Managing Heart Failure in Primary Care: A Case Study Approach

K. Melissa Smith Hayes
Nicole R. Dellise
Editors

Springer

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Editors
K. Melissa Smith Hayes
Assistant Professor
Vanderbilt University School of Nursing
Nashville, TN, USA

Nicole R. Dellise
Director, Structural Heart Program
Director, Center for Advanced Heart Failure Therapy
Centennial Heart
Nashville, TN, USA

ISBN 978-3-031-20192-9 ISBN 978-3-031-20193-6 (eBook)
https://doi.org/10.1007/978-3-031-20193-6

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

K. Melissa Smith Hayes and
Nicole R. Dellise

Dedicated to the past, present, and future heart failure patients we care for, along with our mentors who guide us along the way.

Foreword

It is my honor and privilege to write the foreword for this book that signifies an important contribution to the medical literature, is very much needed, and represents high caliber work from expert authors in the field of heart failure. Heart failure is a global pandemic whose epidemiology is worsening. Unfortunately, recent data suggest that outcomes for these patients at a population level have worsened. Heart failure is a syndrome and hence more complex to diagnose and manage than many other diseases. First, even if the diagnosis is made accurately, the cause of heart failure, which may impact therapy choice, needs to be determined. This requires insights and experience. Second, management is usually complex, requiring individualizing among multiple nonmedical, pharmacological, and device-based interventions. This requires not only insights and experience, but also teamwork. Collaboration, communication, and cooperation between nurses, pharmacists, nutritionists, exercise physiologists, and physicians cannot be overemphasized. No one individual can optimally manage these complex patients' journeys across their lifetime. Third, heart failure has a bidirectional strong association with multiple other comorbidities where heart failure increases the risk of developing and worsening these comorbidities and vice versa. Hence not only some degree of general medical expertise is needed to effectively manage these patients, but also collaboration with other medical specialists is frequently required. Fourth, while science and medicine form the basis of care for these patients, the core depends on compassion and kindness. Patients with heart failure suffer tremendously and sometimes people want to be just heard and understood. Fear of death, fear of breathlessness, fear of suffering, fear of loneliness, etc. are all too human and all too common among patients with heart failure. Addressing these at a humanistic and not merely at a mechanistic level can enhance trust, adherence to self-care, and lifelong relationships between patients, family members, and clinicians. It is with these important perspectives that I find this book to not only be valuable but an essential contribution to the literature. It covers a 360° perspective on a complex topic. Each section and topic are expertly crafted by authors with extensive experience in managing patients with heart failure. I have had the pleasure of working over the years with many of the authors and I can attest to their expertise. This will improve the lives of patients whose clinicians

will have read this book. I wanted to personally congratulate and thank both the editors, Nicole R. Dellise and K. Melissa Smith Hayes, for taking on this challenge and producing a book of this high caliber.

Javed Butler
Distinguished Professor of Medicine, University of Mississippi
Jackson, MS, USA

Senior Vice President, Baylor Scott and White Health
Dallas, TX, USA

President and Chief Research Executive, Baylor Scott
and White Research Institute
Dallas, TX, USA

Preface

The seed for this book was planted a few years ago when we were exploring ways for our nurse practitioner students and primary care colleagues to best receive evidence-based information for taking care of heart failure patients in outpatient clinics. After delivering a presentation titled, "Outpatient Management of Heart Failure in Primary Care," at a national conference, Springer Nature publishing company contacted us to see if we would be willing to expand on this topic for a book. The project became a reality when well-respected colleagues and experts, in both primary care and heart failure, agreed to join us in growing our seed into a multifaceted book to assist primary care providers in providing the best care for the complex needs of the heart failure patient.

It is evident the volume of information needed to safely practice as a primary care provider is vast and often a "deep dive" into specific disease processes such as heart failure is not possible. The incidence and prevalence of heart failure continue to rise, especially as our population is aging and living longer. This increases the probability every clinician in the primary care space will have patients with heart failure at some point in time. It is hoped this book will provide a comprehensive resource for clinicians taking care of heart failure patients. Within the 19 chapters, they can find answers and understanding supported by the most up-to-date evidence and clinical guidelines. In fact, in April 2022 ACC/HFSA/AHA published new heart failure guidelines just in time for us to incorporate the latest findings and strongest evidence throughout the chapters in this book.

In this book, there are five parts. The first part answers the question "What is Heart Failure?" The second and third parts address the clinical assessment of heart failure and heart failure management including transitions of care and goals of care. The fourth part takes a closer look at heart failure and the comorbid conditions that can be challenging to manage in primary care. In each chapter, you will find at least one case study as well as clinical pearls. An entire chapter is dedicated to addressing the medications that should be avoided in the heart failure population. The fifth and final part explores challenging case studies. You will notice neither hypertension nor depression has specific chapters. The treatment of hypertension in heart failure is patient-specific and usually addressed with the medications that are given for heart failure. Depression is common for heart failure patients and should be treated according to published guidelines for depression and practice site-specific protocols.

The number of hours spent on this ambitious endeavor cannot be quantified. All in all, 33 authors (including the two editors) contributed to this book, a vast majority of whom are advanced practice nurses. The authors include 23 advanced practice nurses, 9 heart failure specialist physicians, and one pharmacist. Most, if not all, of the authors have clinical practice responsibilities with either primary care or heart failure populations. Many of the authors hold academic faculty positions as well. Therefore, it is undeniably a generous gift that each of the authors gave to this project and we are sincerely grateful for their contribution and dedication. We can only hope that each time this book is opened, the genius within the pages is recognized and advantageous to not only the provider seeking guidance but ultimately to heart failure patients, who have truly been the motivation behind the hours of work poured into this book.

Nashville, TN, USA — K. Melissa Smith Hayes
Nashville, TN, USA — Nicole R. Dellise

Acknowledgments

It has been our privilege and honor to work with the group of authors that devoted their time and expertise to the content in this book. We are particularly indebted to our authors because the proposal for this book was accepted in the Fall of 2020, at the height of the COVID-19 pandemic in the United States. Over the past three years, they have been healthcare providers at the front lines, faculty members revising curricula for distance learning, family members of the very ill, grieving the loss of loved ones or struggling to work through personal illness. Despite all these responsibilities, each author delivered exceptional work. We recognize their extraordinary efforts and dedicated hours that resulted in the completion of this project.

Among the authors, you will find world-renowned heart failure cardiologists, respected leaders in nursing academia, experienced nurses and advanced practice nurses, expert heart failure pharmacologists, and past presidents of the American Association of Heart Failure Nursing organization and the Heart Failure Society of America. The experience among authors, in both primary care and heart failure, is well highlighted in this book. We are honored to share and disseminate their collaborative work.

To our families and the families of each author, we are very appreciative of the support you gave your loved author as they spent time in the early mornings, evenings, late nights, and weekends to meet deadlines. You too are acknowledged for your patience and understanding during those times. We salute with gratitude our families for all their love and support.

In the ninth hour, our colleague Angela Morehead, DNP, FNP-BC, came to our rescue and assisted greatly in final editing and formatting. We want to acknowledge and thank her immensely for her editing powers and flexibility in helping to finalize the manuscript.

Lastly, a very special thank you to Nathalie L'Horset-Poulain, our Senior Publishing Editor, for inviting us to create this project and guide it to fruition. We also are so thankful for the devoted attendance, direction, and patience Priyadharshini Aruchamy (Project Coordinator) gave to us throughout this process. To the Springer Nature team, we thank you for publishing this important work.

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Editors and Contributors

About the Editors

K. Melissa Smith Hayes, DNP, ANP-BC, CHFN is a board-certified Adult Nurse Practitioner and a certified heart failure nurse. Melissa began her nursing career in 1992 at Vanderbilt University Medical Center in the Medical Intensive Care Unit after graduating from Harding University with her BSN. Melissa earned her MSN degree from Vanderbilt University in 1994 and her DNP degree from Duke University in 2013. Heart Failure became Melissa's primary area of interest in 2001 when she started working in the Vanderbilt Heart Failure Program as a nurse practitioner. Since then, she has maintained a clinical practice in heart failure once a week and is an Assistant Professor of Nursing at Vanderbilt University School of Nursing in Nashville, Tennessee. Melissa teaches in the Adult-Gerontology Primary Care Nurse Practitioner program and the Doctor of Nursing Practice program at Vanderbilt University School of Nursing. Her scholarly interests related to heart failure include the transition of care from hospital to home, post-hospitalization clinic visits, and literacy-appropriate heart failure education. Melissa is actively involved with the American Association of Heart Failure Nurses (AAHFN) and is chair of the Together in Heart Failure (TIHF) website task force which is managed by AAHFN as part of the Heart Failure Patient Foundation. Melissa is a founding member of the Middle Tennessee Heart Failure Journal Club and speaks nationally on the subject of heart failure. When Melissa is not working you are most likely to find her jogging around the block, reading good books, playing with her dog, or spending time with her family and friends.

Nicole R. Dellise, DNP, FNP-BC, CHFN is a board-certified Family Nurse Practitioner and certified heart failure nurse. Nicole is the Structural Heart Program Director and the Director of the Center for Advanced Heart Failure Therapy at Centennial Heart in Nashville, TN. She is also an Instructor of Nursing in the Family Nurse Practitioner Program at Vanderbilt University School of Nursing. Nicole began her career as a heart failure nurse in 2008. She then received her Master's in Nursing from Belmont University in 2012 followed by her Doctorate in Nursing in 2017. Nicole has a strong passion for improving heart failure care across the continuum. She has led hospital-wide heart failure quality improvement projects and developed educational programs for hospital nursing staff. Additionally, Nicole has served as a peer reviewer for a reputable heart failure nursing journal. Nicole is a published author in the area of heart failure. She has spoken locally and nationally. Nicole is a certified yoga instructor and in her spare time, she teaches yoga classes and enjoys spending time with her family and friends.

Contributors

Terri L. Allison, DNP, ACNP-BC, FAANP Assistant Dean for Academics, Doctoral Nursing Practice, Professor, Vanderbilt University School of Nursing, Nashville, TN, USA

Kaushik Amancherla, MD Instructor in Medicine, Division of Cardiovascular Medicine, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

Angelina Anthamatten, DNP, FNP-BC Assistant Professor of Nursing, Vanderbilt University School of Nursing, Nashville, TN, USA

Javed Butler, MD, MPH, MBA President and Chief Research Executive, Baylor Scott and White Research Institute, Dallas, TX, USA

Senior Vice President, Baylor Scott and White Health, Dallas, TX, USA

Distinguished Professor of Medicine, University of Mississippi, Jackson, MS, USA

Leah A. Carr, MSN, CRNP, ACNP-BC Heart Failure Nurse Practitioner, The Heart Group of Lancaster General Health/PENN Medicine, Lancaster, PA, USA

Zachary L. Cox, PharmD, FHFSA Professor, Department of Pharmacy Practice, Lipscomb University College of Pharmacy, Nashville, TN, USA

Heart Failure Clinical Pharmacist, Department of Pharmacy, Vanderbilt University Medical Center, Nashville, TN, USA

Beth Towery Davidson, DNP, ACNP-BC, CCRN, CHFN, FHFSA Advanced Clinical Expert, CardioMEMS™, Heart Failure, Abbott, Pleasanton, CA, USA

Nicole R. Dellise, DNP, FNP-BC, CHFN Director, Structural Heart Program, Centennial Heart, Nashville, TN, USA

Director, Center for Advanced Heart Failure Therapy, Centennial Heart, Nashville, TN, USA

Instructor, Vanderbilt University School of Nursing, Nashville, TN, USA

Krista R. Dobbie, MD Staff Physician, Department of Palliative Medicine and Supportive Care, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

J. Travis Dunlap, PhD, ANP-BC Assistant Professor, Vanderbilt University School of Nursing, Nashville, TN, USA

Melissa Glassford, DNP, FNP-C Assistant Professor, Vanderbilt University School of Nursing, Nashville, TN, USA

Deepak K. Gupta, MD, MSCI Associate Professor of Medicine, Division of Cardiovascular Medicine, Vanderbilt Heart and Vascular Institute, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

Christine M. Hallman, DNP, APRN, ACHPN, NP-C Palliative Care Nurse Practitioner, Palliative Care Services, MedStar Health Washington Hospital Center, Washington, DC, USA

Julie Hannah, MSN, FNP-C Family Nurse Practitioner, Main Street Health, Nashville, TN, USA

Donna Harmon, MSN, ACNP-BC, CHFN Heart Failure Nurse Practitioner, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

Vanderbilt University Medical Center, Nashville, TN, USA

K. Melissa Smith Hayes, DNP, ANP-BC, CHFN Heart Failure Nurse Practitioner, Vanderbilt-Meharry Cardiology, Nashville General Hospital @ Meharry, Nashville, TN, USA

Assistant Professor, Vanderbilt University School of Nursing, Nashville, TN, USA

Leslie W. Hopkins, DNP, APRN, BC, FNP-BC, ANP-C Adult Gerontology Primary Care Academic Director, Associate Professor, Vanderbilt University School of Nursing, Nashville, TN, USA

Amy Howard, MSN, ACNP-BC, CHFN Heart Failure Nurse Practitioner, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

Linda Howerton, MSN, ACNP-BC, CCRN, CHFN Heart Failure Nurse Practitioner, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

Joan King, PhD, ACNP-BC, ANP-BC, FAANP Professor Emeritus, Vanderbilt University School of Nursing, Nashville, TN, USA

Acute Care Nurse Practitioner, Vanderbilt Preanesthesia Evaluation Clinic, Vanderbilt University Medical Center, Nashville, TN, USA

Anupam A. Kumar, MD Clinical Fellow, Division of Cardiovascular Medicine, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

JoAnn Lindenfeld, MD Professor of Medicine, Samuel S. Riven, MD, Director in Cardiology, Vanderbilt University Medical Center, Nashville, TN, USA

Lisa Mendes, MD Professor of Medicine, Division of Cardiovascular Medicine, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

Tara U. Mudd, MSN, APRN, NP-C Instructor, Vanderbilt University School of Nursing, Nashville, KY, USA

Cardiology/Electrophysiology Nurse Practitioner, Norton Heart & Vascular Institute Heart Rhythm Center AFib Clinic,, Louisville, KY, USA

Michelle Mason Parker, MSN, APRN, NP-C Heart Failure Nurse Practitioner, Vanderbilt Heart Outreach Knoxville TN Clinic, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

Douglas J. Pearce, MD, FACC, FHFSA Associate Professor of Medicine, University of Tennessee Health Sciences Center, Nashville, TN, USA

Mary Lauren Pfieffer, DNP, FNP-BC Associate Professor, Vanderbilt University School of Nursing, Nashville, TN, USA

Courtney J. Pitts, DNP, MPH, FNP-BC, FAANP Family Nurse Practitioner Academic Director, Professor, Vanderbilt University School of Nursing, Nashville, TN, USA

Marilyn A. Prasun, PhD, CCNS, CNL, CHFN, FAHA Carle BroMenn Medical Center Endowed Professor, Mennonite College of Nursing, Illinois State University, Normal, IL, USA

Lisa D. Rathman, MSN, CRNP, ACNP-BC, CHFN Heart Failure Nurse Practitioner, The Heart Group of Lancaster General Health/PENN Medicine, Lancaster, PA, USA

Roy S. Small, MD, FACC Medical Director, Clinical Research, The Heart Group of Lancaster General Health/PENN Medicine, Lancaster, PA, USA

Kelly D. Stamp, PhD, NP-C, RN, CHFN, FAHA, FAAN Associate Dean of Academic Programs, Associate Professor, University of Colorado Anschutz, College of Nursing, Aurora, CO, USA

Mark Wigger, MD Assistant Professor of Medicine, Medical Director of the Comprehensive Advanced Heart Failure Outreach Clinics, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

Jessica B. Williams, BSN, RN, CCRN Program Coordinator, CVICU, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

Part I

What Is Heart Failure?

Chapters one and two explore the definitions and pathophysiology of heart failure. These two chapters were designed for the reader to gain a deeper understanding of the complexities of heart failure and the far-reaching burden this disease places on society. The information provides comprehensive background information and sets the stage for subsequent chapters.

Pathophysiology of Heart Failure

1

Joan King

1.1 Introduction

Heart failure is a complex syndrome that historically has been referred to by a number of terms. The most common term has been "congestive heart failure" (CHF). It has also been divided into "left-sided heart failure" and "right-sided heart failure" based on symptomatology. In the past heart failure has also been defined by how well the left ventricle either contracts or fills. If the left ventricle showed signs that it could not contract effectively it was termed systolic failure. If the left ventricle had become very stiff and could not fill adequately, it was termed diastolic failure. Refining the concept of whether it is a "contraction problem" or a "filling problem" has led to focusing on the left ventricular ejection fraction (LVEF). Based on LVEF, heart failure is currently divided into three new categories: Heart Failure with reduced Ejection Fraction (HFrEF), Heart Failure with preserved Ejection Fraction (HFpEF), and a middle level of heart failure called Heart Failure with midrange Ejection Fraction (HFmrEF) [1]. By refining the definition of heart failure with respect to LVEF criteria, it has provided new guidelines for management of patients with heart failure. For the purpose of this book, heart failure will be discussed in terms of HFrEF, HFmrEF, and HFpEF.

J. King (✉)
Vanderbilt University School of Nursing, Nashville, TN, USA

Vanderbilt Preanesthesia Evaluation Clinic, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: joan.king@vanderbilt.edu

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_1

1.2 Definition of Heart Failure

The simplest definition of heart failure (HF) is the failure of the heart to pump enough blood to meet the body's demands. Heart failure is a complex syndrome that involves the interplay between the heart, the systemic and pulmonary vasculatures, the kidneys, and the sympathetic nervous system. With HF each system is impacted. While each system attempts to provide means of correcting the problem, the interplay between systems becomes counter-productive and actually contributes to the pathophysiological process. This pathophysiological process involves a series of complex neurohormonal responses. It represents the vicious cycle of failure that can easily develop if appropriate treatment is not implemented.

Historically heart failure was defined by whether the left ventricle or the right ventricle failed. However, frequently over time both ventricles begin to fail producing a combined failure. Exploring the pathophysiology more closely, it has become evident that in some patients the left ventricle does not contract well during systole, and in other patients the left ventricle is stiff or noncompliant and does fill appropriately during diastole. Clinically the ability to determine how well the heart contracts can be measured by examining the left ventricular ejection fraction (LVEF). Left ventricular ejection fraction represents the percentage of blood pumped out of the left ventricle per beat. Using the LVEF as the marker of left ventricular function, the newest nomenclature for heart failure is Heart Failure with a reduced Ejection Fraction (HFrEF) with an LVEF less than or equal to 40% [2], Heart Failure with a midrange Ejection Fraction (HFmrEF) with an LVEF between 41% and 49% [3], and Heart Failure with a preserved Ejection Fraction (HFpEF) with a LVEF equal to or greater than 50% [1–3]. When patients have HFrEF, the low LVEF implies for any given about of blood in the left ventricle at the onset of systole only 40% or less is actually ejected into the systemic circulation. For example, with HFrEF if there is 100 cc of blood in the left ventricle at the start of systole and the LVEF is only 40%, the amount ejected into the systemic circulation or the stroke volume is only 40 cc. In comparison with HFpEF, the left ventricle is noncompliant and is not filling well during diastole. Hence if the left ventricle hypothetically fills with 50 cc of blood and ejects 50% of that volume, the LVEF is 50%, but the stroke volume is only 25 cc. Hypothetically both examples illustrate a scenario where the stroke volume does not produce a sufficient cardiac output to meet the body's demands. Given the formula for cardiac output (CO) as the stroke volume (SV) times the heart rate (HR) {$CO = SV \times HR$}, in all three forms of HF (HFrEF, HFmrEF, and HFpEF), the stroke volume is not sufficient to produce an adequate cardiac output. By identifying the degree of failure for each patient based on LVEF, it allows clinicians to match the treatment strategy to the degree and type of failure.

1.3 Factors that Govern Systolic Function

There are four main factors that govern systolic function: *preload*, *afterload*, *heart rate*, and *the contractile state of the myocardium*. By definition preload is the amount of blood in the ventricle at the end of diastole just prior to systole. The preload can be measured with a pulmonary artery catheter. By measuring the pressures within a pulmonary artery the pulmonary artery wedge pressure (PAWP) [also called the pulmonary capillary wedge pressure (PCWP)] can be measured. The PAWP reflects the left ventricular end diastolic pressure (LVEDP), or the pressure within the left ventricle at the end of diastole. A normal PAWP is 6–12 mmHg [4]. The afterload is the amount of work the heart must exert to open the aortic valve, and it is measured as the systemic vascular resistance (SVR). The normal range for the SVR is 800–1200 dynes/s/cm^5 [5]. Heart rate also contributes to the ventricular systolic function. As the heart rate increases in response to an increase in sympathetic nervous system (SNS) stimulation, the diastolic filling time is reduced which impacts the left ventricular diastolic volume [6]. If the heart rate becomes too rapid, it has the potential of reducing both the stroke volume and the cardiac output. In addition, a reduction in diastolic filling time also reduces coronary artery perfusion, since the perfusion to the myocardium itself occurs during diastole. This then can lead to a decrease in the function of the myocardium itself. The fourth factor that governs systolic function is the contractile state of the myocardium. Many factors can decrease contractility. Hypoxia, acidosis, ischemia, a prior myocardial infarction, and hypothermia all can decrease the ability of the myocardium to contract effectively. With heart failure there are significant changes in the patient's preload, afterload, heart rate, and contractile state that individually as well as collectively reduce the heart's ability to produce an effective cardiac output.

1.4 Neurohormonal Mechanisms

Adding to the complexity of the pathophysiology of heart failure, the neurohormonal mechanisms involving the SNS and the renin–angiotensin–aldosterone (RAA) system become activated. As the SNS becomes stimulated the arterial vascular tone increases and arterial vasoconstriction is increased. The inherent goal of the SNS stimulation is to improve the blood supply to the vital organs, but at the expense of increasing systemic vascular resistance. In heart failure the increase in systemic vascular resistance contributes to the progression of HF by increasing the workload on the heart. The systemic vascular resistance is calculated as [(MAP-mean RAP)/CO × 80], where MAP is the mean arterial pressure and RAP is the right atrial pressure [7]. Since the systemic vascular resistance represents the amount of work the heart must exert, as vasoconstriction increases the systemic vascular resistance the workload on the heart increases. The workload on the heart also

increases as the heart rate increases. As the preload increases and systemic vascular resistance increases, the force of contraction can increase if the heart is healthy. But for the heart in failure, the increase in the required energy to produce a forceful contraction is limited. The rise in required workload from the increase in preload, systemic vascular resistance, and heart rate increases the myocardial workload to the point that the heart begins to fail and the cardiac output begins to decrease.

The decrease in cardiac output then decreases the oxygenated blood supply to vital organs. One organ that is particularly sensitive to the reduction in cardiac output is the kidney. When the renal perfusion is decreased, the glomerular filtration rate (GFR) decreases and the RAA system is activated. The RAA system then stimulates the release of aldosterone which leads to renal sodium and water retention. Ideally the retention of water increases the preload, with the underlying goal to increase the cardiac output. But with heart failure the increase in preload negatively impacts the heart's ability to achieve an adequate cardiac output. As the preload becomes too great, the force of contraction decreases and the cardiac output declines. The drop in the cardiac output can be plotted on the cardiac function curve noting that as the preload or PAWP rises beyond a point, the cardiac output begins to drop (Fig. 1.1). In addition, the RAA system stimulates the activation of angiotensin II which is a systemic vasoconstrictor. This also causes the release of vasopressin or antidiuretic hormone (ADH) from the posterior pituitary. Both angiotensin II and vasopressin increase the systemic and peripheral vascular resistance, and ADH contributes to a further increase in preload [4]. As the systemic vascular resistance continues to increase, the workload on the myocardium also increases which contributes to a further reduction in the cardiac output.

While both the SNS and RAA systems strive to increase the preload in order to increase the left ventricular end diastolic volume and the subsequent stroke volume and cardiac output, their efforts become counter-productive. Ideally in terms of the Frank Starling law of the heart, by increasing the preload the goal is to achieve the

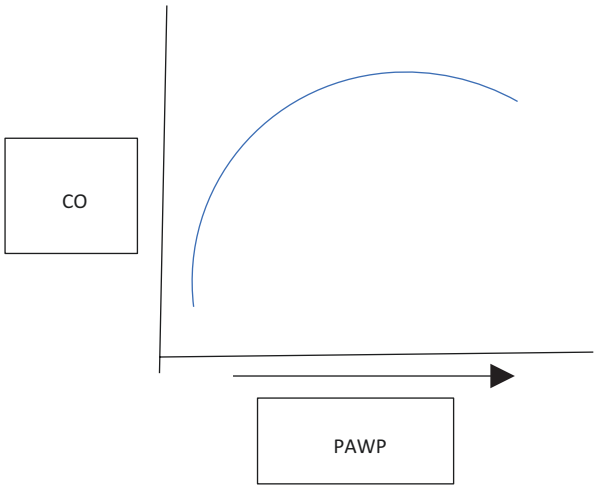

Fig. 1.1 The cardiac function curve: the Frank Starling law of the heart

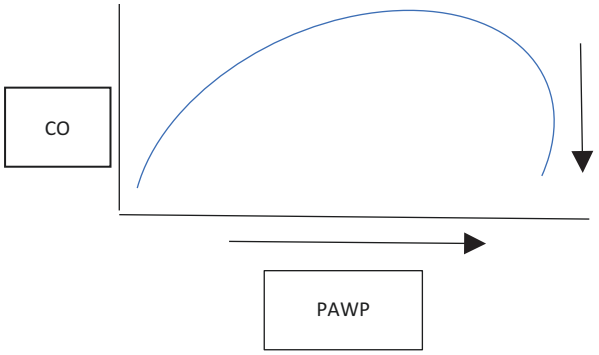

Fig. 1.2 The cardiac function curve with heart failure

ideal alignment of actin and myosin filaments within the cardiac muscle itself, in order to obtain the needed contraction for an effective cardiac output [6]. However, as the preload continues to increase, actin and myosin are no longer in an ideal alignment and the cardiac output begins to decrease (Fig. 1.2). Also in the early phase of HF, atrial and brain natriuretic peptides (ANP and BNP) are released by cardiac myocytes in response to the increase in preload and the subsequent stretch within atria and the ventricles. ANP and BNP then attempt to decrease renal sodium and water reabsorption, as well as produce dilation of the systemic blood vessels [8]. But as the stimulation of the SNS and RAA system continue, the natriuretic peptides fail to counteract the SNS and the RAA system, and the natriuretic peptides become degraded by the enzyme neprilysin [9]. After a given point, which varies for each patient, the cardiac output declines as the left ventricular end diastolic volume, preload, and PAWP increase, and a vicious cycle develops (Fig. 1.2). As the cardiac output drops further, SNS continues to be stimulated, which further increases the systemic vascular resistance, and adds to the workload on the heart. The kidneys continue to activate the RAA system promoting more sodium to be retained, which leads to more fluid retention and the preload continues to increase. The outcome is an added reduction in the cardiac output. Since there is a resistance to the forward flow of blood into the systemic circulation from both an increase in systemic vascular resistance and a decrease in contractility, venous congestion develops in the pulmonary bed, and oxygen exchange decreases. As the hypoxia within the pulmonary circulation increases, the pulmonary vascular resistance (PVR) increases. This then increases the workload on the right ventricle. However, the right ventricle is not a strong pumping chamber, and the venous congestion progresses into the right atrium and then into the general venous circulation. Clinically this results in an elevated central venous pressure (CVP), elevated jugular venous distension (JVD), and hepatomegaly. The increase in preload also takes a toll on the left ventricle. As the preload continues to increase, the left ventricle dilates. And as the systemic vascular resistance forces the left ventricle to work against higher systemic pressures, it causes the left ventricle to increase in muscle mass or hypertrophy. As the neurohormonal components continue to be stimulated, they become more counter-productive. Plotting the cardiac output on the cardiac

function curve, it becomes apparent that for every unit increase in PAWP there is a further decrease in the cardiac output (Fig. 1.2).

While the cardiac function curve helps to illustrate the negative consequences of too high a PAWP, it is important to note that the cardiac function curve is not stagnant. Normal SNS stimulation and positive inotropic drugs can move the cardiac function curve up and to the left and improve the cardiac output. But in heart failure, hypoxia, negative inotropic drugs, ischemia, and too great a preload or systemic vascular resistance can move the cardiac function curve down and to the right. As the cardiac function curve moves down and to the right, it implies that as the preload or PAWP increases there is an actual further decrease in the cardiac output. Specifically with HF, an increase in the preload, as measured by an increase in the PAWP, decreases contractility which moves the cardiac function curve down and to the right even more. Graphically Fig. 1.3 demonstrates the more the left ventricle fails, the greater the shift in the cardiac function curve. Hence in HF for any increase in the PAWP there is a further decrease in the cardiac output (from A to B in Fig. 1.3).

Ideally the compensatory mechanisms within the neurohormonal responses should restore the cardiac output and subsequently meet the body's metabolic demands. However, the SNS and the RAA system continue to become counterproductive. The heart rate increases making the myocardium work harder, and as tachycardia develops it reduces diastolic filling time. The SNS stimulation also increases circulating catecholamines which may promote dysrhythmias. The increase in systemic vascular resistance continues to make the left ventricle work against higher pressures. The kidneys continue their role of trying to improve their blood supply through the RAA system. Hence the preload is increased even more, the systemic vascular resistance is increased, and the heart begins to dilate and hypertrophy. As the myocardium hypertrophies, it decreases the coronary artery perfusion and can potentiate myocardial ischemia. In addition, prolonged SNS

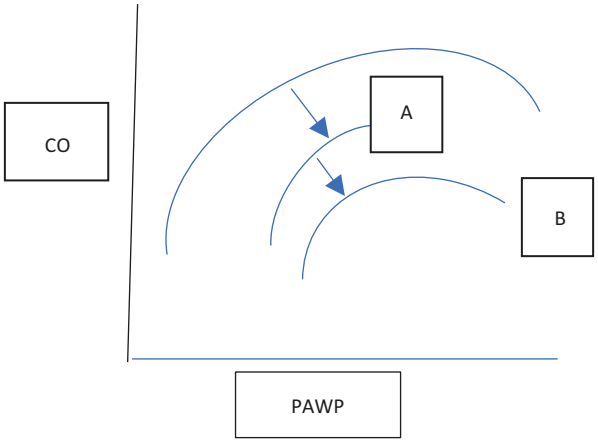

Fig. 1.3 Decreases in cardiac output with heart failure

stimulation, prolonged angiotensin II, and secretion of aldosterone produce changes in the myocardial fibers which results in negative remodeling of the myocardium. This negative remodeling, which actually changes the shape of the heart muscle itself, further reduces the cardiac output and contributes to further progression of HF [5]. Without appropriate medical and nursing interventions, a vicious cycle ensues with chronically elevated heart rate, increase in fluid retention, and a continual downward spiraling cardiac output and decompensated HF develops. Understanding the neurohormonal responses and the complexity of the pathophysiology provides the foundation for the treatment of HF patients. Chapter 6, discusses the treatment of HFrEF which includes beta-blockers help to curtail the SNS stimulation and angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) angiotensin receptor-neprilysin inhibitors (ARNi) and mineralocorticoid receptor antagonists (MRA) impact the RAA system, and diuretics and sodium-glucose transporter 2 inhibitors (SGLT2i) can begin to help to reduce fluid retention [1].

For patients who fail to respond to treatment and develop acute decompensated heart failure (ADHF) or whose cardiac output has dropped dramatically, cardiogenic shock may develop. Hemodynamically cardiogenic shock is defined as a cardiac index less than 2.2 L/min/kg/m^2 [10, 11]. A classic symptom of cardiogenic shock is pulmonary edema. As the hydrostatic pressure within the pulmonary circulation becomes greater than the colloidal osmotic pressure, fluid leaks into the interstitial spaces and into the alveoli. If a patient is intubated or begins productive coughing, pink frothy sputum may be evident. Other clinical manifestations of cardiogenic shock are an elevated PAWP above 15 cm water pressure, profound hypotension with a systolic BP less than 90 mmHg, an elevated SVR, and bilateral pulmonary infiltrates [11]. Also the vital signs will reflect both an effort to increase heart rate, but a drop in SaO_2 and extreme shortness of breath will develop if the patient is not already intubated. Because of the compensatory mechanisms still trying to rescue the circulatory system, there will be a decrease in renal perfusion and hence a decrease in GFR and urinary output.

1.5 Correlation of Pathophysiology and Symptomology

Focusing on symptomatology, it is often beneficial to think about symptoms stemming from an increase in blood volume within the lungs, or pulmonary venous congestion, as well as an increase in blood volume within the general venous circulation. As the left ventricle fails in its ability to pump blood forward into the systemic circulation, it increases venous congestion within the pulmonary circulation. As the pulmonary venous congestion increases, it decreases the ability to achieve adequate oxygen exchange. Specifically, as the hydrostatic pressure within pulmonary vessels increases, it forces fluid to leave the vascular bed and cross into the interstitial space and then into the alveoli. This then inhibits oxygen exchange and contributes to the patient's sense of being short of air (SOA) and dyspnea on exertion (DOE). As HF worsens, the shortness of air can progress to orthopnea,

paroxysmal nocturnal dyspnea (PND), and dyspnea at rest [12], and a progressive dry cough may develop especially when the patient is recumbent [13]. In addition, the patient may note an increase in fatigue as the HF progresses. Physical assessment findings that parallel these symptoms include a drop in oxygen saturation (SaO_2), the presence of bilateral crackles or adventitious breath sounds, dullness to percussion noting a possible pleural effusion, and the evidence of pulmonary congestion on chest X-ray. In addition, as the left ventricle becomes less compliant, S3 and/or S4 may be heard. An S3 may be heard during the passive flow of blood from the left atrium into the left ventricle, and an S4 may be heard when the left atrium contracts or during "atrial kick." When both S3 and S4 are heard it is called a summation gallop. The dilation of the left ventricle from the increase in preload and hypertrophy of the myocardium related to the increase in SVR may be evident on chest X-ray as cardiomegaly and on 12 Lead ECG as left ventricular hypertrophy.

As venous congestion within the pulmonary circulation increases, it increases the pressure within the pulmonary bed itself, which increases the workload on the right ventricle. As the right ventricle begins to fail, the venous congestion is reflected back into the general venous circulation. While the venous circulation is a high capacitance system and it can handle an increase in volume with little change in pressure, eventually the increase in venous congestion produces venous distension within the liver and the portal veins and lower extremities. Physical examination then begins to note an elevated CVP and an increase in JVD, liver enlargement or hepatomegaly, ascites, and dependent edema. As the volume within the liver increases, pressing on the liver may produce a rise in the JVD by 1 cm or greater which is called a positive hepatojugular reflux [12]. Other patient symptoms that reflect HF are the increase in fluid retention noting that a 2.2 pound increase in weight reflects 1 L of retained fluid, and a decrease in perfusion to the gastrointestinal track may produce symptoms of abdominal distention and pain and anorexia.

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Heart Failure Across the Population

2

Joan King

2.1 Epidemiology

Over 6.2 million adults 20 years of age or older have been diagnosed with heart failure [1]. However, heart failure is frequently viewed as primarily a disease of aging, with 75% of those having heart failure being over the age of 65, and with 10% of individuals 80 years of age or older developing heart failure [2]. In terms of incidence, individuals over the age of 80 are six times more likely to develop heart failure than adults between the ages of 46–64 [3]. Given the statistics pointing to heart failure as a syndrome impacting the older adult, the normal changes that occur with aging take on greater significance. Within the cardiovascular system, age-related changes that occur include a decrease in ventricular and arterial compliance which leads to impaired diastolic filling within the ventricles and an increase in peripheral vascular resistance, respectively. As discussed in Chap. 1, both a decrease in diastolic filling and an increase in vascular resistance are key factors in the development and progression of heart failure. Changes in the SA node with a decrease in pacemaker cells can also lead to dysrhythmias that may complicate the management of heart failure. The progression of atherosclerosis as one ages also can lead to the development of coronary artery disease and myocardial infarctions or ischemic events, both of which may lead to heart failure. Within the sympathetic nervous system (SNS) there is a decrease in SNS stimulation, which can contribute to a decrease in stroke volume and cardiac output and an overall decrease in cardiac reserve [3].

In terms of the impact on society, there are more than one million new cases of heart failure diagnosed yearly [1, 2], with more than a current annual cost of

J. King (✉)
Vanderbilt University School of Nursing, Nashville, TN, USA

Vanderbilt Preanesthesia Evaluation Clinic, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: joan.king@vanderbilt.edu

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_2

$30.7 billion [4]. By 2030 the annual cost of heart failure is expected to be $70 billion, with an expected eight million individuals having heart failure [5]. This places a huge burden on patients, their families, as well as society. And in spite of current treatment strategies the mortality rate is 22–40% within the first year of hospitalization [6] and 42% within 5 years [7]. There are also gender differences with a higher mortality rate for men (59%) than women (45%) [3]. In 2018 alone there were 379,800 deaths attributed to heart failure [4]. While heart failure is more prevalent generally in men, it is more prevalent for women in nursing homes [3]. In terms of ethnic differences, non-Hispanic Black patients have a higher incidence of heart failure, including the highest death rate per capita [8] which may be attributed to their higher incidence of hypertension, diabetes, and genetic factors [6].

2.2 Etiology

In exploring the etiology of heart failure, heart failure frequently is divided into ischemic and non-ischemic causes. Two-thirds of the patients with Heart Failure with a reduced Ejection Fraction (HFrEF) have ischemic heart failure related to coronary artery disease and subsequent myocardial infarction or an ischemic event [7]. Current statistics indicate that appropriately 50% of hospital admissions are related to HFrEF [1]. However, for those admitted with Heart Failure with a preserved Ejection Fraction (HFpEF), the underlining etiology is most often a non-ischemic event [9]. These non-ischemic events frequently are attributed to impaired ventricular filling secondary to a decrease in ventricular compliance [10]. The most common cause of non-ischemic heart failure is hypertension, which can be defined as both a cause of heart failure and a modifiable risk factor [6, 11]. However non-ischemic heart failure may also develop as the result of severe valvular dysfunction such as aortic or mitral stenosis or regurgitation, a stunned myocardium as in Takotsubo, dilated, hypertrophic, or peripartum cardiomyopathy or as the result of congenital heart defects [9]. Other causes of non-ischemic heart failure include post-drug administration as with doxorubicin, or post-radiation treatment, as well as autoimmune diseases such as lupus, rheumatoid arthritis, or infiltrative diseases such as amyloidosis or sarcoidosis which can cause restrictive cardiomyopathy [7]. Anemia, hyperthyroidism, and hypothyroidism may also lead to non-ischemic heart failure. Pericardial pathology such as cardiac tamponade or pericardial constriction can also lead to non-ischemic heart failure [9]. But structural changes are not the only etiology for the development of non-ischemic HF. Atrial fibrillation with the loss of atrial kick and subsequent rapid ventricular rates can reduce both the stroke volume and the cardiac output. Obstructive sleep apnea and the associated increase in workload on the heart can also lead to the development of heart failure. For patients in the intensive care unit (ICU), positive pressure ventilation and positive end-expiratory pressure (PEEP) reduce preload and can lead to reduced stroke volume and cardiac output. But there are also a number of modifiable risk factors that can contribute to the development of heart failure. These include diabetes, cigarette smoking, elevated cholesterol, obesity as well as the use excessive use of alcohol,

and the use of cocaine or amphetamines [6, 7]. For the older adult, self-treatment with NSAIDs or COX-2 inhibitors can attribute to the development of heart failure [3].

2.3 Classification and Stages of Heart Failure

While heart failure can be categorized as either ischemic or non-ischemic in terms of etiology, there are a number of approaches to stratifying a patient's heart failure (HF) based on symptomatology. The two most commonly used classification systems are the ACC/AHA Stages of Heart Failure (ACC/AHA stages) and the New York Heart Association Functional Classification (NYHA class) (Table 2.1).

Comparing the two major classification systems, the ACC/AHA system begins by specifically focusing on patients who are *at risk* for developing heart failure. The goal for Stage A is to intervene early in a patient's management history in order to prevent comorbidities or address modifiable risk factors that may lead to heart failure [6]. This would include managing a patient's hypertension and facilitating the achievement of recommended blood pressure goals, as well as focusing on the appropriate goals for other comorbidities. These comorbidities frequently include diabetes, weight control, hyperlipidemia, and obstructive sleep apnea. Inherent in the application of the ACC/AHA stages is the incorporation of patient education with an emphasis on both the short-term goals and the long-term consequences of poorly controlled comorbidities [6]. As providers develop guideline-directed medical therapy (GDMT) plans for each patient, it is important that psychosocial issues that may impact a patient's ability to physically, psychologically or financially adherence to any GDMT be addressed. For example, in Stage A, a provider may include specific recommendations to reduce the intake of carbohydrates and limit

Table 2.1 The ACC/AHA stages of heart failure and the NYHA functional classification system

ACC/AHA stages of heart failure
A. High risk: For developing HF but without any structural changes or damage and no symptoms
B. Pre-HF: Presence of structural heart disease but no evidence of increase in filling pressures or persistently elevated troponin levels
C. Symptomatic HF: Presence of structural heart disease with *prior or current* HF symptoms that are responsive to treatment
D. Advanced HF: Symptoms that interfere with activities of daily living that are refractory to conventional therapy and may require specialized interventions such as ventricle assist devices, transplantation, or palliative care
NYHA functional classification
I. No physical limitations: Ordinary physical activity does not cause symptoms
II. Slight physical limitations with symptoms of HF with normal physical activity
III. Pronounced physical activity limitations with minimal exertions causing symptoms
IV. Unable to perform any physical activity without HF symptoms or HF symptoms at rest

Heidenreich et al. [8], LaRue and Joseph [7], Bashore et al. [2], Jennings [12]

the usage of salt. While these recommendations are very valid, the provider needs to assess whether the patient can afford to make the necessary changes. For some patients in lower socioeconomic levels replacing canned or processed foods with fresh fruits and vegetables and high-quality protein may not be financially feasible. Transportation, work schedules, and family demands also need to be taken into consideration when GDMT plans are developed. For example, while recommending a weekly exercise schedule to facilitate blood pressure, weight, and glucose control, issues related to feasibility need to be addressed. Questions that need to be explored include time constraints from both work and family responsibilities, safety, or physical limitations that may limit the ability to exercise. Addressing and incorporating physical and psychosocial restraints into GDMTs facilitates the development of patient specific plans of care, with the goal of increasing patient adherence.

While the NYHA classification system does not explicitly address the at-risk population, the same issues related to supporting patient adherence apply. As a patient develops symptoms of heart failure, both within the ACC/AHA and the NYHA systems, it is important that the social determinants of health are addressed in the development of patient specific GDMT plans. As a patient becomes more symptomatic and more frequent clinic visits are needed, individualized social determinants need to be continually addressed. As already stated issues such as transportation, work, and family responsibilities have the potential to derail well-developed treatment plans, as well as language barriers and insurance issues. Even the use of telehealth access has social and economic implications for each patient. Computer access and internet feasibility and knowledge have the ability to either support the goals of treatment or isolate the patient even more from the health care system. As new GDMT plans are developed, it is important that the patient fully understands how the changes in treatment are directed toward optimizing the patient's health status within the complex pathophysiology of heart failure. The patient also needs to recognize that they are a vital member of their heart failure team. Their adherence to any given plan of care is critical, as well as their willingness to openly communicate problems and issues that may develop. The ultimate goal within each ACC/AHA stage or NYHA class is to try and prevent the downhill spiral into refractory heart failure. Given the complexity of the pathophysiology of heart failure, addressing the psychosocial and economic determinants to health care makes developing individualized GDMT plans both challenging and rewarding. Whether a provider uses the ACC/AHA or the NYHA system or both, addressing the psychosocial and economic determinants of a patient's ability to adhere to a recommended treatment plan is critical.

In comparing the AHA/ACC system to the NYHA system, which classification system a clinician ascribes to may be determined by the work environment or setting, or it may be decided by which classification system works best for a given level of acuity. In some clinics, both systems may be used. However, there are operational differences between the two. Within the ACC/AHA system, as the patient progresses from Stage A to Stage D, they never return to an earlier stage. For example, a patient within the ACC/AHA framework cannot go from Stage C back to Stage B. If a patient meets the criteria for Stage C, even if their symptoms improve or have

resolved, by definition the patient is still in Stage C. In comparison since the NYHA system focuses on the level of physical activity needed to produce signs or symptoms of heart failure, it does allow a patient to move from one class to another as their clinical status changes. This implies within the NYHA framework a patient may be admitted because of extreme shortness of breath, problematic fluid retention, and a significant weight gain and be classified as a NHYA Class III, but be discharged as a NHYA Class II once stabilized [7]. For that same patient, they may also be classified as an ACC/AHA Stage C. Upon discharge the patient remains a Stage C. Retaining the Stage C classification serves to help other care providers recognize how symptomatic the patient had become, but at discharge a NYHA Class II implies the patient has been stabilized. Thus pairing the two classification systems together can provide more data as to where the patient is along the heart failure trajectory.

A third method for classifying a heart failure patient is the Killip classification system. This system incorporates hemodynamic parameters along with clinical symptoms. As Table 2.2 notes, the Killip classification system incorporates the pulmonary artery wedge pressure (PAWP) and the cardiac index (CI) along with physical assessment findings noting if a patient is dry or wet and warm or cold. Combining these data points allows the clinician to more narrowly stratify each heart failure patient. This implies the patient must have a pulmonary artery catheter in place in order to obtain both the PAWP and cardiac index data, making the Killip classification system a stratification system specific to an intensive care setting [7].

By using specific hemodynamic parameters that correlate cardiac index and PAWP with fluid status, the Killip classification system focuses on acutely decompensated heart failure (ADHF) patients. Since all ADHF patients are not alike, by dividing ADHF patients into four more narrowly defined classes, it seeks to guide the use of GDMT pharmacological interventions and sets specific goals for at least four different levels of acuity for ADHF patients. For example, if a patient is admitted to the ICU in Killip Class II and is warm but wet, then the GDMT may focus on the appropriate use of IV diuretics given if other parameters such as creatinine levels are stable . As with both the ACC/AHA and the NYHA systems, the ultimate

Table 2.2 Killip classification system

Class I
Warm and dry, PAWP < 18 mmHg
CI > 2.2 L/min/m^2
Class II
Warm and wet, PAWP > 18 mmHg
CI > 2.2 L/min/m^2
Class III
Cold and dry, PAWP < 18 mmHg
CI <2.2 L/min/m^2
Class IV
Cold and wet, PAWP > 18 mmHg
CI < 2.2 L/min/m^2

LaRue and Joseph [7]

goal is to stabilize the patient. In this example the patient would be initially classified as a Killip Class II (warm and wet) to the Killip Class I warm and dry status as the patient stabilized. As one group of authors has done, the classes within the Killip classification system can be somewhat correlated with the NYHA system [7]. Specifically, for a given patient Killip Class I has the potential of correlating with NYHA Class II. Killip Class II may correlate with NYHA Class III, and depending upon the patient's status Killip Class II, III, and IV all may correlate with NYHA Class IV. Hence it is possible to correlate these two classification systems, and the ACC/AHA classification system can also be correlated with NHYA system. However, both the ACC/AHA system and the NYHA system are very broad in comparison to the Killip classification system. Also, both the ACC/AHA and NYHA systems rely on the subjective signs and symptoms as well as objective physical findings, whereas the Killip classification system incorporates specific hemodynamic data points to support the physical assessment findings of warm vs cold and dry vs wet. This makes the Killip classification system more goal specific for intensive care settings.

While each system has its advantages, all three systems have limitations since subjective and objective findings are incorporated into each category. In particular both the ACC/AHA and the NYHA systems are very global in stratifying patients within their respective final stages [13]. Hence other classification systems have emerged in an effort to better stratify patients who are in ADHF. As new frameworks are developed to help differentiate different levels of acuity within ADHF, the goal of each framework is to provide more guidance for pharmacological and device support. While these newer classification systems may not be used in the outpatient clinical setting, it is paramount that health care providers stay abreast of new stratification systems in order to understand progress notes and discharge summaries that elaborate on the patient's heart failure progression during any given hospitalization. As more specific stratification schemes of ADHF are developed and appropriate research supported GDMT developed, it allows all clinicians the opportunity to obtain a clearer picture of each patient's heart failure trajectory.

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Part II

Clinical Assessment of Heart Failure

Understanding heart failure symptomatology and performing skilled physical exam techniques is the cornerstone for developing conclusive diagnoses and optimal treatment plans for the heart failure patient. Chapters three and four supply in-depth instructions for comprehensive history taking and thorough physical assessment. Chapter five will expand knowledge of what to expect when referring a suspected heart failure patient to cardiology. Complex clinical reasoning to explore differential diagnoses along with cardiac testing is discussed.

Comprehensive Heart Failure History

3

Leah A. Carr, Lisa D. Rathman, and Roy S. Small

3.1 Introduction

In 2021, the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, and the Japanese Heart Failure Society proposed a new universal definition of heart failure: "Heart failure is a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion" [1]. The authors defined a new classification of heart failure based on left ventricular ejection fraction (LVEF), describing normal or less than normal ejection fraction (EF) [1]. Patient reported symptoms and clinical manifestations of heart failure are similar regardless of their ejection fraction [1]. The underlying pathophysiology of the subtypes of heart failure is vastly different and dictates the evaluation and ultimately the treatment [1, 2].

Patients with risk factors should be screened periodically by their primary care providers for clinical symptoms associated with heart failure. Mild myocardial dysfunction and structural changes can exist for years without being clinically detected [3, 4]. A comprehensive clinical history and symptom assessment is essential because early recognition and intervention can prevent adverse outcomes [4, 5]. The American College of Cardiology and American Heart Association developed a staging system for heart failure through which most patients will progress during the course of the disease process [5]. Disease progression through the heart failure

All authors are from The Heart Group of Lancaster General Health/PENN Medicine.

L. A. Carr · L. D. Rathman (✉) · R. S. Small
The Heart Group of Lancaster General Health/PENN Medicine, Lancaster, PA, USA
e-mail: Leah.Seitz1@pennmedicine.upenn.edu; lisa.rathman@pennmedicine.upenn.edu; roy.small@pennmedicine.upenn.edu

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_3

stages can be delayed and perhaps prevented, but generally, not reversed [5]. Once structural disease has been established, there is rarely a mechanism for complete correction [4]. Progression from one stage to the next is clinically relevant as it is associated with a reduction in overall survival (Table 3.1) [5].

Cardiomyopathies are defined as changes in the myocardium secondary to metabolic, mechanical, or electrical dysfunction within the heart [4]. Cardiomyopathies can be classified into three main subgroups with the different etiologies falling into one of these categories (Table 3.2) [2, 4, 6].

Table 3.1 ACC/AHA stages of heart failure [5]

Stage	Definition	Examples
A	At risk for heart failure: no structural changes/functional heart disease or abnormal biomarkers and no past or present signs and symptoms of heart failure	• Hypertension • Diabetes/metabolic syndrome • Obesity • Atherosclerotic vascular disease • Substance abusers (alcohol, illicit drugs) • Family history of cardiomyopathy • Exposure to cardiotoxic agents
B	Pre-heart failure: structural heart changes or evidence of increased filling pressures but no signs or symptoms of heart failure	• Previous MI • Left ventricular hypertrophy/remodeling • Valvular disease
C	Symptomatic heart failure: patients with current or previous symptoms/signs of HF	• Heart failure signs and symptoms • Symptoms of heart failure at rest/activity despite guideline directed medical therapy
D	Advanced heart failure: refractory, end stage heart failure	• Marked heart failure symptoms at all times • Recurrent hospitalizations and decompensations

Table 3.2 Three major cardiomyopathy categories and most common etiologies [2, 4, 6]

Cardiomyopathy	Common etiologies
Dilated cardiomyopathy	• Idiopathic • Peripartum • Ischemic • Infectious (viral, bacterial, parasitic) • Alcohol, illicit substances, toxins • Chronic persistent tachycardia-(metabolic) • Developmental (such as non-compaction) or familial (for example, arrhythmogenic right ventricular dysplasia) • Autoimmune • Valvular (mitral or aortic regurgitation)
Hypertrophic cardiomyopathy	• Longstanding, persistent hypertension • Hypertrophic obstructive cardiomyopathy • Small vessel disease from diabetes mellitus
Restrictive or infiltrative cardiomyopathy	• Amyloidosis • Sarcoidosis • Hemochromatosis • Scleroderma

There may be an overlap within these subtypes. For example, both amyloidosis and longstanding uncontrolled hypertension can present as dilated cardiomyopathies. Valvular disease can present as dilated cardiomyopathy or restrictive depending on the specific lesion.

3.2 History: Etiology and Precipitating Factors of Heart Failure

3.2.1 Risk Factors

It is important to assess all common risk factors associated with the development of heart failure. This history section will give a closer look into the topics that are imperative to consider when gathering a history for someone who is suspected of having heart failure.

Early identification and modification of risk factors can prevent the development and progression of heart failure [5]. Some of the most common risk factors that lead to the development of left ventricular (LV) dysfunction include advancing age, obesity, hypertension, dyslipidemia, diabetes, obstructive sleep apnea, and alcohol or illicit substance use [4]. This section will review factors that are important to consider when taking a history of a patient suspected of having heart failure.

3.2.2 Coronary Artery Disease (CAD)

Myocardial ischemia should be considered in all patients presenting with new onset of heart failure [2, 4, 6]. Approximately 50% of patients diagnosed with heart failure have an underlying ischemic cardiomyopathy [7]. Patients with a new diagnosis of heart failure should be assessed for signs and symptoms of CAD [2, 4, 5, 7]. Risk factors should be addressed and signs/symptoms evaluated [3].

3.2.3 Valvular Heart Disease

Mitral regurgitation (MR) is a frequent cause of heart failure which may be the result of a structurally abnormal valve (primary) or due to annular dilatation with incomplete coaptation of the valve leaflets (secondary or functional MR) [8]. A history of rheumatic fever should prompt consideration of valvular heart disease. Aortic stenosis may be due to a congenital defect (bicuspid aortic valve) or degenerative (calcific) disease [2, 3, 9]. Endocarditis may cause severe valve dysfunction and is a particular concern in patients with a history of intravenous drug abuse or an indwelling catheter [3].

3.2.4 Hypertension

Patients with a longstanding history of persistent or untreated hypertension are at an increased risk for developing a hypertensive cardiomyopathy [2]. These hearts remodel due to the longstanding increased afterload by increasing LV wall thickness and mass [2]. They develop restrictive filling and may manifest as heart failure with preserved EF (HFpEF) as the disease progresses [3].

3.2.5 Endocrine

Numerous endocrine conditions are associated with LV dysfunction and heart failure. Diabetes mellitus (DM) (Types 1 and 2), hypo or hyperthyroidism, growth hormone excess, pheochromocytoma, hyperaldosteronism, and Cushing's syndrome are all potential causes of LV dysfunction and heart failure [2, 4, 10]. Patients who have diabetes mellitus are prone to developing coronary artery disease and resultant myocardial ischemia [5, 11]. DM is also a risk factor for the development of HFpEF [11, 12]. Uncontrolled diabetics tend to have more frequent heart failure decompensations due to hyperosmolar stress and increased infection risk [3, 11, 12].

3.2.6 Pregnancy

Heart failure and left ventricular dysfunction can occur in both the peripartum and postpartum phases of pregnancy [2, 13, 14]. If it occurs within the first year after the delivery of a child, it is termed postpartum cardiomyopathy. These women tend to have no history of prior heart disease or peripartum preeclampsia [3, 13, 14]. Women with peripartum cardiomyopathies frequently recover within the first 6 months. Those who do not recover are advised against additional pregnancies [3, 13, 14].

3.2.7 Family History/Genetics

Approximately 10–15% of heart failure patients have a genetic mutation likely to be related to their cardiomyopathy [2–4]. Heritable cardiomyopathies include hypertrophic obstructive cardiomyopathy, Fabry's disease, or muscular dystrophies including the laminopathies [15–18]. It is very important for those who have a family history of sudden cardiac death to have a cardiac evaluation as well as genetic testing if indicated [2, 3]. Hereditary TTR amyloid is due to a genetic mutation, which regulates the metabolism and structure of transthyretin [18]. It is important for family members of affected individuals to undergo genetic testing [2, 16].

3.2.8 Illicit Substances and Toxic Agents (Chemotherapy, Drugs, Alcohol)

A crucial part of history taking for newly identified cardiomyopathies is to identify past and present alcohol consumption and/or illicit drug use [19]. Alcohol is directly cardiotoxic and chronic consumption of excessive alcohol can cause an alcohol-induced cardiomyopathy [5, 19]. Similarly, drug-induced cardiomyopathies are seen with long-term methamphetamine, cocaine, and other stimulant use, which can directly cause myocardial remodeling and dysfunction, as well as induce LV dysfunction through coronary artery disease [2, 3, 19]. There is about a 35% chance that a cardiomyopathy due to excessive alcohol consumption will resolve if the patient can abstain from drinking [6]. Chapter 16 of this book delves further into a review of alcohol and drug inducted cardiomyopathies.

Chemotherapy agents pose a significant risk for both acute and chronic myocardial damage. Some commonly used drugs that contribute to myocardial dysfunction are anthracyclines (such as doxorubicin or Adriamycin) or cyclophosphamide (Cytoxan) [2, 4, 19]. Comorbidities such as advanced age, preexisting heart disease, or prior radiation increase the risks associated with chemotherapy [3, 19]. Cardiotoxicity may be a direct effect of the drug (for example, anthracyclines, tyrosine kinase inhibitors, or monoclonal antibodies) or a secondary effect from vascular damage and cardiac ischemia (fluorouracil) [19]. Some chemotherapy agents can cause cardiac arrhythmias, myocarditis, or pericarditis [19]. Immune checkpoint inhibitors are monoclonal antibodies, which target host immune regulation receptors and can precipitate acute myocarditis [20, 21].

3.2.9 Myocarditis

Acute myocarditis may be a result of a viral infection (SARS COVID-19 or more traditional viruses) or an inflammatory process (giant cell myocarditis or sarcoidosis) [2, 20–23]. Most viral myocarditis cases are sequelae from upper respiratory or gastrointestinal illnesses [20, 23]. It is important to establish the connection with a prior viral illness as it may allow for more direct serologic testing and specific diagnosis [20]. Evidence of myocardial inflammation has been found in 2–3% of college athletes recovering from COVID infection [24]. There have been rare case reports of mostly younger adults with myocarditis or pericarditis associated with the mRNA vaccines with reports of four to five cases per one million vaccinations [25]. Approximately 50% of patient with an acute viral myocarditis will recover their cardiac function within 6–12 months of their index diagnosis [6]. HIV, parasites, Chagas, bacterial, and fungal infections can also cause acute myocarditis [3, 20].

3.2.10 Connective Tissue and Systemic Disorders

Autoimmune diseases which can lead to cardiomyopathies include systemic lupus erythematosus, scleroderma, and polymyositis [2, 4]. These patients will often present with heart failure in the setting of preserved left ventricular function [3].

3.2.11 Anemia

Anemia is a highly correctable cause of heart failure [26]. Anemia secondary to iron deficiency is a common condition that can cause heart failure exacerbations [26]. It is important to evaluate and treat the underlying etiology [26, 27]. Untreated severe anemia causes increased myocardial oxygen demand as well as increases peripheral tissue oxygen demand to meet metabolic oxygen requirements [3, 26].

3.2.12 Nutritional Deficiencies

Nutritional deficits such as thiamine deficiency can lead to the development of a dilated cardiomyopathy and heart failure [28, 29]. Thiamine insufficiency can occur among individuals who are on fad diets, as well as those who have prolonged hospitalizations with inadequate nutritional support [28, 29]. There are two types of thiamine deficiency: dry beriberi and wet beriberi. Dry beriberi manifests as primarily neurological complications, whereas wet beriberi involves cardiac deficits [28, 29]. The cardiovascular complications with wet beriberi include low cardiac output failure, systemic vasodilation, peripheral edema, and fluid retention [28, 29]. The focus of management for thiamine deficient patients with heart failure needs to be normalization of this nutritional abnormality with adequate supplementation of thiamine, which is available in both intravenous and oral formulations [28].

3.2.13 Arrhythmias

Patients with incessant, uncontrolled tachycardias can develop a dilated cardiomyopathy [5]. It is typically the supraventricular tachycardias such as uncontrolled atrial fibrillation or flutter that lead to cardiac remodeling [12, 30, 31]. Ventricular tachycardia can occur in patients with dilated cardiomyopathies and heart failure [5]. Persistent frequent ventricular ectopy is associated with LV dysfunction. Patients with tachycardia-induced cardiomyopathies often have reversibility of their cardiac dysfunction if successfully controlled [3, 5, 12, 30, 31].

3.2.14 Idiopathic

After a comprehensive medical work-up is completed, there are still times when a definitive etiology or causative factor cannot be identified [2]. These cases are termed idiopathic cardiomyopathies and account for 10–20% of all heart failure cases [3].

In summary, an all-inclusive health history is essential in the setting of any new heart failure diagnosis. Subsequent history taking at all future clinic visits should be completed to ensure the patient's heart failure is controlled and properly treated in order to prevent future exacerbations.

3.3 History: Symptoms of Heart Failure

An all-inclusive history of symptoms is essential to make a prompt diagnosis of heart failure. No single historical element or symptom has been proven to be diagnostic of heart failure [5]. A comprehensive history will aid in determining the acuity, etiology, and progression of heart failure.

Symptoms commonly observed in heart failure patients include those due to congestion from excess fluid accumulation and reduced cardiac output (Table 3.3) [5, 32].

The most common symptoms heart failure patients report are dyspnea and fatigue. Dyspnea is reported in >50% of heart failure patients and is the most common complaint in the hospitalized subset of patients [33, 34]. Dyspnea and fatigue are nonspecific with a broad spectrum of differential diagnoses. In the heart failure patient in particular, dyspnea and fatigue are due to congestion and low cardiac output, respectively.

Table 3.3 Common symptoms of heart failure [5, 32]

Congestion (excess fluid volume)	Reduced cardiac output
• Dyspnea (rest or exertional)	• Fatigue
• Paroxysmal nocturnal dyspnea	• Nausea
• Edema	• Weakness
• Orthopnea	• Early satiety or anorexia
• Early satiety or anorexia	• Decreased exercise tolerance
• Cough	• Poor concentration or memory
• Abdominal bloating	• Sleepiness
• Weight gain	• Unexplained weight loss
• Abdominal or epigastric discomfort	• Muscle wasting
• Nausea	• Malaise
• Chest discomfort	• Sleep disturbance (Cheyne–stokes respiration)
• Bendopnea	

Fatigue and exercise intolerance affects nearly 85% of all heart failure patients [33, 34]. The cause is often multifactorial and difficult to treat [33]. In the heart failure patient, orthopnea is highly suggestive of congestion with a high sensitivity rate [35]. In the ESCAPE trial, orthopnea (≥2 pillow) was an indicator of elevated pulmonary capillary wedge pressure [32]. Paroxysmal nocturnal dyspnea is another reportable symptom that is commonly seen in the volume-overloaded patient [34, 36]. Both orthopnea and paroxysmal nocturnal dyspnea have a high specificity [33]. The absence of either of these symptoms has a high negative predictive value.

Bendopnea is a novel heart failure symptom first defined by Thibodeau et al. in 2014 [37]. It occurs when a sitting patient develops dyspnea within 30 s of bending at the waist to touch his or her feet [37]. Several clinical trials have demonstrated that bendopnea is associated with increased cardiac filling pressures and risk for heart failure hospitalization [37, 38]. Bendopnea is not diagnostic for heart failure alone and can occur in patients with pulmonary disease or morbid obesity [37].

Peripheral edema due to right heart congestion is another common feature of heart failure reported by >50% of patients [34]. It typically develops gradually with >5 L of excess fluid before pitting edema is seen [39]. Generally, low albumin or sitting with legs not extended is associated with more prominent edema. Edema can vary from mild ankle or foot swelling to significant swelling of the legs, scrotum, abdomen, sacrum, and periorbital space. It may help in judging treatment response to grade the degree of pitting [1, 3–5] as well as the extent (for example, ankle vs extending to the knee or thigh). Peripheral edema is not specific to heart failure alone and can occur due to other conditions such as venous insufficiency, liver cirrhosis, or chronic lymphedema [34].

Gastrointestinal complaints such as nausea, abdominal bloating, early satiety, and anorexia are commonly reported by heart failure patients [33]. These complaints may stem from low cardiac output due to poor gut perfusion or fluid volume overload and vascular congestion in the peri-abdominal space.

During each patient encounter, it is important to re-evaluate patient symptoms to assess for progression or improvement as a result of therapy. A careful interim history may prevent heart failure hospitalizations and disease advancement. Some patients have a tendency to minimize their symptoms, which can sometimes be discerned with careful questioning or confirmation with other household members [40]. Patients will unconsciously alter their daily activity to avoid symptoms or dismiss their limitations as a normal result of aging or reduced fitness. Multiple factors such as including age, mentation, and comorbid conditions may influence a patient's ability to recognize early symptoms of heart failure [40].

3.4 History Taking: Assessment of Symptom Severity

A comprehensive assessment of symptoms is important to determine a patient's functional limitations. The New York Heart Association functional class helps clarify the severity of patient symptoms (Table 3.4) [5].

Table 3.4 New York Heart Association (NYHA) functional class

NYHA class 1	No limitation in physical activity
NYHA class 2	Slight limitation in physical activity
NYHA class 3	Marked limitation in physical activity
NYHA class 4	Symptoms at rest; inability to carry out any physical activity without shortness of breath or discomfort

Adapted from nomenclature and criteria for the diagnosis of diseases of the heart and great vessels. 9th ed. Little, Brown, and company [41]

The American Heart Association and American College of Cardiology (AHA/ACC) recommends patient management and treatment based on patient's AHA/ACC stage (Table 3.5) and NYHA functional classification [5]. Patients with ACC/AHA stage C and D heart failure should be assigned a NYHA class at baseline and with each subsequent patient encounter, as the patient's functional status will change over time [5]. Worsening NYHA functional class is associated with increased morbidity and mortality [1]. Providers should target management and interventions to improve patient symptoms and quality of life. Guideline directed medical therapy will mitigate disease progression and improve prognosis.

3.5 Sample History Taking: Etiology, Risk Factor Assessment, and Symptoms

Mr. HF is a 58 year male with a history of myocardial infarction 5 years ago with a stent to his right coronary artery, hypertension, hyperlipidemia who presents to his primary care office with vague complaints of fatigue and decrease in exercise tolerance. He has a family history of ischemic heart disease in his paternal family line. He has no significant history of autoimmune disease, connective tissue disorders, anemia, alcohol/illicit substance abuse, or recent viral illnesses. Table 3.5 highlights additional history questions and symptoms to address during the encounter with Mr. HF.

Table 3.5 Heart failure clinical history pertinent questions/review of systems to explore

Cardiovascular	• Chest pain or pressure • Angina • Palpitations or irregular heartbeat
Pulmonary	• Shortness of breath at rest • What activities cause dyspnea on exertion? How many flights of stairs before dyspnea occurs? • What is the most strenuous activity you are able to do? • Paroxysmal nocturnal dyspnea • Orthopnea (Do you sleep in bed? How many pillows do you use at night or do you need to prop yourself up to sleep?) • Snoring or witnessed apnea by significant other? Have you been diagnosed or tested for sleep apnea? • Cough
Gastrointestinal	• Early satiety/anorexia • Abdominal bloating • Abdominal pain • Constipation/diarrhea • Nausea/vomiting
Neurologic	• Anxiety/depression • Confusion
Renal	• Nocturia
General symptoms	• Recent weight loss/gain • Fatigue/weakness • Daytime sleepiness • Edema
General history	• Tobacco use • Illicit drug use • Alcohol intake • Current medications/OTC including PRN use of nitroglycerin • Regular exercise • Pertinent family history

3.6 Conclusions

Heart failure is a progressive and chronic illness. Patients with heart failure suffer substantial symptoms such as shortness of breath and edema, which impact patient quality and duration of life. A thorough assessment of patient's history and symptoms is essential not only for a timely diagnosis but ongoing clinical management to improve outcomes.

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Physical Exam for Presence and Severity of Heart Failure

4

Jessica B. Williams, Donna Harmon, and JoAnn Lindenfeld

4.1 Introduction

Over six million Americans have heart failure (HF) [1], thus the ability to perform a careful and accurate physical examination to determine the presence and severity of HF is important for cardiologists and also for primary care providers who provide most of the care for these patients. Due to the progressive nature of HF and the frequent occurrence of acute exacerbations, a careful physical examination for HF signs should occur with each patient encounter. These physical examination skills, in addition to careful history taking, allow daily assessment of the hospitalized HF patient during an acute exacerbation but are also important for assessing changes during an outpatient visit. The physical examination may provide clues to the etiology of HF but for most patients determining the etiology also requires a careful history, an electrocardiogram, and blood testing along with additional studies such as echocardiography, coronary angiography, magnetic resonance imaging (MRI), and other tests.

Depending on the level of severity, physical manifestations of HF may present in almost every organ system. For the purpose of this chapter, we have focused on physical examination findings and techniques that apply *primarily* to the evaluation of HF. The physical examination is especially helpful for assessing the severity of HF and the presence of congestion but some of the physical examination findings discussed below also suggest specific syndromes or etiologies.

J. B. Williams (✉) · J. Lindenfeld (✉)
Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: jessica.b.williams@vumc.org; joann.lindenfeld@vumc.org

D. Harmon
Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA

Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: donna.harmon@vumc.org

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_4

In the following discussion, we review specific physical examination findings critical to the evaluation of HF and then discuss how to combine all the exam findings for an overall assessment.

4.2 General Inspection

General inspection rapidly provides important information about the HF patient including problems that may be caused by HF or may be exacerbating HF. General inspection includes inspection of the skin color and nail beds for evidence of cyanosis and/or clubbing, inspection of breathing, level of distress, and the overall nutritional status of the patient. Table 4.1 provides a summary of the key general inspection findings to look for in the HF patient. Is the patient "pink" or "blue?" A pink color of the lips, mucous membranes, fingers, and toes indicates that there is normal blood oxygenation. "Central cyanosis" occurs when the lips, mucous membranes, and extremities appear "blue" and implies hypoxemia. Central cyanosis is accompanied by peripheral cyanosis as all of the arterial blood is less than normally oxygenated [2]. Peripheral cyanosis without central cyanosis may indicate severe peripheral vasoconstriction resulting in slow blood flow in the periphery allowing marked oxygen uptake and cyanosis in the periphery only. Pulmonary congestion due to HF does not usually cause hypoxemia unless there is an associated respiratory condition or there is severe pulmonary congestion. Clubbed nail beds may also be noted and indicate a chronic hypoxic condition which may be due to respiratory disease or a chronic right to left intracardiac shunt as most often occurs in congenital heart disease [3]. Clubbed nail beds are often red, sponge-like, and swollen. The

Table 4.1 General inspection

	Finding	Suggests
Skin color	Central and peripheral cyanosis	Hypoxemia
	Peripheral cyanosis	Low cardiac output and peripheral vasoconstriction
	Pale skin—Best seen in conjunctivae, creases of palms	Anemia
	Jaundice	Liver dysfunction
Nail beds	Clubbing	Chronic hypoxemia
Breathing	Short of breath at rest	Pulmonary congestion
	Short of breath lying flat	Pulmonary congestion
	Short of breath bending over	Pulmonary congestion
	Short of breath walking into examining room	Pulmonary congestion
Nutrition	Evidence of cachexia	Muscle loss included temporal and thenar muscle loss If due to heart failure indicates end-stage heart failure

usual concave angle between the nail bed and the nail becomes flat or convex so that the nails look like upside-down spoons.

As part of the inspection, the patient's eyes should be evaluated for jaundice or "scleral icterus." Scleral icterus begins to be noticeable when the bilirubin exceeds 3 mg/dL in adults. It is the conjunctivae that take on the yellow color, not the sclerae so this would be better termed "conjunctival icterus." Jaundice may be caused by hepatic congestion due to HF but the presence of jaundice is unusual in HF unless there is severe right-sided HF. Thus the presence of jaundice in the patient with HF should stimulate consideration of other causes of jaundice [4].

Next is the evaluation of the patient's breathing. Does the patient seem physically comfortable or is there evidence of respiratory distress? Is the patient short of breath at rest or with walking into the examining room? Is the patient able to lie flat without shortness of breath? Shortness of breath due to HF at rest indicates severe pulmonary congestion. If the patient cannot lie flat without shortness of breath (orthopnea) there is very likely an elevated pulmonary capillary wedge pressure causing pulmonary congestion.

Is the patient cachectic? Cachexia is defined by loss of body weight and muscle mass that is noted generally in all muscles but may be easiest to see muscle loss in temporal muscles, supraclavicular muscles, and interosseous muscles of the hands [5]. Cachexia may be caused by several medical problems other than HF such as cancer and severe lung disease. When cachexia is due to HF alone it indicates that the HF is severe [6].

Is the patient alert and interacting normally? Severe HF may result in poor cerebral perfusion, especially in the upright position, but the relationship between cerebral blood flow, cardiac output, and cognitive dysfunction is complex and requires additional study [7, 8]. If there is a significant change in mental status and the patient is confused or disoriented it may indicate a severe drop in cardiac output. Cardiogenic shock and other signs of poor perfusion (discussed below) should be immediately assessed. Depression is common in HF patients and a general assessment of mood and alertness may suggest a further evaluation for depression [9]. While a "flat affect" may be common in depression, the diagnosis of depression requires a careful history. Women with HF are more likely to have depression than their male counterparts. Interestingly, female caregivers of male HF patients are also more likely to suffer depression than male caregivers of female HF patients [9, 10].

Frailty is highly prevalent in HF patients occurring in as many as 50% [11]. Frailty is "a syndrome characterized by an exaggerated decline in function and reserve in multiple physiological systems, resulting in a lower homeostatic tolerance of stressors and increased sensitivity and vulnerability to a wide range of adverse outcomes" [12]. Although patients are often said to be "frail" by general inspection, general inspection is an insensitive method of detecting frailty. Frailty is most often evaluated in two ways—with the Fried criteria that consist of five criteria including historical features, gait speed, and handgrip strength, or with a general questionnaire that combines multiple comorbidities [11]. Other frailty tests have been devised for specific situations. Many general inspection findings suggest frailty including loss of muscle mass (sarcopenia), slow gait speed, and difficulty

getting up from a sitting position. However, it is important to understand that low body mass index and frailty are not synonymous, and frailty may be present even in obese HF patients. Recently, it has been reported that frail women are less likely to manifest muscle loss than frail men [13]. As frailty is a sign of poor clinical outcomes including mortality, it will be important to utilize the physical examination as part of the assessment of whether treatment of HF results in improved frailty [14].

4.3 Heart Rate and Rhythm, Blood Pressure, and Arterial Pulse

4.3.1 Heart Rate and Rhythm

Assessment of the heart rate (HR), the quality of the arterial pulse (AP), and blood pressure (BP) are all important in the assessment of HF patients. Bradycardia is generally defined as a HR <60 beats/min, while tachycardia is defined as an HR >100 beats per min (bpm), but changes between 60 and 100 bpm may also be important. For example, an outpatient whose resting HR is generally 70 bpm should be carefully evaluated (as discussed below) if the HR is 88 bpm. A rapid heart rate, or tachycardia, may be important for several reasons. A rapid HR may indicate an arrhythmia such as new atrial fibrillation or may be a sign of worsening HF because the increased HR is caused by sympathetic activation due to a low cardiac output or worsening pulmonary congestion or both. Finally, in a patient taking beta-blockers, a substantial increase in HR may indicate non-compliance with the beta-blockers [15]. In HF patients with sinus rhythm there is a direct correlation between higher heart rate and mortality [16]. Bradycardias may indicate an arrhythmia such as heart block or sick sinus syndrome that may exacerbate HF, especially if a new finding. However, a HR below 60 is not always abnormal.

Atrial fibrillation is a common cause of exacerbation of HF and the palpated pulse is usually "irregularly irregular." Frequent premature atrial or ventricular beats may also be irregularly irregular so an irregularly irregular pulse is not diagnostic of atrial fibrillation. The assessment of HR may provide a clue to the cause of new or worsening HF—tachycardias with a rate >120 that have been present for several weeks may cause left ventricular dysfunction and a drop in ejection fraction—a condition termed "tachycardia-mediated cardiomyopathy." New premature atrial beats, which may precede atrial fibrillation are often a sign of high intracardiac filling pressures or congestion.

When there is a rapid, irregularly irregular rhythm in atrial fibrillation the provider should be aware that the peripheral HR may not accurately reflect the actual number of ventricular contractions. With a rapid HR, the left ventricle may not have time to fill, if the beats that are very close together, and thus no peripheral pulse is noted for those beats. For example, the actual heart rate may be 140 but the peripheral pulse is 110. As the ventricular response to atrial fibrillation slows there is less and less discrepancy between the apical and peripheral pulses as there is more time for filling with each beat. Listening to the heart and palpating the peripheral pulse simultaneously will detect this situation.

A "regularly irregular" HR may also signal a hemodynamic diagnosis. For example, pulsus alternans describes the situation when every other heartbeat is not palpable or is markedly diminished [17]. Pulsus alternans is detected by noting a palpable pulse on every other beat identified either with an electrocardiographic tracing or by cardiac auscultation. In patients with HF, the alternating pulse amplitude is due to alternating fluctuation of left ventricular contraction and is a sign of very severe HF and thus is a poor prognostic finding. Pulsus alternans is a rare but important examination finding and does have causes other than HF [18].

Pulsus paradoxus, described below, may also lead to intermittently palpable pulse creating the impression of an irregular HR. However, pulsus paradoxus is rarely detected by palpating the radial pulse as the pressure differences of 10–20 mmHg between beats are below most examiner's detection abilities.

4.3.2 Blood Pressure

Blood pressure (BP) should be measured at each visit and at home if possible. Appropriate sphygmomanometer cuff size and patient positioning are simple, yet important for accurate blood pressure measurement. A larger size cuff is necessary to adequately assess BP in obese patients. Both the systolic and diastolic pressures are important as is the pulse pressure (systolic minus the diastolic BP). Systolic BP is often low in patients with HF and reduced ejection fraction (HFrEF) and may prevent up-titration of medical therapies that lower the BP. However, in the absence of dizziness or orthostatic dizziness a systolic BP of 90–100 mmHg may not preclude further therapy. A narrow pulse pressure (<30 mmHg) usually indicates a very low cardiac output and severe HF [19]. Another useful calculation from the BP is the proportional pulse pressure which is the pulse pressure divided by the systolic BP. A value <25% has good sensitivity and specificity for low cardiac output [20].

In the initial evaluation, orthostatic BP should be measured especially in older patients. The most current consensus guidelines for the detection of orthostatic BP at home and in the clinic are outlined in Table 4.2 [21]. Orthostatic hypotension is defined as a reduction of at least 20 mmHg in systolic BP or 10 mmHg in diastolic BP within 3 min of standing [21]. In the patient with supine hypertension (defined

Table 4.2 Recommendations for determination or orthostatic hypotension in clinic and at home (modified from [21])

In clinic	At home
BP/HR monitoring after 5 min supine Repeat BP/HR testing after 1 and 3 min of standing *Alternate method*: BP/HR monitoring after 5 min seated Repeat BP/HR testing after 1 and 3 min of standing	BP/HR monitoring after 5 min supine or before arising in the AM Repeat BP/HR testing after 3 min of standing Repeat BP/HR testing while standing when symptomatic Check orthostatic vitals for 7 days prior to clinic appointment [9]

BP blood pressure, *HR* heart rate

as a supine systolic blood pressure of >150 mmHg or diastolic blood pressure >90 mmHg), a 30 mmHg decrease in systolic blood pressure or 15-point fall in diastolic blood pressure has been suggested as the magnitude of blood pressure fall is dependent on the baseline blood pressure [21]. Many medications for HF and other comorbidities cause hypotension and may exacerbate symptoms of orthostatic hypotension.

One unusual BP finding is that of pulsus paradoxus which is present when the systolic blood pressure drops by more than 10 mmHg with each inspiration. Pulsus paradoxus is rarely diagnosed with palpation of the peripheral pulse and is most often detected using changes in systolic blood pressure with inspiration. Pulsus paradoxus occurs when the heart is compressed, for example, by a pericardial effusion, and the blood flow increase into the right ventricle during inspiration limits the blood flow to the left ventricle as total intracardiac space is relatively fixed. Thus, the stroke volume decreases with inspiration and systolic BP drops with inspiration. The greater the intrapericardial pressure, the more left ventricular filling is limited and the greater the drop in stroke volume and systolic pressure. Pulsus paradoxus may also occur with severe respiratory distress due to underlying lung disease. Assessment for pulsus paradox should be done if the patient is acutely ill and a pericardial friction rub is heard or suspected.

4.4 Venous Congestion: Jugular Venous Pulse, Hepatojugular Reflux, Peripheral Edema, Hepatic Congestion, and Ascites

Venous congestion results from elevation of pressures on the right side of the heart and generally is caused by right ventricular failure with elevation of the right ventricular end-diastolic pressure that results in elevation of right atrial pressure that is transmitted to the venous system. Venous congestion is most often assessed using the jugular venous pulse, the presence and extent of peripheral edema, hepatic congestion, and ascites each of which are described below. Very rarely tricuspid stenosis may result in high right atrial pressures without elevation of right ventricular end-diastolic pressure.

4.4.1 Jugular Venous Pressure and Hepatojugular Reflex

Assessment of the jugular venous pressure (JVP) is one of the more difficult parts of the physical examination to learn due to the low pressures in the venous system, the undulating nature of the venous waves, and variations in the size of the patient's neck. With continued practice, the JVP provides valuable information about volume status of the HF patient. The JVP is the pressure within the thoracic vena cava and is a good estimate of the right atrial pressure. The JVP is synonymous with central venous pressure (CVP) [22].

Table 4.3 Tips for assessing jugular venous pressure (modified from [19])

Identify the top of the JVP usually with the patient sitting upright
Use the right side of the neck with indirect light such as the flashlight on your phone Usually the right side is most accurate but examining both sides on first examination is helpful
Have the patient turn their head slightly to the left
Make sure the patient is breathing normally and not "holding their breath"
The carotid pulse can be felt but the JVP can rarely be felt
If the tip of the JVP cannot be seen, lower the head of the examining table until it can be seen
If the JVP cannot be seen, utilize the hepatojugular reflux test to see if the top of the JVP is visible

Tips for examining the JVP are provided in Table 4.3. In measuring JVP, the examiner will begin on the patient's right side with the patient lying at a 45-degree angle or the angle at which the top of the JVP is easily visualized. The reader is referred to an excellent video of the examination of the JVP [23]. The head should be turned slightly to the left and the chin tilted up. An indirect light source is valuable to place the jugular vein in relief to make it more easily visualized. The right internal jugular vein is used for measurement as it sits directly above the right atrium and the assessment is not confounded by venous valves often found in the left jugular vein. First, locate the sternocleidomastoid muscle, which extends between the end of the clavicle and the earlobe. Next, find the external jugular vein's pulsation just lateral to the internal jugular vein and look for the highest pulsation at the site of the internal jugular vein. Measure this distance in centimeters (cm). Then, extend a ruler horizontally from this point and a vertical ruler from the sternal angle, measuring the vertical distance above the sternal angle. The sternal angle of Louis sits 5 cm above the right atrium, adding this amount to the previous measurement for a total JVP in cm of water. At the same time, the examiner can assess for positive hepatojugular reflex, which is discussed later.

When the top of the jugular vein is difficult to see, a helpful test is the hepatojugular reflux sign [24]. Although this is called the hepatojugular reflux sign a more accurate name would be abdominojugular reflux sign as pressure may be applied anywhere over the abdomen and not just over the liver. Using the palm of the hand, the examiner places sustained pressure on the abdomen asking the patient to continue to breathe. The abdominojugular reflux sign is said to be positive when there is an increase in the JVP of greater than 3 cm, sustained for greater than 15 s. A positive abdominojugular reflux sign indicates right ventricular failure as the right ventricle cannot eject the extra blood that is returned to it with compression of the abdomen. A positive abdominojugular reflex sign indicates right ventricular failure, but the examiner must determine from the history and other physical signs if the right ventricular failure is due to left ventricular failure or another cause. In patients presenting with dyspnea, the abdominojugular reflux is useful in predicting HF and suggests elevated pulmonary capillary wedge pressure (>15 mmHg).

The jugular venous waveform includes a, c, and v waves with the "a" wave representing the pressure generated by right atrial contraction, The "c" wave is usually much less visible than the "a" and "v" waves and represents right ventricular contraction causing the closed tricuspid valve to bulge toward the right atrium during RV isovolumetric contraction. The "v" wave represents venous filling of the right atrium when the tricuspid valve is closed. One finding that is quite common in patients with HF is an exaggerated c-v wave that results from tricuspid regurgitation [21]. Many additional diagnoses may be made with further assessment of the a and v waves and their corresponding x and y descents seen in the jugular venous pulse. The reader is referred to two excellent descriptions [23, 24]. The JVP is generally reported as a "mean" JVP so the examiner must assess the overall mean of the three waves. It should be noted that 1 cm of water is equivalent to 0.73 mmHg so a JVP of 20 cm of water is equivalent to 15 mmHg. The estimation of JVP in a patient with known HF is generally a good indication of elevations in left-sided filling pressures, but substantial discordance between left- and right-sided pressures does occur [25].

4.4.2 Peripheral Edema

Peripheral edema occurs when fluid builds up in the interstitial space in the legs. Edema begins to appear when there is retention of approximately 2–3 L of fluid [26]. Edema may be "pitting" or non-pitting. Pitting means that pressing a finger into the area of edema creates a "pit" that takes time to resolve and both the depth of the "pit" and the time it takes for resolution are part of the assessment of the severity of the edema (see below). Pitting edema is much more common than non-pitting edema which is seen in lymphatic obstruction and severe hypothyroidism. Causes of pitting edema include HF, medications (particularly dihydropyridine calcium channel blockers) [27], bilateral deep venous insufficiency, nephrotic syndrome, severe chronic kidney disease, bilateral deep venous thrombosis, and chronic immobility [26, 28].

In HF patients, peripheral edema is due to chronically elevated jugular venous pressure. The chronically elevated venous pressure results in disruption of the interstitial space allowing more space for fluid retention and resulting in an imbalance between hydrostatic and oncotic pressures, further worsening fluid retention [29]. As the edema accumulates preferentially in dependent areas, it is noted in the lower extremities in patients who are ambulatory and over the sacrum in patients who are bedbound. As fluid retention continues, the edema progresses up the leg and even to the presacral region or higher in ambulatory patients. The amount of fluid accumulation is dependent on the chronicity of the elevation in jugular venous pressure, the degree of elevation of jugular venous pressure, disruption of tight bonds in the interstitial space, and renal function.

There is no well-validated method of assessing peripheral pitting edema. Most grading schemes involve applying pressure, with a finger, to the area of edema and noting an indentation [30]. Pitting is said to occur when the indentation does not immediately resolve. The most common technique is to use either the thumb or

Table 4.4 Assessment of pitting edema (modified from [30])

1.		Press firmly with your thumb for at least 2 s on each extremity	
(a)		Over the dorsum of the foot	
(b)		Behind the medial malleolus	
(c)		Lower calf above the medial malleolus	
2.		Record indention recovery time in seconds	
	Indentation	*Visual distortion*	*Disappears*
1+	≤2 mm (slight)	None	Rapidly
2+	2–4 mm (deeper)	Minimal	10–15 s
3+	4–6 mm (noticeably deep)	Noticeable	May last >1 min
4+	6–8 mm (very deep)	Gross distortion	May last as long as 2–5 min

index finger to apply pressure to the edematous area and observe the depth of the indentation and the time it takes for the pitting to resolve. Pitting is usually reported on a scale of 1–4+ as outlined in Table 4.4. In addition to the 1–4+ score, the extent of the edema is expressed as the location describing the highest extent of the pitting edema. For example, "2+ edema is reported to the mid-thigh." The presence of peripheral edema is neither sensitive nor specific for the diagnosis of HF. However, the use of a grading scheme allows some assessment of the amount of excess fluid and can be used to assess the response to diuresis.

4.4.3 Hepatic Congestion and Ascites

The most common abdominal findings in the HF patient are hepatic congestion and ascites. When the jugular venous pressure is elevated there is elevated pressure in the liver resulting in hepatic congestion and enlargement. A normal liver does not usually extend below the right costal margin. Using percussion and palpation, beginning at the right midclavicular line, the liver may be either palpated or percussed below the costal margin and the extension below the costal margin (1 cm, 2 cm, etc.) provides a rough measure of hepatic congestion. Also, percussion can be used to track upward in the midclavicular line to determine the distance between the upper and lower margins of the liver. Six to twelve centimeters reflects a normal liver size. When the liver is congested the patient may often complain of pain over the liver or pain with palpation of the liver. In the setting of severe tricuspid regurgitation, a systolic pulse may be palpated over the liver reflecting the large "V" wave of the tricuspid regurgitation.

Ascites occurs with chronically elevated venous pressures. Using percussion with the patient in the supine position, ascites is suggested by tympany over the umbilicus and dullness over the lateral abdomen and flanks. Ascites is also detected using the fluid wave test and the "shifting dullness" test. To detect a fluid wave the patient should be supine, and one examiner places the ulnar surface of one hand into the mid-abdomen of the patient. The second examiner places the fingertips of the left hand along one flank while tapping the other flank with the right hand. When

there is ascites a "fluid wave" will be felt by the left hand indicating ascites. The test for shifting dullness is also done with the patient supine [31]. The abdomen is percussed from the umbilicus to the flank and the point at which the percussion changes from tympany to dullness is marked. The patient is then asked to turn on his/her side away from the examiner and percussion is performed again marking the change from tympany to dullness. "Shifting dullness" is present when during percussion the region of dullness shifts when the patient is turned from a supine position to a lateral position suggesting the movement of ascitic fluid. The detection of shifting dullness generally requires 500 mL of ascites [32].

4.5 Pulmonary Congestion: Lung Examination

The comprehensive lung exam is an important part of the initial examination as well as the daily examination in any HF patient. Pulmonary congestion is a primary concern in the setting of HF and can manifest in a variety of pulmonary signs.

4.5.1 Respiratory Rate, Pattern, and Quality

Observation of respiratory rate at varying levels of activity, such as walking to the exam room, climbing on the exam table, or with conversation as well as with position changes during the exam can point to HF severity. Tachypnea, even in the absence of other common indicators of pulmonary congestion (discussed below), is an important sign of respiratory distress that is often brought on by pulmonary congestion. Tachypnea (respiratory rate $\geq$ 18 breaths/min) may appear initially during exertion and may be an early sign of HF exacerbation [33]. It is important to measure the respiratory rate as tachypnea may be present despite the absence of apparent respiratory distress.

A specific pattern of breathing, Cheyne–Stokes respiration, occurs in HF patients especially those with advanced HF, generally indicates a poor prognosis [34] and is characterized by intermittent hyperpnea alternating with brief apnea. Cheyne–Stokes respiration is often considered a nocturnal breathing pattern, however, in more advanced stages of HF, it may be observed while patients are sitting upright and awake [35].

4.5.2 Lung Sounds

The HF patient may present with different types of lung sounds. The most common sounds heard over the lungs of HF patients are c*rackles* (*rales*) which are fine, high-pitched crackling or rattling sounds that occur during inspiration. They are often compared to the sound of salt hitting a hot pan, cellophane crumpling, or the sound of rubbing two pieces of hair together close to the ear. Crackles due to HF are often clear with cough and represent fluid in the alveolar space. Crackles or rales that do

not clear with cough may be evidence of intrapulmonary interstitial fibrosis that occurs with interstitial lung disease. Rales are generally heard only when the HF is decompensated and even with decompensation rales are frequently not present especially after diuresis is initiated. Rales improve with the upright position so when the congestion is not severe rales may not be heard when the patient is sitting upright. With mild pulmonary congestion, rales may be heard first at the bases of the lung but as left atrial pressure increases and the pulmonary congestion progresses the crackles are heard higher in the lung fields. The absence of crackles does not mean that pulmonary capillary wedge pressure (PCWP) is normal. If fact rales may be absent when PCWP is chronically elevated due to hypertrophied lymphatics that carry away excess interalveolar fluid [36].

Wheezes can be heard on inspiration and/or expiration and are a result of bronchial inflammation that reduces the diameter of the bronchus. Wheezes may be caused by pulmonary congestion although they are more common with pulmonary processes such as exacerbation of chronic obstructive lung disease or asthma. Pleural effusions may also occur in the decompensated HF patient due to elevations in central venous pressure. When pleural effusions are due to HF they are often bilateral and somewhat larger on the right than the left. If unilateral pleural effusions are generally right-sided [37]. Pleural effusions can be detected by careful clinical examination. Pleural fluid interferes with transmission of low-frequency vibrations and results in diminished tactile fremitus. Fremitus is the vibration that can be felt or heard on the chest wall by talking or breathing. Asymmetric chest expansion, diminished fremitus, dullness on percussion, decreased or absent breath sounds, and reduced vocal resonance have a high sensitivity and specificity for the presence of a pleural effusion [38].

4.6 Cardiac Examination: Examination of the Precordium, Heart Sounds, Heart Murmurs, Extra Sounds, and Rubs

4.6.1 Inspection and Palpation of the Precordium

The point of maximal impulse (PMI) or apical impulse is normally in the left midclavicular line and represents the apex of the left ventricle [39]. A PMI lateral to the midclavicular line suggests cardiac enlargement. To locate the PMI, start by examining at the fifth intercostal space in the midclavicular line. Whether it is visible or not, lightly place the pads of your fingers over this area to palpate the PMI. If the PMI remains elusive, have the patient lie in a left lateral position to allow the left ventricular apex to move closer to the precordium [40].

The PMI should be about the size of a quarter and should produce a tapping sensation with each systole [39, 40]. If the PMI is larger and displaced laterally or the impact is sustained this suggests ventricular enlargement and hypertrophy, respectively [40]. The normal PMI is palpated as a brief "tap" on the chest wall. A "sustained" apical impulse is present when that "tap" has a duration of ≥50% of systole. The sustained systolic impact can be described as a lift or a heave and

indicates left ventricular hypertrophy. In addition to assessing impact, the PMI may be displaced laterally to the midclavicular line suggesting cardiac enlargement. A dyskinetic PMI is one where the PMI occurs at a different time than the remainder of the cardiac movement and suggests left ventricular wall motion abnormalities.

The right ventricle is best palpated along the left sternal border with the palmar digital surface of the hand. A right ventricular lift occurs when the impulse is sustained (lasting 50% of systole) and indicates right ventricular hypertrophy [40].

Light palpation of the precordium will rarely reveal a palpable murmur termed a "thrill" which is the transmission of a murmur that is at least grade IV/VI and to the chest wall.

4.6.2 Heart Sounds [39–41]

Heart sounds consist of high- and low-frequency sounds. High-frequency sounds are associated with the closing or opening of the heart valves, while low-frequency sounds reflect the diastolic filling events of the ventricle. During the examination, the clinician should listen for heart sounds followed by listening for heart murmurs as identification of S1 and S2 allows the auscultator to accurately identify systole and diastole (Fig. 4.2).

Heart sounds consist of S1 (the first heart sound), S2 (the second heart sound), S3 (the third heart sound), and S4 (the fourth heart sound). S1 and S2 are "normal" heart sounds, while S3 and S4 are usually abnormal or "extra" heart sounds. S1 and S2 are medium to high-pitched sounds associated with valve closing, while S3 and S4 are low-pitched sounds associated with abnormal filling patterns of the left or right ventricle. The diaphragm of the stethoscope has a flat surface that is designed to pick up high-pitched sounds while the bell of the stethoscope is designed to detect low-pitched sounds. The bell can also detect high-pitched sounds if it is pressed tightly against the skin to create a tight, flat surface of the skin against the bell.

The locations on the chest where specific heart sounds and murmurs for specific valves are referred to as "listening points" are shown in Fig. 4.1. The time between S1 and S2 is shorter than the timing between S2 to S1. This makes systole and diastole easy to differentiate. However, as the HR increases, systolic and diastole become nearly equal so that the pauses between S1 and S2 and S2 to S1 are similar making it difficult to determine which is S1 and S2. The carotid upstroke occurs between S1 and S2 and helps identify S1 and S2 (Fig. 4.2). The S1, a high-pitched sound, signifies the closure of the mitral and tricuspid (atrioventricular) valves and is heard using the stethoscope's diaphragm. The S1 is best heard at the mitral (apex) and tricuspid (left lower sternal border) listening points (Fig. 4.1). The clinician will listen for two audible components known as the mitral first heart sound (M1) and tricuspid first heart sound (T1) which are the closing sounds of the mitral and tricuspid valves, respectively. The splitting of S1 may be difficult to hear and changes in S1 splitting are rarely diagnostic. However, the intensity of the S1 may

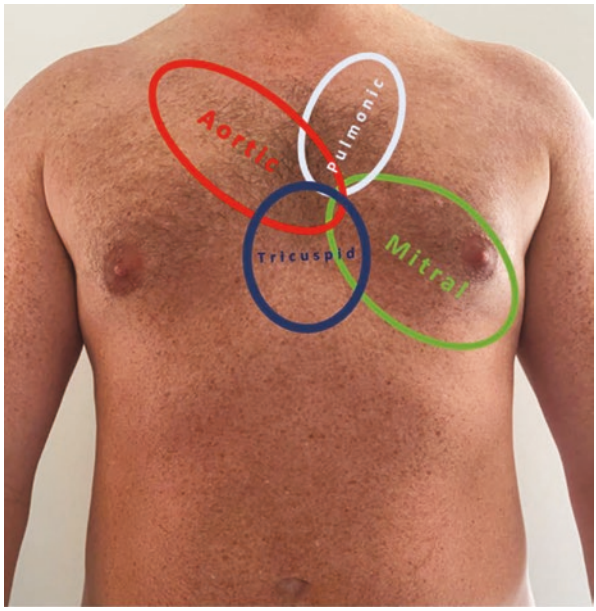

Fig. 4.1 Listening points for the cardiac examination. These positions suggest the best areas for heart aortic, pulmonic, mitral, and tricuspid valve sounds and murmurs

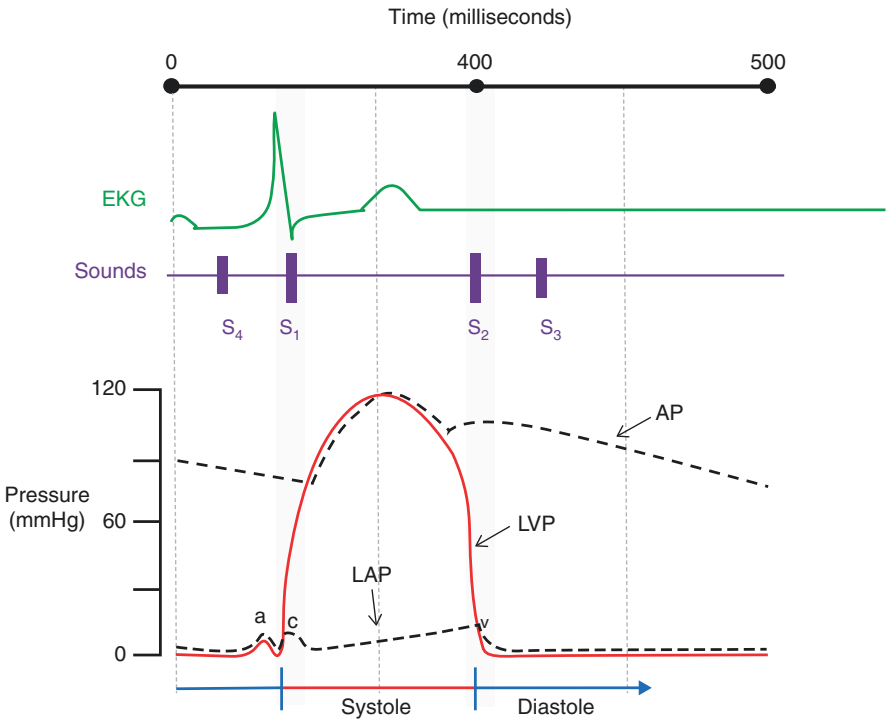

Fig. 4.2 Timing of heart sounds with aortic, left ventricular, and left atrial pressures. *LAP* left atrial pressure, *LVP* left ventricular pressure, *AP* aortic pressure, *Press* pressure, *S1* first heart sound, *S2* second heart sound, *S3* third heart sound, *S4* fourth heart sound

be diminished with prolongation of the PR interval of the ECG as the prolongation allows more time for the atrioventricular valves to be closing following atrial contraction resulting in much softer closing sounds with ventricular contraction. Poor ventricular contractility may also decrease the intensity of S1 due to a decreased force of ventricular contraction and the elevated atrial pressures that result in a smaller ventricular-atrial gradient. A loud S1 (due to the increased M1) is a hallmark of mitral stenosis as the mitral gradient leaves the valve still wide open when a ventricular contraction begins causing a wide open mitral valve to be forcibly shut by ventricular contraction. The S2 results from the closure of the aortic (A2) and pulmonic (P2) (semilunar) valves. They are high-pitched so are best heard with the diaphragm of the stethoscope in the aortic area (upper right sternal border) and pulmonic (right-left sternal border) listening points. An S2 split may or may not be audible but is heard best at the pulmonic listening point as the P2 is generally softer than the A2. In a normal cardiac cycle, the aortic valve closes before the pulmonic valve creating a split S2. With inspiration drawing more blood into the right ventricle the P2 occurs later. In a normal heart the splitting of the S2 increases with inspiration and narrows with expiration. Several abnormalities of S2 splitting can be helpful to suggest a diagnosis. For example, with pulmonary hypertension, the pulmonary circulation becomes less compliant and the pulmonary valve closes earlier creating a narrow splitting of S2. With an atrial septal defect, the splitting of the S2 is fixed. With severe aortic stenosis, there is limited motion of the aortic valve creating a very soft A2 and a "single" S2. Finally left bundle branch blocke causes later left ventricular ejection and thus later aortic valve closing so that the pulmonic component (P2) occurs before A2 resulting in a paradoxical S2 with increased splitting during expiration rather than inspiration. Paradoxical splitting of the S2 may also occur with right ventricular pacing as the left ventricular contraction occurs later.

The S3 and S4 are both low-frequency sounds and are heard best with the bell of the stethoscope over the apex of the heart and the patient in the left lateral decubitus position. The S3 occurs during the early diastolic filling phase of the ventricle and the S4 is a result of atrial contraction, thus occurring in late diastole (Fig. 4.2). Both sounds result from the vibration of the ventricular muscle as diastolic flow is abruptly limited with elevated filling pressures. The S3 can be physiologic, as in children, pregnant women, or athletes with a large stroke volume and low heart rate. Except for in these situations, it is generally pathologic and indicates HF. An S3 may develop or get louder when the HF is decompensated and there is excess intravascular and intracardiac volume which may get softer or even disappear with diuresis. The S4 is almost always pathologic and is most often noted when there is a forceful atrial contraction such as occurs with left ventricular hypertrophy. The S3 and S4 are referred to as extra sounds or "gallops" as the four heart sounds together, especially with tachycardia, mimic the sounds made by the hooves of a running horse. In a patient without overt HF, the presence of an S3 predicts the development of HF [42] and in the patient with HF, it portends a worse prognosis [19].

4.6.3 Heart Murmurs [39–41]

After assessing the heart sounds the clinician focuses on evaluating murmurs. It is important to identify S1 and S2 to determine if murmurs are systolic or diastolic. Systolic murmurs are audible between S1 and S2 and diastolic murmurs start with S2 and then S1. Murmurs are generated by turbulence of flow across a valve. Excess turbulence of blood flow in systole may be generated across semilunar valves with an either valvular or subvalvular obstruction or valvular regurgitation. The turbulence of blood flow occurs across the atrioventricular (mitral or tricuspid) valves with regurgitation during systole or obstruction during diastole. Murmurs are assigned a numerical grade from I to VI according to the loudness of the murmur. Turbulence most often occurs when a valve is abnormal or with subvalvular obstruction. However, when blood flow across a semilunar valve is high (such as with pregnancy, anemia, or hyperthyroidism) turbulence may be present even across a normal valve.

During auscultation, the clinician will assess each murmur for location, timing, duration, quality, intensity, pitch, radiation, and respiratory phase variation (Table 4.5). For systolic murmurs, the change in murmur intensity following a pause in the cardiac cycle should also be assessed. The clinician should listen in the aortic, pulmonic, tricuspid, and mitral areas which are identified in Fig. 4.1. In addition to listening to these areas in the supine patient, the clinician should listen over the left ventricular apex with the patient in the left lateral decubitus position in order to hear the murmur of mitral stenosis. In each area, the clinician determines if the murmur is systolic or diastolic. In addition to timing with the heart sounds as described above, systolic murmurs occur with the carotid pulse. The duration of the systolic murmurs may be early, or mid-holosystolic. Systolic ejection murmurs such as the murmur of aortic stenosis end before the S2, while holosystolic murmurs (such as mitral or tricuspid regurgitation) may continue into the S2 as the ventricular pressure is still higher than atrial pressure for a short time after the semilunar valves close. The intensity of the murmur is graded from I to VI with a grade I murmur

Table 4.5 Qualities of murmurs to evaluate

Evaluation	Specifics
Location	Listening points
Timing	Systolic or diastolic
Duration	Early, mid, late or pansystolic or diastolic
Quality	Ejection type Regurgitant type
Intensity	Grades I–VI
Pitch	High, medium, low
Radiation	Does it radiate to neck, to the back?
Respiratory variation	Does it increase with inspiration?
Post pause (such as the in the beat immediately post-PVC)	Intensity

Table 4.6 Grading of the intensity of heart murmurs

Grade	Description
1	Faintest sound that can be detected
2	Soft but readily detectable
3	Louder than grade 2 but not associated with a palpable thrill
4	Easily detected murmur associated with a palpable "thrill"
5	Very loud murmur audible with the stethoscope placed lightly on the chest
6	Extremely loud murmur audible with the stethoscope off of the chest

being very faint, a grade IV murmur being palpable (called a thrill), and a grade VI murmur can be heard with the stethoscope only partially touching the chest (Table 4.6). It is important to note that a "thrill" always signifies a pathologic murmur. The radiation of murmurs often provides clues to their etiology. For example, aortic stenosis usually radiates to both carotids as the turbulent flow. The murmur of mitral regurgitation often radiates into the axilla. Respiratory variation is particularly valuable in identifying tricuspid regurgitation. Following inspiration, the systolic murmur of tricuspid regurgitation is often increased in intensity because of the extra blood inspiration is drawn into the right ventricle. However, if right atrial and right ventricular end-diastolic pressure are already very high, inspiration may have no effect on the volume in the right ventricle and the murmur of tricuspid regurgitation may not increase. Finally, the systolic murmurs of aortic stenosis and subaortic stenosis both increase following a pause in the cardiac cycle as the increased filling of the ventricle increases the aortic valve gradient and the turbulence of flow. The murmur of mitral regurgitation, however, does not increase following a pause in the cardiac cycle. The most common systolic murmurs in the patient with heart failure are those of mitral and tricuspid regurgitation, aortic stenosis, and subvalvular aortic stenosis. Evaluating the response of these murmurs to such maneuvers as a handgrip, squatting, and Valsalva maneuver, and following a pause in the cardiac cycle may help differentiate these murmurs. For a more extensive description of heart murmurs the reader is referred to additional references [39, 41].

4.6.4 Pericardial Friction Rub and Other Extra Sounds

Other cardiac sounds include pericardial friction rubs, clicks, and snaps. A pericardial friction rub signifies inflammation of the pericardial sac and is often the hallmark of pericarditis. Friction rubs are high-pitched, scratchy sounding, and are present in systole and diastole. Classic friction rubs have three components that reflect the times of most movement of the heart within the pericardial sac—systole and early and late diastole. However, three components of the friction rub are not always audible. The friction rub is often best heard with the patient sitting up and leaning forward bringing the heart close to the chest wall.

A mitral opening snap is generally used to describe the sharp and high-pitched opening of the mitral valve in early diastole and reflects the high-pressure gradient across the mitral valve in early diastole opening the restricted valve with force.

Clicks are sometimes present secondary to prosthetic valves with variability depending on the type, position, and normal function. The mechanical heart valve will have an opening and closing click and sometimes are audible without the stethoscope. Specific valves may be identified by their characteristic sounds. Ejection clicks are high-pitched sounds heard when the native aortic or pulmonary valves undergo maximal opening and are heard closely following the first heart sound. An aortic ejection click most often indicates a bicuspid aortic valve. Clicks may also be caused by mitral valve prolapse, but these are not referred to as ejection clicks as they often occur later in systole when a portion of the mitral valve prolapses causing a clicking or snapping sound. The characteristic feature is that the timing of the click may change with a Valsalva maneuver [43]. The Valsalva maneuver decreases the ventricular volume causing the mitral valve to prolapse earlier moving the click from late to mid or early systole. It is important to understand that the sign that the Valsalva maneuver has been successful in reducing left ventricular volume is an increase in heart rate.

4.7 Putting It All Together: Assessment of Congestion and Perfusion

The physical examination, along with the history, is often sufficient to establish the diagnosis of HF. In some cases, the physical examination may also suggest the etiology of heart failure—for example, when a murmur of aortic stenosis is heard. The physical examination is always valuable in assessing the daily status of the hospitalized patient with acutely decompensated heart failure and in assessing the outpatient with chronic HF. The physical examination findings specific for left ventricular failure, right ventricular failure, and low cardiac output are outlined in Table 4.7 [19]. The presence of crackles or rales is the only direct examination finding of elevated left ventricular pressures (left ventricular failure), but signs of right ventricular failure, in the patient with heart failure, are an indirect reflection of elevation in left-sided pressures. The signs of congestion, both right- and left sided define a

Table 4.7 Signs of right- and left-sided venous and pulmonary congestion

Right-sided (venous) congestion	Left-sided (pulmonary)	Low cardiac output
Elevated JVP	Rales	Cool extremities
Bilateral pitting edema		Narrow pulse pressure
Ascites		Proportional pulse pressure <25%
Hepatojugular reflux		“Thready” pulse
Tricuspid regurgitation		Pulsus alternans (rare)

patient who is “wet” or” dry” and the signs of low cardiac output define the patient as “warm” or “cold” allowing the examiner to place the patient into a specific hemodynamic profile that predicts prognosis and defines a treatment path [19, 44].

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The Cardiology Referral for Heart Failure: Work-up and Expectations

5

Kaushik Amancherla and Lisa Mendes

Case Scenario

Mr. Smith is a 53-year-old gentleman referred to the cardiology clinic for evaluation of exertional shortness of breath and lower extremity edema. His primary care provider is concerned that he may be developing heart failure. Mr. Smith's medical history is notable for type 2 diabetes mellitus, hypertension, and rheumatoid arthritis that are all well controlled. At today's visit he tells the cardiologist he was previously very active but in the past several weeks became short of breath walking two blocks. He also experiences occasional skipped heartbeats and has noticed swelling in his legs throughout the day. He denies chest pain, lightheadedness, or sudden loss of consciousness. He does not smoke tobacco, drink alcohol, or use recreational drugs. There is no family history of coronary artery disease or heart failure. His sister and mother have Hashimoto's thyroiditis. His only medications are metformin 1000 mg daily and amlodipine 10 mg daily.

On physical examination, Mr. Smith is a fit appearing man in no acute distress. His blood pressure is 110/80 mmHg, HR 90 bpm, and BMI 24 kg/m^2. His JVP is elevated at 12 cm and there are crackles at the lung bases. On cardiac examination, the apical impulse is normal in position but a soft S3 is heard at the apex. There is no hepatomegaly on abdominal examination. The extremities are warm with mild to moderate leg edema. An ECG was notable for sinus rhythm with left bundle branch block and frequent ventricular premature contractions. On chest X-ray the heart was normal in size with mild vascular congestion.

K. Amancherla · L. Mendes (✉)
Division of Cardiovascular Medicine, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: kaushik.amancherla@vumc.org; lisa.a.mendes@vumc.org

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_5

5.1 Initial Clinic Evaluation

5.1.1 General Approach

The history and physical examination are key components of the initial encounter with a patient that has suspected heart failure. The cardiovascular medicine (CVM) specialist will inquire about symptoms consistent with elevated left- and right-sided filling pressures, volume overload, and low output state, in addition to other clinical information that may be helpful in determining the etiology of a patient's heart failure including chest pain, palpitations, or fever. A detailed, 3-generational family history of coronary artery disease, heart failure, and sudden cardiac death will be obtained [1]. Medications including nonprescription formulations will be reviewed as will social habits such as tobacco, alcohol and recreational drug use.

5.1.2 Physical Exam

The physical examination will be focused on findings associated with heart failure and the neurohormonal changes that result from reduced cardiac output. The cardiology provider will measure height, weight, body mass index (BMI), blood pressure, and heart rate. An increased heart rate may be compensatory if cardiac output is reduced and the pulse pressure (difference between systolic and diastolic blood pressure) may be narrow due to peripheral vasoconstriction. If left atrial and ventricular pressures are elevated, crackles or rales may be appreciated on auscultation of the lungs. Elevation in right-sided filling pressures will be associated with jugular venous distention, and pressure in the right upper quadrant of the abdomen may result in further engorgement of these veins if the liver is congested (hepatic jugular reflux). On cardiac examination, the apical impulse may be displaced to the left if the heart is enlarged. A third heart sound (S3 gallop) is associated with systolic dysfunction and has been found to have the highest association with heart failure [2]. The murmurs of mitral and tricuspid regurgitation are common and may be more prominent in patients with decompensated heart failure. Lower extremity edema can be associated with sodium and water retention as well as venous congestion. Although these findings are helpful in making a clinical diagnosis of heart failure, the absence of these findings does not exclude this diagnosis and the CVM specialist may order additional laboratory testing and imaging when the suspicion of heart failure remains high [3].

5.1.3 Diagnostic Testing

Routine laboratory testing often obtained at the initial visit includes a compete blood count, metabolic panel, thyroid function, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP). An

electrocardiogram will be obtained to assess for abnormalities that may be associated with heart failure such as infarct patterns, arrhythmias, and conduction abnormalities. The chest radiograph may show chamber enlargement and signs of pulmonary congestion.

The imaging modality most widely utilized to characterize heart function is a transthoracic echocardiogram (TTE) [1]. TTE is noninvasive and uses sound waves to accurately assess chamber dimensions, wall motion, valve function, and hemodynamics, in addition to left ventricular systolic and diastolic function. Three-dimensional imaging has further improved chamber size and systolic function quantification and measurement of myocardial strain can provide clues to potential etiologies of left ventricular dysfunction. If echocardiography is inconclusive, cardiac magnetic resonance imaging (CMRI) is another noninvasive imaging modality that is available at most major medical centers and is the method of choice for quantitating ventricular chamber size and function, and valvular regurgitation [1]. In addition, this imaging method can assess myocardial perfusion and viability and myocardial tissue for inflammation and infiltration, providing useful diagnostic and prognostic information.

5.2 Case Scenario: Diagnostic Testing

Case Scenario

After the initial visit Mr. Smith's routine laboratory testing is normal except for an elevated BNP of 249. A transthoracic echocardiogram (TTE) is performed and is notable for normal left ventricular cavity size and wall thickness but severely reduced left ventricular ejection fraction (LVEF) of 30–35% with akinesis of the inferior and lateral walls. The atria are mildly enlarged but there is no significant valve disease. The inferior vena cava is dilated consistent with elevated right-sided filling pressures.

5.2.1 Assessment for the Etiology of Heart Failure

Heart failure can be caused by a wide range of disorders that affect the myocardium, pericardium, valves, and vasculature. The first step in the diagnostic process is to determine if the patient has predominantly systolic or diastolic dysfunction as quantification of the LVEF is key to both determining the etiology of heart failure and planning treatment. In the United States, the most common causes of HFrEF are coronary artery disease (CAD), hypertension, and nonischemic cardiomyopathy [1]. CAD and HTN are also common etiologies to heart failure with preserved EF (HFpEF) in addition to older age, female gender, diabetes, and obesity.

5.2.2 Assessment for Coronary Artery Disease

Both invasive and noninvasive testing can be used to assess patients with suspected CAD and newly diagnosed heart failure (Table 5.1). The choice of testing depends on a number of factors including the pretest probability of CAD, the ability of the patient to exercise, and the baseline ECG. For patients able to exercise with an intermediate probability of CAD and normal baseline ECG, exercise stress testing with ECG monitoring is an appropriate choice. Exercise testing not only can assess for ischemia but can also provide useful prognostic information as measured by functional capacity [4].

The presence of a left bundle branch block, ST-segment deviation, ventricular paced rhythm, and left ventricular hypertrophy can limit the interpretation of ECG results with exercise, and in these instances, echocardiography or myocardial perfusion imaging is recommended to overcome the limitations associated with ECG interpretation alone [5]. In patients not capable of exercising, pharmacological stress in conjunction with echocardiography or myocardial perfusion imaging has been shown to have sensitivity and specificity for detecting CAD similar to exercise testing with imaging [5]. Pharmacologic stress echocardiography most often involves the use of dobutamine, a β_1-agonist that increases heart rate and contractility similar to exercise [6]. With myocardial perfusion imaging, a coronary vasodilator such as adenosine or regadenoson is administered. These agents dilate normal

Table 5.1 Overview of testing for diagnosing CAD

Testing for ischemia	Advantages	Disadvantages
Exercise ECG	Provides information on functional capacity	Less sensitive when compared with imaging modalities
Exercise/ pharmacologic echocardiography	No exposure to radiation; widely available; higher sensitivity in comparison to ECG alone	Quality of imaging dependent on experience of sonographer
Exercise/ pharmacologic nuclear stress test	Higher sensitivity in comparison to echocardiography	Exposure to radiation; more expensive than echocardiography
Coronary CTA	High negative predictive value for stenotic coronary lesions $\geq 50\%$	Requires the use of iodinated contrast, limiting its use in patients with kidney disease and those with iodine allergies
Cardiac MRI	Allows for comprehensive simultaneous assessment of biventricular function and presence of scar	Requires specific expertise
Coronary angiography	Considered the gold standard in evaluating for the presence of CAD	Invasive procedure

ECG electrocardiogram, *CTA* computed tomography angiography, *MRI* magnetic resonance imaging

coronary arteries without significantly changing flow in diseased vessels. The resulting heterogeneity in flow can be detected by perfusion imaging [7].

The most common imaging modalities for assessing CAD in conjunction with exercise or pharmacologic stress are echocardiography and single-photon emission computed tomography (SPECT) or positron emission tomography (PET). With echocardiography wall motion is monitored during stress with ischemia defined as a new or worsening wall motion abnormality. Myocardial perfusion can also be assessed with single-photon emission computed tomography (SPECT) or positron emission tomography (PET). With SPECT imaging, a radioisotope technetium-99m is injected at peak exercise or after administration of a coronary vasodilator. In the normally perfused heart the radioisotope is equally distributed throughout the myocardium. In patients with ischemia, there will be regional decrease in uptake with stress that will partially or completely fill in with rest. A persistent defect at rest and with stress is consistent with myocardial infarction. PET myocardial perfusion imaging utilizes rubidium-82 or N13-ammonia as the radioisotope. PET imaging is more sensitive and specific than SPECT for the detection of CAD, provides superior imaging, and is associated with lower radiation exposure to the patient. However, it is more expensive than SPECT and can only be offered at centers that have a cyclotron to generate the radioisotope [5].

In recent years, there has been increasing use of coronary computed tomography angiography (CCTA) and cardiac magnetic resonance imaging (CMRI) in the evaluation of ischemic heart disease [8, 9]. Due to advances in CT technology, the anatomy of coronary arteries can be accurately visualized. CCTA has a high negative predictive value for stenotic coronary lesions ≥50% in comparison to functional stress testing. CCTA does require the administration of intravenous contrast which should be avoided in patients with chronic kidney disease and those with allergies to iodinated contrast. Its diagnostic accuracy is also decreased if there is significant coronary artery calcification which can be seen in patients with advanced atherosclerotic disease. Similar to CCTA, stress CMRI also has a high negative predictive value [9]. Stress CMRI is a pharmacologic stress test performed either with a vasodilator, such as adenosine or regadenoson, to detect abnormalities in perfusion or with dobutamine to detect regional wall motion abnormalities. CMRI also allows for comprehensive evaluation of biventricular function and the presence of infarcted tissue or scar. Studies have shown its diagnostic accuracy to be at least as good as other stress imaging modalities and it is capable of providing useful prognostic information [10, 11].

The gold standard for the evaluation of ischemic heart disease is coronary angiography as it allows direct visual assessment of the extent and severity of coronary artery disease. The American College of Cardiology and the American Heart Association guidelines for heart failure recommend coronary angiography for patients with a high pretest probability of CAD and who are candidates for revascularization [1]. Coronary angiography does carry a small but not insignificant risk (0.1–0.2%) of complications such as vascular injury, renal failure, stroke, and myocardial infarction. However, risk–benefit ratio favors coronary angiography when

noninvasive testing is inconclusive or when defining coronary anatomy will provide useful prognostic information and potential treatment with revascularization [12, 13].

The decision between an invasive and noninvasive approach to assess for CAD in patients with new-onset heart failure is controversial and variation exists among institutions and physicians. Testing should be determined by the patient's probability of CAD, the potential complications versus benefits, and patient preferences.

5.3 Case Scenario: Invasive Testing

Case Scenario
Mr. Smith was subsequently referred for left heart catheterization and coronary angiography due to the presence of regional wall motion abnormalities (hypokinesis of the inferior and lateral walls) potentially secondary to multivessel CAD. On coronary angiography, he was noted to have a 30% stenosis in his left anterior descending artery and non-obstructive disease in his other coronaries.

5.3.1 Work-up for Nonischemic Cardiomyopathy

When the work-up for ischemic heart disease as a cause of newly diagnosed heart failure is negative, the focus shifts to searching for nonischemic causes (Table 5.2). The differential for nonischemic cardiomyopathy is broad and includes familial, metabolic abnormalities, toxins including cancer therapies, tachycardia-mediated, peripartum cardiomyopathy, infectious causes, and inflammatory heart disease [1].

The history and physical exam play a crucial role in directing the diagnostic work-up of nonischemic cardiomyopathy. Familial cardiomyopathy represents a significant proportion of patients previously diagnosed with idiopathic dilated cardiomyopathy (DCM), with studies suggesting up to 50% of patients with idiopathic DCM actually have familial DCM [14]. In addition, it is estimated that approximately 40% of cases of familial DCM have an identifiable genetic cause [14]. For this reason, a 3-generational family history is highly recommended for patients with idiopathic DCM [1]. When a potential case of familial cardiomyopathy is identified, patients should be referred for genetic testing. If a known genetic variant for cardiomyopathy is identified, additional family members should undergo screening and appropriate genetic counseling [14].

Additional testing should be directed at the suspected cause based on the initial clinical evaluation. Screening for hemochromatosis, HIV, inflammatory and infiltrative diseases, and toxins is reasonable in selected patients presenting with heart failure [1].

In many cases, additional imaging may be needed to identify a potential etiology [15]. CMRI not only provides a comprehensive assessment of ventricular size, wall thickness, and function, but also provides detailed information regarding tissue composition. T1 and T2 mapping and late gadolinium enhancement (LGE) are all

Table 5.2 Causes of nonischemic cardiomyopathy

Autoimmune/ inflammatory	Dermatomyositis Polymyositis nodosa Rheumatoid arthritis Sarcoid Systemic lupus erythematosus
Genetic	Familial cardiomyopathy Duchenne's muscular dystrophy Friedreich's ataxia Arrhythmogenic right ventricular dysplasia
Infections	Viral, bacterial, fungal, and parasites, including HIV, COVID-19, Chagas disease
Infiltrative diseases	Amyloid Hemochromatosis
Nutritional deficiencies	Thiamine, L-carnitine, niacin
Metabolic	Obesity Diabetes Thyroid disease Abnormalities in growth hormone Anemia
Toxins	Alcohol Cocaine/methamphetamine Chemotherapy Medications: Plaquenil, clozapine, phenothiazines
Miscellaneous	Peripartum Stress-induced Tachycardia induced Radiation

CMR imaging techniques that help identify myocardial edema, infiltration, and fibrosis [16]. There are several typical patterns of LGE seen in patients with nonischemic cardiomyopathies that may help secure a diagnosis when combined with the clinical presentation. Patchy subepicardial LGE is typical for myocarditis, whereas patchy mid-wall and epicardial lesions with a predilection for the basal septum are more typical of sarcoid heart disease [16, 17]. Cardiac amyloid is associated with diffuse subendocardial LGE and iron deposition can be diagnosed with T2 mapping [18]. These differential patterns can guide further diagnostics and treatment.

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and SPECT are advanced imaging modalities that can complement CMRI in diagnosing the etiology of nonischemic cardiomyopathy. In cases of suspected cardiac sarcoid where CMRI cannot be performed or is inconclusive, FDG-PET can provide useful diagnostic and therapeutic information. FDG-PET evaluates for active inflammation and can help diagnose cardiac sarcoidosis at an early stage when therapy is likely to be most effective [17, 19]. In patients with suspected hereditary or

wild-type (ATTR) amyloidosis, technetium 99 m-pyrophoshphate scan, a form of SPECT imaging, can detect cardiac transthyretin protein deposition. Moderate to severe uptake of the radiotracer in patients without monoclonal protein on serum and urine analysis is sufficient to make a diagnosis of ATTR cardiac amyloid without biopsy [18].

Endomyocardial biopsy (EMB) can provide valuable information to the etiology of new-onset heart failure but is typically only pursued in patients where a histopathologic diagnosis is critical for guiding treatment strategies. EMB is recommended in patients presenting with unexplained acute heart failure requiring inotropes or mechanical circulatory support, and patients with new-onset heart failure and electrical instability [20]. These presentations raise suspicion for giant cell myocarditis or fulminant acute myocarditis and confirmation of the diagnosis can result in life-saving therapies. EMB may also be useful in patients where there is a strong suspicion of cardiac sarcoid but noninvasive imaging techniques are inconclusive [21]. In patients with HFpEF suspected of having amyloid heart disease, EMB can assist with amyloid fibril typing in cases where the diagnosis cannot be confirmed by other hematologic and imaging methods [22]. Complications of EMB include vascular injury and myocardial perforation [1]. EMB is also limited by sampling error due to the patchy nature of many inflammatory and infiltrative heart diseases.

5.4 Case Scenario: Diagnosis

Case Scenario

The lack of significant obstructive CAD suggests that ischemic heart disease is not the primary cause of Mr. Smith's newly diagnosed heart failure. His history of rheumatoid arthritis and family history of autoimmune disease raised suspicion for the possibility of cardiac sarcoidosis which can be associated with other autoimmune disorders. He underwent FDG-PET, which showed a large perfusion defect in the lateral wall and high uptake of FDG in the basal septum. These findings were suggestive of cardiac sarcoidosis. He was subsequently started on corticosteroid therapy with improvement in symptoms and left ventricular function. Since sarcoid is a multisystem disease, the cardiologist and primary care provider (PCP) coordinated care to pursue chest computed tomography and pulmonary function tests (to assess for pulmonary involvement). The PCP also referred the patient to ophthalmology to assess for uveal involvement and closely followed up with the patient each month to ensure adequate blood glucose control in the context of corticosteroid use.

5.4.1 Putting It All Together

Signs and symptoms of heart failure should result in a prompt referral to CVD specialist for assistance with diagnosis and treatment. The differential diagnosis for heart failure is broad and ranges from genetic causes to inflammatory heart disease.

Ischemic heart disease is the leading cause of heart failure in the United States, but choosing the optimal noninvasive stress test or deciding between stress testing and coronary angiography is a nuanced process that is dependent on many patient and institution specific factors. Advances in cardiac imaging have greatly improved the ability to diagnose the etiology of heart failure noninvasively and for many cardiac diseases have replaced the need for EMB. Taken together, evaluation of a patient with new-onset heart failure by an experienced CVD specialist can help navigate through these decision pathways to definitively diagnose the patient and initiate life improving treatment. Once a definitive diagnosis is made, frequent communication and collaboration between the CVD specialist and the PCP is critical in providing the best care for the patient.

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for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012;59(22):1995–2027.
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Part III

Heart Failure Management

Chapters six and seven are designed to highlight guideline directed medical therapy and enhance the understanding of treatment variations between Heart Failure with Reduced Ejection Fraction versus Heart Failure with Preserved Ejection Fraction. Chapter eight is focused on navigating self-care strategies, social determinants of health, and transitional care that can be particularly challenging for the heart failure population. Heart failure continues to have a high morbidity and mortality rate. Chapter nine provides insight and guidance for goals of care and end-of-life discussions.

Heart Failure with Reduced Ejection Fraction

6

Terri L. Allison and Beth Towery Davidson

6.1 Introduction

Heart failure (HF) is a syndrome that results in the inability of the heart to meet the metabolic demands of the body. Heart failure with reduced ejection fraction (HFrEF), previously called congestive heart failure due to its prominent clinical feature of fluid volume overload, or congestion, is defined as "a clinical diagnosis of heart failure with an ejection fraction <40%" and is often associated with left ventricular enlargement [1]. A proposed universal definition of HFrEF qualifies the diagnosis as a clinical syndrome that includes symptomatic HF with left ventricular ejection fraction (LVEF) ≤ 40% and presence of either elevated natriuretic peptides (i.e., brain natriuretic peptide [BNP]) or objective evidence of pulmonary or systemic congestion, i.e., via right heart catheterization [2]. Heart failure with preserved ejection fraction (HFpEF) represents approximately half of patients diagnosed with HF. HFpEF is currently defined as an LVEF ≥50% [1]. Treatment for HFpEF is available and addressed in a subsequent chapter. Heart failure with mildly reduced or midrange ejection fraction (HFmrEF) is defined as LVEF 41–49% with evidence of spontaneous or provoked increase in left ventricular filling pressures [1]. Patients with HFmrEF may benefit from similar therapies used in the treatment of HFrEF. Patients with HFrEF may have improvement in LVEF following implementation of goal-directed medical therapies (GDMT); however, these patients often continue to have changes in cardiac structure and function [1].

T. L. Allison (✉)
Vanderbilt University School of Nursing, Nashville, TN, USA
e-mail: terri.allison@vanderbilt.edu

B. T. Davidson
Advanced Clinical Expert, CardioMEMS™, Heart Failure, Abbott, Pleasanton, CA, USA
e-mail: bethdavidsondnp@comcast.net

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_6

Guideline-directed medical therapy should be continued in this subset of patients with HFrEF despite improvements in ejection fraction.

In this chapter, the epidemiology, etiology, diagnostic testing, GDMT, and device options for management of HFrEF will be presented.

6.2 Epidemiology

A predominant cause of HFrEF is coronary artery disease (CAD) and myocardial infarction (MI) although numerous other causes can result in left ventricular dilation and enlargement. Heart failure incidence and prevalence increases with advancing age and, based on the most recent data, approximately six million people ≥ age 20 have HF. Prevalence is expected to increase 46% by the year 2030 [3]. Older adult women (≥ age 80) and black men and women demonstrate the highest prevalence of heart failure [3]. Of heart failure hospitalizations, 50% are related to HFrEF. Heart failure is a chronic and progressive syndrome and 15–20% of patients diagnosed with HFrEF will develop worsening heart failure within 18 months of diagnosis [4]. Additionally, hospitalization due to HF exacerbation increases mortality risk by approximately 10% for each hospitalization [5].

6.3 Etiology

Heart failure can occur because of diseases of the pericardium, myocardium, endocardium, heart valves, coronary arteries, and/or certain metabolic or infectious disorders [6]. Etiology is often categorized into two classifications of cardiomyopathy (CMP): ischemic cardiomyopathy (ICM) and nonischemic cardiomyopathy (NCIM) [1]. The term dilated cardiomyopathy (DCM) is frequently used synonymously with NICM; however, the term DCM does not encompass all causes of NICM. Older studies examining outcomes of patients with HFrEF due to ICM versus DCM were mixed and the relationship between the etiology of HFrEF and outcome was unclear [7]. Patients with ICM or NICM can develop HFrEF. A data analysis of the Prospective Comparison of Angiotensin-receptor-neprilysin inhibitor (ARNI) with Angiotensin converting-enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial demonstrated no differences in cardiovascular death or HF hospitalization between ICM and NICM groups when controlled for New York Heart Association (NYHA) functional class, and demographic, risk, and comorbid factors [8].

Cardiomyopathy can be classified according to anatomic or functional features (Table 6.1). Coronary artery disease and myocardial infarction (MI) cause myocardial remodeling and myocyte hypertrophy and destruction, resulting in ICM [9]. Dilated cardiomyopathy occurs as a consequence of myriad disorders affecting the

heart where the end result of the disease process is damage to the myocardium manifested as ventricular dilation and reduced myocardial contractility in the absence of hypertension or valvular disease [1, 10]. Other types of NICM occur as the result of processes that cause myocyte damage, infiltration, or fibrosis of myocardial tissues causing myocardial stiffening and restriction, or a thickening and hypertrophy of the myocardium [11].

Table 6.1 Classification of cardiomyopathy [1, 9–13]

Classification by disease type/ phenotype	Etiology
Ischemic cardiomyopathy (ICM)	Coronary artery disease
	Myocardial infarction
Nonischemic(NICM)/dilated cardiomyopathy (DCM)	Idiopathic
	Familial/genetic
	Hypertension
	Toxins:
	• Alcohol
	• Cocaine
	• Chemotherapy, i.e., anthracyclines
	• Ephedra, methylphenidate
	• Anabolic steroids
	• Thoracic radiation
	Nutritional:
	• Anorexia nervosa
	• Thiamine deficiency
	• Obesity
	Dystrophinopathies:
	• Duchenne muscular dystrophy
	• Becker's muscular dystrophy
	Tachycardia-induced cardiomyopathy
	LV noncompaction (LVNC)
	Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Hypertrophic cardiomyopathy (HCM)	Idiopathic
	Familial/genetic
Restrictive/infiltrative cardiomyopathy	Amyloidosis
	Sarcoidosis
	Connective tissue disease:
	• Lupus erythematosus
	• Scleroderma
	• Hemochromatosis
Valvular cardiomyopathy	Mitral, tricuspid, pulmonary, or aortic valve disease
	Rheumatic heart disease

(continued)

Table 6.1 (continued)

Classification by disease type/ phenotype	Etiology
Peripartum cardiomyopathy	Pregnancy or postpartum associated heart failure
Inflammation or infection	Viral myocarditis:
	• Coxsackie
	• Parvovirus
	• Adenovirus
	• Echovirus
	• Influenza
	• HIV
	• SARS-CoV-2 (COVID-19)
	Protozoal infection:
	• Chagas disease
	Spirochete infection
	• Syphilis
	Giant cell myocarditis
Metabolic/endocrine disorders	Diabetes mellitus
	Hyperthyroidism
	Hypothyroidism
Stress-induced cardiomyopathy (Takotsubo)	Physical or emotional stress (catecholamine surge)

LV left ventricle, *HIV* human immunodeficiency virus

6.4 Prevention

A multitude of risk factors and disease processes increase the possibility a person will develop heart failure. Preventive strategies focus on elimination or management of modifiable risk factors (Table 6.2) [1, 14]. While many risk factors may not be eliminated, maintaining a healthy lifestyle is the most significant approach to preventing HF [15, 16]. Primary care providers (PCPs) play an essential role in recognizing HF risk factors among their patient population, implementing interventions to address modifiable risk factors and monitoring for development of or progression to HF. A team-based approach that evaluates the social determinates of health impacting treatment decisions and considers the patient's goals and preferences should be incorporated when developing plans of care [1].

Individuals with American College of Cardiology/American Heart Association (ACC/AHA) Stage A HF (Table 6.3) are at high risk for development of HF but have no structural cardiac changes or HF symptoms. Prevention strategies to ameliorate HF risk focus on management of comorbid disease processes and lifestyle and behavioral factors. The most significant comorbid diagnoses that promote progression of HF are hypertension, diabetes mellitus, metabolic syndrome, and history of

Table 6.2 HFrEF risk factors [1, 10]

Modifiable
• Hypertension
• Diabetes mellitus
• Metabolic syndrome
• Atherosclerotic disease
• Dyslipidemia
• Smoking/tobacco use
• Physical inactivity
• Overweight/obesity
• Excessive alcohol consumption
• Cardiotoxic over the counter or medicinal substances in excessive doses or prolonged use, e.g., anabolic steroids, amphetamines, ephedra, decongestants, nonsteroidal anti-inflammatories
Nonmodifiable
• Cardiotoxic chemotherapy, e.g., anthracyclines, trastuzumab, cyclophosphamide
• Thoracic radiation
• Family history of sudden cardiac death
• Family history of premature CAD: age < 55 males, age < 65 females
• Conduction system disease, e.g., atrial fibrillation
• Muscular dystrophy

atherosclerotic cardiovascular disease (ASCVD), particularly MI or CAD [1, 14]. Hypertension control is the most effective strategy in preventing new onset HF [17].

Assessment of ASCVD risk is the basis for determining primary prevention strategies [15]. Asymptomatic adults aged 40–75 should be screened; screening adults > age 20 every 4–6 years should be considered. Eight primary preventive measures have been shown to avert ASCVD events leading to HF progression and include weight reduction if overweight or obese (BMI $\geq$ 25.9 kg/m^2), increased physical activity, blood pressure, cholesterol and glycemic control, smoking cessation, adherence to a healthy diet, and renal function monitoring, as well as implementation of guideline-based pharmacologic interventions for management of comorbidities [15, 16]. Family history of premature ASCVD (age < 55 males, age < 65 females); metabolic syndrome; chronic kidney disease; chronic inflammatory conditions, e.g., lupus, rheumatoid arthritis, HIV/AIDS; history of premature menopause (< age 40); history of preeclampsia; high-risk race or ethnicity (South Asian ancestry); hypertriglyceridemia; extracardiac vascular disorders, e.g., erectile dysfunction, claudication, or peripheral arterial vascular disease (PAD) are factors that revise a patient's 10-year ASCVD risk estimation and should be included in patient assessment. Individuals with HF Stages B–D (Table 6.3) should also undergo aggressive management of cardiovascular risk factors as secondary prevention strategies to avoid HF progression [16].

Table 6.3 Heart failure stages and functional classification [1]

ACC/AHA stages of HF			NYHA functional classification
A	*At-risk for heart failure* At high risk for HF without current or previous signs/symptoms of HF and without structural heart disease or abnormal biomarkers	None	
B	*Pre-heart failure* Structural heart disease without current or previous signs/symptoms of HF without abnormal biomarkers	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
C	*Symptomatic heart failure* Structural heart disease with prior or current signs/symptoms of HF with structural heart disease, or evidence of increased filling pressures, or risk factors and increased BNP or cardiac troponin in absence of competing diagnosis	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
		II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
		IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest
D	*Advanced heart failure* Refractory HF despite attempts to optimize GDMT	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

ACC American College of Cardiology, *AHA* American Heart Association, *NYHA* New York Heart Association

6.5 Outpatient Management

6.5.1 Diagnosis and Evaluation

The typical primary care provider managing 2000 patients is likely to have 40–50 patients with HF and roughly five newly diagnosed cases per year [18]. Although relatively common, the individual practitioner will likely not become an expert in HFrEF diagnosis. Clinical diagnosis can present a major challenge as patients may exhibit a variety of signs and symptoms, many of which are not specific to HF. Patients with HF often have several comorbid conditions, further complicating the clinical presentation [19]. Additionally, individuals not typically thought to be predisposed to HF, e.g., young adults, pregnant or postpartum women, may be misdiagnosed.

6.5.2 Patient History

A detailed history is important to identify any cardiac and noncardiac disorders that may contribute to the development or progression of HF [1]. Elements of the patient history should include chief complaint, history of present illness (HPI), past medical history, family history, social history and habits, review of systems, and a functional assessment (Table 6.4). Risk assessment can be useful to estimate subsequent

Table 6.4 Heart failure patient history [20]

HPI	Chief complaint Signs/symptoms Hospitalizations Emergency department visits Medications & supplements Allergies/intolerances	
Past medical history	*Cardiac conditions* Coronary artery disease Myocardial infarction Cardiac surgery/procedures Hypertension *Infiltrative disease* Amyloidosis Sarcoidosis *Hereditary disease* Cardiomyopathy Hemochromatosis Sickle cell trait Thalassemia *Dysrhythmias* Devices Pacemaker Cardiac resynchronization therapy (CRT) Implanted cardioverter defibrillator (ICD)	*Noncardiac conditions* Diabetes mellitus Hyper/hypothyroidism Peripheral vascular disease *Connective tissue disorders* Lupus erythematosus Scleroderma *Infectious disease* Hepatitis C Human immunodeficiency virus (HIV) Chronic obstructive pulmonary disease (COPD) Renal insufficiency/chronic kidney disease Mediastinal irradiation Pheochromocytoma Anemia Obesity
Family history	Coronary artery disease Cerebrovascular accident or transient ischemic attack Cardiomyopathy (3 generations for idiopathic/familial) Sudden cardiac death Hypertension Hyperlipidemia	
Social history/social determinates of health	Social support system Family Marital status Care partner Childcare Financial resources/strain Insurance/access to care Education Work/profession	Tobacco/alcohol Illicit drugs Religion/culture Transportation Food insecurity Health literacy Mental health Exposure to adversity Violence Trauma Personal safety Housing/utilities

mortality risk, including utilization of biomarkers and a variety of risk models that guide treatment plans [1, 21, 22]. Available risk score models frequently used in the chronic HF population include the Seattle Heart Failure Model, Heart Failure Survival Score, and the CHARM and CORONA Risk Scores [1]. Functional assessment and ability to complete activities of daily living are helpful in assessing the overall degree of limitation. The 6-min walk can be easily evaluated in all settings and is a measure of exercise capacity that can be trended over time following the initial diagnosis of HF [23] Functional assessement often correlates with NYHA heart failure classification and should be monitored over time to evaluate changes in severity of illness, including signs and symptoms of decompensation [1].

6.5.3 Physical Exam

A primary goal in assessment of the patient with HF is to determine the extent and severity of disease. Physical examination focuses primarily on the cardiovascular and pulmonary systems. Volume status, vital signs, and weight should be evaluated at every patient encounter [1]. Orthostatic hypotension can be common and may be related to vasodilation, low cardiac output, and/or volume depletion.

The HF-focused exam includes [24]:

- General inspection—skin/nailbed color, mental status, respiratory effort.
- Jugular venous pressure (JVP)—normal <8 cm when assessed at 45-degree angle.
- Heart sounds/murmurs.
- Lung sounds.
- Hepatojugular reflux (HJR)/abdominojugular test—increase in JVP when manual pressure applied over the liver.
- Peripheral edema/skin temperature.

A variety of abnormal assessment findings may be seen in the HF population. Findings may include tachycardia and tachypnea, elevated JVP, rales or crackles, decreased breath sounds, S3 heart sound, displaced point of maximal impulse (PMI), ascites, HJR, reduced strength of peripheral pulses, cyanosis, and cardiac cachexia [20]. Tachycardia is typically a compensatory response to low cardiac output. Cardiac enlargement is detected by palpation, with the PMI laterally displaced or presence of a precordial heave. A third heart sound, S3, is associated with congestion and may be one of the earliest signs of cardiac decompensation due to HF [24]. Murmurs are indicative of valvular dysfunction. Mitral regurgitation can occur with increased LV mass and dilation of the valve annulus. Both elevation of JVP and positive HJR reflect venous congestion [20, 24]. Respiratory rate and pattern reflect the degree of pulmonary compromise. Crackles from transudative fluid in the alveolar spaces may be auscultated, but clear breath sounds do not exclude the presence of pulmonary edema [1]. Peripheral edema is most common in the lower extremities, ankles, and feet. In severe, untreated fluid volume overload, anasarca may occur. Cool and mottled extremities are associated with low cardiac output. Cardiac cachexia and muscle wasting are not well understood but are a poor prognostic sign

[25]. See also Chap. 4 for more details of the physical exam for presence and severity of HF.

6.5.4 Diagnostic Evaluation

If a diagnosis of HFrEF is suspected, initial evaluation includes measurement of natriuretic peptides, electrocardiography, and chest X-ray. Signs of congestion and cardiomegaly on chest X-ray are sensitive for HF [25]. Transthoracic echocardiogram remains the gold standard for evaluation of ejection fraction (EF), left and right ventricular mass, chamber size, valvular dysfunction, and pericardial effusion [1]. Routine, repeat measurement of left ventricular (LV) function is not warranted in the absence of a change in clinical status [1]. New patient HF evaluation should also incorporate laboratory analysis to establish baseline levels and evaluate for disorders that contribute to or exacerbate HF and includes electrolytes, hepatic and renal function, thyroid function, diabetes mellitus, and anemia. Genetic testing is warranted for familial or genetically transmitted disorders affecting the myocardium. Based on the 2017 HF guidelines, measurement of natriuretic peptides should be utilized to assist in the diagnosis or exclusion of HF, to aid in the determination of prognosis, and for risk stratification [26].

The etiology of HFrEF is often ischemia; newly diagnosed patients typically require an evaluation for CAD. Left heart cardiac catheterization (LHC) with coronary angiography is the benchmark diagnostic tool for identification of obstructive epicardial CAD. Noninvasive evaluation may be considered for patients who are deemed low risk for atherosclerosis. Cardiac magnetic resonance imaging (cMRI), positron emission tomography (PET), or technetium pyrophosphate scintigraphy (PYP) may be indicated, depending upon clinical presentation and suspicion of specific underlying illness, such as myocarditis or amyloidosis [25]. Right heart catheterization (RHC) to evaluate hemodynamic status and cardiopulmonary exercise stress testing (CPXT) to evaluate functional capacity are utilized to assess degree of cardiac decompensation, response to GDMT, and when evaluating an individual's candidacy for advanced therapies, such as ventricular assist devices (VAD) and cardiac transplantation. Endomyocardial biopsy is not routinely performed but can be helpful in diagnosing myocarditis, post-transplant rejection, or other infiltrative processes (Table 6.5) [1].

6.5.5 Clinical Presentation

Patients with HF may present initially with a wide variety of symptoms that are vague and nonspecific, confounding the diagnosis. Dyspnea, at rest or with exertion, and fatigue are often the predominate symptoms prompting an individual to seek treatment. Additional cardinal symptoms include fluid retention, orthopnea, and paroxysmal nocturnal dyspnea. Patients may complain of abdominal pain and early satiety due to splanchnic and liver congestion [1, 28]. Bendopnea, shortness of breath when

Table 6.5 Diagnostic tools for evaluation of HFrEF [1, 25–27]

Laboratory studies	Diagnostic imaging
Natriuretic peptides	12 Lead EKG
Biomarkers (e.g., troponin, ST2)	Chest X-ray
Complete blood count	2D echocardiogram
Basic metabolic profile	Cardiac catheterization
Hepatic function panel	Stress testing
Iron studies	MRI
Urinalysis	PET
Thyroid function tests	PYP scan
Hemoglobin A1c	CPXT
Lipid panel	Endomyocardial biopsy
Genetic testing	

Table 6.6 Signs and symptoms of left and right ventricular failure [1, 28, 30]

LV failure	RV failure
Shortness of breath	Jugular venous distention
Tachypnea	Edema
Orthopnea	Abdominal distension
Benopnea	Hepatomegaly
Cough	Ascites
Crackles/rales	Anorexia/early satiety
Pleural effusion	Nausea
	Right upper quadrant pain
	Anasarca

bending forward, is associated with advanced NYHA classification and greater mortality [29]. Signs and symptoms may be defined based upon the primary targets of congestion. Left-sided symptoms are primarily reflected in the lungs and pulmonary system whereas right-sided symptoms appear in the peripheral vasculature (Table 6.6).

6.5.6 Guideline-Directed Medical Therapy

Utilization of GDMT is centered upon specific treatment recommendations as categorized by the ACC/AHA heart failure staging system and NYHA classification (Table 6.3) [1]. GDMT for HFrEF focuses on patients with Stage C and D HF. NYHA class will vary based upon changes in clinical condition and symptoms. Overall management goals include symptom control, prevention of disease progression, and reduction of HF hospitalization rates and mortality.

The landscape of evidence-based medications for HFrEF continues to evolve but the cornerstone remains neurohormonal blockade to counteract the deleterious effects of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). Angiotensin converting enzyme inhibitors, ARBs, ARNI, and aldosterone antagonists/mineralocorticoid receptor agonists (AA/MRA) all have morality benefit in patients with HF [1, 26]. Based on the totality of data

surrounding ARNI, sacubitril/valsartan (the first and only commercially available ARNI in the USA) is the preferred RAAS antagonist in HFrEF [31]. Although ACEI and ARB medications are used interchangeably and are considered to have a "class effect," only three beta blockers are approved for use in HF—bisoprolol, carvedilol, and metoprolol succinate [1]. Diuretics are commonly prescribed to manage congestion and volume overload and are solely for symptom control. Hydralazine in combination with nitrates is an alternative for those patients who have contraindications or intolerance to ACEI/ARB/ARNI and in special populations, such as African Americans. Digoxin may be prescribed to improve symptoms and reduce HF hospitalization rates. Ivabradine acts at the level of the sinoatrial node to lower heart rate without compromising blood pressure and was demonstrated to improve HF hospitalization rates in the Systolic Heart Failure Treatment with the I_f Inhibitor Trial (SHIFT) [32].

Additional therapies continue to gain Food and Drug Administration (FDA) approval as new pathological targets have been identified to improve symptoms and/or outcomes for patients with HFrEF, such as the guanylyl cyclase (sCG) stimulators and the sodium-glucose co-transporter-2 (SGLT2) inhibitors [31]. Vericiguat, a sCG stimulator, received FDA approval in January 2021 and is the first treatment for chronic heart failure approved specifically for patients following a hospitalization for HF or in need of outpatient intravenous (IV) diuretics. Based on the results of the pivotal, phase III Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) trial, vericiguat is indicated to reduce the risk of cardiovascular death and HF hospitalization among patients with symptomatic chronic HF [33]. Vericiguat is adjunctive therapy to baseline GDMT and works through the nitric oxide pathway to increase smooth muscle relaxation and vasodilation [34].

Although the complete mechanism of action remains unclear, SGLT2 inhibition has repeatedly shown benefit among the HFrEF population in patients with and without diabetes mellitus [31]. SGLT2 inhibition promotes diuresis and natriuresis (sodium loss), leading to reduction in preload, blood pressure, arterial stiffness, and afterload, thereby improving subendocardial blood flow. SGLT2 inhibition is also associated with a shift to ketone-based myocardial metabolism and preservation of renal function [35]. Two SGLT2 agents, empagliflozin and dapagliflozin, have an approved indication for HF. SGLT2 inhibition received a Class IA recommendation with publication of the 2022 HF guideline to reduce HF hospitalization and reduce cardiovascular mortality [1]. Table 6.7 outlines the aforementioned indications and neurohormonal targets along with the appropriate agents that are recommended for HFrEF medical therapy [36].

6.5.7 Initiation, Titration, and Optimization

HF medical regimens are increasing in complexity and patients often have multiple comorbid conditions, complicating management for both patients and clinicians. The current treatment algorithm for GDMT in HFrEF Stage C and D is depicted in Fig. 6.1.

Table 6.7 Indications for medical therapy in HFrEF. Adapted [36]

Indication/therapy target	Agent
RAAS inhibition	ACEI, ARB, ARNI AA/MRA (spironolactone, eplerenone)
SNS inhibition	Beta blockers (bisoprolol, carvedilol, metoprolol succinate)
SGLT2 inhibition	SGLT2 inhibitors (dapagliflozin and empagliflozin)
Guanylyl cyclase stimulator (sCG stimulator)	Soluble sCG stimulator (vericiguat)
HR/HF hospitalization reduction: Beta adrenergic receptors Sodium/potassium ATPase pump HCN-gated channel	Beta blockers Cardiac glycosides (digoxin) HCN-gated channel inhibitor (ivabradine)
Congestion: Sodium inhibition in the nephron	Diuretics (loop, thiazide)
Vasodilation: Arterioles (afterload) Intracellular cyclic-GMP (preload)	Hydralazine + nitrates (African Americans, or ACE/ARB/ARNI intolerant)

RAAS renin-angiotensin-aldosterone system, *SNS* sympathetic nervous system, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin 2 receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor, *MRA* mineralocorticoid receptor agonist, *SGLT-2* sodium-glucose cotransport-2, *HR* heart rate, *HF* heart failure, *HCN* hyperpolarization-activated cyclic nucleotide, *DCT* distal convoluted tubule, *GMP* guanosine monophosphate

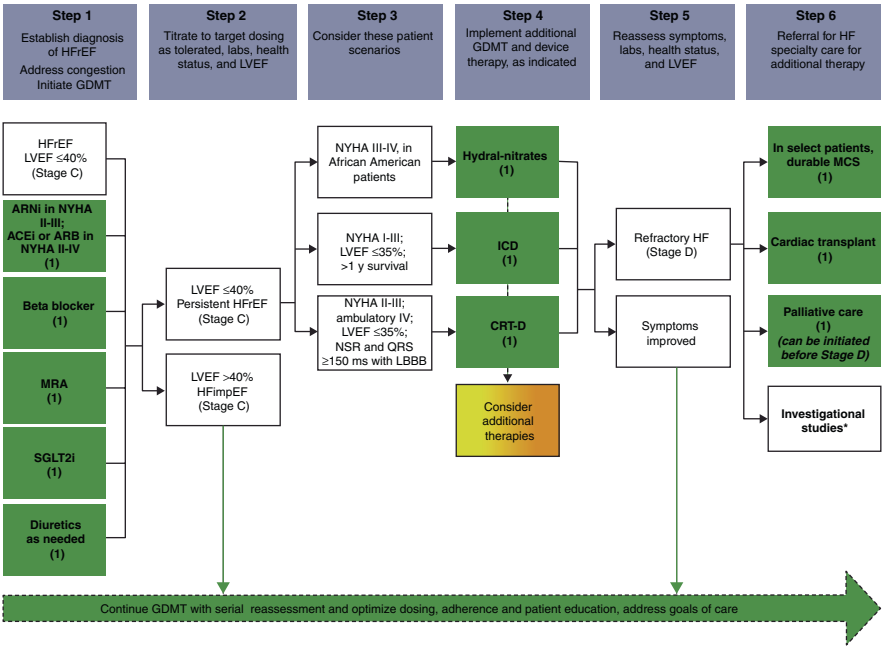

Fig. 6.1 Treatment algorithm for GDMT [1]. [Reprinted from Journal of Cardiac Failure, 79 (17), Heidenreich P, Bozkurt B, Aguilar D, et al. AHA/ACC/HFSA Guideline for the Management of Heart Failure, e263–e421, copyright (2022), with permission from Elsevier]

GDMT is shown to reduce morbidity and mortality within 30 days of initiation [37]. Optimizing GDMT and promoting patient adherence remains a challenging task for clinicians. Despite clear guidelines for the management of HFrEF, results from the Change the Management of Patients with Heart Failure (CHAMP-HF) registry showed major gaps in utilization of evidence-based medical therapy, highlighting a significant opportunity to improve clinical care and outcomes for the HFrEF population [38]. Practical strategies to promote adherence and optimize GDMT include [1, 6, 31, 39]:

- Prioritize therapies with the greatest therapeutic benefit: ARNI, beta blockers, AA/MRA, and SGLT2 inhibitors.
- Initiate medications at low doses and up-titrate as tolerated.
- Minimize diuretics to the lowest possible dose to maintain euvolemia.
- Avoid medication up-titration if volume depleted or HF decompensated.
- Schedule medication dosing to avoid excessive fluctuations in blood pressure or hypotension.
- Monitor renal function, electrolytes, and cardiac-specific biomarkers (BNP, NTproBNP, Troponin) to assess for HF exacerbation and aide clinical decision making.
- Assess affordability and access to prescribed medication regimen.
- Reconcile medications at every visit. Discuss side effects and reinforce benefits.
- Simplify regimen when possible; deprescribe all nonessential medications and supplements.
- Employ "teach back" method to assess recall and understanding. Include caregivers in patient education.

6.5.8 Adjunctive Therapies

Patients with HFrEF may benefit from adjunctive therapies to augment GDMT and improve quality of life. Revascularization procedures are recommended for patients with coronary ischemia, suitable coronary anatomy, and viable myocardium. Hyperkalemia is a clinical adverse effect of RAAS inhibition, often limiting initiation or up-titration of ACE inhibitors, ARBs, AA/MRAs, or ARNI. Potassium binders may be considered to allow continuation of GDTM. Omega-3 polyunsaturated fatty acid supplementation is a reasonable consideration to reduce mortality and cardiovascular hospitalizations. Mitral valve surgery or transcatheter mitral valve repair is indicated for patients with secondary, or functional, mitral regurgitation [1].

Many adjunctive therapies have not improved outcomes in the HFrEF population. Anticoagulation is not recommended without the presence of comorbid conditions, such as atrial fibrillation or prior thrombotic/embolic event. Statins are not beneficial when solely prescribed for the diagnosis of heart failure. Nutritional supplementation and hormonal therapies, other than to correct confirmed deficiencies, are not recommended. Continuous inotropic infusions are not indicated except for palliation or as a "bridge" to advanced therapies [1]. Medications known to adversely influence the clinical status of patients with HFrEF should be avoided,

including calcium channel blockers, most antiarrhythmic medications, nonsteroidal anti-inflammatory agents, and thiazolidinediones [1].

6.5.9 Nonpharmacological Interventions

In addition to standard medical therapy, nonpharmacological interventions managed collaboratively by the primary care and cardiology clinicians can augment HF patient stability, quality of life, adherence, and patient engagement in self-care (Table 6.8).

6.5.10 Device Therapy

The therapeutic benefits of device therapy for the treatment of HFrEF are well established and a subset of patients will be candidates for implantable devices once GDMT is optimized [41–43]. Implantable device therapy should only be considered in patients receiving optimal GDMT.

Implantable cardioverter defibrillators (ICDs) protect HF patients from sudden cardiac death (SCD) due to cardiac dysrhythmias; however, frequent shocks may decrease quality of life and result in significant stress and anxiety [1]. Use of antiarrhythmic medications, catheter ablation of arrhythmogenic myocardium, and refined ICD and cardiac resynchronization therapy (CRT) programming can decrease the frequency of dysrhythmias requiring shocks to restore normal sinus rhythm [6].

Wearable cardiac defibrillators (WCD) are available for patients at risk for sudden cardiac death who do not qualify for ICD implantation. WCDs provide an option for protection when the risk of SCD is unclear, such as after acute MI and coronary revascularization procedures in the setting of low EF, prior to initiation of GDMT, those awaiting mechanical circulatory support implantation and/or cardiac transplantation, and patients with an active contraindication to device implantation, such as infection [44].

In approximately one third of patients, HF progression is associated with a prolongation of the QRS interval and asynchronous contraction between the right and

Table 6.8 Nonpharmacologic interventions for heart failure [1, 40]

Individualized patient education
Weight management
Physical activity/cardiac rehabilitation
Smoking cessation
Alcohol moderation/restriction
Avoid excessive sodium intake
Fluid restriction (as indicated)
Continuous positive airway pressure (CPAP) for sleep apnea
Primary disease prevention screenings (mammogram, colonoscopy, etc.)
Influenza/pneumococcal/COVID-19 vaccination

left ventricle, resulting in decreased efficiency of cardiac performance. Cardiac resynchronization therapy can improve ventricular function, decrease mitral regurgitation, reverse ventricular remodeling, and improve EF [1]. More recently, device therapy options have expanded to select patients with low to moderate EF and a narrow QRS complex (Table 6.9). Although the exact mechanism of action differs slightly between devices, all are designed to modulate the SNS [45–47].

HF hospitalization and readmission rates remain a target for improved clinical outcomes. Despite the Hospital Readmission Reduction Program (HRRP), 30- and 90-day readmission rates increased from 2010 to 2017 [48]. Ambulatory pulmonary artery pressure monitoring can largely reduce hospitalization for patients with NYHA class II and III heart failure [49, 50]. Wireless implantable hemodynamic monitoring allows for improved heart failure management by early detection of changes in pulmonary pressures. The CardioMEMS™ HF System (Fig. 6.2) is the first and only FDA-approved wireless heart failure monitoring system proven to reduce hospitalization for both HFrEF and heart failure with preserved ejection fraction (HFpEF) [50, 51].

Table 6.9 Novel devices for HFrEF with narrow QRS complex [45–47]

Device	Barostim™	Optimizer® Smart	Cardionomic™ Pulmonary Neuromodulation System (CPNS)
Manufacturer	CVRx	Impulse Dynamics	Cardionomic
Mechanism of action	Activates baroreceptors in carotid artery, increases parasympathetic tone, decreases sympathetic drive	SNS modulation to increase contractile force, no increase in oxygen consumption	SNS stimulation to increase contractility and MAP, no change in heart rate
Indication	• EF < 35	• EF 25–45	• EF < 50
	• NYHA II or III	• Narrow QRS	• SBP > 80
	• NO indication for CRT	• NO indication for CRT	• NO CRT/ICD
	• NT pro BNP < 1600		• NSR
Insertion	Carotid stimulator and pulse generator; requires vascular surgeon and electrophysiology	Pulse generator and 2 leads—placed by electrophysiology	IJ insertion, 16 Fr—placed by interventional cardiology or electrophysiology
Clinical benefits	• Increased QoL	• Increased QoL	• "Device inotropy"
	• Increased 6 MWT	• Increased 6 MWT	• Increase SV, contractility, MAP
	• Improvement in NYHA Class	• Improvement in NYHA Class	
	• Decreased BNP	• Increased peak VO_2	
Cost	$35K	$23K	TBD
FDA approval	August, 2019	March, 2019	FDA approved pilot study initiated April, 2021

Mitral regurgitation (MR) is common in the HFrEF population as LV dilatation leads to poor coaptation of the mitral valve, known commonly as functional or secondary MR. Severity of functional MR is strongly associated with decreased quality of life and increased heart failure hospitalization and mortality [52]. Management of valvular heart disease has dramatically changed with the advent of transcatheter valve procedures. MitraClip™ is a minimally invasive, catheter-based device which grasps and coapts the mitral valve leaflets, thus reducing MR throughout the cardiac cycle [53]. MitraClip™, depicted in Fig. 6.3, provides a

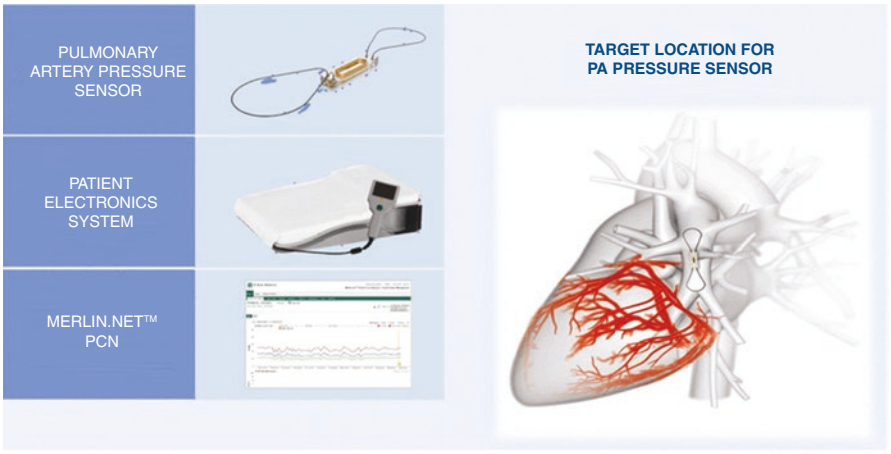

Fig. 6.2 CardioMems™ HF System. [Abbott, Abbott "A," CardioMEMS, HeartMate, HeartMate 3, and MitraClip are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, © 2021. All rights reserved]

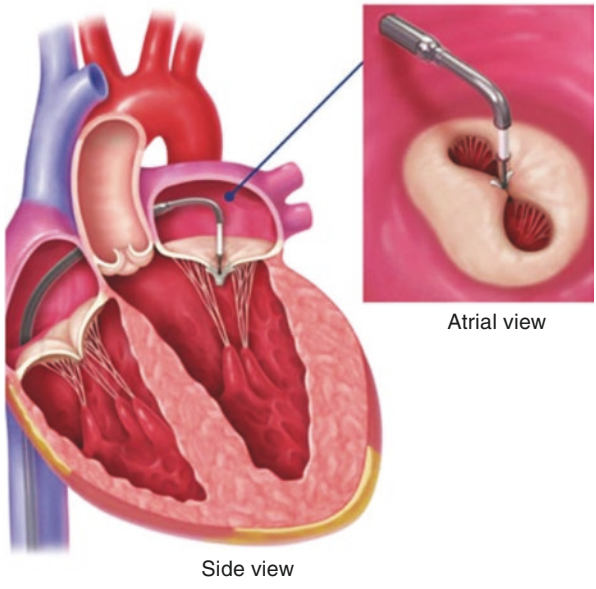

Fig. 6.3 MitraClip™ transcatheter mitral valve repair (TMVr) [54]. [Abbott, Abbott "A," CardioMEMS, HeartMate, HeartMate 3, and MitraClip are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, © 2021. All rights reserved]

safe and effective option for patients, reducing all-cause mortality and HF hospitalization while improving quality of life [54].

6.6 Putting It All Together

6.6.1 Case Study

6.6.1.1 Subjective HPI

A. Johnson is a 62-year-old, African American male recently discharged from the hospital with a new diagnosis of nonischemic cardiomyopathy, ACC/AHA Stage C, NYHA class III. He had a left heart cardiac catheterization (LHC) while hospitalized and was found to have nonobstructive CAD. His LVEF is 25–30% per transthoracic echocardiogram (TTE) and found to have moderate mitral regurgitation. He denies syncope and/or presyncope. No chest pain, palpitations, orthopnea, dyspnea, PND, lower extremity edema, or abdominal bloating.

6.6.1.2 Past Medical History

Hypertension, uncontrolled.
Obesity—BMI 31 kg/m^2.
Obstructive sleep apnea (untreated).
No history of tobacco or substance abuse.
Reports adherence with medications and dietary restrictions.

6.6.1.3 Current Medical Regimen

Aspirin 81 mg daily.
Atorvastatin 20 mg once a day.
Carvedilol 3.125 mg twice daily.
Sacubitril/valsartan 26/24 mg twice daily.
Spironolactone 12.5 mg daily.
Furosemide 80 mg once daily.

6.6.1.4 Review of Systems

No acute distress.
Daily weights stable.
Denies nausea & early satiety.
Dyspnea with moderate exertion but has improved.
Occasional palpitations with activity

6.6.2 Objective

Objective: Vital signs: BP 138/78 HR 82; RR 20, oxygen saturation 98% on room air; Temp 98.7 °F. Weight 212 pounds. Physical exam: Lungs clear, JVP 4–6 cm

at 90°F, no HJR. Heart regular rate and rhythm, IV/VI apical systolic murmur, PMI laterally displaced. No LE edema, bilaterally extremities are warm.

Labs results (day of visit): Sodium 145 mmol/L; Potassium 4.0 mmol/L; BUN 17 mg/dL; Creatinine 1.24 mg/dL (eGFR 77.0 > =6.0 mL/min/1.73 m^2), NTproBNP 200 pg/mL.

TTE (2 weeks ago) LVEF 25–30%, LVIDD 6.0 cm, mild-moderate mitral regurgitation no other valvular abnormalities.

EKG: Sinus rhythm, left bundle branch block.

6.6.3 Assessment

Mr. Johnson presents to office post hospital discharge. Symptomatically and hemodynamically stable. He is warm and euvolemic with adequate blood pressure and heart rate for uptitration of GDMT.

6.6.4 Plan

1. Increase carvedilol 6.25 mg twice daily for improved heart rate control and improved afterload reduction.
2. Add Dapagliflozin 10 mg daily.
3. No other medications changes on this visit.
4. Lifestyle modification—weight loss.
5. Referral for sleep apnea evaluation and CPAP consideration.
6. Return to clinic in 1 month with repeat labs BMP, NTproBNP.
7. Repeat echocardiogram in 3 months—Electrophysiology referral if EF not improved.

6.6.5 Heart Failure with Reduced Ejection Fraction: Clinical Considerations

- Initiate comprehensive, disease modifying GDMT at time of diagnosis.
- Start with low doses, prioritize beta blocker up-titration.
- Benefits of ARNI/BB/MRA/SGLT2i are demonstrated within 30 days of initiation.
- Cumulative benefits of GDMT within 30 days are incremental and additive, with an overall relative risk reduction >75%.
- Median survival with GDMT at maximally tolerated doses is extended approximately 6 years.
- [1, 55].

6.7 Conclusion

Heart failure with reduced ejection fraction continues to increase in incidence with significant morbidity and mortality accompanied by diminished quality of life despite advances in targeted, evidence-based medical and device therapies. HF remains a substantial burden to patients, caregivers, clinicians, and the health care system. As clinical presentation is often insidious and nonspecific, accurate evaluation and diagnosis can be challenging for primary care teams. Implementation of primary prevention strategies to aggressively manage risk factors may prevent new-onset HF. Adherence and rapid adoption of GDMT and device therapies can significantly improve clinical outcomes and decrease the overall economic burden of HF associated with repeat hospitalizations. Primary care teams can play a vital role in the complex management of heart failure and should refer to cardiology and/or specialized heart failure programs when patients fail GDMT and/or have recurrent HF hospitalizations.

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Heart Failure with Preserved Ejection Fraction

7

Anupam A. Kumar and Deepak K. Gupta

7.1 Introduction

Heart failure (HF) is a syndrome caused by diverse etiologies which results in an inability of the heart to generate sufficient blood flow to meet the metabolic demands of the body or to do so at the expense of elevated filling pressure. The signs and symptoms of HF, specifically the resulting volume overload, have been recognized for centuries as "dropsy." It was not recognized until as late as the 1930s that the heart contributed to this condition. Subsequent studies over the following decades showed reduced left ventricular ejection fraction (LVEF) was a marker of systolic dysfunction and a possible cause [1]. In the 1970s to 1990s it was reported that despite similar signs and symptoms of HF, some patients did not manifest reduced LVEF. Therefore, the culprit was believed to be the dysfunction of ventricular diastole, leading to the term "diastolic HF" [1].

The nomenclature of HF with "preserved ejection fraction" was popularized over the ensuing decades, particularly following the report of the CHARM-Preserved study in 2003; this found that candesartan lowered hospital admissions but did not impact mortality in patients with HFpEF [2]. The term HFpEF is also preferred over "diastolic HF" due to the frequent presence of abnormal systolic mechanics seen by strain and tissue Doppler imaging, indicating HFpEF is not due to isolated abnormalities in diastolic function [3].

With greater recognition of the syndrome of HFpEF, as well as population-wide increases in risk factors for HFpEF, its prevalence has been increasing. Nevertheless, HFpEF remains a challenge to diagnose and treat, which has been attributed to

A. A. Kumar · D. K. Gupta (✉)
Division of Cardiovascular Medicine, Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: Anupam.a.kumar@vumc.org; d.gupta@vumc.org

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_7

heterogeneity in both etiology and presentation. In this chapter, the epidemiology and diverse etiologies of HFpEF, strategies for diagnosis and ruling out clinical mimics, and to date, limited treatment strategies will be reviewed.

7.2 Definition

The American Heart Association, American College of Cardiology, and European Society of Cardiology all generally define HFpEF as the presence of symptoms and signs of HF with an LVEF equal to or exceeding 50% [4, 5].

Diastolic dysfunction defined by echocardiography is helpful but not sufficient for diagnosis in the absence of HF symptoms and signs. Grade 1 diastolic dysfunction without features of the HF syndrome is not diagnostic of HFpEF; however, it is a marker of increased risk of progression to overt HF. Grade 2 and 3 diastolic dysfunction, however, typically indicate increased filling pressure and are more likely to signal the presence of HF in the appropriate clinical context [5].

HF with recovered ejection fraction, in which the LVEF was previously documented to be reduced but has since recovered, is thought to be a distinct entity with different pathophysiology [6]. Additionally, HFpEF is thought to be related to primarily left-sided dysfunction and is also distinct from isolated right HF with preserved LVEF, as can be seen in pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, and other pulmonary and systemic disorders [6].

7.3 Epidemiology

HFpEF is an increasingly common form of HF, accounting for approximately 50% of all patients with HF [7, 8]. This estimate is expected to rise with the aging population in the United States and the increasing prevalence of comorbidities that contribute to its development, e.g., hypertension, diabetes mellitus, and obesity [7, 8].

Outcomes in patients with HFpEF remain poor. Hospitalized patients with HFpEF have a markedly reduced median survival compared with the general population. For example, hospitalized patients with HFpEF between the ages of 65 and 69 years have a median survival of 4 years compared with 18.7 years in the general population [9]. The dismal 75.7% 5-year mortality of hospitalized HFpEF patients is similar to survival in HFrEF patients [9]. Patients with HFpEF compared with HFrEF, however, have a higher rate of noncardiac causes of death [10].

Patients with HFpEF also have a high rate of 30-day readmission following HF hospitalization. In a 2018 study of Medicare beneficiaries, the 30-day readmission rate among HFpEF subjects was 22.3%. Similar to the mortality discussion above, there was a higher rate of noncardiac causes for readmission compared with individuals with HFrEF [11].

7.4 Etiology

HFpEF is a syndrome and not a discrete disease such that multiple etiologies for HFpEF exist. The clinical evaluation of a patient with HFpEF requires consideration of underlying contributors to the syndrome, which may involve the exclusion of diagnoses, including amyloidosis, other myocardial deposition diseases, sarcoidosis, and Fabry's disease [5, 7].

Most cases of HFpEF can be attributed to a constellation of traditional cardiometabolic risk factors, such as hypertension, obesity, diabetes, and chronic kidney disease. Although these are common in patients with HFrEF as well, obesity and insulin resistance may be relatively stronger contributors to the onset of HFpEF compared with HFrEF, based on data from epidemiologic cohort studies [12].

Several risk factors for the development of HFpEF have been identified. Prior studies have established that the incidence of HFpEF increases with age [8]. Additionally, compared with HFrEF, there is a high proportion of women among patients with HFpEF; this may also be a factor of age, however [8]. Coronary artery disease (CAD) is a common comorbidity in HFpEF and is associated with increased mortality and deterioration of LVEF over time [13]. Whether CAD is causative in this subset of patients is unclear but diastolic dysfunction can certainly be caused by myocardial ischemia [13]. Hypertension has also been linked to the development of HFpEF in numerous studies [14].

Obesity is also an important risk factor for the development of HFpEF. Among patients with HFpEF in the United States, over 80% are overweight or obese [15]. There is debate on causality, but evidence suggests that HFpEF patients with increased abdominal adiposity may be at a higher risk of mortality [16].

The etiology of HF, regardless of LVEF, is heterogenous but results in common pathophysiologic outcomes; the primary clinical insult (or insults) results in myocardial dysfunction leading to increased intracardiac filling pressures and exertional symptoms. The heterogeneity of etiology, phenotypes, and neurohormonal activation appears to differ between HFpEF compared with HFrEF, which may underlie the discordant results for clinical trials of medications with proven efficacy to improve outcomes in HFrEF, but not HFpEF [17].

HFpEF was traditionally thought to be a sequelae of systemic hypertension chronically increasing afterload, resulting in left ventricular hypertrophy (LVH). LVH would eventually result in myocardial stiffness and impaired diastolic relaxation and compliance. It has been observed, however, that HFpEF can develop without convincing hypertrophy or diastolic dysfunction on an echocardiogram. Moreover, echocardiogram findings of hypertrophy or abnormal myocardial relaxation could be found in patients without clinical HF [18].

Over the last decade, further studies have led to a paradigm shift in thinking about the etiology and pathophysiology of HFpEF. A prospective study by Shah et al. [19] utilized machine learning techniques to identify three primary phenotypes of patients with HFpEF:

1. Younger patients with normal B-type natriuretic peptide (BNP) and moderate diastolic dysfunction.
2. Diabetic, obese patients with severe diastolic dysfunction.
3. Older patients with chronic kidney disease, arrhythmias, pulmonary hypertension, and RV dysfunction.

These three groups differed substantially in clinical features, hemodynamics, cardiac structure, and outcomes. The third group above fared the worst over time when examining survival free of cardiovascular hospitalization and death [19]. A study by Cohen et al. [20] used latent class analysis to similarly classify subjects enrolled in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) study into three clinical phenogroups similar to those found by Shah et al. Importantly, there were significant differences in circulating biomarkers, cardiovascular characteristics, prognosis, and responses to spironolactone [20]. These data reinforce the impact of etiologic and phenotypic heterogeneity on attempts to effectively study, diagnose, and treat patients with this complex syndrome.

In addition to macrovascular CAD described above, coronary microvascular dysfunction has been proposed as a possible mechanism underlying HFpEF pathology. This is thought to be a downstream result of systemic inflammation caused by diabetes, obesity, and other common comorbidities in HFpEF. In a study of 151 HFpEF patients without revascularizable macrovascular CAD, 75% had coronary microvascular dysfunction defined as reduced coronary flow reserve by stress echocardiography [21]. Patients with microvascular dysfunction were more likely to have a history of current or prior smoking suggesting this is a possible risk factor. Interestingly, patients with coronary microvascular dysfunction also had evidence of peripheral endothelial dysfunction defined by reactive hyperemia index measured using arterial tonometry. This suggests, as have numerous studies, that systemic vascular dysfunction is an important aspect of etiology and pathophysiology in HFpEF [22]. Systemic arterial stiffness has been demonstrated in patients with HFpEF and appears to worsen during exercise [3].

Skeletal muscle abnormalities, including mitochondrial dysfunction, have also been identified in patients with HFpEF. Therefore, exercise intolerance in patients with HFpEF may be mediated by both cardiac and noncardiac systemic causes [23].

7.5 Prevention

Prevention of HFpEF largely focuses on the management of the most common modifiable risk factors in this population: hypertension, obesity, and diabetes [24]. In 2016, the AHA launched a campaign called "Life's Simple 7" centered around cardiovascular prevention that provides a useful framework that can be applied here as well. The "Simple 7" includes smoking cessation, weight loss, exercise, dietary control, improvement of blood pressure, lowering cholesterol, and improved glucose control [25].

7.6 Diagnosis of HFpEF

Accurate diagnosis of HFpEF can be challenging due in part to phenotypic heterogeneity and the diversity in clinical presentation. HFpEF often presents without overt findings of congestion at rest and is more often exertional shortness of breath, particularly in the outpatient setting. Though very sensitive for HF, exertional dyspnea is poorly specific and found in many non-HF and noncardiac conditions [26]. This is particularly true among elderly patients who often present with many comorbidities that could result in exertional intolerance, which adds to the diagnostic uncertainty in ambulatory settings outside of decompensation events [26]. Objective testing that may aid in the diagnostic approach for HFpEF is summarized below.

7.6.1 Natriuretic Peptides

In the evaluation of the patient presenting with acute dyspnea, circulating levels of natriuretic peptides are recommended to be measured as low values have high negative predictive value for excluding a cardiac etiology, i.e., HF [27]. A few caveats of particular relevance to HFpEF are that natriuretic peptide levels are inversely related to body mass index (BMI), such that lower natriuretic peptide thresholds may be needed with higher BMI in the exclusion of cardiac causes of dyspnea. Additionally, natriuretic peptide levels are also inversely associated with LVEF, such that natriuretic peptide levels are typically not as high in patients with HFpEF compared with HFrEF despite a similar severity of symptoms and signs of HF [27].

7.6.2 Echocardiography

Transthoracic echocardiography is often the first diagnostic step when evaluating a patient with concern for HF [5, 27]. Echocardiography, which is more readily available compared with other imaging modalities such as cardiac magnetic resonance

(CMR), not only provides the requisite information regarding LVEF but also yields insight into other pathologies, such as valvular and pericardial disorders [7]. Echocardiogram findings suggestive of HFpEF are reflective of elevated filling pressures, i.e., elevated E/e' ratio, left atrial enlargement, and higher pulmonary artery systolic pressure. Other echocardiographic findings often found in patients with HFpEF include reduced mitral annular tissue early diastolic tissue velocity (e'), right ventricular dilatation or dysfunction, and reduced LV global longitudinal systolic strain [28].

7.6.3 Invasive Diagnostics

The "gold standard" for diagnosis of HFpEF is invasive cardiopulmonary exercise testing, although this is often reserved for when the diagnosis is unclear [7]. Exercise testing is particularly useful in patients who are clinically euvolemic but are limited by exertional dyspnea and in whom another diagnostic test such as natriuretic peptide level, transthoracic echocardiography, or stress testing does not establish a diagnosis. Resting hemodynamics may be normal in these patients but exercise may provoke marked physiologic derangements leading to increased intracardiac filling pressures and exertional limitations [28].

Right heart catheterization hemodynamics are obtained at rest and with a graded exercise protocol. Exercise is usually performed to fatigue with an upright or supine bicycle. Hemodynamics are diagnostic of HF in a patient with preserved LVEF if pulmonary capillary wedge pressure is ≥15 mmHg at rest and/or ≥25 mmHg with exercise [7]. Given the cost, invasiveness, and requirement for expertise, however, this test is best reserved for cases of diagnostic uncertainty after the initial workup [28].

7.6.4 Cardiac Magnetic Resonance

Cardiac magnetic resonance imaging (CMR) also has utility as a screening tool, particularly in the evaluation of other causes of HF that may present similarly to HFpEF, including amyloid, sarcoid, hypertrophic cardiomyopathy, and Fabry's disease [29]. Echocardiography may be insufficiently sensitive for the detection of other pathologies in patients with HFpEF, many of whom have comorbid conditions that limit echocardiographic image quality such as obesity, lung disease, and atrial fibrillation [5, 29]. In addition to improved endomyocardial border definition and the ability to evaluate all segments of the myocardium, CMR with gadolinium contrast and parametric mapping techniques allow for in vivo tissue characterization [29]. A study of 154 patients with HFpEF who underwent CMR found that 42 (27%) had previously unknown pathologies such as epicardial or microvascular CAD, hypertrophic cardiomyopathy, or constrictive pericarditis [30]. Patients who were found to have new diagnoses on CMR also had a higher likelihood of adverse outcomes (hazard ratio 1.92, $p = 0.03$) [30]. Though not widely available, the ability to

pair CMR with exercise testing may have added value in the evaluation of patients with suspected HFpEF. For example, the HFpEF-Stress trial of 75 patients with suggested diastolic dysfunction on echocardiography found that real-time cardiac MR with exercise allowed for highly accurate identification of HFpEF, as evidenced by impaired left atrial emptying during diastole and reduced left atrial strain during exercise in patients with HFpEF [31]. Left atrial long axis strain was the best predictor of HFpEF in this study [31].

7.6.5 Diagnostic Algorithms

Reddy et al. developed a scoring system using readily available clinical and echocardiographic data; the components and scoring system are shown in Fig. 7.1 [28]. In patients with high [6–9] or low [0–1] scores, the diagnosis of HFpEF is with reasonable certainty ruled in or out, respectively. Patients with intermediate scores [2–5] may benefit from further diagnostic testing [28].

The H_2FPEF score in their initial study was effectively able to distinguish HFpEF from noncardiac causes of dyspnea and assist in determining the need for further diagnostic testing in cases with remaining uncertainty [28].

Another diagnostic algorithm Heart Failure Association Pre-Test assessment, Echocardiography & natriuretic peptide, Functional testing, Final etiology (HFA-PEFF) score has also been developed [32]. The algorithm starts with the pre-test probability of HFpEF (based on risk factors and symptoms) and incorporates functional, morphological, and biomarker domains to determine the likelihood of HFpEF. It was validated in two HFpEF cohorts with a high score (5–6 points)

	Clinical variable	Values	Points
H_2	Heavy	BMI > 30 kg/m^2	2
	Hypertensive	2 or more BP meds	1
F	Atrial fibrillation	Paroxysmal/persistent	3
P	Pulmonary hypertension	Doppler echocardiogram with estimated right ventricular systolic pressure> 35 mm Hg	1
E	Elder	Age > 60	1
F	Filling pressure	Doppler echocardiogram with E/e′ > 9	1
H_2FPEF Score			Sum (0-9)

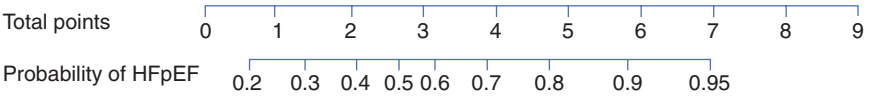

Fig. 7.1 Description of the H_2FPEF score [28]. [Reprinted from: Circulation, 138(9), Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction, 861–70, copyright (2018) with permission from Wolters-Kluwer]

demonstrating high specificity (93%) and positive predictive value (98%). A low HFA-PEFF score had a sensitivity of 99% to rule out HFpEF with a negative predictive value of 73% [32]. In the 36% of evaluated patients with intermediate scores, more diagnostic testing, such as exercise echocardiography or invasive hemodynamics, was needed. The authors postulated that the low negative predictive value may have been driven by low BNP levels in patients with obesity, leading to low HFA-PEFF scores. In obese patients or patients with an otherwise high pre-test probability of HFpEF and low HFA-PEFF scores, further testing may be helpful. Additionally, the algorithm's complexity may limit its clinical utility and the authors noted a desire for simplification in future iterations [32].

7.7 Clinical Mimics of HFpEF

Ruling out cardiac causes of HFpEF-like clinical syndromes has important implications not only for diagnosis but also for management. This section discusses cardiac clinical syndromes that can mimic HFpEF (Table 7.1).

7.7.1 Cardiac Amyloidosis

Cardiac amyloidosis is an underdiagnosed condition that shares many clinical features with HFpEF; namely, HF symptoms, thickened myocardium, and diastolic dysfunction. Consistent with prior autopsy and imaging studies, a recently published prospective endomyocardial biopsy study of patients with HFpEF found that 14% had previously unknown amyloid deposition [33–35]. Patients found to have amyloidosis were more likely to be older, with lower blood pressure and BMI, and have fewer comorbidities. Patients with cardiac amyloid were also more likely to have higher troponin and B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) levels [33–35].

Underdiagnosis of cardiac amyloidosis has particularly important implications for patients with transthyretin mutations given the availability of new treatment options with demonstrated efficacy for prolonging survival. Early detection and advances in therapies for light chain amyloidosis have also translated into improvements in survival rates [36].

Table 7.1 Examples of HFpEF clinical mimics

Examples of HFpEF clinical mimics
Cardiac amyloidosis
Hypertrophic cardiomyopathy
Sarcoidosis
Constrictive pericarditis
Stiff left atrial syndrome
High-output cardiac failure
Valvular heart disease

The unrecognized inclusion of patients with cardiac amyloidosis may have contributed to the failure of clinical trials to show the benefit of pharmacologic therapies in HFpEF. For example, neurohormonal antagonists such as inhibitors of the renin-angiotensin-aldosterone system and beta-blockers may be poorly tolerated and may have deleterious effects in patients with cardiac amyloidosis [37].

Evaluation of a patient with symptoms and signs of HFpEF should include consideration of cardiac amyloidosis to align indicated therapies for the correct diagnosis. Clinical red flags for cardiac amyloid that should prompt further investigation include increased LV wall thickness in the absence of a history of hypertension, electrocardiogram with low QRS amplitude, current or prior history of bilateral carpal tunnel syndrome, lumbar spinal stenosis, biceps tendon rupture, or peripheral neuropathy; older patients with lower blood pressure and BMI (as found in the study above by Hahn et al.); and macroglossia [38]. On laboratory evaluation, persistent and mildly increased troponin levels and an unexpected increased BNP/NT-proBNP should lead to consideration of cardiac amyloidosis. Additionally, echocardiogram findings of marked hypertrophy or reduced global longitudinal systolic strain with apical sparing may be indicative [37].

Diagnostic workup for cardiac amyloid should include an echocardiogram with strain as an initial step (as in all HFpEF patients). If there is elevated clinical concern based on the above criteria, noninvasive imaging workup with technetium pyrophosphate PET scanning (to evaluate for possible aTTR amyloid) and/or cardiac MRI can be considered. Laboratory workup includes evaluation for AL amyloidosis including urine and serum protein electrophoresis with kappa/lambda ratio quantification as well as the measurement of free light chains. If after these studies there continues to be diagnostic uncertainty and clinical suspicion, an endomyocardial biopsy may be needed [37, 38].

7.7.2 Hypertrophic Cardiomyopathy

Left ventricular hypertrophy is a common finding in HFpEF and more generally with chronic hypertensive heart disease. Hypertrophic cardiomyopathy is often a challenging diagnosis to make given the diversity of hypertrophic phenotypes and presence with or without left ventricular outflow tract obstruction and mitral valve leaflet systolic anterior motion. CMR imaging with gadolinium contrast allows a more precise measurement of wall thickness and localization of hypertrophy, especially in areas poorly visualized by echocardiography (inferolateral, apical, and anterolateral walls), as well as detection of fibrosis/scarring. CMR features that are indicative of HCM include asymmetric LVH and late gadolinium enhancement in segments of wall thickening [29]. Studies have shown the presence of late gadolinium enhancement (LGE) in 65% of patients with HCM; the increasing extent of LGE portends a worse prognosis in these patients [30, 39]. Younger patients with HFpEF, a history of malignant arrhythmias such as ventricular tachycardia or ventricular fibrillation, and a personal or family history of sudden cardiac death may increase the diagnostic suspicion of HCM as a cause of clinical HF with normal LVEF.

7.7.3 Other Cardiomyopathies

Infiltrative or inflammatory cardiomyopathies such as sarcoidosis, myocarditis, and hemochromatosis can also be clinically mistaken for HFpEF in earlier stages before the development of reduced LVEF. An echocardiogram may be insufficiently sensitive to distinguish these conditions from more typical HFpEF and may necessitate advanced imaging techniques. CMR with gadolinium contrast and more modern parametric mapping techniques is often helpful for evaluating the myocardium for these conditions [29].

In patients with high clinical suspicion for cardiac sarcoidosis, who may have known biopsy-proven pulmonary sarcoid or other concerning findings such as conduction system disease or malignant tachyarrhythmias, FDG-PET can be considered to assess for active sarcoid lesions. In the absence of convincing noninvasive imaging, an endomyocardial biopsy can be considered.

Restrictive cardiomyopathies present similarly and are caused by rigid, nondilated ventricles with decreased myocardial compliance and therefore reduced diastolic filling. It can be seen in patients with the infiltrative cardiomyopathies described above, endomyocardial fibrosis, systemic disorders such as hypereosinophilic syndrome, or with prior chemotherapy and radiation [40].

7.7.4 Pericardial Disorders

Diseases of the pericardium can also present with indolent dyspnea and volume overload, causing misdiagnosis as HFpEF. Constrictive pericarditis results from inflammation, scarring, or calcification of the pericardium which then becomes noncompliant. The noncompliant pericardium impairs diastolic filling of the ventricles with reciprocal changes observed during respiration between the right and left ventricles. Risk factors for constrictive pericarditis include prior cardiac surgery, pericarditis, or mediastinal radiation, though its etiology is commonly idiopathic [41]. Pericardial thickening or calcification can be seen on noninvasive imaging such as cardiac CT or MRI, though this finding is insensitive. Simultaneous invasive measurement of both right and left heart hemodynamics allows for better diagnosis and distinguishing between constrictive and restrictive pathologies.

7.7.5 Stiff Left Atrial Syndrome

This syndrome is a complication of extensive catheter ablations or MAZE procedures for atrial fibrillation in which the formed scars create stiffness of the atrium. This results in hypertension of the left atrium which can present as HF symptoms and preserved LVEF. Right heart catheterization alone will show elevated pulmonary capillary wedge pressure and elevated pulmonary artery pressures. However, simultaneous right and left heart catheterization reveals a high wedge pressure resulting from left atrial hypertension but a discordantly normal or low left

ventricular end-diastolic pressure, confirming the diagnosis [42]. Direct left atrial pressure measurement with transseptal puncture may be needed as well. A similar hemodynamic profile of elevated pulmonary pressure could be seen with mitral valve disease (which should be ruled out by echocardiography) or pulmonary vein stenosis, which can also be a complication of catheter ablation [42].

7.8 Medical Management

Unfortunately, compared with HFrEF, there is a dearth of evidence-based treatment options for HFpEF that convincingly reduce adverse clinical outcomes. To date, with the exception of the empagliflozin trial (EMPEROR-Preserved) most large, randomized studies of therapeutics in HFpEF have been neutral with regard to clinical outcomes, with some post-hoc and subgroup analyses suggesting benefit in selected populations (Fig. 7.2), which has informed recommendations in the guidelines [27, 43].

7.8.1 Diuretics

As in HFrEF, symptomatic management is largely centered around the management of hypervolemia with diuretics. Although diuretics have not been shown to have a mortality benefit, maintenance of euvolemia does appear to reduce rates of rehospitalization based on studies with implantable pulmonary artery pressure monitors, discussed below [44].

Drug class	Summary of Key Trials	Guideline Statements
Sodium-glucose co-transporter-2 (SGLT-2) inhibitors	EMPEROR-Preserved, included patients with HF and LVEF > 40%, revealed an˜21% reduction in the primary endpoint, a composite of HF hospitalization and CV death.	The use of SGLT2 inhibitors can be beneficial to decrease HF hospitalizations and CV mortality for patients with HFpEF (Class IIa, Level of Evidence: B-R).
Beta blockers	Two randomized controlled trials of a total of 888 patients, SENIORS (2009) and J-DHF (2013) failed to find beneficial effects of beta blockade on call-cause mortality and HF hospitalization.	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF *(Class IIa, Level of Evidence: C).*
ACE Inhibitors /Angiotensin-receptor blockers	CHARM-Preserved (2003): In 3023 patients with LVEF > 40%, NYHA II-IV symptoms and prior cardiovascular hospitalization, there was no difference in cardiovascular mortality but there was a mild, but non-statistically significant, reduction in heart failure hospitalizations (15.9 vs 18.3%, p = 0.07 non-adjusted/p = 0.05 after adjustment).	The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF *(Class IIa, Level of Evidence: C).*
	I-Preserve (2008): In 4128 patients with LVEF ≥ 45% and NYHA II-IV, there was no difference in the composite outcome of all-cause mortality and CV hospitalization. There was a modest reduction in cardiovascular hospitalization (hazard ratio 0.95, p = 0.044).	The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF *(Class IIb, Level of Evidence: B-R).*
Mineralocorticoid Receptor Antagonists	TOPCAT (2014): In 3445 patients with LVEF ≥ 45% and signs/symptoms of HF, there was no difference in the composite outcome of CV mortality, abortedcardiac arrest, or HF hospitalizations with spironolactone compared to placebo. There was a modest reduction in HF hospitalization (12% vs 14.2%). Subsequent post-hoc analyses suggested low levels of medication consuming among Eastern European subjects and suggested benefit among the North American cohort.	In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30mL/min, creatinine <2.5 mg/dl, potassium <5.0 mEq/l), aldoaterone receptor antagnists might be considered to decrease hospitalizations *(Class IIb, level of Evidence B-R).*
Angiotensin-receptor/neprilysin inhibitors	PARAGON-HF (2019): In 4822 patients with LVEF ≥ 45%, NYHA II-IV, and symptoms of HF requiring diuresis within 30 days with recent HF hospitalization or elevated BNP, there was no difference in the composite outcome of HF hospitalization or CV mortality. Subgroup analyses suggested benefit for subject with LVEF below the median 57% (HR 0.78, CI 0.64-0.98).	For HEpEF patients with LVEF on the lower end of the spectrum, ARNi may be considered to decrease hospitalizations (Class IIb, level of Evidence B-R).

Fig. 7.2 Summary of key HFpEF clinical trials and related guideline statements [27, 43]

7.8.2 Aldosterone Antagonists

The primary results of the TOPCAT study were published in 2014 but the trial remains a source of debate. The initial study of 3445 patients with HFpEF with LVEF ≥45% did not show a benefit for spironolactone over placebo in reducing the composite primary endpoint of cardiovascular mortality, aborted cardiac arrest, or HF hospitalizations, yet there was a statistically significant reduction in HF hospitalizations alone (hazard ratio 0.83 [95% CI 0.69–0.99], $p = 0.04$) [45]. In a post-hoc analysis excluding the cohort from Eastern Europe (Russian and Georgian subjects, specifically) due to concern for lower drug adherence in this group and atypical or misdiagnosed HFpEF (based on significantly lower event rates), treatment with spironolactone was superior to placebo for the primary endpoint [46, 47].

The 2022 ACC/AHA/HFSA Focused Update Guideline for the Management of Heart Failure included a Class IIb recommendation for consideration of aldosterone antagonists in selected patients with HFpEF (LVEF ≥45%) who had elevated BNP or HF hospitalization within 1 year, glomerular filtration rate > 30 mL/min, creatinine <2.5 mg/dL, and potassium <5 mEq/L [43].

7.8.3 Angiotensin Receptor-Neprilysin Inhibitor

After the demonstration of the efficacy of sacubitril/valsartan in patients with HFrEF, this medication was subsequently tested in patients with HFpEF in the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial. In the treatment group, there was a nonsignificant decrease in the primary outcome (HR 0.87 [95% CI 0.75–1.01], $p = 0.059$) [48]. A subgroup analysis of the subjects below the median LVEF of 57% did show a significant benefit, however. A pooled analysis spanning the spectrum of HFpEF and HFrEF patients indicated the clinical benefit of sacubitril/valsartan varied by LVEF, with efficacy in patients with HF and LVEF below normal (in the mid-range or borderline preserved) and that women were more benefit at even higher LVEF than men [49]. Given these analyses, the FDA recently approved sacubitril/valsartan for use in patients with HFpEF with LVEF below normal (up to ~60%) and the 2022 ACC/AHA/HFSA guidelines provide an IIb recommendation [43].

7.8.4 Sodium-Glucose Co-transporter (SGLT) Inhibition

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors have shown a clear benefit in patients with HFrEF in two large randomized trials [50]. Results from a larger phase 3 study of empagliflozin (EMPEROR-Preserved), which included patients with HF and LVEF >40%, revealed an ~21% reduction in the primary endpoint, a composite of HF hospitalization and CV death. Therefore, 2022 ACC/AHA/HFSA guidelines recommend (IIa) the use of SGLT2 inhibitors in these patients [43].

7.8.5 Pulmonary Artery Pressure Monitoring

Patients with difficult to control hypervolemia and frequent readmissions for decompensation can be considered for implantation of a wireless pulmonary artery pressure monitor. The CardioMEMS heart sensor (Abbott Laboratories, Illinois, USA) was evaluated in a single-blinded, randomized controlled trial of 550 subjects with HF, of whom 119 had LVEF over 40%. After implantations during a right heart catheterization, patients were randomized to management using daily pressure readings versus standard care with daily weight monitoring. In the subgroup of patients with HFpEF, CardioMEMS monitoring was associated with a statistically significant reduction in the rate of HF hospitalization at 6 months and throughout follow-up (average 17.6 months). This remains one of the only interventions to the date shown to have a clear benefit in reducing HF readmissions in patients with HFpEF [44].

7.8.6 Cardiac Rehabilitation

Cardiac rehabilitation is an underutilized intervention among patients with HF. In patients with HFpEF, participation in cardiac rehabilitation was associated with improved outcomes in a retrospective propensity matched survival study [51]. The Centers for Medicaid and Medicare Services does not yet, however, cover cardiac rehabilitation for patients with HFpEF in the absence of another indication, e.g., post-cardiac surgery, post-MI, post-PCI, or chronic stable angina.

7.8.7 Coronary Revascularization

As noted above, CAD is common in patients with HFpEF though the mechanistic and causative links between the two common diseases have not been firmly established. Despite this, evidence suggests that coronary revascularization in HFpEF decreases mortality and limits the deterioration of LVEF over time [13]. Despite this common association, it has not been established whether HFpEF patients should routinely be referred for noninvasive stress testing or angiography in the absence of acute coronary syndrome or symptoms attributable to flow-limiting epicardial coronary artery stenosis [13].

7.8.8 Hypertension Management

In patients with HFpEF, effective management of hypertension can result in improved cardiac function and a decrease in myocardial mass [18]. Systolic blood pressure < 120 or < 130 mmHg, however, has been associated in large registries with a higher risk of mortality. Trials of antihypertensives and neurohormonal blockade have largely been negative [52]. This suggests that hypertension control is

likely important in patients with HFpEF with poorly controlled hypertension, but optimal blood pressure targets remain unclear. Therefore, current recommendations for blood pressure management in patients with HFpEF follow those provided by the ACC/AHA [53].

7.8.9 Atrial Fibrillation Management

The 2022 AHA/ACC/HFSA guidelines provide a IIa recommendation for the management of atrial fibrillation in patients with HFpEF with the goal of symptom improvement [43]. Chapter 10 of this book covers management of atrial fibrillation for heart failure patients.

7.8.10 Referral for Clinical Trials

Given the relative lack of proven therapies with a mortality benefit in HFpEF, all patients should be considered for participation in clinical trials; this is particularly important in patients refractory to the aforementioned therapies. Other causes of HFpEF-like syndrome (such as cardiac amyloidosis) should ideally be ruled out to avoid pathologic heterogeneity that has likely plagued many negative prior studies.

In addition to trials of potential pharmacologic therapies, studies that provide mechanistic characterization and deep phenotyping of HFpEF patients are critical to further our understanding of this condition.

7.9 Case Study

A 77-year-old woman with a history of hypertension, atrial fibrillation requiring cryoablation, mild-moderate mitral regurgitation, obesity (BMI ~ 31 kg/m^2), obstructive sleep apnea, bilateral carpal tunnel syndrome, and psoriatic arthritis presented with worsening exertional dyspnea, fatigue, and lower extremity edema. She had previously been very active, participating regularly in water aerobics without limitations. Shortly after a three-week bout of a flu-like illness, she had increasing exercise intolerance and new bilateral leg edema, which was progressive over several months. She did not have orthopnea, paroxysmal nocturnal dyspnea, or palpitations. Her hypertension had been gradually worsening over this time as well. She was taking once-weekly hydrochlorothiazide for edema without improvement.

Her PCP referred her for echocardiography which showed preserved LVEF (70%) with normal wall thickness and grade 2 diastolic dysfunction. E/e' ratio was 14 with an estimated pulmonary artery systolic pressure of 30–35 mmHg. The right ventricle was normal size with normal systolic function. Left and right atria were

enlarged with moderate to severely increased left atrial volume index at 48 mL/m^2. Valve assessment revealed mild-moderate mitral regurgitation, trace aortic regurgitation, and trace tricuspid regurgitation. Her H2FPEF score was 7. She was referred to cardiology.

For further workup, she underwent a coronary angiogram which did not show epicardial coronary artery disease. She also underwent an invasive hemodynamic study which showed an increase in pulmonary capillary wedge pressure from 14 to 27 mmHg with exercise. The left ventricular end-diastolic pressure was similar to PCWP, ruling out pulmonary vein stenosis and stiff left atrium resulting from ablation.

To evaluate for other pathologies, she was screened for AL amyloidosis with normal serum protein electrophoresis and urine protein electrophoresis. Serum-free light chains were unremarkable. Holter monitoring did not show recurrent atrial fibrillation or atrial flutter to explain her symptoms.

Her diuretics were intensified, and a regular exercise regimen was recommended, which improved her lower extremity edema and gradually improved her exercise tolerance and fatigue. Cardiopulmonary exercise testing 6 months following these interventions was reassuring with normal peak oxygen consumption of 16.8 mL/kg/min (108% max predicted). She continues to follow up with her PCP and cardiologist. SGLT2 inhibition was added for persistent symptoms, which has led to weight loss, reduction in diuretic dose, and a further improvement in her symptoms. Further workup may include a technetium pyrophosphate scan to screen for transthyretin amyloid, given her history of bilateral carpal tunnel syndrome.

7.10 Conclusion

HFpEF is a challenging but increasingly common condition seen in cardiac patients. Given the numerous clinical mimics, it is important to carefully rule out conditions such as amyloidosis and sarcoidosis, which have proven treatments. Additionally, careful diagnosis of HFpEF itself using invasive or noninvasive exercise hemodynamics is often warranted given nonspecific symptoms in patients who are not actively congested and/or in obese individuals in whom natriuretic peptide levels may be below thresholds typically defined for HF. Despite limited randomized evidence, there may be a benefit to therapies including mineralocorticoid receptor antagonists and angiotensin-receptor/neprilysin inhibitors in selected groups of patients with HFpEF.

Pearls for Primary Care: When to Refer to Cardiology?
Referral for cardiology evaluation and management is particularly appropriate when there is diagnostic uncertainty or failure to respond to diuretics and blood pressure control.

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Transitions of Care and Self-Care Strategies for the Heart Failure Patient

8

Kelly D. Stamp and Marilyn A. Prasun

8.1 Introduction

The prevalence of heart failure (HF) is projected to increase by 46% by 2030, which will increase the prevalence to greater than 8 million individuals having HF [1]. Interestingly hospital discharges for a primary diagnosis of HF between 2010 and 2013 are reported to have declined from 4.4 to 4.1 per 1000 and then increased between 2014 and 2017 to 4.9 per 1000 [2]. Thirty-day readmission rates revealed a similar increase [2]. Following a HF hospitalization 43% were rehospitalized 4 times within 1 year [3]. Black males are reported to have the higher hospitalization rates when compared to whites with Hispanic males presenting significantly younger [1, 4]. Patient mortality increases significantly with each subsequent hospitalization and HF rehospitalization is greatest among those who were previously hospitalized [5, 6]. A good transition from the hospital to home is critical to reducing risk for readmission and ensuring quality patient outcomes.

8.2 Transition from Hospital to Home

Transitioning a patient from the hospital begins at admission and extends past discharge. Patients with HF are vulnerable during this period following hospitalization with reports of readmission rates ranging between 20.6% and 25.3% in the United States [7]. Transition of care interventions among patients with HF have been

K. D. Stamp (✉)
University of Colorado Anschutz, College of Nursing, Aurora, CO, USA
e-mail: KELLY.STAMP@CUANSCHUTZ.EDU

M. A. Prasun
Illinois State University, Mennonite College of Nursing, Normal, IL, USA
e-mail: maprasu@ilstu.edu

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_8

examined and no single intervention has demonstrated a consistent reduction in 30-day readmissions [8]. However, key components of a quality transition include comprehensive planning while the patient is hospitalized, timely post-discharge follow-up, and ongoing support by phone or home visits [9, 10]. Transition of care should be multifaceted and individualized to the patient and caregiver needs. Patient safety is paramount and is dependent on quality and clear, timely communication among all healthcare providers prior, during, and following transition [11].

Development of a comprehensive plan of care using shared decision-making is critical at the outset of the hospitalization. The plan of care should extend to after the patient is discharged and include plans to optimize guideline-directed medical therapy (GDMT), determination of dry weight, diet, regular exercise, and treatment of comorbidities. Palliative and supportive care for symptomatic patients should be discussed with the patient. The plan of care should be mutually agreed upon with the patient and communicated to all care providers [12].

A multidisciplinary team approach has been shown to be effective in implementing the plan of care and transitioning patients with HF [8]. Programs vary in the model and membership, yet can include but are not limited to a HF provider, nurse, pharmacist, dietician, social worker, and primary care provider (PCP). Nurses are in an optimal position to holistically implement and facilitate transition of care both within the hospital and the outpatient setting. Ideally a patient and their caregiver will meet and receive care and education from the multidisciplinary team while hospitalized and will continue to remain in contact and follow up with the team on an outpatient basis. Each team member shares their expertise such as a pharmacist can provide extensive education and bring insight into medications, side effects, cost, and strategies to facilitate adherence whereas a social worker can identify potential resources that will assist the patient and caregiver. The nurse can serve in a wide array of roles to coordinate care, educate, address questions, follow-up, and facilitate communication. Another model that has demonstrated effective transition is the case management model which provides services during and following hospital discharge [13]. Case managers who are typically nurses work one-on-one with the patient and their caregiver. The nurse serves as a liaison with other providers while coordinating care and providing close monitoring and follow-up. Home-based nursing inventions have also shown promise to improve patient outcomes. A multidisciplinary team approach, case management, and in-home nurse models are reported to be effective and have reduced readmissions of patients with HF [8, 13, 14].

Education is a critical component of the plan of care for the patient with HF and should be provided and reinforced on each encounter with the patient thereafter [15]. Patient-centered education for HF is reported to reduce readmission and improve HF-related knowledge, self-care behaviors, and quality of life [16]. Educational topics should include monitoring and responding to changes in signs and symptoms, dietary restrictions, weight and reporting changes, remaining physically active, medications and adherence, stress management and social support, and when to call their provider. Additional topics relevant to the patient and caregiver based on their individual needs should be included. Utilization of teach-back techniques during education is helpful to ensure patient understanding by providing them an opportunity to demonstrate and verbalize what they learned about self-care. Self-care strategies in HF will be further discussed later in this chapter.

Scheduling of the follow-up visit with the patient's provider within 7 days is recommended [15]. The appointment ideally should be scheduled prior to leaving the hospital to avoid delays in evaluation. During discharge, the patient receives a lot of information they have to process; therefore, scheduling the appointment and providing them with a written reminder will facilitate timely follow-up. Receiving a diagnosis of HF or experiencing a readmission for a HF exacerbation can be overwhelming for the patient and caregiver. Patients report fatigue, depression, and perceived low quality of life prior to hospital discharge which can make following recommendations difficult [17]. Facilitating timely follow-up and quality communication among all providers promotes a safe transition for a complex patient. Early follow-up can address potential barriers and gaps in care, thereby preventing readmissions to the hospital.

Telephone follow-up has been incorporated into many transitional care programs. Telephone follow-up can serve to review the treatment plan, address questions, assess symptoms and weights, and encourage adherence to recommendations [18]. Again, the patient and caregiver may feel overwhelmed with the information provided during the hospital course. Telephone follow-up is an opportunity to address any concerns and review recommendations and why they are important in promoting optimal outcomes. The frequency and duration of phone follow-up varied in the literature [18, 19]. Refer to Table 8.1 for links to examples of discharge and follow-up tools.

Table 8.1 Transitional care and follow-up resources

American Heart Association Readmission and Discharge Checklist [20]	https://www.heart.org/-/media/files/professional/quality-improvement/target-heart-failure/targethf-readmission-checklist-ucm_496868.pdf?la=en https://www.heart.org/-/media/files/professional/quality-improvement/target-heart-failure/targethf-discharge-checklist-ucm_496869.pdf?la=en
American Association of Heart Failure Nurses Guide for patients after discharge [21]	https://cdn.ymaws.com/www.aahfn.org/resource/resmgr/patient_empowerment_tool_br.pdf
Heart Failure Society of America Clinician Guide [22]	https://staywell.mydigitalpublication.com/publication/?m=58494&i=540965&p=8&ver=html5
Agency for Healthcare Research and Quality Telephone follow-up [23]	https://www.ahrq.gov/patient-safety/settings/hospital/red/toolkit/redtool5.html
American Heart Association Guide for Telephone follow-up [24]	https://www.heart.org/-/media/files/professional/quality-improvement/target-heart-failure/targethf-telephone-followup-form-ucm_496870.pdf?la=en

Note the above is not an exhaustive list and serves as an example of resources

8.3 Community Resources

Management of HF is complex and can be challenging for patients and caregivers. Recognition of community resources and referral is important to promote optimal patient outcomes. Resources will vary based on geographic location. Consideration of the patient's social determinates is critically important and can significantly influence access to needed services and support [25]. Routine screening of patients' needs and having a list of resources is best practice [25].

All patients should be screened to determine their healthcare needs. This may occur in various ways, through the hospital setting, follow-up by the provider, or in the outpatient setting with referrals to other necessary services. Documentation in the plan of care and communication to all healthcare providers is needed. Although a variety of screening tools are available the provider should select a tool that is most appropriate for their individual practice that can be incorporated into daily practice. The Accountable Health Communities' social needs tool was developed by the Centers for Medicare and Medicaid Services and provides assessment of individual patients [26]. This tool has 10 questions assessing unmet needs which include housing, food insecurity, transportation needs, utility needs, and safety [26]. Similar to other screening tools utilized in clinical practice, the findings can guide referrals to community services and resources. Currently there is limited evidence to support a specific tool and more research is warranted [27].

Table 8.2 Heart failure community resources

Hospital based	Dietician both inpatient and outpatient services Social services Cardiac rehabilitation Support group (general cardiac and/or heart failure) Home health services
Addition and behavioral	Behavioral and/or mental health services Smoking cessation programs Alcohol Anonymous and drug treatment programs
Community social service	County and state supported services (in home assistance) Durable medical suppliers
Exercise	Silver Sneakers YMCA
Food service	Food pantries (location, distribution times) Meal service (soup kitchen, local mission) In-home meals (meals on wheels)
Housing/Shelter	Local shelters
Pharmacy	Drug assistance programs
Senior services	Office of aging
Transportation	Hospital-based transportation Medical access public transportation Taxi or local car service

Note the above is not an exhaustive list and serves as an example of potential resources

Based upon identified patient needs referrals to resources should be started. Refer to Table 8.2 as an example of a community resource list. Contact numbers and addresses should be included and reviewed annually. Based upon the assessment, services can be reviewed with the patient and referrals made. The patient should be provided with the agency and contact information. Follow-up on the referral should occur to ensure the patient has accessed and obtained the needed service.

In addition to community services, there are web resources that can provide evidence-based education to both the patient and caregiver. The HF Patient Foundation affiliated with the American Association of Heart Failure Nurses offers opportunities to network and access healthcare providers who can address questions regarding self-care. With advancing technology and expanding access to the internet apprising patients and caregivers of safe quality sites can further enhance their knowledge and understanding of self-care behaviors. Refer to Table 8.3 for a list of web-based patient resources.

Table 8.3 Patient and caregiver websites

American Association of Heart Failure Nurses provides patient educational material regarding HF diagnosis, symptoms, risk factors, and life-style modifications [28]	https://www.aahfn.org/default.aspx
Center for Disease Control (CDC) provides information regarding the incidence of heart failure and risk factors and smoking cessation programs [29]	https://www.cdc.gov/heartdisease/heart_failure.htm https://www.cdc.gov/tobacco/basic_information/for-health-care-providers/quitlines-other/index.html
Heart Failure Patient Foundation provides educational resources for patients and caregivers, opportunities for networking, and access to healthcare providers to address self-care questions. Supported by the American Association of Heart Failure Nurses [30] Heart Failure Society of America provides patient educational information regarding diagnosis, treatment, and life-style modifications [31]	https://www.heartfailurepf.org/ https://hfsa.org/patient
The American Heart Association provides patient educational material regarding life-style modifications and self-care [32]	https://www.heartfoundation.org.au/conditions/heart-failure-resources-for-patients
The Global Heart Hub is an organization that has brought together cardiovascular patient directed organizations from around the world to share educational material and advocate for patients and caregivers [33]	https://globalhearthub.org/patient-councils/hfpatientscouncil/

8.4 Initial Post-discharge Clinic Visit

Patients with HF presenting after hospitalization whether it is following a new diagnosis or following a HF exacerbation will have experienced changes to their treatment plan, recommended life-style modifications, and most likely will require additional time and/or support from other team members (nurse, pharmacist, social services). Access and review of the patient's hospital records, diagnostic tests, procedures, and discharge summary prior to the appointment will facilitate patient evaluation and implementation of the treatment plan. Having a clear well-developed evidence-based treatment plan that is shared and communicated to the patient and family will facilitate adherence. When reminding the patient of their appointment encourage them to write down any questions or concerns, to ensure they are addressed during their appointment. Continued education and review of information will be necessary to promote understanding. Remember this is a stressful time and many patients with HF discharged from the hospital are depressed, fatigued, and perceive a poor quality of life [17].

When the patient is newly diagnosed with HF, confirmation of the diagnosis should be made with current or prior signs or symptoms. In addition, a structural or functional cardiac abnormality should be corroborated by either an elevated

natriuretic peptide level (either B-type natriuretic peptide level [BNP] or N-terminal pro-B-type natriuretic peptide [NT-proBNP]) or objective evidence of pulmonary or systemic congestion [34]. Patients meeting these criteria are considered Stage C and patients without current or prior signs and symptoms are considered Stage B or pre-HF [34]. Patients with severe symptoms and who are either intolerant or refractory to guideline-directed medical therapy (GDMT) are Stage D advanced HF [34]. Assigning New York Heart Association (NYHA) functional class is recommended at baseline and after treatment throughout the continuum of care. The NYHA functional class serves to characterize symptoms and functional capacity on a scale from I to IV. Patients with increased NYHA functional class (II–IV) are recommended to undergo further optimization of GDMT if possible [34]. All patients should have their HF staged and NYHA functional class assigned.

8.4.1 History

A complete history is important in evaluating the patient post-hospital discharge in determining precipitating events, signs, and symptoms and potential cardiac disorders and/or comorbidities that contributed to the hospitalization. Dyspnea and fatigue that occurs at rest or with activity are cardinal symptoms of HF. During transition from the hospital to follow-up, the patient's fluid state is a primary concern. However, some patients may have difficulty articulating symptoms and equate them to the aging process or some other factor such as being out of shape. The history should include the history of present illness, past medical history, family history, personal history, review of systems and functional assessment. If the patient is known to the provider, the history may be more focused on precipitating events and present illness. When interviewing the patient, it is critically important to question the occurrence of symptoms, severity, and factors that exacerbate their symptoms. Questions such as do their symptoms occur at rest or with activity? Do they wake up at night with symptoms of shortness of breath? How many pillows do they sleep with or is the head of their bed elevated? Have they noted a change in weight (gain or loss)? Have they noticed swelling in their abdomen, hands, feet, or legs? Potential precipitating factors should also be assessed such as, but not limited to, sleep disorder breathing, anemia, arrhythmia, infection, or change in medication. Among patients with a HF exacerbation assessment of dietary, uncontrolled comorbidity, missed or nonadherence to prescribed medications or exacerbating medication such as NSAIDs should be evaluated. If family members or a caregiver is present for the appointment, they may provide additional insight into the patient's signs and symptoms of prior hospitalization and following discharge. A quality history takes time, attention to detail, and a trusting open rapport with both the patient and family.

A risk assessment is recommended which may include B-type natriuretic peptide levels [15, 35]. Prior hospital discharge or on initial return to the office obtaining a natriuretic peptide level is helpful in establishing post-discharge prognosis and can be a point of comparison when following the patient post-discharge [35]. Of note

patients who have been prescribed an angiotensin receptor–neprilysin inhibitor (ARNI) must only have NT-proBNP drawn since BNP is a substrate of neprilysin and will result in an artificially elevated reading. A variety of validated risk assessment tools to examine morbidity and mortality are available for both HF reduced ejection fraction (HFrEF) and HF preserved ejection fraction (HFpEF) online to assess patients with chronic HF [36, 37]. Patients following their initial diagnosis of HF often have several questions regarding their prognosis and risk assessment tools can be helpful.

8.4.2 Physical Examination

Physical examination of patients with HF includes a focused evaluation of the cardiac and pulmonary systems with components of the integumentary and gastrointestinal systems. All initial and return appointments should include weight, body mass index (BMI), blood pressure (BP), heart rate (HR), and respiratory rate (RR) [15]. The patient's vital signs should fall within a normal range and if they do not then adjustments to the treatment plan should be considered. Orthostatic BP and HR should be evaluated on return and provide important insight into the patient's volume status [15]. The patient's HR, rhythm, and character should be evaluated. An elevated HR can indicate dehydration, low cardiac output, and/or a stress response whereas a low HR could suggest bradycardia, heart block, arrhythmia, or response to beta blocker therapy. Ventricular and atrial arrhythmias are common in patients with HF. Providers should inspect the head, neck, and chest when beginning their examination. Assessment for jugular venous distention with the patient's head elevated above 45° signifies increased central venous pressure indicative of congestion [15, 38]. The abdominojugular test should be performed if jugular venous distention is present and is associated with an elevated wedge pressure and right ventricular HF [38]. Cardiac enlargement may be detected when palpating the precordium with an apical impulse displaced laterally to the left and downward. A clear S_1 and S_2 should be auscultated. However, some patients with HF may have a third heart sound (S_3) that persists when sitting up is associated with diastolic dysfunction and fluid volume overload [38]. A fourth heart sound may also occur (S_4) but is not a sign of failure but instead decreased ventricular compliance. When an elevated HR occurs in this instance the two sounds merge, and a summation gallop is heard [38]. Murmurs suggest valvular disease. In HF particularly advanced murmurs are frequently present.

Ideally in patients with stable HF clear breath sounds should be heard. When there is accumulation of fluid it can lead to pulmonary crackles. Initially, late inspiratory crackles are present typically in the bases of the lungs; later as the patient becomes more congested diffuse crackles can be heard across the chest [38]. Although the absence of crackles does not exclude pulmonary edema. Pulmonary compromise is also reflected in the respiratory rate and pattern. Tachypnea or Cheyne-Stokes with diaphoresis, tachycardia, and extremity coldness can reflect compromise and decompensation [39].

Patients with HF may or may not present with edema. When present, it is often detected in the abdomen, feet, ankles, hands, or sacral area. The patient's skin may appear either pallor or cyanosis and cool to touch. Patients may not report abdominal complaints but may have accumulated significant fluid either as ascites or visceral edema. Symptoms associated with abdominal fluid retention include indigestion, nausea, vomiting, and diarrhea [38]. For more details on physical exam findings, refer to chapter "Physical Exam for Presence and Severity of Heart Failure" in this book.

8.4.3 Assessment of Weights

While hospitalized patients should have received education and instructions on self-care behaviors and life-style modifications, patients are often instructed to weigh their self each day typically upon rising in the morning after they urinate. Consistent assessment is critical in determining if there is a meaningful change in weight. Variance between hospital, home, and office scales can result in confusion. If the patient was fluid volume overloaded when presenting to the hospital their weight should have declined. Unfortunately, many times patients are discharged from the hospital before they have reached their dry weight [40]. Establishing a dry weight range for the patient using their home scales and when to call with changes is important. This should be clearly documented in the patient's medical record to be used as a reference point when the patient calls the office. Assisting the patient in understanding how fluctuations in weight can occur and the importance of reporting symptoms regardless of their weight is key. Regular review of weight diaries by the provider is important. Discussing times of increased weight and jointly identifying potential contributing factors are educational opportunities. Additional patient monitoring of self-care activities will be discussed later in this chapter.

8.4.4 Medication reconciliation

Medication reconciliation is an important activity in the initial follow-up appointment and after any changes to the patient's treatment plan. Although errors in medications can occur at any time they are reported to be as high as 50% in adult and elderly patients discharged from the hospital [41]. Patients should be instructed to bring in *all* their medications (i.e., anything they are taking which includes over-the-counter medications or supplements as well as medications they have discontinued) to their appointment. A nurse or pharmacist can assist with the review and reconciliation process. Unfortunately, patients sometimes fail to discontinue old medications and begin new ones, or during hospitalization medications are changed due to formularies resulting in the patient potentially taking duplicate medications from a single drug class. A complete review of all medications, frequency, and dose should be undertaken with the patient. Examining prescription refill patterns also provides insight into the patient's prior adherence patterns. Ensuring the patient has a clear understanding of their medications, the reason for the medications, and a process that facilitates

adherence is key. During the initial follow-up further optimization of GDMT may be undertaken as part of the treatment plan. This process should be reviewed with the patient and joint decision making occur. It is important to identify and address all barriers that may prevent the patient from taking their medications as prescribed. Patients should be instructed on potential side effects of their medications, to not discontinue their medications without medical direction, and to contact the office if there are questions or a change in status occurs. Optimization of GDMT should occur every two weeks if possible until the patient has reached target-tolerated dosing.

8.4.5 Diagnostics and Laboratory Testing

A major goal in managing the newly diagnosed patient with HF or the patient who experienced an exacerbation is to determine, if possible, the underlying cause or precipitating event. Depending upon the extent of evaluation during the hospitalization will determine the need for diagnostic evaluation following hospital discharge. Transthoracic doppler echocardiogram combined with doppler flow studies is one of the most valuable tools in evaluating the patient with HF [15]. However, repeated measurement in the absence of a status change or treatment interventions should not be performed [15]. Patients who are suspected of having coronary disease and would be candidates for revascularization should undergo coronary angiography [15].

Patients admitted to the hospital with HF typically undergo laboratory testing and should include complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, calcium, magnesium, glucose, fasting lipid profile, liver function, thyroid stimulating hormone, and either BNP or NT-proBNP levels [15, 35]. Review of previous laboratory diagnostics, comorbidities, and patient assessment will guide requests for testing post-discharge from the hospital. Laboratory testing should be coordinated and communicated with all providers to avoid duplication. Serial monitoring of laboratory tests includes renal function and electrolytes with changes in the patient's fluid state and optimization of GDMT. For ACEI, ARB, or ARNI class medications and aldosterone receptor antagonists such as spironolactone, potassium and renal function should be monitored at the time of initiation and then closely monitored thereafter to minimize the risk of hyperkalemia and renal insufficiency [15].

8.4.6 Optimization of Guideline-Directed Medical Therapy

Guideline-directed medical therapy (GDMT) is critically important to ensure optimal outcomes of patients with HF. Current recommendations are based on evidence and all patients with HF should be treated based on current evidence, yet treatment plans must be individualized to the patient [15]. Providers should review current GDMT to stay up to date on any recommendations or changes [15, 35]. Studies reveal many patients are placed on GDMT but medication doses are not increased to recommended levels [42, 43]. Incremental increases in the patient's HF

medications while carefully monitoring for any adverse events is an important role of the patient's provider and can have a significant impact on the patient's outcome. With each visit identifying any opportunities to optimize the patient's treatment plan should be discussed and considered.

8.5 Self-Care Strategies for the Heart Failure Patient

Prior research has shown that one way to improve a patient with HF's quality of life and outcomes is through the performance of self-care. In this section, we will explore self-care strategies for the patient with HF by first understanding the definition of self-care and how the self-care of patients with HF is affected by family/caregiver relationships, cultural influences, and self-efficacy. We will end the section with overall strategies for promoting HF self-care with considerations encompassing these areas listed above.

8.5.1 Definition of Self-Care and the Importance of Symptom Monitoring

Self-care has been defined by Riegel et al. as a process that influences one's actions to maintain physiologic stability, help one to perceive their symptoms of worsening HF, and then manage those symptoms through a treatment regimen [44]. Self-care has been identified to have 3 separate components that are linked together and necessary to maintain a homeostasis. The first process in self-care is *maintenance*, which consists of adherence to treatment and behaviors. For example, following the prescribed medication regimen, diet restrictions (i.e., low salt), and performing exercise (i.e., walking) [44]. The next step in the process of self-care is one being able to perceive their symptoms (*symptom perception*). This involves listening to their body (i.e., pants fitting too tight, shortness of breath when performing activities that do not normally cause shortness of breath, etc.). In addition to perceiving symptom(s), one needs to recognize and interpret it as a problem or not being normal for them and labeling it as such. Lastly, a person with HF needs to perform the final process of self-care, which is *management*. In the management phase, a person with HF will respond to the symptom.

It is important to note that patients with HF make these decisions about their self-care based on the circumstances occurring, and their environmental elements that influence the problem, such as patient's decision about what to eat at home may be very different when faced with making this decision in a different environment, surrounded by different support systems. For example, a person may follow a low sodium diet while at home, but they attend a family event where low-sodium foods are not available, so they choose to eat with others and therefore consume a higher sodium diet than normal. This is an example of how normally individuals who are adherent and successful with their HF regimen may fail due to the circumstances that surround them [44]. Many times individuals will make decisions about their care based on past experiences with the symptom and treatment of that symptom.

However, at times other factors may influence their decision-making such as age-related cognitive decline, comorbid conditions, gender, living situation, and social support. These are all examples that a provider should keep in mind regarding how complicated one's decision-making can be when performing self-care and ways that we as healthcare providers can support a patient in their self-care process.

8.5.2 Role of Family Caregiver with Promoting Self-Care

The care of a patient with HF can occur in many settings, such as the outpatient clinic, provider's office, or in a hospital setting. However, the actual maintenance and management of these patients occur in their home by themselves or with family caregivers. Since the patient spends most of their time managing their condition of HF in the home, it is important to assess the contributory factors to being successful or not with their self-care in a home setting. This section will examine the role of the family caregiver as it pertains to HF self-care, as well as the impact that the caregiver can have on the patient with actually performing their self-care.

Caregivers help patients with their medication management, dietary restrictions, schedule appointments, watch for and report untoward symptoms such as edema and/or shortness of breath, and daily weighing [45]. They may also help the patient with calling their provider when necessary and assist with titrating their diuretic or other medications as directed, essentially serving to interface between the patient and clinicians. Given the ways that caregivers help with all aspects of self-care, it is easy to see how they can play an important role in positively or negatively affecting patients with regard to performance of their self-care behaviors. Family theory and research can provide some helpful information on the importance of the role that family caregivers have on patients who are managing their condition of HF.

The way a family communicates and adapts to and solves problems can affect the patient's ability to adhere to their self-care regimen. One theory that explains the interactions between family and a patient with a chronic illness such as HF is the Self-Determination Theory (SDT), which is a theory of motivation. Motivation to perform self-care is an essential factor for achieving behavioral change [46]. There are two types of motivation described by SDT, which are autonomous and controlled regulation [46, 47]. Autonomous regulation occurs when a person performs the behavior because they value it and feel that they have the ability to integrate it into their daily living whereas controlled regulation occurs when a person with HF performs the behavior because they feel pressured by another person, which could be verbally (e.g., "you should") or by being made to feel guilty for not performing the behavior [48, 49]. Prior studies using interventions to underpin the SDT theory have shown that caregivers who provide autonomous support to patients with HF tend to have higher levels of adherence to their low sodium diets and medication adherence with higher motivation and confidence to perform their self-care [50, 51]. Also, caregivers mood can affect a patient with HF's motivation to perform self-care maintenance. Patients who had caregivers with higher levels of depression and anxiety had worse self-care maintenance and at times could effect a patient's engagement in their self-care and self-efficacy for performing self-care [52].

Educational interventions which include the family member/caregiver with the patient have more positive, sustained effects than those that only include education of the patient with HF [50, 51, 53, 54]. Therefore, healthcare providers should include family members in education related to care of the HF patient and help the family member understand how providing supportive, autonomous communication to the patient can promote successful outcomes.

8.5.3 Cultural Influences of Self-Care

Person-related factors such as culture and ethnicity can play a role in one performing their recommended self-care regimen. Prior studies have been completed to evaluate the influence of cultural beliefs and practices on performing self-care behaviors [55–60]. Providers need to consider a person's cultural beliefs when providing self-care education so they can help tailor the education and self-care practices to be sustainable within a person's way of life.

8.5.4 Health Literacy, Self-Care Education, and Self-Efficacy

HF self-care education can improve patient's knowledge to learn the skills necessary to manage this progressive, chronic condition. With knowledge comes empowerment and a feeling of personal control and confidence to manage the symptoms of their disease. However, knowledge alone without providing patients and caregivers with the necessary skills, strategies, and support to make lifestyle changes can result in failure for the patient leading to decreased self-efficacy for managing their condition. It is beneficial for HF patients to receive specialized education and training in self-management (medication management, nutrition, exercise) [61]. However, education in the presence of low health literacy can lead to poor outcomes such as nonadherence to performing self-care behaviors [62]. Prior research has found that there are levels of health literacy. One is critical health literacy, which is the ability to critically analyze information provided and use that information to make decisions about self-care. When a person has low levels of critical health literacy it has been shown to be an independent predictor of patients performing fewer self-care behaviors [62]. Providing educational interventions about symptom management, perception, and maintenance is one way to improve health literacy, self-efficacy, and self-care confidence for performing self-care in patients with HF [63].

8.5.5 Overall Self-Care Strategies for Managing a Patient with Heart Failure

Patients with HF vary in their ability to perform self-care [64]. However, there are some factors that can facilitate or serve as barriers to patients being successful with

following their regimen and monitoring their status. Some of the things that providers can consider when working with patients who have HF is to recognize that one of the main barriers to taking diuretics is the fear that they will have an accident when outside of the house or the side effect of getting up to go to the bathroom all night and lacking sleep. In many cases this can lead to patients skipping their dose and having worsening symptoms. Providers can mitigate this barrier by educating the patients about strategies regarding when to take their diuretic so that it does not interfere in their daily life. For instance, recommend that they plan ahead and take their diuretic at least a few hours before leaving the house so that most of their diuresis will have subsided before outside activities begin. Second, to schedule their diuretic no later than 5–6 p.m. in the evening so going to the bathroom frequently won't interfere with their sleep.

A barrier to weighing themselves daily or monitoring for swelling was forgetfulness. Providers can educate their patients with HF to make weekly diaries and place the diary somewhere they will see it every day. Ask them to write their weight down so they can see the trend of weight loss or gain. In addition, we know through prior research that patients have a difficult time assessing edema. Talk with them about things they can measure, such as whether their pants, socks, pantyhose, or shoes become tighter than normal or their clothing is fitting more tightly than normal. Hand your patient written instructions that they can refer to often because they tend to forget what is said during the office visit. Following a low-sodium diet is often difficult for patients with HF especially when they eat out or want to attend social events. In the case of attending social events talk with them about that it is okay to eat before they go so the temptation to eat salty foods is lessened or they can bring their own dish so they know there will at least be one thing that they can safely eat. When eating out, talk with them about reviewing the menu for items that contain fresh foods and ask the chef or cook to leave the salt out of the dish when preparing the meal. Let them know that chefs are adept at taking special orders for dietary restrictions or allergies.

8.6 Putting It All Together

John Jones is a 58-year-old black man who has had a long history of hypertension and diabetes mellitus. He experienced a myocardial infarction and was treated with PTCA and stent to the right coronary artery 3 years prior. He has worked at the local factory filling rail cars for the past 19 years. He is married with two children, one in high school and one in her first year of college. He was admitted to General Hospital 3 days ago for progressive increase in shortness of breath and was found to have heart failure (HF) with an ejection fraction of 22%. He was placed on guideline-directed medical therapy (GDMT) and underwent a cardiac catheterization with no further intervention required. He has been noted to have intermittent PVCs. His new medications include Entresto 24/26 mg twice daily, Carvedilol 25 mg twice daily, Spironolactone 25 mg daily, dapagliflozin 5 mg daily and furosemide 40 mg daily.

He is scheduled for follow-up with his primary care provider in 1 week and cardiologist in 3–4 weeks.

Considerations:

- New diagnosis
- New medications
- Home support
- Communication/Hand off

To facilitate this patient's transition to home, nurses and providers must take into consideration the above factors. With a new diagnosis of HF, patients may or may not fully appreciate what that means. Ensuring evidence-based education is provided to both the patient and his significant other using teach-back prior to discharge is critical. The patient not only has been given a new diagnosis but will be required to make many life changes (diet, activity, medications). HF education should begin on admission and continue through discharge and each follow-up outpatient visit [15]. Assess what the patient and significant other know regarding HF and build their knowledge. Throughout the hospital course and discharge process shared decision making is key. With the new medications ensure the patient has a good understanding of what medications have been discontinued, what medications he should continue from the past, and what new medications have been added. Review the medications, purpose, side effects, what to do in the event of side effects, and the importance of taking them as prescribed. Discuss with the patient his prescription plan and determine if the patient can afford and is willing to obtain the new medications. Although the medications listed are GDMT if the patient cannot afford them or if there are other barriers address them prior to discharge. Consider getting the prescriptions filled as the patient is leaving the facility or at his local pharmacy to be picked up on his way home.

Home support is essential to ensure a good successful transition home. Depending upon the hospital facility an array of services may be considered. Regardless of the services (care coordination, home health, remote monitoring, and/or phone follow-up), contact with the patient soon after discharge anywhere from 1 to 7 days has been found to be beneficial [14]. A multidisciplinary transitional program individualized to the patient population can have a positive impact in reducing readmissions [14].

Patients are most vulnerable during the first week following discharge [7]. Timely, accessible information regarding the patient's diagnosis, weight, symptoms, and treatment plan needs to be shared with the healthcare team. Quality communication with healthcare providers facilitates and promotes positive patient outcomes.

At General Hospital Mr. Jones and his wife received over 1 h of HF education. He received printed literature, weight diaries, and a scale. He met with the registered dietician who discussed his diet as it related to his diabetes and HF. The pharmacist at the hospital met with Mr. Jones and reviewed his medications, provided

him an updated medication list, and assessed the cost of his new prescriptions. Currently Mr. Jones is amendable to filling and taking his recommended medications as prescribed. His follow-up appointment was scheduled in 5 days with his Primary Care Provider (PCP) and numbers were given to call should he have symptoms or questions. Cardiac rehabilitation will reach out to the patient in the next 6 weeks to schedule Phase II. Home health was scheduled to evaluate following discharge. The HF team contacted the patient via phone 3 days following discharge and reviewed his treatment plan and addressed questions. When home health arrived 4 days following discharge the patient's weight had continued to decline and the patient appeared dry. A call was placed to his PCP and his diuretic dose was reduced and a basic metabolic panel was ordered. The patient and his wife had several questions regarding his medications and diet, which the home health nurse addressed, and the requested laboratory test was drawn. The following morning the patient was evaluated by his PCP and his laboratory results were reviewed and his renal function displayed a slight decline. His PCP will continue with his reduced dose of diuretic. The patient and his wife both verbalize questions and would like to connect with other people with a similar diagnosis. A list of reliable resources was provided, and they connected with the HF Patient Foundation and Together in HF. On their return appointment with the Cardiology provider the patient's symptoms were stable and he was tolerating his current treatment plan.

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Goals of Care for the Heart Failure Patient

9

Christine M. Hallman and Krista R. Dobbie

9.1 Case Study: Setting the Stage

Mr. Smith is a 64-year-old male with past medical history of hypertension, diabetes mellitus, and continued tobacco abuse. He had significant coronary artery disease and underwent four vessel coronary artery bypass grafting approximately 10 years ago. He now has continued ischemic cardiomyopathy with an ejection fraction of 10%; Heart Failure with Reduced Ejection Fraction (HFrEF). He has evidence of right-sided heart failure (HF) as well. Due to his refusal to stop smoking he is not a candidate for a left ventricular assist device or heart transplant. He has been admitted to the hospital three times in the last six months with acute decompensated heart failure. Unfortunately, he is also showing evidence of cardio-renal syndrome with an elevated creatinine of 2.5. He is readmitted a fourth time with acute decompensated systolic and diastolic heart failure and hypervolemia. His creatinine is now 3.8. His cardiologist attempts to mention hospice care, to which Mr. Smith replies, "I'm not ready for hospice care." What do you do next? How do you attempt to discuss goals of care and code status with Mr. Smith? What conversations could you have had earlier to help Mr. Smith process the terminal nature of his heart disease?

C. M. Hallman (✉)
Palliative Care Services, MedStar Health Washington Hospital Center, Washington, DC, USA
e-mail: christine.m.hallman@medstar.net

K. R. Dobbie
Department of Palliative Medicine and Supportive Care, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: dobbiek@ccf.org

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_9

9.2 Palliative Care in Heart Failure

9.2.1 What Is Palliative Care?

Formally, the World Health Organization (WHO) (2020) defines palliative care as: "An approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual [1]."

Historically, palliative care has been viewed as only being applicable to patients at the end of life and most commonly associated with cancer diagnoses [1–4]. However, due to the labile nature and unpredictable course of heart failure, this view has evolved and the importance of integrating palliative care into the management of heart failure is now being recognized throughout the disease trajectory, often suggesting introduction of services at diagnosis [3, 5–7]. Palliative care is both a philosophy of care and a medical approach to care and may be provided in conjunction with other life-prolonging and guideline-directed medical therapies. Palliative care should not be confused with the hospice benefit which requires a physician to declare a life expectancy of less than 6 months [3, 4, 7, 8]. Hospice will be discussed in more detail later in this chapter. Palliative care services include: pain management, symptom management, identification and clarification of patients' goals of care by means of advance care planning, coordination of care, psychosocial support and spiritual support; thereby offering a holistic model of care and a patient-centered approach [1, 3, 9, 10].

Palliative care services may be provided by either specialists or general practitioners and are offered in various settings such as the acute care setting, ambulatory care setting, or at home [1, 10, 11]. Due to the lack of specialty trained palliative care providers, there is a growing belief that all clinicians providing care for patients with heart failure should possess the basic skills needed to deliver competent primary palliative care. Therefore, an emphasis is currently being placed on the importance of incorporating the principles of palliative care into clinical and didactic training programs [6, 8, 9, 11, 12].

9.2.2 Why Is Palliative Care in Heart Failure Important?

The recommendation for the early integration of palliative care in heart failure is suggested by all major cardiovascular societies and is included in national heart failure treatment guideline recommendations published by the American College of Cardiology Foundation (ACCF) as well as the American Heart Association (AHA) [7, 11, 13–16].

Heart failure carries a five-year mortality rate of nearly 50% and places patients at a higher risk for sudden cardiac death [3, 9, 15]. In addition to the five-year 50% mortality rate, the average survival for patients with HF is just 16 months following the first hospital admission, making this worse than the expected survival rate for

numerous cancers [3, 8, 11]. Furthermore, it is estimated that the cost of caring for heart failure is approaching $100 billion dollars and is the costliest diagnosis incurred by Medicare [6, 9, 11, 15].

Studies have shown that patients with heart failure experience symptom burdens that are comparable, if not worse, than those experienced by patients living with cancer [7, 9, 16]. The most commonly reported symptoms experienced by patients living with heart failure include: peripheral edema, dyspnea, fatigue, anorexia/early satiety, anxiety, spiritual and psychosocial distress, caregiver burden, depression, and pain; though pain is often overlooked and thereby is undertreated in heart failure [5, 7, 9, 10]. The Center to Advance Palliative Care (CAPC) website serves as an excellent resource of information for clinicians providing palliative care across specialties. This website offers numerous evidence-based assessment tools that can aid providers in the clinical assessment of patients and evaluates their palliative care needs [17].

When initiated early and utilized appropriately, the holistic approach of palliative care has been shown to increase quality of life, improve survival, decrease physical and emotional symptom burden, decrease cost of caring, decrease the numbers of hospitalizations and unwanted advanced therapies at the end of life, and facilitate earlier referrals to hospice [3, 4, 6, 9–11, 18, 19].

9.3 Current State of Palliative Care in Heart Failure

Despite being included in both international and national heart failure treatment guidelines, the use of palliative care in heart failure is grossly underutilized [8, 13]. It is estimated that less than 10% of end-stage heart failure patients receive a palliative care consultation [8]. This is problematic as cardiac patients in the last month of life utilize acute care services at a higher prevalence than patients living with cancer [8]. The current barriers that have been identified to integrate palliative care into heart failure management include: scarcity of specialty palliative care providers, lack of generalist palliative care training, difficulty in prognostication, the need for identifiable "triggers," advancement of late-stage heart failure therapies, lack of disease state awareness, and institutional barriers [6–9, 13, 15, 16].

9.3.1 How and When to Refer to Palliative Care for the Primary Care Provider

Primary care providers should approach and assess each patient with heart failure on a case by case basis and refer to specialty palliative care providers based on individual patient need, regardless of where the patient is in the course of the disease trajectory [6, 16]. Some triggers for referral include: increasing symptom burden, psychosocial or spiritual distress, worsening ejection fraction, repeat hospital admissions, patient-reported decrease in quality of life, decrease in functional status, initiation of palliative inotropes, implantable-cardioverter defibrillator (ICD)

placement, refractory to medical therapy, not a candidate for advanced therapies, need for goals of care discussion, or need for hospice care [6, 8, 10, 13, 19].

For a patient with heart failure, it is never too early to refer to palliative care for introduction of services [7, 13, 16]. The introduction of services allows for early and ongoing support and the degree of palliative care involvement may vary based on need throughout the disease trajectory [7]. Not only does palliative care serve as another layer of support to the patient, but involving palliative care also ensures adherence to heart failure management and practice guidelines [7, 11, 13–16].

9.4 Goals of Care Discussions in Heart Failure

9.4.1 Components of Goals of Care Conversations

Goals of care discussions are ongoing conversations that occur between clinicians, patients, and families in the setting of a chronic and progressive illness such as heart failure and may occur with or without specialist palliative care involvement [19, 20]. Goals of care conversations should be initiated at diagnosis of such conditions and continue throughout the trajectory of the illness and be updated on a regular basis [20–22]. These discussions provide an opportunity for providers to discuss prognosis and treatment options and afford patients the opportunity to ask questions and clarify any misconceptions related to their current medical condition [19]. It has been shown that advanced care planning is associated with lower risk of inpatient hospital deaths, lower costs, and higher utilizations of hospice care [23].

In addition to ensuring patients' prognostic awareness, goals of care discussions are centered around understanding patients' goals, values, and preferences in the context of such illness and may also include conversation related to completion of advance directives, appointment of a healthcare proxy, resuscitation status, symptom management, and preferences for end of life care [19, 20, 22, 24]. Goals of care conversations help to foster an environment of shared decision-making and allow for the development of individualized care plans that are aligned with patients' goals and values [20, 22, 24].

9.4.2 Current State of Goals of Care Conversations

Similar to the recommendations put forth by national societies for the integration of palliative care, it is also recommended that goals of care are discussed on an annual basis and after any change in functional status. These conversations should be documented in the electronic medical record so they are accessible to the entire care team [6, 10, 16, 25, 26]. Despite these recommendations, it is believed that only 12–17% of patients with heart failure have engaged in goals of care conversations with their providers and most patients with heart failure have not completed formal advance directives [6, 8, 20, 22]. The barriers to engaging in goals of care conversations have been identified and are well documented. These barriers include: (a) lack of

provider confidence in facilitating such conversations; (b) lack of provider education in executing the conversation; (c) difficulty in the prognostication of HF making timing for initiation of such conversations unclear; (d) uncertainty around appropriate clinical triggers for goals of care conversations; (e) provider belief that patients do not want to discuss preferences for end-of-life care; (f) lack of tools to help facilitate conversations; (g) lack of time; (h) fear of taking, "hope," away from the patient; (i) uneasiness in discussing end-of-life [4, 13, 20, 21, 26].

Engaging in routine and ongoing goals of care discussions along with the development of a patient value-driven care plan increases quality of life, decreases symptom burden, decreases unwanted advanced therapies at the end of life, decreases financial burden to both the patient and the healthcare system at large, and leaves the patient and families with a more auspicious outlook on hospice care and better prepared for end-of-life situations [4, 13, 19, 24, 26]. The importance of these conversations is so great that in 2016 the Center for Medicare and Medicaid Services began reimbursing providers for engaging in these discussions and may serve as a motivating factor for primary care providers [20, 25].

9.4.3 How to Initiate Goals of Care Conversations

Once the need for a goals of care conversation is recognized, goals of care conversations in the primary care setting should be planned in advance and should be scheduled to allow for an adequate amount of time so that the conversation is not rushed and all parties are given sufficient time to provide information and ask questions [20–22]. Prior to entering into a goals of care conversation, the clinician should engage in a thorough review of the patient's chart and become familiar with all necessary and pertinent medical information that may factor into future complex medical decision-making [20]. It is also important to inform patients and families of the nature of the visit prior to the scheduled appointment day to enable them to come prepared to enter into such conversation [20].

At the time of the scheduled meeting, the clinician should set the agenda and begin by assessing the prognostic awareness of the patient and family followed by providing a medical update and clarifying any information that may have been misinterpreted by the patient [20, 21]. Throughout the meeting, the clinician should engage the patient by asking open-ended questions while taking time to acknowledge and respond to any emotion [20]. After all of the information has been presented and the patients' goals and values have been identified, the clinician should recommend a medically appropriate plan of care that is congruent with the stated wishes [20]. If any changes are made to the patients' plan of care following a goals of care conversation, the outcome of the conversation should be documented in the electronic medical record and communicated to all members of the patients' care team [14, 20, 26]. It is important to recognize that these conversations should be iterative and may not occur in a single setting but rather require a set of subsequent meetings to fully complete the conversation and facilitate decision-making [20, 21].

9.5 Special Considerations for Goals of Care Conversations in Heart Failure

9.5.1 Difficulties in Discussing Goals of Care

These authors advocate that goals of care discussions are especially important in heart failure patients due to the many life sustaining technological devices such as aortic balloon pumps, temporary left ventricular support (i.e., Impella device by Abiomed), ventricular assist devices (LVAD), palliative inotropes, dialysis, and extra-corporal membranous oxygenation (ECMO). These devices or therapies may be placed urgently when a patient is in cardiogenic shock and may make a transition to hospice care more difficult or ineligible for hospice care. Tragically, these devices may result in a "bridge to nowhere" if the patient is unable to improve and is not a candidate for long-term mechanical circulatory support or transplant. For families of these patients, end of life care that has these forms of technological life support has been associated with increased family anxiety, depression, poorer quality of life, and overall less satisfaction with the dying process [27]. Therefore, clear goals of care discussions early in the disease process and preferably in the outpatient setting may prevent initiation of these devices when a hospice transition may have been more appropriate.

These discussions can take many forms including simple advance care planning conversations defining a medial power of attorney or completion of a living will. A medical power of attorney or healthcare power of attorney is a person whom the patient trusts to make healthcare decisions for them when they are unable. This is a simple discussion and a way in which to begin a goals of care conversation. An advance directive is "the general term that refers to the various documents that could include a living will, instruction directive, health care proxy or health care power of attorney" [28].

More involved and complex goals of care conversations include determining code status, deactivation of devices, and discussions about transitioning to a hospice level of care. To reiterate, the American Heart Association recommends an "Annual Heart Failure Review" much like an annual wellness visit. The goal is to have continued ongoing conversations about symptom burden, quality of life, estimation of prognosis, patient's goals, review of therapies, and anticipatory planning for future events [26]. By continuing ongoing conversations, this allows patients and their loved ones to redefine their goals as their illness progresses. Why are these conversations so difficult? Heart failure is a terminal and progressive condition. However, patients are often unaware that their heart failure cannot be cured and will continue to worsen over time. Unlike cancer, the primary care physician or cardiologist cannot show the patient a CT scan that visually shows progression of disease. There is no evidence that the patient can physically see that allows them to process that their heart failure is indeed progressing. Secondly, patients are readmitted to the hospital, undergo diuresis, and discharged back to home with their shortness of breath improved and their edema resolved. This gives patients and families a false sense of security that with each admission the disease will be kept in check and managed.

How can the patient believe they are actually dying from a terminal illness if each time the healthcare team makes them feel better? Therefore, before even having a meaningful conversation regarding goals of care, the medical provider must educate and explain the terminal nature of heart failure to the patient and family.

Patients and families need concrete examples of how to understand their disease is, in fact, progressing. Clinicians understand that heart failure disease progression is evidenced by recurrent readmission rates, hypotension that may result in intolerance to heart failure medications, volume overload refractory to diuresis, worsening cardio-renal syndrome, hyponatremia, and increasing symptom burden. A very simple and accurate prognostication tool is the surprise question. "Would you be surprised if this patient was alive 1 year from now?" If the answer is yes, then the clinician should be explaining the terminal nature of heart failure to patients and embark on serious goals of care discussions [29]. Explaining heart failure to patients can be simply telling them that progression of their disease means that they will begin to have more frequent admissions, the oral medications may no longer work at removing their fluid accumulation, and their blood pressure may be too low to continue to take the medications that are helping their failing heart. It is important for patients to process that disease progression means that they will spend less time at home and be more frequently admitted to the hospital. If patients truly understand recurrent readmissions are a very poor prognosis, they can begin to think about when they may want to remain at home and transition to a hospice level of care. This is a process. A process of continuing to reevaluate what each admission means and how the disease is progressing. If patients understand the significance of multiple readmissions earlier in their disease trajectory, they can begin to consider an earlier transition to hospice [29].

9.5.2 Code Status Discussions

Code status discussions can be very complicated discussions in patients with heart disease. Patients may have had successful resuscitation in the past. They may have had their defibrillators discharged resulting in restoring life sustaining rhythms and prolongation of their life. They may come to falsely believe that if their heart stops, simple shocks will result in restoring their health. In this author's opinion, for these reasons, code status discussions are more difficult and challenging discussions in cardiac patients rather than other disease populations. It is important to understand that most patients hospitalized with heart failure will want resuscitation in the event of cardiac arrest [30]. Krumholz found that of patients hospitalized with heart failure, only 23% did not wish for resuscitation, and of those 23% of patients, 40% would go on to change their minds after their hospitalization ended [30]. Therefore, code status should be continued to be readdressed throughout the patient's illness and with each decline in clinical status. A patient may insist on remaining full code due to past experiences with resuscitation. These authors suggest, rather than try to convince the patient to change their mind, a useful discussion at this point is to discuss "what if." What if you are alive but remain on life support? What if you are

alive but have an anoxic brain injury? What is meaningful quality of life for you and when would you want the medical team to remove life support? Would your family know what to do? When would you want life sustaining support removed? This now introduces the concept that not all resuscitation will restore the patient back to full functional capacity. It also begins a dialogue of what is meaningful quality of life for the patient and what would they want in a "worst-case" scenario if they continue to remain full code.

9.5.3 Defibrillator Device Deactivation

Implantable cardioverter defibrillators (ICD) are placed most commonly for primary prevention in patients with severe HF who are at risk for sudden cardiac death due to ventricular arrhythmias. While these devices increase survival by treating life-threatening ventricular arrhythmias, they do not add quality of life to the patient. Patients who have been previously shocked may not wish to have additional shocks in the future. Unfortunately, there is little information regarding the risk of defibrillator shocks at end of life [31]. However, one study revealed that 19% of patients received a shock in their last month of life and 8% in their last hour of life [31]. Deactivating a patient's ICD simply means to disable the shocking functionality. This renders the device unable to treat ventricular fibrillation or ventricular tachycardia with shocks. It is important to recognize that disabling the shock function does not interfere with the resynchronization therapy function or bradycardia pacing function. It is important to explain to patients that deactivation of the device will not result in death at the time of deactivation and that pacing functionality remains intact. Also, the device deactivation is easy and painless [32].

Many hospices prefer defibrillators be deactivated at the time of signing consents for admission to hospice care. This prevents unwanted shocks during the dying process. However, discussing device deactivation with patients can prove to be a difficult conversation and anxiety provoking for both the healthcare provider and the patient. The authors have found it helpful to first ask patients if their device has ever been discharged. Asking this question helps provide some insight into their illness and experiences with their defibrillator. If the answer is yes, patients may be actually relieved to deactivate their device. Some patients have shared with the authors that the shocks were painful, they received multiple shocks, and they lived in fear of when they may be shocked again. For these patients, device deactivation may actually improve their quality of life by lessening anxiety and fear. If the answer is no, these patients may be fearful that deactivating their device may hasten or cause death. It is imperative to reassure these patients that pacemaker function will remain intact. Explaining the dying process, and the unlikely event that their defibrillator may fire, can reassure the patient that device deactivation will not result in imminent death.

The patient has a right to refuse device deactivation. They are still entitled to enroll in hospice care with an active device. In the situation where patients refuse device deactivation, the hospice agency should ensure that a magnet is delivered to

the home. In a patient receiving multiple shocks at the end of life, a magnet placed over the device pocket on the chest wall will stop the shocks. Device deactivation conversations can also be revisited over the course of the hospice admission and patient's illness. Just like code status, patients may change their minds at a later date and request that the hospice agency deactivate their device.

9.6 Hospice and End of Life Best Practices

9.6.1 Hospice Care

Hospice care is specialized care for patients at the end of their life. The hospice model of care emphasizes expert control of symptoms to ensure the best quality of life for the patient rather than aggressive life-prolonging care. Also, hospice care aims to support both the patient and caregivers emotionally with grief support and bereavement support to the family after the patient dies. Hospice care has been shown to alleviate symptoms and improve patient and family satisfaction [33]. Some studies have shown that hospice care is associated with improved survival benefit [34].

The Centers for Medicare and Medicaid Services (CMS) define hospice care as "a comprehensive, holistic program of care and support for terminally ill patients and their families. Hospice care changes the focus to comfort care (palliative care) for pain relief and symptom management instead of care to cure the patient's illness" [35]. To enter into hospice care, two physicians (the primary care physician or cardiologist and the hospice medical director) certify that the patient has a life expectancy anticipated to be six months or less. The patient signs a consent electing the Medicare Part A Hospice benefit for their hospice diagnosis and waives the right for all future Medicare payments related to their hospice diagnosis/illness. They are electing hospice care for their terminal diagnosis and waive additional hospitalizations and life prolonging therapies. There are several levels of hospice care including routine home care, continuous care at home, and inpatient respite care or inpatient care [35]. Hospice care provides medications for comfort, nursing and physician care, medical equipment, hospice aide, social services, spiritual counseling, and counseling to the family before and after the death of the patient. CMS eligibility criteria for heart failure includes patients with New York Heart Association Class IV symptoms at rest who have already been optimally treated for their disease and yet symptoms such as angina and dyspnea persist. They are not candidates for surgical procedures, or they have turned down such procedures. They have an ejection fraction of 20% or less but this is not required. Supportive symptoms that would support eligibility include but are not required are supraventricular or ventricular arrhythmias, history of cardiac arrest or resuscitation, syncope, brain embolism of cardiac origin, or concomitant HIV disease [36]. Hospice care for heart failure patients includes continuation of their oral medications and opioids for symptom management. Not all hospices can provide continued inotrope support or intravenous medications due to cost constraints and this should be considered when choosing hospice agencies especially if a patient is already receiving an inotrope.

Compared to cancer patients, heart failure patients are referred to hospice care late, usually within twelve days of their death compared to twenty days for cancer patients [37]. This study also found that heart failure patients were more likely to be referred to hospice care from inpatient hospitalizations or nursing facilities which may indicate that these referrals are being advocated by healthcare providers rather than patient preferences [37].

9.6.2 Barriers to Hospice Care Referral

Due to the difficulty with prognostication of the trajectory of heart failure, healthcare providers may wait until the patient is actively dying to consider referral to hospice care. Lack of early advance care planning conversations and the patient's poor understanding of the terminal nature of heart failure only add to these barriers. As previously stated, therapies such as mechanical circulatory support or inotropes may complicate hospice referral. Some hospices may be unfamiliar with left ventricular assist devices and lack confidence in their ability to care for these patients, thereby refusing admission to hospice unless the device is deactivated. Inotropes present a financial problem in that smaller hospices may not be able to cover the cost of this therapy. Smaller hospices may require infusions to be stopped or after the present infusion is completed, they will not re-order the inotrope. Having healthcare teams partner with their local hospice providers is essential to help troubleshoot these therapeutic barriers. This also ensures the healthcare provider is familiar with what services their local hospices can provide.

Late referral to hospice services has been associated with poor family satisfaction, lack of care coordination, and decreased awareness of the dying process and when death is imminent [38]. How can you as a provider help prepare a patient for hospice care? Introduce the concept of hospice care *BEFORE* you are ready to refer a patient. This can be done by providing "information only" conversations in conjunction with explaining that heart failure is a terminal disease. "I'm not referring you to hospice care at this time, but I want you to be aware of their services so you can think about when this may be a good option for you." Providing this information early introduces the possibility of an alternative to readmission to the hospital and empowering the patient to think about when they may want to choose hospice care as an option. A sample conversation may commence as follows, "I want you to be aware that as your disease progresses you may reach a point where you no longer wish to come to the hospital. I would like to provide you with information regarding hospice care, so you realize that there are other alternatives to readmission as your disease worsens. I want you to have time to think about this option and decide when hospice care might be the right choice you." Empowering the patient with information early, allowing time to process this information, and giving the patient control over when they would like to be admitted to hospice may help result in the patient being able to choose hospice care when appropriate for them.

9.7 Case Study: Putting It All Together

Referring back to the case at the beginning of the chapter, the question remains how could we have better cared for Mr. Smith? As his ejection fraction began to worsen and even before his creatinine began to climb, palliative medicine could have been consulted for introduction of services. Ideally, education about terminal heart failure and what to expect would be the basis to begin a basic goals of care discussion. Mr. Smith could have completed a medical power of attorney and started to process that as his disease advances, he would require more frequent admissions. Code status discussions could be initiated; however, the healthcare team would understand that he would most likely choose to be full code during those early discussions. The palliative care team would continue to follow him and evaluate him with each admission for increasing symptom burden and address symptoms that were contributing to worsening quality of life and help the primary team manage these symptoms. As his kidney function started to decline, early information regarding hospice care could be provided as an alternative form of care for end-stage disease. Ultimately, the goal would be to let Mr. Smith decide when he would be ready for hospice referral. Code status and goals of care would continue to be readdressed with each subsequent admission. This would be an iterative process with no agenda, rather simply a dialogue between Mr. Smith and his healthcare team to assess where he was in the process of accepting his terminal illness. As he became more ill, the healthcare team would recommend a do not resuscitate order, educate about the dying process, aggressively manage symptoms, and suggest considering more of a comfort-based plan of care. The healthcare team would recommend a referral to hospice care when they believed he has six months or less to live with his heart failure. He may not be ready at that time, but the team would agree to continue to reevaluate hospice care as an alternative to aggressive care that was now failing Mr. Smith. With palliative care referral early in his disease process, Mr. Smith would have education about the terminal nature of heart failure, many goals of care conversations and code status discussions, early information regarding hospice care and symptom management. This would have given him time to process his disease and empowered him to choose hospice care when he knew he was dying of his heart failure.

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Part IV

Heart Failure and the Management of Co-morbidities in Primary Care

Heart Failure has a strong association with multiple other comorbidities. Chapters 10 through 18 were designed to guide clinicians through complex decisions that are involved when heart failure patients have multiple chronic conditions. A case study is embedded in each chapter to highlight complexities. The chapters in this section do not include hypertension or depression. The treatment of hypertension in heart failure is patient-specific and usually addressed with the medications that are given for heart failure. Depression is common for heart failure patients and should be treated according to published guidelines for depression and practice site-specific protocols.

Atrial Fibrillation and Heart Failure

10

Tara U. Mudd

10.1 Introduction

In clinical practice, atrial fibrillation (AF) is the most common cardiac arrhythmia. By 2030, it is anticipated that the incidence and prevalence of AF will more than double, to 2.6 million and 12.1 million respectively [1]. Atrial fibrillation is a cardiac dysrhythmia that is characterized by abnormal electrical signals originating in the atria that fire rapidly with uncoordinated atrial activation and consequently, ineffective atrial contraction as no one single signal can depolarize the atria completely. As a result of the uncoordinated atrial activation, the ensuing ventricular response is characteristically irregularly irregular.

Atrial fibrillation and heart failure (HF) often occur in conjunction. The presence of one increases the likelihood of the other and each can be caused by the existence of the other [2]. This is the case in both heart failure with preserved ejection fraction (HFpEF) as well as reduced ejection fraction (HFrEF). Data from the original Framingham Heart Study examined over 10,000 individuals with new onset AF or HF between 1980 and 2012, and among 1737 individuals with new AF, 37% had HF [3]. Patients face greater mortality risk in the presence of both AF and HF compared with neither condition, particularly among those with HFrEF [3].

Atrial fibrillation is classified as paroxysmal, persistent (including early and longstanding persistent), or permanent. Paroxysmal AF includes those episodes that terminate spontaneously within 7 days. If AF is present for more than 7 days, it is termed persistent. Early persistent AF encompasses those episodes that last for more than 7 days but less than 3 months in duration. Longstanding persistent AF is continuous AF of more than 12 months. Finally, permanent AF is AF for which a decision has been

T. U. Mudd (✉)
Norton Heart & Vascular Institute Heart Rhythm Center AFib Clinic, Louisville, KY, USA
e-mail: tara.mudd.1@vanderbilt.edu

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_10

made by the patient and their provider not to pursue restoration of sinus rhythm by any means. “Chronic” AF is no longer used, as the disease state of AF itself is chronic.

The symptoms associated with atrial fibrillation can vary significantly from patient to patient. Many often report palpitations or the sensation of heart racing. Chest discomfort/pressure, dyspnea, edema, dizziness, lightheadedness, syncope, fatigue, and exertional intolerance are also common complaints. Many of these symptoms may also overlap with those related to their heart failure and it can often be difficult to determine if one or both of their comorbidities are responsible for their complaints.

10.2 Atrial Fibrillation-Induced Heart Failure

There are multiple ways in which AF can cause or worsen HF. Patients who have AF often have heart rates that are either too fast or too slow. Tachycardia and bradycardia, or other abrupt changes in the heart rate and rhythm, can potentially decrease cardiac output. Those who have persistent tachycardia related to their AF may develop tachycardia-induced cardiomyopathy [2]. Chronically elevated rates may produce significant structural changes in the heart including dilation of the left ventricle, marked reduction in left ventricular ejection fraction (LVEF), elevated filling pressures, and increased systemic vascular resistance [4, 5]. In most cases, LVEF returns to baseline once the tachycardia is controlled although in some cases LVEF may not return to baseline. In those who have preexisting cardiomyopathy, persistently elevated heart rates may cause further worsening of their cardiac function. The diagnosis of tachycardia-induced cardiomyopathy is typically made following the initiation of rate lowering therapy or restoration of normal sinus rhythm and then reevaluating the patient’s cardiac function [6]. It is also important to exclude other potential causes of cardiomyopathy such as ischemic heart disease.

As noted above, patients with AF have loss of atrial systole, also called atrial “kick.” Atrial systole promotes optimal ventricular filling. In the setting of diastolic heart failure, peak left ventricular filling occurs in late diastole and is more sensitive to the loss of effective atrial contraction. Finally, activation of neurohormonal vasoconstrictors, including angiotensin II and norepinephrine, can contribute to adverse hemodynamic changes. Some studies suggest angiotensin II is involved in the electrical and structural remodeling of the atrial myocardium [7, 8]. Structural remodeling of the atria includes fibrosis that perpetuates the development and maintenance of AF. Further, the presence of AF results in remodeling of the atrium over time, explaining the well-established concept that AF begets AF. The longer a patient has been in continuous AF, the less likely it is to terminate spontaneously and the harder it is to restore and maintain normal sinus rhythm [9].

10.3 Heart Failure Induced Atrial Fibrillation

The fibrillatory conduction throughout the atria is the result of various foci in the heart firing rapidly. The most common site of the rapid atrial firing that triggers AF is in the pulmonary veins (PV). When the atrium is stretched, as may be the case in those who present with volume overload and increased left atrial pressure, the likelihood of rapid firing from the PVs increases due to the stretch of sensitive ion channels [10]. Once AF has been induced, the patient will be more prone to have recurrent AF in the future, even in the absence of volume overload due to the electrical and structural remodeling of the atria as discussed above. Thus, the cyclical relationship between AF and HF begins [9].

10.4 Other Causes of Atrial Fibrillation

Aside from HF, there are other potential causes for AF. Non-modifiable risk factors include genetics, age, and sex. Several mutations have been identified that are responsible for familial AF, and those with a first degree relative with a history of AF have a 40% increased risk of developing it themselves [11].

A community-based cohort study in Olmstead County, Minnesota, found that the age-adjusted incidence of AF per 1000 person-years increased significantly between 1980 and 2000 from 4.4 to 5.4 in men and from 2.4 to 2.8 in women [12]. Screening for thyroid disease is also important in the patient with AF, particularly hyperthyroidism. Modifiable risk factors for AF include obesity, decreased physical activity, smoking, diabetes, sleep apnea, alcohol consumption, and hypertension [13]. Many of these are also independent risk factors for the development of HF [13].

Other cardiac abnormalities associated with AF include ischemic heart disease, mitral valve disease, hypertrophic cardiomyopathy, and dilated cardiomyopathy. Less often, you will find restrictive cardiomyopathies such as amyloidosis or constrictive pericarditis. Special attention should be paid to those with mitral valve disease. A stenotic or regurgitant mitral valve can cause left atrial enlargement and structural changes that perpetuate AF. The more severe the valvular insufficiency becomes, the more likely the patient will develop persistent and refractory AF [14].

10.5 Special Considerations

Patients with AF have a fivefold increase in stroke risk compared with those without AF, and special consideration must be given to these patients to prevent thromboembolic complications [15, 16]. Of those strokes that result from AF, 90% of them are due to a thrombus originating in the left atrial appendage. The use of the CHA_2DS_2-VASc score can assist in estimating thromboembolic risk in patients with AF to determine who would benefit from anticoagulant therapy [15, 16] (Fig. 10.1).

The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA_2DS_2-VASc

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74y	1
Sex **C**ategory (ie female gender)	1

LV = left ventricular; TE = thromboembolism.

Fig. 10.1 CHA_2DS_2-VASc scoring system (Reprinted from Chest, 137(2), Lip G et al., Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach, 263–272, 2010, with permission from Elsevier [16])

In adults with AF, thromboembolic risk is higher in females than in males, but female sex is associated with increased risk primarily in those with at least two non-sex risk factors [17, 18]:

- For CHA_2DS_2-VASc ≥ 2 in males or ≥3 in females (two or more non-sex risk factors), the benefit of oral anticoagulation (OAC) outweighs bleeding risk [15, 16, 19].
- For CHA_2DS_2-VASc 1 in males or 2 in females, the risk of thromboembolism varies depending on the non-sex risk factor. Age of 65–74 has the greatest effect on risk and use of OAC is recommended [15–17].
- For CHA_2DS_2-VASc score of 0 in males or 1 in females, the thromboembolic risk is low and OAC is not recommended [15–17].

In selecting anticoagulation, novel oral anticoagulants (NOACs: dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) [20].

It is also imperative to consider individual bleeding risk when making the decision to initiate anticoagulation. The HAS-BLED score was developed to estimate the 1-year risk for major bleeding (intracranial, hospitalization, hemoglobin decrease >2 g/L, and/or transfusion) [21, 22]. Patients with AF are divided into 3 risk stratifications. A score of 0 indicates low risk, 1–2 indicates moderate risk, and ≥3 indicates high risk [21, 22] (Fig. 10.2). Evaluating both the bleeding risk and the stroke risk is important to maximize appropriate anticoagulant therapy yet minimize adverse events resulting in net clinical benefit for the patient [21].

Clinical Characteristics Composing the HAS-BLED Bleeding Risk Score

Letter	Clinical Characteristic[a]	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1 or 2

HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly(> 65years), Drugs/alcohol concomitantly; INR = international normalized ratio.

Fig. 10.2 HAS-BLED bleeding risk score (Reprinted from Chest, 138(5), Pisters R et al., A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation, 1093–1100, 2010, with permission from Elsevier [21])

10.6 Treatment of Atrial Fibrillation and Heart Failure

For patients with AF, goals of therapy should include prevention of arterial thromboembolism (namely stroke), control of symptoms, and prevention of heart failure and/or hemodynamic compromise. Effective treatment and management of patients with atrial fibrillation and heart failure often require multidisciplinary collaboration between primary care and various subspecialties of cardiology, including but not limited to, electrophysiology, general cardiology, and advanced heart failure.

In a patient who presents with acute decompensation, initial strategy must focus on achieving euvolemia, preventing stroke/systemic embolism, and controlling the heart rate [23]. This may require admission for inpatient treatment depending on the severity of the decompensation. If the patient has HFpEF and they present with pulmonary congestion or hypotension, rate control can be attempted first with non-dihydropyridine calcium channel antagonists, including diltiazem or beta blockers. In those with HFrEF, digoxin or intravenous amiodarone (in an inpatient setting) may be used. Avoid use of beta blockers and nondihydropyridine calcium channel blockers until stabilization of the decompensated HF as their negative inotropic properties may worsen the clinical condition. In most cases, slowing the ventricular response in AF will improve the clinical status of the patient [23]. Cardioversion in the setting of acutely decompensated HF is not likely to be successful and should only be considered after attempts to rate control and/or decrease pulmonary congestion have failed [24]. Careful attention must also be paid to those patients who have not been adequately anticoagulated since these patients have an increased risk of embolization following cardioversion [25]. In these situations, a transesophageal echocardiogram is used to exclude thrombus in the left atrium/left atrial appendage [26].

Once the patient has been stabilized, attention can be turned to overall treatment goals of AF, specifically, rate versus rhythm control. If rate control is selected, goals

of therapy target adequate control of the heart rate while the patient remains in AF [27]. For patients who have HFpEF, calcium channel blockers may be more appropriate, while beta blockers and/or digoxin should be used in those with HFrEF [27]. Oral amiodarone can be used for rate control if other medications are not successful or other comorbidities prevent optimal titration as in hypotension [27]. Careful monitoring for long-term side effects of chronic amiodarone use is imperative and includes baseline, bi-annual, and annual monitoring for pulmonary, hepatic, thyroid, and ocular toxicity [28]. The guidelines for amiodarone surveillance include the following: (1) 12 lead electrocardiograms (ECG) at baseline and then only if symptoms and physical exam dictate, (2) Chest X-ray should be done at baseline and every 12 months (chest X-ray every 6 months is not needed if no pulmonary symptoms are present), (3) Pulmonary Function Testing with DLCO is needed at baseline and then only if abnormal findings are present on the annual chest X-ray or the patient is symptomatic, (4) Liver function testing (LFT) and Thyroid Stimulating Hormone (TSH) testing should be done at baseline, at 6 months, and every 12 months while patients are taking oral amiodarone. If the patient has any visual impairment an eye exam should be done at baseline and then again if visual changes arise [28]. In rhythm control, treatment strategies focus on maintenance of sinus rhythm often utilizing various medications, procedures (catheter and surgical based), and risk factor modification [29].

10.7 Heart Failure and Rhythm Control

Maintenance of sinus rhythm is preferred to AF for most patients with reduced EF. Rhythm control can be achieved with the use of antiarrhythmic drug therapy, catheter ablation, or surgical ablation [29]. Long-term maintenance of sinus rhythm is significantly influenced by how long the patient has been in AF, the size of the left atrium, and the patient's engagement in risk factor modification. The initial approach to rhythm control includes electrical cardioversion and choosing an appropriate antiarrhythmic drug [29]. For those with HFrEF, amiodarone, sotalol, or dofetilide is recommended [29]. Other antiarrhythmic medications, including propafenone, dronedarone, and flecainide, have been associated with poor outcomes in HF patients [29].

As in those patients with HFrEF, rhythm control is also preferred to rate control for most patients with HFpEF [30]. Those strategies mimic those noted above. However, in patients that have preserved ejection fraction, consideration can be made to use propafenone or flecainide as antiarrhythmic therapy as long as the patient does not have evidence of any ischemic heart disease [29]. In addition, use of nondihydropyridine calcium channel blockers may also be used to assist with rate control [31]. Digoxin is used more cautiously in HFpEF [31].

10.7.1 Antiarrhythmic Medications

Dofetilide has a favorable side effect profile and efficacy, but its use is limited due to strict guidelines for administration and dose adjustments based on renal function. It is typically initiated in a hospital to monitor the QT interval at peak dosing [29]. Sotalol also has a favorable side effect profile and can be used in those with mild renal dysfunction, but should be avoided in those with EF <30% [29]. In those with HF or a structurally abnormal heart, sotalol should also be initiated in an inpatient setting [29]. Amiodarone can be started in an outpatient setting and is appropriate to use in those with renal failure. It should be noted that amiodarone takes several weeks to reach therapeutic benefit and has the potential for significant long-term side effects [29]. In patients with more persistent AF, the use of both antiarrhythmic therapy and cardioversion is recommended, as medical therapy alone is unlikely to restore sinus rhythm [29] (Table 10.1). Due to the potential for significant short- and long-term side effects, initiation of antiarrhythmic therapy should be done in close consultation with a cardiology provider.

Table 10.1 Antiarrhythmic drugs for atrial fibrillation [29]

	Mechanism	ECG effects	Contraindications
Class 1c			
Flecainide	Blocks fast inward sodium channels	Prolongs PR and QRS	Ischemic or structural heart disease, sinus node dysfunction, 2nd or 3rd degree AV block or bundle branch disease without a pacemaker
Propafenone	Blocks fast inward sodium channels, mild beta blocker, and L-type channel blockade	Prolongs PR and QRS	Ischemic or structural heart disease, sinus node dysfunction, 2nd or 3rd degree AV block or bundle branch disease without a pacemaker potent CYP2D6 inhibitor or inducers
Class III			
Sotalol	Nonselectively antagonizes beta-1 and beta-2 adrenergic receptors and prolongs action potential phase 3	Prolongs QT intervals	Asthma, CrCl <40 mL/min, LV dysfunction; QTc >450 ms; sinus bradycardia <50 bpm, 2nd or 3rd degree AV block without pacemaker
Dofetilide	Prolongs action potential phase 3	Prolongs QT intervals	CrCl <40 mL/min; QTc >440 ms
Multichannel blockers			
Amiodarone	Inhibits sodium, potassium and long-lasting calcium channels and beta-adrenergic receptors	Prolongs PR, QRS, and QT intervals	Avoid in advanced pulmonary disease; severe hepatic impairment; thyroid dysfunction
Dronedarone	Inhibits sodium, potassium, and long-lasting type calcium channels and beta-adrenergic receptors	Prolongs PR, QRS, and QT intervals	Permanent atrial fibrillation, recent decompensated or advanced heart failure, QTc >500 ms; severe hepatic impairment

10.7.2 Catheter Ablation

In patients who continue to have symptomatic recurrent atrial fibrillation, or are intolerant of antiarrhythmic therapy, referral to a cardiac electrophysiologist is recommended for evaluation for catheter ablation (CA) [31]. Patients with heart failure have a high recurrence of AF and more frequently require repeat ablation procedures [31]. The catheter ablation versus standard conventional therapy in patients with left ventricular dysfunction and atrial fibrillation (CASTLE-AF) trial randomized 363 patients to CA or medical therapy. The participants had symptomatic paroxysmal or persistent AF, NYHA Class II, III, or IV HF; an LVEF ≤35%; failure or unwillingness to take antiarrhythmic therapy; and prior placement of an implantable cardioverter defibrillator (ICD). After a median follow-up of nearly 38 months, the primary composite end point of death from any cause or hospitalization for worsening HF occurred in fewer patients in the CA group and fewer patients in the CA group died from any cause. The AF burden (time in AF) was monitored using their ICD and was significantly lower in those having had CA versus medical therapy [32].

It is important to note that catheter ablation may be used in conjunction with antiarrhythmic therapy. The goal of CA in this subset of patients should be to reduce AF burden and improve HF-related symptoms which may require multiple treatment modalities [32].

10.8 Heart Failure and Rate Control

If rhythm control cannot be achieved and treatment goals focus on rate management, those patients with HFrEF should receive beta blockers as first-line therapy [31]. Initial choices of beta blocker can include carvedilol, extended-release metoprolol succinate, or bisoprolol [33]. Generally, it is recommended to optimize the dose prior to considering a second agent for the treatment of atrial fibrillation. Digoxin may also be used but may be less efficacious than beta blockers. Avoid use of nondihydropyridine calcium channel blockers such as verapamil or diltiazem. The adequacy of rate control in AF should be assessed in a resting state as well as typical exertion for the patient [34]. A heart rate goal of ≤80–90 beats/minute at rest and ≤110–115 beats during moderate exercise is advised [34].

If rate control with beta blockers and digoxin cannot be achieved, then it may be reasonable to consider the use of amiodarone, either alone or in combination with other rate lowering medications. Amiodarone should be avoided for chronic rate control due to its potential for long-term side effects [34].

Finally, if the above noted strategies fail or are contraindicated for the patient, rate control can be achieved with ablation of the atrioventricular node and subsequent permanent pacemaker placement [34]. If the LVEF is <45%, strong consideration should be made for cardiac resynchronization therapy with a biventricular or His bundle pacing system as opposed to the standard right ventricular pacing system [34].

10.9 Putting It All Together

10.9.1 Case Study

Jean is a 73-year-old female who presents for a routine wellness exam. Her past medical history includes hypertension, diastolic heart failure, hypothyroid, obstructive sleep apnea, and hyperlipidemia. Her current medications include Lisinopril 10 mg daily, furosemide 20 mg daily as needed for swelling, levothyroxine 75 mcg daily, and atorvastatin 10 mg daily. She has a CPAP for treatment of her sleep apnea and reports approximately 70% compliance with use. Past surgical history includes cholecystectomy 5 years ago. She is married and lives with her husband. She worked as a church secretary for 20 years and is now retired. She remains very active in her church and with her five grandchildren. She routinely walks one to two miles per day in the early mornings, 3–4 times per week. She has never smoked and does not drink alcohol. She consumes 2–3 caffeinated beverages per day, mainly coffee. Pertinent family history includes her mother who died of a stroke and a brother who has had myocardial infarction with coronary artery bypass grafting at the age of 67.

In the office, she notes that she largely has been feeling well but in the last 2–3 months, she has felt more tired than usual and has trouble keeping up with her grandchildren. She finds that she short-winded after completing her morning walks and has attributed this to "getting older." She has also noted that her ankles have a "sock ring" when she takes them off in the evenings. She has used her prn furosemide on a few occasions "if it gets really bad." She has good urine output when she takes this. Her last dose of furosemide was about 1 week ago. She denies any chest discomfort, paroxysmal nocturnal dyspnea, or orthopnea. She sometimes notes her heart rate is increased during periods of emotional stress or if she's "really pushing it" with activities. She has had no syncope or near syncope. She has been taking all of her medications as directed and without difficulties.

10.9.2 Objective

Height is 5′2″ and her weight is 160 lbs (BMI 29.26). Blood pressure is 128/72 mmHg and her pulse is 113. She is afebrile. Upon examination, she is noted to have an irregularly irregular rhythm and 1–2+ bilateral lower extremity edema. Other physical exam findings include: lungs = fine bibasilar rales; abdomen = no distention; neck = negative for thyromegaly or JVD; neurologic = normal coordination and gate. She had lab work done a week prior to her appointment which included a lipid panel, basic metabolic panel, TSH, free T4, and Vitamin D level. All were within acceptable range with the exception of TSH of 0.23 and free T4 of 2.5 An ECG is performed due to irregularly irregular rhythm noted and shows atrial fibrillation with rapid ventricular response. She had a previous echocardiogram 5 years prior as part of her clearance for cholecystectomy which showed left ventricular systolic function of 50–55%, grade I diastolic dysfunction, mild concentric left ventricular hypertrophy, mild left atrial enlargement, and trace to mild mitral regurgitation. She has never previously had an ischemic evaluation.

10.9.3 Assessment

Newly diagnosed atrial fibrillation with elevated rates and associated symptoms of fatigue, exertional dyspnea, and increased lower extremity edema for the last 2–3 months. She has evidence of fluid overload on exam concerning for exacerbation of diastolic heart failure versus declining left ventricular systolic function, but does not appear acutely decompensated. Contributing factors to atrial fibrillation include age, history of hypertension, history of diastolic heart failure, suboptimal treatment of obstructive sleep apnea, medication-induced hyperthyroid state, and possibly her family history. Her mother died due to complications from a stroke, which could have been caused by undiagnosed atrial fibrillation. She also has a first degree relative with ischemic heart disease.

10.9.4 Plan

Initial plans should include stroke risk reduction and improved rate control. Once achieved, attention should focus on rhythm management. Based upon her age, sex, and past medical history, her CHA_2DS_2-VASc score is 3 (Female; age 73, and history of hypertension) which warrants initiation of anticoagulation. She does not have any active contraindications to anticoagulation and apixaban 5mg BID will be initiated for stroke risk reduction. Dosing of apixaban based upon her age <80, body weight of >60 kg, and normal renal function. Due to concerns of worsening left ventricular dysfunction, selection of rate control medication should not include nondihydropyridine calcium channel blockers. Jean will be initiated on metoprolol succinate 50 mg once daily every evening. A common side effect of metoprolol succinate is somnolence and evening dosing may ameliorate those complaints and improve adherence.

Due to noted hyperthyroid state on pre-visit labs, levothyroxine dose will be lowered to 50 mcg twice daily with plans for repeat TSH and free T4 in 6 weeks.

She should return to the clinic in 1 week for follow-up and repeat ECG to evaluate effectiveness of rate control. If her rates are better controlled and she still exhibits lower extremity edema, consider initiation of low-dose diuretic therapy based upon proBNP result and blood pressure response to beta blocker initiation. If rates are not controlled, consider further titration of beta blocker or if patient is becoming hypotensive, initiate low dose of digoxin at 0.125mg daily and another 1 week follow-up for ECG and further lab work including BMP and digoxin level.

Once Jean is adequately rate controlled, obtain echocardiogram to evaluate left ventricular function and left atrial size. At this point, it would be appropriate to engage in co-management of the patient with cardiology.

After 4 weeks of therapeutic anticoagulation, proceed with cardioversion. If she becomes unstable during those four weeks, would proceed with transesophageal echocardiogram to rule out left atrial thrombus and proceed with cardioversion to sinus rhythm if no thrombus is found.

Considering female sex and complaints of exertional dyspnea and fatigue, as well as family history of ischemic heart disease, obtain a nuclear stress test to evaluate for ischemia once patient has returned to sinus rhythm. As she is an avid walker, exercise nuclear stress test would be recommended over pharmacologic stress test.

Her blood pressure is currently in an acceptable range but may lower with the addition of beta blocker therapy.

Due to increased risk of atrial fibrillation with untreated or suboptimal treated sleep apnea, she will follow up with her sleep medicine specialist for further titration and adjustment of her CPAP.

10.9.5 Clinical Pearls

Though her AF may be induced from her hyperthyroid state, the persistent nature of her atrial fibrillation likely initiated atrial remodeling and she will be significantly more prone to recurrent and more persistent AF in the future. Consideration should be made to referring her for more advanced therapies for her atrial fibrillation including initiation of antiarrhythmic drug therapy and catheter ablation.

Patients who present with newly diagnosed atrial fibrillation in the setting of heart failure exacerbation often require close monitoring and follow-up. While a thorough evaluation of risk factors is imperative to the long-term success of rhythm management, these conversations may be delayed to subsequent follow-ups once the patient is stable. It is helpful to provide the patient with education materials to review once they get home, as the quantity of material covered may be difficult to maintain. One strategy is to provide the patient with a simple one-page document outlining common modifiable risk factors for atrial fibrillation and what items require more focus (Fig. 10.3).

NORTON
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Risk Factors For Atrial Fibrillation	OK	Needs Work
Sleep Apnea *If you **have been** diagnosed with sleep apnea, it is very important that you use your sleep device, as prescribed by your sleep specialist, routinely. You should continue follow up with your sleep specialist at least once a year.* *If you **have not** been diagnosed with sleep apnea, but have symptoms suggestive of sleep apnea - as determined by your health care provider - it is important that you have a sleep study done to determine whether or not you have sleep apnea, and treat it if necessary.*		
High Blood Pressure *It is important to take your medications as prescribed by your physician. On **average**, you should keep your blood pressure below* **130/80.**		
Diabetes *It is important to keep your diabetes under very tight control. Whether your diabetes is managed by your primary care provider, or an endocrinologist, you should follow up with them at routine intervals to make sure your blood sugar is staying very well controlled. Your A1C should be less than 7%.*		
Body Mass Index (BMI) *Being overweight can increase your risk of afib. Your BMI is calculated using your height and weight. A normal BMI is between 18.5-24.9. A BMI between 25-29.9 is considered overweight. A BMI greater than 30 is considered obese. It is important to aim for a healthy weight. If necessary, we may refer you to our Norton Health & Wellness Center to assist you in achieving a healthy weight by changing your diet.* (**Your Current BMI is: _____**)		
Exercise *Maintaining an active lifestyle is a good way to decrease your risk of afib. Starting out, a good goal is __ minutes of low intensity (walking, water aerobics, etc.) __ times a week, gradually increasing the amount of time and number of days you are exercising. Ultimately, the American Heart Association recommends at least 150 minutes per week of moderate exercise. This can be 30 minutes a day, five days a week. You can even divide your time into two or three segments of 10-15 minutes per day.*		
Alcohol Intake *Men should have no more than 1-2 drinks/day and women no more than 1 drink/day. Some patients are sensitive to even the smallest amounts of alcohol, so your provider may recommend complete abstinence of alcohol.* **(1 drink = 1 can of beer, 5oz. wine, 1.5oz. shot of liquor)**		
Tobacco *If you use tobacco products (cigarettes, cigars, smokeless tobacco, etc.), we **STRONGLY** encourage you to stop completely. We have resources to help you quit. Stopping smoking is the single best thing you can do to improve your overall health.*		
Cholesterol *You should have your cholesterol checked at routine intervals. Generally, the guidelines for your cholesterol are: Total Cholesterol <200, LDL <130, HDL >50 (women) >40 (men), Triglycerides < 150. Your doctor may have more specific targets for you based on your risk factors for other medical problems.*		

Fig. 10.3 Example patient checklist to modify risk factors for atrial fibrillation. Used with permission

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Cardiorenal Syndrome, Chronic Kidney Disease, Anemia, and Heart Failure

11

Michelle Mason Parker and Mark Wigger

11.1 Cardiorenal Syndrome

11.1.1 Definition

Cardiorenal syndrome (CRS) was first formally defined in 2004 as the interaction between the renal and circulatory systems with fluid volume. Therapies used in the treatment of acute heart failure to reduce congestion are limited by decreasing renal function [1]. This definition has since evolved as it did not fully encompass the complex bidirectional relationship these two organs share. In 2008, the Acute Dialysis Quality Initiative used a consensus approach to further define CRS which was expanded upon by Ronco et al. into the 5 categories listed in Table 11.1 [2]. This current definition is based on the acuity of presentation and the originating organ of dysfunction wherein acute or chronic dysfunction in one organ causes acute or chronic dysfunction in the other organ as well as possible systemic disorders affecting both organs in Type 11.5 [3].

There is certainly some overlap between these 5 phenotypes which can make accurate identification more difficult, and common comorbidities such as hypertension, vascular disease, diabetes mellitus, and chronic inflammation can further complicate this clinical picture [4]. However, acknowledgment of the pathophysiologic interactions between the heart and kidneys can help promote the delivery of goal-directed therapies, such as the use of diuretics and renin-angiotensin-aldosterone system (RAAS) inhibitors. Modest fluctuations in serum creatinine with these

M. M. Parker (✉)
Vanderbilt Heart Outreach, Knoxville, TN, USA
e-mail: michelle.m.parker@vumc.org

M. Wigger
Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: mark.a.wigger@vumc.org

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_11

Table 11.1 Defining CRS based on the consensus conference of the acute dialysis quality initiative [2, 3]

Category of CRS	Definition
Type 1: Acute cardiorenal syndrome	Heart failure resulting in acute kidney injury
Type 2: Chronic cardiorenal syndrome	Heart failure resulting in chronic kidney disease
Type 3: Acute renal-cardiac syndrome	Acute kidney injury resulting in heart failure
Type 4: Chronic renal-cardiac syndrome	Chronic kidney disease resulting in heart failure
Type 5: Secondary cardiorenal syndrome	Systemic process resulting in both heart failure and kidney disease

therapies do not have the same negative impact on patient outcomes as true acute kidney injury and may not require medication discontinuation as often as once thought (see the section on treatment below).

The exact prevalence of each phenotype of CRS is difficult to estimate since most are treated on an outpatient basis where data is less readily available. CRS Type I is the most studied due to the frequency of hospitalizations in this subgroup. Approximately 40% of patients hospitalized from heart failure also have Type I CRS [4, 5]. At least 30% of all heart failure patients are thought to have moderate to severe renal impairment [6]. One analysis showed acute CRS (Type I and III) carries the highest risk of death [7]. Type IV CRS had better survival than either acute form.

11.1.2 Pathophysiology

There are several pathological mechanisms explaining the development of CRS including hypoperfusion, neurohormonal alterations, hemodynamic changes, and inflammation [4]. Hypoperfusion was the first of these to be explored but may not account for CRS as much as previously thought. In this theory, the reduced pumping function of the heart creates inadequate forward flow leading to prerenal hypoperfusion [4, 6]. The kidneys receive up to 25% of total cardiac output so heart failure can have a profound effect [6]. While this could play a role in some more advanced heart failure cases (patients with a cardiac index less than 1.5), patients with heart failure with preserved ejection fraction (HFpEF) and those with hypertension, not hypotension, have also been noted to have CRS Type I or II indicating low cardiac output is not the sole explanation [8]. Elevated intra-abdominal pressures from fluid retention can also cause renal compression and reduced perfusion leading to decreased GFR which may explain why CRS can be seen in those with and without reduced cardiac output [9, 10].

The relationship of neurohormonal feedback likely plays a larger role in CRS wherein decompensated heart failure leads to elevated renal venous pressures related to increased fluid volume [11], which leads to RAAS activation which causes preglomerular vasoconstriction and further neurohormonal activation. The activation of the

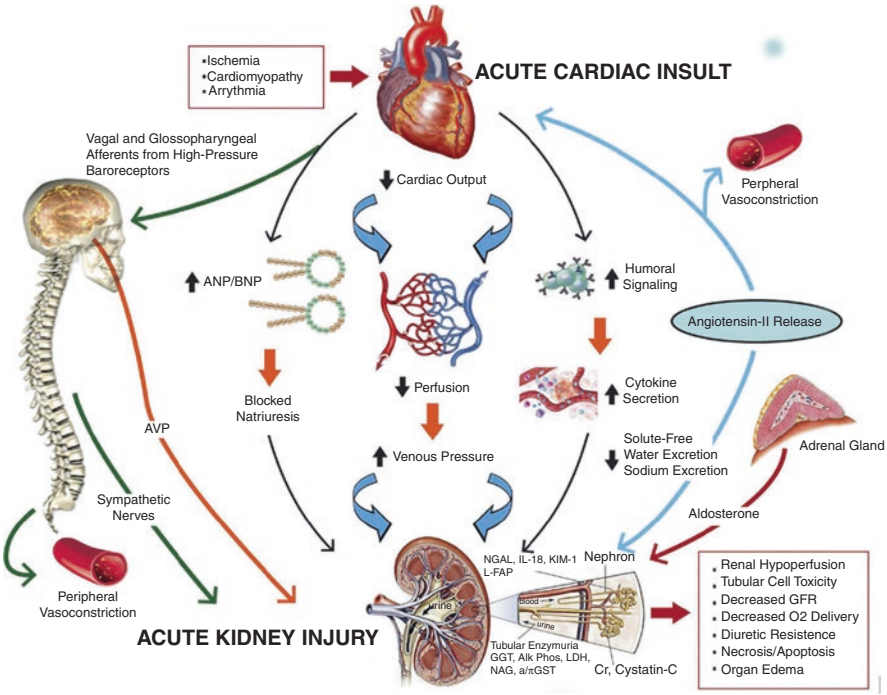

Fig. 11.1 Pathophysiology of neurohumoral and inflammatory pathways involved in cardiorenal syndrome (Reprinted from Seminars in Nephrology 31 (1), Ismail et al., Cardio-renal syndrome type 1: epidemiology, pathophysiology, and treatment, 18-25, 2012 with permission from Elsevier [12]). HAS-BLED bleeding risk score (Reprinted from Chest, 138(5), Pisters R et al., A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation, 1093–1100, 2010, with permission from Elsevier [13])

neurohormonal axis results in increased proximal tubular sodium and water reabsorption resulting in both oliguria and worsening congestion (see Fig. 11.1). This also leads to increased reabsorption of urea leading to a rise in BUN disproportionate to creatinine levels which is further discussed in the biomarker section below [6].

Hemodynamic alterations are associated with CRS as well. Right atrial (RA) pressure is increased with baseline renal dysfunction; however, increased central venous pressure (CVP) has also been associated with transient decreases in glomerular filtration rate (GFR) indicating that increased circulating fluid volume leads to temporarily decreased renal function in those with or without prior renal dysfunction [10, 14].

Persistent RAAS activation is also associated with increased inflammatory markers. This mechanism is associated with Type III and IV CRS wherein increased tumor necrosis factor-alpha, interleukin-1, and interleukin-6, which are elevated in acute kidney injury, can cause cardio-depressant effects such as a reduction in left ventricular ejection fraction (LVEF) [4]. Type IV CRS, also called uremic cardiomyopathy, is

related to fibroblast growth factor-23 (FGF-23) [15]. FGF-23 causes LV hypertrophy leading to reduced capillary density, microvascular ischemia, and heart failure. Figure 11.1 illustrates how the above mechanisms can all work together in creating dual-organ dysfunction while originating from different sources [12].

11.1.3 Differential Diagnosis

Diagnosis and proper classification of CRS require in-depth clinical knowledge as well as a general understanding of both heart failure and renal insufficiency. Obtaining a detailed patient history and review of symptoms is paramount to know if the patient is in heart failure (refer to Chap. 3) and then CRS should be considered based on the testing below. Without thorough patient assessment, CRS can mimic or even simultaneously occur with acute kidney injury (AKI) or chronic kidney disease (CKD), the latter of which will be discussed in a section later in the chapter. This confusion can lead to inadequate medical therapy when basing treatment decisions on lab values alone.

AKI is defined as having a change in serum creatinine of 0.3 mg/dl or higher [16]. Other staging and classifications such as RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) have been created to help further stage severity of AKI based on creatinine and urinary output (UOP) as shown in Table 11.2 [12]. AKI is associated with "an abrupt (within hours) decrease in kidney

Table 11.2 Acute kidney injury classification/staging. (Reprinted from Clinical Biochemist Reviews, 37(2) Makris & Spanou, Acute kidney injury: Definition, pathophysiology, and clinical phenotypes, 85–98, 2016 with permission from the Editor of Clinical Biochemist Reviews [16])

RIFLE criteria for classification/staging AKI			AKIN criteria for classification/staging AKI		
Stage	GFR criteria	Urine output criteria	Stage	Serum creatinine criteria	Urine output criteria
Risk	1.5-fold increase in sCr or >25% decrease in GFR	UO <0.5 mL/kg/h for 6 h	Stage 1	Absolute increase in sCr ≥0.3 mg/dL (≥26.5 μmol/L) or ≥1.5 to 2.0-fold from baseline	UO <0.5 mL/kg/h for 6 h
Injury	2.0-fold increase in sCr or >50% decrease in GFR	UO <0.5 mL/kg/h for 12 h	Stage 2	Increase in sCR >2.0 to 3.0-fold from baseline	UO <0.5 mL/kg/h for 12 h
Failure	3.0-fold increase in sCr or >75% decrease in GFR or sCr >4.0 mg/dL with an acute increase of 0.5 mg/dL	UO <0.3 mL/kg/h for 24 h or anuria for 12 h	Stage 3	Increase in sCr > threefold from baseline or increase of sCr to ≥4.0 mg/dL (≥354 μmol/L) with an acute increase of at least 0.5 mg/dL (44 μmol/L)	UO <0.3 mL/kg/h for 24 h or anuria for 12 h
Loss	Complete loss of kidney function for >4 weeks				
ESKD	End-stage kidney disease for >3 months				

function which encompasses both injury (structural damage) and impairment (loss of function)." These abrupt changes can also occur with CRS which should be considered in patients with heart failure.

11.2 Diagnostic Tools

11.2.1 Biomarkers

Diagnostic testing including cardiac and renal biomarkers and other imaging can help diagnose CRS and distinguish between it and primary renal disease. Cardiac biomarkers commonly used in the assessment of heart failure and CRS include troponin, a measure of cardiac injury, and brain natriuretic peptide (BNP), a measure of wall tension [4]. Troponin elevation is associated with an increased risk of heart failure death in both patients with and without ischemia [17]. It is commonly used in acute/emergency medicine or inpatient evaluation, but troponin can be useful in some outpatient situations as well. Assessment of BNP has a Class 1A recommendation based on current heart failure guidelines for assessment or diagnosis of heart failure. N-terminal pro-B-type natriuretic peptides (NT pro-BNP) are an inactive protein cleaved off BNP and necessary for evaluation of wall tension/heart failure in patients receiving drug therapy with neprilysin inhibitors such as sacubitril-valsartan, because the drug leads to rising BNP levels for several weeks after initiation leading to inconsistent results [18]. NT pro-BNP is not affected by sacubitril and is therefore more reliable for comparison. It is important to note that both BNP and NT pro-BNP are often elevated at baseline in patients with CKD due to primary renal excretion which can further complicate this clinical picture [18]. Cystatin C may also be beneficial in evaluating CRS and can be useful in predicting cardiac mortality; however, this cardiac and renal biomarker is less used in clinical practice currently [4].

Renal biomarkers associated with CRS include serum creatinine, blood urea nitrogen (BUN), and glomerular filtration rate (GFR). Serum creatinine is sensitive and varies vastly with age, gender, muscle mass, medication usage, and hydration [16]. Serum creatinine does not mark true tubular damage; instead, it reflects GFR. The GFR is a more consistent measurement when weight and age are taken into consideration but is less useful with acute fluctuations in renal function. Therefore, creatinine is considered the "imperfect gold standard" for routine monitoring of renal function [16]. Availability of a patient's baseline creatinine is key to interpretation [19]. BUN is a marker of prerenal azotemia and can be disproportionately elevated in CRS and corresponds with increased mortality of heart failure that is independent of creatinine or GFR [4, 6, 13]. Ngal is a biomarker currently used in Europe to help distinguish between CRS and AKI but is not commonly used in the United States as of 2019 [4]. Urinalysis (UA) is also beneficial since a dipstick for blood or protein suggests underlying primary renal disease. Increased urine albuminuria is a known sign of glomerular and tubular damage [20]. Most often, a UA will be unrevealing in type I and II CRS without underlying renal dysfunction with a few rare exceptions [6].

11.2.2 Imaging

Other diagnostic imaging is useful in the diagnosis of CRS. An echocardiogram is a noninvasive and frequently used tool for assessing overall cardiac function and can also provide insightful findings on physiological changes associated with congestion. Dilated inferior vena cava is a good indicator of fluid volume overload [21]. With E' related to mitral inflow velocity, E directly correlates with pulmonary capillary wedge pressure (PCWP) in which an E'/E ratio greater than 15 is associated with a PCWP greater than or equal to 18 [22] also indicating increased volume. Decreased ejection fraction, increased pulmonary artery pressure, and increased right ventricle diameter are all independently associated with an increased incidence of CRS [4]. Global longitudinal strain (GLS) has also been shown useful in predicting mortality in patients with CKD even with preserved EF [23].

Renal Ultrasound (US) is a necessary tool for the evaluation of renal insufficiency and can also lend clues helpful to diagnosing CRS. It can help determine the chronicity of CRS based on renal size, echogenicity, and cortical thickness [24]. Small kidneys are often indicative of underlying renal dysfunction as opposed to CRS alone [6]. One study showed discontinuous renal flow patterns plus increased right atrial pressure are indicative of CRS and had the poorest 1-year prognosis [25]. This renal congestion is also associated with decreased diuretic efficiency [26] which will be discussed more under the treatment section later in this chapter.

Cardiac MRI is considered the gold standard for cardiac structural assessment and evaluation of ventricular function in general. In Type IV CRS, myocardial fibrosis is associated with increased diffuse late gadolinium enhancement which may serve as a warning sign for heart failure outcomes in the patient with CKD [27].

11.3 Treatment

Unfortunately, no specific therapy exists to correct CRS or independently increase GFR; however, correction of the underlying condition has been shown to improve outcomes, i.e., improvement of cardiac function can lead to improvement in GFR in patients with Type I and II CRS, much like improvement in renal function can improve cardiac function in Type III and IV CRS [27]. Therefore, the use of guideline-directed medical therapy for heart failure should be continued in most cases, despite down-trending renal biomarkers, to give the patient the best chance for cardiac recovery and survival (see medication consideration section below).

11.3.1 Diuretics

Management of fluid overload is the primary treatment for mitigating the vicious cycle of CRS. Over 90% of patients with acute heart failure require diuretics [4]. While studies have never been able to prove a true mortality benefit to diuretic use in patients with heart failure via a randomized controlled trial, a Class Ia recommendation endorses the use of loop diuretics for immediate relief of heart failure

symptoms based on expert opinion [17]. Even though a rising creatinine can be associated with loop diuretic use and rising creatinine is also associated with worse clinical outcomes, recent studies such as the ESCAPE trial prove that a rise in creatinine due to heart failure treatment did not result in reduced outcomes so long as it resulted in a resolution of congestion [28, 29]. This is referred to as a functional increase in creatinine. Furthermore, elevated renal biomarkers should not deter diuretic use when clinical congestion is present [28]. Despite the initial rise in creatinine, many patients will return to baseline after decongestion, and some may even improve beyond their baseline due to decreased intra-abdominal pressure and decreased RV dilation as previously discussed in the pathophysiology section.

11.3.2 Diuretic Resistance

Unfortunately, heart failure patients with and without underlying renal dysfunction may struggle with diuretic resistance, defined as a lack of responsiveness to therapy. However, it is generally true that the higher the renal insufficiency, the higher the diuretic dose needed to create a response. This can be caused by several reasons in CRS. First, intestinal absorption of loop diuretics is decreased with abdominal edema [30]. This is true with one of the most commonly used loop diuretics in heart failure, Furosemide. Furosemide absorption varies significantly from one patient to another with average bioavailability of only about 50% [31]. Other oral loop diuretics such as bumetanide and torsemide average closer to 90% absorption which leads to a more predictable response [30]. Other causes of diuretic resistance include decreased diuretic delivery to kidneys due to decreased renal blood flow and increased sodium reabsorption from RAAS activation and/or dietary indiscretion with high sodium intake [4]. Below is a list of helpful tips for increasing diuretic response in patients with resistance (see Table 11.3).

It is important to understand that the diuretic threshold must be broken to elicit a response. This may require a dose increase or temporary use of IV diuretics to

Table 11.3 Tips for overcoming diuretic resistance [21, 30]

• Increase loop diuretic dose by 50–100%
• Change furosemide to bumetanide or torsemide (see Chap. 19 for more information)
• Make sure the patient is on an aldosterone antagonist as part of GDMT
• Advise patient to adhere to a low-sodium diet
• Add a thiazide-like diuretic such as metolazone before loop diuretic dose administration to inhibit sodium reabsorption in the distal tubule (watch for electrolyte abnormalities including hypokalemia)
• Supine position following diuretic administration may be helpful
• Consider heart failure program referral for frequent dose adjustment, lab monitoring, and/or advanced fluid monitoring device implant such as Cardiomems to guide therapy
• Discourage NSAID use as this can counteract diuretic effectiveness
• Consider ER or admission for intravenous diuretic administration
• Remember it is good practice to recheck electrolytes in 1 week following diuretic adjustments

achieve, but diuretic resistance is usually reversible with the correct strategy [21]. Note that increasing the frequency of diuretic dosing is only helpful once an effective dose is identified. For example, if 20 mg of furosemide does not increase UOP, increase it to 40 mg instead of 20 mg twice daily [30].

11.4 Chronic Kidney Disease and Heart Failure

11.4.1 Definitions and Staging of CKD

Underlying chronic kidney disease (CKD) creates a different patient scenario than CRS Type I and II. CKD involves a gradual loss of kidney function and loss of glomerular filtration ability which is graded based on glomerular filtration rate and the presence of disease. The stages of chronic kidney disease are outlined below (Fig. 11.2). Other factors for diagnosis include the presence of albuminuria, urine sedimentation, or structural abnormalities for greater than 3 months [32].

11.4.2 Prevalence with Heart Failure

Heart failure and CKD are commonly found in conjunction with one another. With each stage of CKD, the prevalence of heart failure also increases [32]. An estimated 44% of patients undergoing hemodialysis (HD) have comorbid heart failure. As the stage of CKD progresses, the mortality risk also increases for both patients with HFpEF and HFrEF [32].

11.4.3 Prevention of Heart Failure in a Patient with CKD

Uncontrolled hypertension and diabetes mellitus are both considered risk factors for both CKD and heart failure. House et al. [32] demonstrated that tight blood pressure control, defined as a systolic blood pressure less than 120, in patients with CKD may help prevent new-onset heart failure. In the RENAAL (Reduction of Endpoints

Fig. 11.2 Stages of chronic kidney disease [32]

in Non-insulin dependent diabetes with Angiotensin II Antagonist Losartan) trial, a relative risk reduction (RRR) of 32% was observed in first heart failure hospitalization [33]. Poor glycemic control in CKD was found to be an independent risk factor for the development of heart failure [32]. SGLT2 inhibitors have shown to have a class effect in slowing the progression of CKD and reducing the risk of hospitalization in those with and without prior history of heart failure [34] as seen in the Empa-Reg Outcome trial with a 39% RRR for heart failure hospitalization [35].

11.5 Medication Limitations with CKD and Heart Failure

Although CKD and heart failure frequently coincide, patients with both conditions are less likely to receive GDMT for heart failure due to concerns of hypotension, kidney function, and hyperkalemia [32]. Unfortunately, since most study criteria for commonly used medications have excluded patients with a creatinine of 2.5 or higher, there is limited evidence to support the use or discontinuation of GDMT in this patient population [4]. However, most drug classes show continued benefits up to stage IV CKD. See considerations for each of the four main heart failure therapy classes below.

11.5.1 Beta Blockers

Beta blockers may be the best studied for heart failure GDMT with CKD. At least three clinical trials with a good population of patients with CKD showed a mortality benefit with the use of metoprolol, bisoprolol, and to a smaller extent carvedilol [32]. Atenolol, nadolol, and sotalol are excreted by the kidneys and have not proven to have mortality benefits with heart failure, so these drugs would not be preferred for either patient population. It should be noted that metoprolol is somewhat dialyzable, and consideration may be given to dose timing based on the dialysis schedule.

11.5.2 RAAS-Altering Medications

Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin II Receptor Blockers (ARBs), and Angiotensin Receptor-Neprilysin Inhibitors (ARNIs) are known to be underutilized, under-prescribed, and underdosed in the CKD population [20]. These medications may help slow the development of kidney disease with accompanying proteinuria, but frequently cause an acute rise in creatinine that may lead to dose reduction or even drug discontinuation in patients with CKD. Benefits of using ACE/ARBs in patients with CKD were noted in the CONSENSUS trial which showed a decreased mortality and decreased symptoms of heart failure despite a doubling of creatinine in 11% of subjects [36]. In the majority of these subjects, the creatinine returned to 30% of baseline which is consistent with other trials in the HFrEF population [4]. The benefit of RAAS inhibition did not outweigh the risk,

however, in the HFpEF population with CKD [32]. The only available ARNI, sacubitril/valsartan, has been studied the least in heart failure with CKD, and available data is mixed. In a small sample size, it showed preservation of GFR but also an increase in albuminuria compared to valsartan alone [32].

Close monitoring is recommended with consistent use of ACE/ARB/ARNIs, especially with CKD. A basic metabolic panel should be drawn at baseline and repeated 1–2 weeks later following initiation and titration of dose and then every 3–6 months based on current guidelines [37]. If creatinine increases over 50% of baseline or is over 3.0, GFR is less than 25, or potassium is over 5.5, it is recommended to reduce the dose by 50% and repeat labs in 1 week. Consideration should be given to other causes of worsening renal function including over-diuresis or intrinsic kidney disease. If ACE/ARB/ARNI cannot be tolerated due to worsening renal function, combination therapy with hydralazine and isosorbide dinitrate may be used, although this is more beneficial in African American population as opposed to other ethnicities [38]. Keep in mind that azotemia alone in the setting of diuresis should not lead to a dose decrease or withdrawal of ACE/ARB/ARNI as this can lead to worsening heart failure outcomes [32].

11.5.3 Mineralocorticoid Receptor Antagonists (MRAs)

Mineralocorticoid receptor antagonists, also termed aldosterone antagonists, although known to be generally well tolerated in stages I-III CKD, are another class of heart failure therapy that has not been well studied in CKD stages IV and V [32]. The RALES (Randomized Aldactone Evaluation Study) study set criteria as EF less than 35%, creatinine less than or equal to 2.5, and potassium less than or equal to 5.0 and revealed similar benefits to mortality reduction in groups with GFR less than 60 as GFR greater than 60. However, the population with GFR less than 60 saw a higher incidence of hyperkalemia, reduction of GFR by 30% or more, dose reduction, or drug discontinuation [32, 39]. Continuing studies are underway to evaluate the safety and effectiveness of MRA use in patients undergoing HD [32]. Monitoring of BMP after 1 week and every 3–6 months is the typical practice for stable patients.

11.5.4 Sodium-Glucose Cotransporter 2 (SLGT2) Inhibitors

Sodium-glucose cotransporter 2 (SLGT2) inhibitors, created as glucose-lowering drugs for type II diabetes mellitus, have demonstrated benefits for both HFpEF and HFrEF. These medications have been added to guidelines as a recommended therapy for HFrEF as of 2021 for patients with and without diabetes [17]. Unlike some of the other heart failure therapies mentioned in the sections above, studies have paid particular attention to renal outcomes for patients with CKD and the results are promising. SLGT2 inhibitors are not only safe for all stages of CKD but also slow the progression of CKD [20]. An acute fall in GFR is often noted initially in the first 2 weeks of therapy followed by stabilization with decreased risk that the patient will reach ESRD, indicating a renal protective mechanism is at work.

11.6 Ultrafiltration and Dialysis with Heart Failure

Patients undergoing dialysis for ESRD, both with and without heart failure, are at high risk for frequent fluid and potassium fluctuation. Ultrafiltration is the process of fluid removal during dialysis sessions [40]. The amount of fluid withdrawn is dependent on the rate of filtration, length of sessions, and frequency of sessions. For patients with heart failure, increased frequency of dialysis sessions, such as short daily sessions, has been shown to decrease LV mass and lower the risk of cardiovascular death and hospitalization [32]. Particular benefit has been seen in patients who undergo home hemodialysis which can be both scheduled and as needed/PRN. A 41% decrease in heart failure, cardiomyopathy, fluid overload, and hospitalizations has been seen in this group [32, 41]. Limited data is available to determine the best practice between peritoneal dialysis and in-clinic hemodialysis in this patient population. Studies for using ultrafiltration for fluid removal in non-dialysis heart failure patients have not consistently demonstrated benefit compared to diuretics, nor is it considered to be more renal protective [20].

11.7 Renal Transplant Considerations for Heart Failure

Patients undergoing renal transplant have approximately an 18% chance of developing heart failure in the next 3 years [32]. Heart failure therapy in this population has not been thoroughly studied; however, one trial showed that lisinopril in renal transplant recipients with heart failure decreased LV mass index. Despite limited data available in this unique population, standard GDMT including loop diuretics should not be withheld. For patients with heart failure before renal transplant, outcomes are mixed. There is an increased risk of mortality and graft rejection of the new organ with prior heart failure, but some types of heart failure including uremic cardiomyopathy may significantly improve post-transplant. Patients may also be a candidate for dual-organ (heart and kidney) transplant in those who have end-stage disease of both organs [32, 42].

11.8 Hyperkalemia in CKD and Heart Failure

Hyperkalemia is a frequent complication of CKD and one of the most common reasons for de-escalation or discontinuation of RAAS inhibitors and MRAs as mentioned above which leads to worsening heart failure outcomes. Patiromer [32, 43] and zirconium cyclosilicate [32, 44] have been shown to lower potassium and prevent hyperkalemia when taken daily. Further data is needed to prove whether this will improve GDMT utilization in heart failure, but this may be a strategy to consider for some patients.

11.9 Anemia, Heart Failure, and CKD Considerations

11.9.1 Incidence and Associations

Anemia, heart failure, and CKD are heavily intertwined conditions. The risk of developing anemia increases with both heart failure and CKD. For heart failure, the incidence of anemia goes up with each New York Heart Association (NYHA) functional class, seeing an average of 9% anemia in NYHA Class I and up to 79% in NYHA Class IV [45]. Anemia incidence increases as GFR decreases in CKD [46]. While anemia is only rarely the cause of heart failure directly, it has been shown to worsen outcomes including hospitalizations and mortality. Anemia also increases the risk of developing heart failure in patients with CKD [45].

11.9.2 Pathophysiology of Anemia in Heart Failure

Several mechanisms are suspected to cause anemia with heart failure. First, increased circulating cytokines with heart failure may lead to anemia of inflammation/anemia of chronic disease [45]. Increased plasma volume seen in heart failure may also create dilutional anemia which can be corrected and fluctuates with diuresis. ACE inhibitors have been shown to decrease erythropoiesis in the SOLVD trial which may cause or worsen anemia [47]. CKD and CRS are both known causes of anemia due to erythropoietin production seen with reduced kidney function [45]. Additionally, iron deficiency anemia is found in both the CKD and heart failure populations.

11.9.3 Diagnosis

Common anemia symptoms of dyspnea and fatigue may be mistaken as symptoms of heart failure, which is one of the reasons laboratory screenings are important to detect and diagnose anemia. Complete blood counts with differential, iron studies including serum iron, transferrin, iron saturation, ferritin, creatinine, C-reactive protein, erythrocyte sedimentation rate, serum B12, and folate levels should be drawn at baseline heart failure or CKD diagnosis, and anytime anemia is suspected [45]. Gastrointestinal blood loss should always be ruled out. Identification of the cause of anemia is key to treatment, especially when iron deficiency is suspected. If the cause cannot be identified based on lab results, a hematology referral should be considered.

11.9.4 Iron Replacement

Iron replacement is indicated in anemia with heart failure or CKD when hemoglobin is less than 10 and iron saturation is less than 20%, or ferritin is less than 41 [45, 46]. Ferritin may be sustained in patients with heart failure and can be misleading if

assessed independently of other labs [45]. Several large studies including a meta-analysis in 2019 showed that intravenous (IV) iron replacement decreased heart failure hospitalizations, improved NYHA class and 6-minute walk tests, improved ejection fraction, and lowered BNP and CRP levels in heart failure patients and should be used for saturation less than 17% [45]. Although no randomized controlled trials have compared oral iron supplementation with IV iron replacement, experts recommend the use of IV iron due to better absorption and more efficient correction of iron levels in heart failure patients [45]. Erythropoietin stimulating agents (ESAs) and blood transfusion may be used in severe anemia that does not respond to iron infusion. ESAs are contraindicated in patients with a history of stroke, thromboembolic events, and malignancy [45].

11.10 Conclusion

Cardiorenal syndrome and chronic renal failure in the setting of heart failure, often complicated by anemia, create two different patient profiles with separate considerations for each; however, the overlap is hard not to see. Careful focus on underlying etiology is important to correct management and improve patient outcomes. Primary care providers are key to reducing and identifying risk factors, initiating GDMT, providing patient support, follow up on labs and other testing, and communicating among specialty services. The two case studies below identify two different patients who will likely enter the primary care clinic; will you be able to tell them apart?

Case Study 1: Cardiorenal Syndrome Type II and Diuretic Resistance

Subjective: Ms. Jones is a 68 year-old female with the following past medical history/problem list: Heart failure with reduced ejection fraction, NYHA Class II; status post-ICD implant for primary prevention of sudden cardiac death; dilated, ischemic cardiomyopathy; coronary artery disease, status post-coronary artery bypass grafting >10 years ago; hypertension; diabetes mellitus, type 2.

Family history: Coronary artery disease in her father and paternal grandmother.

Social history: She lives at home with her husband. They have three grown children. Homemaker. Denies alcohol, tobacco, and illicit drug use.

Medications: Carvedilol 3.125 mg BID; Sacubitril/Valsartan 24/26 mg BID; Spironolactone 25 mg daily; Furosemide 80 mg BID; Metformin 1000 mg BID; Aspirin 81 mg daily; Atorvastatin 80 mg QHS.

Allergies: NKDA.

Case Scenario

Chief complaint: The patient called requesting an appointment due to worsening shortness of breath and her "fluid pill not working anymore."

HPI: Ms. Smith returns for episodic visit complaining of increased shortness of breath with mild activity, 11 lb weight gain in 1 week, and lower extremity edema. She has recently returned from a vacation with her grandchildren where she admits she did not watch her sodium intake and ate out almost every day. She states, "I've been taking my furosemide, but it just doesn't seem to be working as well as it used to." She normally limits sodium intake to 2 g daily and fluid intake to 2 l daily and reports taking all medications as prescribed. She admits to bloating, early satiety, 3-pillow orthopnea, and less than expected urinary output. She denies any recent ER visits, hospitalizations, chest pain, or palpitations. No fever, dark or foul-smelling urine, frequency, urgency, frank hematuria, or hesitation.

Objective

Vital signs: BP 102/65; HR 89; oxygen saturation 97% on room air; Temp 98.2°. Weight 172 lbs (last recorded office weight was 161 lbs)

Physical exam: JVD 10 cm. Normal S, S2 without S3 or murmur. Normal work of breathing at rest. Lung sounds decreased in bilateral bases. Abdomen distended but still soft and non-tender. 1 + bilateral lower extremity pitting edema to mid-calves

Labs

Today—Sodium 134; Potassium 4.6; BUN 32; Creatinine 1.8; Pro BNP 3560

2 months ago—Sodium 137; Potassium 3.9; BUN 22; Creatinine 1.2; Pro BNP 540

Diagnostics

The most recent echo 2 months ago showed a stable EF of 35%.

Assessment

Ms. Jones is having a mild acute chronic heart failure exacerbation with NYHA Class III symptoms complicated by an acute decrease in renal function with a rise from baseline creatinine from 1.2 to now 1.8 over the last 2 months. Her pro-BNP is also elevated much higher than baseline. On exam, she appears to have increased abdominal pressure and congestion which is likely causing diuretic resistance to her furosemide and associated lab fluctuations.

Plan

Change furosemide 80 mg BID to bumetanide 4 mg in the morning and 2 mg in the afternoon for the next week starting today. Repeat visit with BMP in 5–7 days. Call in 1–2 days if urinary output does not increase with medication change or if shortness of breath or swelling continues to worsen.

Check weight daily upon waking after emptying the bladder and before eating or drinking. Call for further weight gain of 2 lbs overnight or weight loss greater than 10 lbs in 1 week.

Resume a low sodium diet and reduce fluid intake to 1.5 L/day until symptoms improve.

Return to the clinic for a recheck of symptoms in about 1 week. Would consider the addition of an SGLT2 inhibitor at the next visit for heart failure, diabetes, and renal protective benefits and decrease bumetanide to 2 mg BID (once the goal is reached) with an additional 2 mg PRN for a weight gain of 2 lbs overnight or 5 lbs in 1 week.

Clinical Pearls

- Although this patient is experiencing acute symptoms of both cardiac and renal symptoms, she does not need to be treated as an inpatient or go to ER for IV diuretics unless oral medications do not help or symptoms worsen.
- Changing furosemide to bumetanide should improve diuretic resistance and drug absorption. Increasing the dose temporarily will also be beneficial.
- SGLT2 inhibitor benefits heart failure, diabetes, and renal function.
- Lab monitoring expectations—creatinine will likely rise slightly at the next visit from increased diuretic use, but symptoms and BNP should improve. Renal function will then return to baseline over the next few weeks. Would trend labs every 2 weeks. If creatinine does not return to baseline in the next 1–2 months would consider a nephrology referral.
- Monitor NT pro-BNP while taking sacubitril/valsartan.

Case Study 2: The Complex Interaction of CKD, HF, and Anemia

Subjective: Mr. Greene is a 55 year-old male with a past medical history/problem list: poorly controlled hypertension 20+ years; microscopic hematuria 10 years; nephrolithiasis; depression, obesity

Family history: Hypertension

Social history: Tool and dye maker. Divorced with 2 grown children. Denies current alcohol, tobacco, and illicit drug use. History of 1 ppd smoker for 30 years.

Medications: Lisinopril 20 mg daily, amlodipine 5 mg daily, hydrochlorothiazide 25 mg daily, sertraline 20 mg daily

Allergies: NKDA

Case Scenario

Chief complaint: Increased shortness of breath, swelling in ankles, and a metallic taste in the mouth for 2 months.

HPI: Since his last visit 9 months ago, the patient has noticed shortness of breath with walking short distances, swelling in the ankles, and a metallic taste in the mouth for about 2 months. He has checked his BP at home a couple of times and says it averages 150s/90s. He has also noted weight gain of about 15 lbs, bloating, and poor appetite. He states, "I just feel so tired all the time now." He denies any missed doses of medications, lightheadedness, chest pain, or palpitations. No recent illness or hospitalizations.

Objective

Vital signs: BP 145/100; HR 102; oxygen saturation 96% on room air; Temp 98.0°. Weight 258 lbs

Physical exam: JVP elevated 12 cm; displaced apical beat (mid-axillary line); loud S3; lung fields clear, dull at both bases; liver edge 6 cm below costal margin; No ascites; 2+ Ankle edema

Labs: Serum creatinine 2.8 mg/dl; BUN 30; eGFR 26%; Potassium 4.0; Total CO_2 28; Hemoglobin 10.3; (add diff showing anemia). Total cholesterol 216, LDL 146, triglycerides 362; fasting glucose 122; Albumin-creatinine ratio >300; Urinalysis 3+ protein, 5–10 rbc, No rbc cast–trace granular cast

No prior labs for comparison in the last 12 months.

Assessment: This patient has labs indicative of chronic renal insufficiency and anemia. He also has signs and symptoms of new-onset heart failure.

Plan: The patient needs an echocardiogram to better assess for LV dysfunction and referral to cardiology for management. He also needs a nephrology referral for CKD stage IV based on GFR. Would stop HCTZ and begin furosemide 80 mg BID for better diuresis. Would decrease lisinopril and begin hydralazine 100 mg TID for tighter BP control. Needs iron levels checked and replaced if indicated for anemia. Reduced sodium diet. A renal US for secondary hypertension workup and assessment of intrinsic kidney disease. Avoid nephrotoxins including NSAIDs.

Clinical Pearls

- Diuresis is less effective with low-dose thiazide-like diuretics alone in the setting of CKD; he will need a higher dose loop diuretic to break the threshold and begin diuresis.
- Current guidelines recommend reducing, not discontinuing ACE/ARB, with isolated elevated creatinine reading. Would add hydralazine for blood pressure coverage while further evaluation takes place. Would add isosorbide dinitrate if the echo reveals HFrEF.

- Stabilization including appropriate diagnosis of renal disease, aggressive HTN management, and fluid volume likely to improve cardiac symptoms and quality of life.

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Diabetes and Heart Failure

12

Angelina Anthamatten

12.1 The Bidirectional Link Between Diabetes and Heart Failure

Coronary artery disease (CAD) and heart failure (HF) are major complications of diabetes mellitus (DM) [1], and type 2 diabetes mellitus (T2DM) and HF are common comorbidities [1, 2]. Unfortunately, HF has been described as an "often neglected complication of diabetes" [3, p. 3]; however, it is essential to consider its significance, as it has been included among the most serious complications of DM [1]. Further, a bidirectional link between diabetes and HF has been identified [3].

Diabetes has been identified as a risk factor for HF, and HF is also a risk factor for diabetes [2]. Diabetes is associated with at least a doubling in the risk of cardiovascular (CV) disease [4]. Historically, CV risk in diabetes has been considered primarily related to atherosclerotic disease [4], but heart failure is now considered the most common and morbid cardiovascular complication of T2DM [4, 5]. Thus, providers should consider the potential for DM in those with HF, as well as HF for those with DM. The incidence of DM has been found to be substantially higher for those with HF than the general population, and there is a two- to fourfold increased risk of HF in individuals with DM compared with those without DM [2].

Both HF and DM have complex pathophysiology, and there is an interplay between many mechanisms of these diseases [3]. Diabetes can contribute to structural and functional changes in the myocardium that lead to the development and progression of HF [3]. Diabetes-associated HF is highly complex, with "multiple mechanisms and consequent manifestations" evident at systemic, cardiac, and cellular/molecular levels and predispose the heart to myocardial dysfunction, including impaired cardiac relaxation, compliance, and contractility [1, p. 340].

A. Anthamatten (✉)
Vanderbilt University School of Nursing, Nashville, TN, USA
e-mail: angel.anthamatten@vanderbilt.edu

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_12

Some processes that have been linked with diabetes-associated HF pathology include hyperglycemia; hyperinsulinemia [1–3]; insulin resistance; inflammation, oxidative stress [1–3, 5]; alterations in the renin-angiotensin-aldosterone system (RAAS); advanced glycation end products (AGEs); and autonomic, endothelial, and mitochondrial dysfunctions [1–3].

In addition to T2DM being a risk factor for the development of HF, there is also risk for adverse outcomes for those with established disease [2]. Patients with HF and DM are known to have worse clinical outcomes than patients with HF without DM, including increased risk of hospitalization, readmission, and mortality, as well as worse health-related quality of life [2]. A scientific statement by the American Heart Association/Heart Failure Society of America (AHA/HFSA) [2] highlighted, "Identifying and implementing optimal treatment strategies for patients living with DM and HF is critical to improving outcomes in this high-risk population" (p. e294). Fortunately, there have been new developments in pharmacotherapy for T2DM, with certain drugs demonstrating significant benefits for cardiovascular disease and HF.

12.2 Management of Type 2 Diabetes Mellitus

The prevalence of diabetes in the general population is significant—according to the Centers for Disease Control (CDC) 2020 statistics report, 37.3 million people have diabetes, with T2DM being the most common type and accounting for 90–95% of diagnosed cases [6]. Options for the treatment of T2DM are evolving, and there is enhanced understanding of complex pathophysiology, specific roles of drugs, and patient-specific factors [7–9].

12.2.1 Evidence-Based Recommendations

There are many valuable resources to help providers stay abreast of growing medication options for the treatment of T2DM (Table 12.1), such as the American Diabetes Association's (ADA) Standards of Medical Care in Diabetes, which offers routinely updated, evidence-based recommendations [10], and the American

Table 12.1 Examples of evidence-based resources for management of diabetes mellitus

American Diabetes Association Standards of Medical Care in Diabetes	Available online: https://diabetesjournals.org/care (also available as free mobile application)
AACE/ACE Diabetes Management Algorithm	Available online: https://pro.aace.com/disease-state-resources/diabetes
Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement from the American Heart Association and the Heart Failure Society of America	Available online: https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000691

Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE), which published a clinical practice guideline and updated consensus statement and algorithm for management of T2DM [11, 12]. Both the ADA and AACE/ACE highlighted the importance of clinical judgment, considering benefits and risks, and individualizing therapy [10, 11]. A writing group of experts associated with the AHA and HFSA stated, "Although there are separate, dedicated guidelines for the management of DM and HF as isolated conditions, there is insufficient guidance on caring for patients with both DM and HF" [2, p. e294]. Thus, this group collaborated to publish a scientific statement that reviewed and summarized pertinent information for clinicians, including clinical considerations regarding pharmacologic options for the management of T2DM for those with HF [2].

12.2.2 Individualized Therapy

There is not one "best" medication for T2DM that will uniformly and optimally work for all patients—each drug has risks and benefits that must be weighed in the context of individual factors and preferences. What may be best for one person may not be a good fit for another. There are a variety of pharmacologic options, with differences in mechanisms of action, anticipated efficacy/degree of hemoglobin A1c lowering, administration requirements, adverse effect profiles, safety data, and costs.

A variety of factors are considered when choosing the best medication option for an individual; several are outlined in Fig. 12.1. When individualizing therapy, several key components of medication profiles can be considered, including mechanism of action, anticipated efficacy, contraindications, cautions, adverse effect profile (such as hypoglycemia risk and weight effects), cost (which may vary or change), and additional benefits of therapy (such as CV benefits). The ADA's Standards of Medical Care also highlighted consideration of patient burden [10]. A patient and provider can partner to determine the best therapy decisions for the individual and incorporate the patient's preferences and priorities. For example, cost may be most important for one patient, while avoidance of weight gain may be priority for another. Further, the optimal therapy for a patient can change over time, so it is prudent to continually review individual factors and other information (such

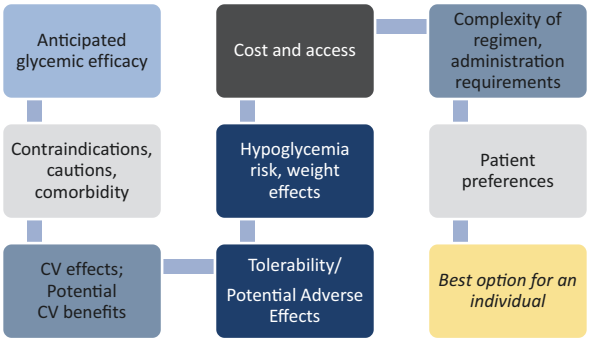

Fig. 12.1 Some key considerations when choosing a medication for type 2 diabetes

as available therapy options, current research and recommendations, cost, health parameters and comorbidities, etc.) to determine if changes are needed.

There are many potential adverse effects of various T2DM drugs; two that are commonly highlighted are hypoglycemia and weight gain. Prevention of hypoglycemia is important for all, but there are additional cautions about potential detrimental effects for older adults and those with cardiovascular disease [10]. In fact, severe hypoglycemia is recognized as a predictor of macrovascular events, adverse clinical outcomes, and mortality in patients with T2DM [13]. Other potential adverse effects of various diabetes drugs include gastrointestinal symptoms, fluid retention, vitamin B12 deficiency, fracture, diabetic ketoacidosis (DKA), genitourinary infections, and joint pain. Some potential adverse effects of various therapies are included in the sections on drug classes below, as well as in Table 12.2.

Efficacy, affordability, weight effects, hypoglycemia risk, and ease of use are among factors that are commonly considered when selecting drug therapy for T2DM. Insulin is considered the most potent antihyperglycemic agent, but there are also other non-insulin options that can have robust glucose-lowering effects [11]. Non-insulin therapies with the greatest anticipated HbA_{1c} reductions include glucagon-like peptide 1 receptor agonists (GLP-1 RA), metformin, sulfonylureas, and thiazolidinediones (TZDs) [14, 15]. If cost is the determining factor, some drugs are expected to have lower costs, such as metformin, sulfonylureas, and pioglitazone [15]. When weight loss is primary, a GLP-1 RA or sodium–glucose cotransporter 2 inhibitors (SGLT-2i) may be preferred [14]. The hypoglycemia risks associated with insulin and sulfonylureas can be significant, but several other classes have lower hypoglycemia risks (Table 12.2).

Some drugs for T2DM may also offer benefits for other conditions, such as HF, atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and diabetic kidney disease (DKD) [10]. For example, SGLT2 inhibitors and GLP-1 RA have been highlighted for demonstrated benefits for those with ASCVD [10]. Certain SGLT-2 inhibitors have shown benefits for HF (such as empagliflozin, dapagliflozin, canagliflozin), and these drugs also demonstrated reduced chronic kidney disease (CKD) progression in cardiovascular outcomes trials (CVOTs) [10]. Many options are administered orally, whereas some are injected (most GLP-1 RAs and insulins), and one inhaled rapid-acting insulin is available at the time of writing.

12.2.3 Cardiovascular Safety

There has been an increased focus on cardiovascular safety of diabetes therapies in recent years. In addition, standards of trial design and evaluation have evolved [28], which presents both benefits and challenges. First, it is important to be aware of an important event that significantly impacted our understanding of cardiovascular effects of drugs for T2DM. Prior to 2008, there was a lack of robust research evaluating long-term cardiovascular outcomes with therapies for DM; however, in 2008, the FDA issued guidance for industry to perform CVOTs for all new medications for T2DM. This paved the way for “dramatic growth in clinical investigations

Table 12.2 Some considerations for select pharmacologic therapies for type 2 diabetes mellitus [2, 8, 10, 11, 14–27]

Class	Examples	Anticipated efficacy/average HbA1c reduction	Hypoglycemia risk	Potential weight effects	Anticipated cost (may vary or change)	Other select considerations
Biguanide	Metformin Metformin ER	Higher ~1.0–1.5%	Neutral	Mild loss (~2 pounds) or neutral	Lower	Endo/Renal: consider factors that could increase risk for lactic acidosis; carefully review cautions for renal insufficiency [17], such as caution if <45 mL/min/1.73 m^2, avoid eGFR <30 mL/min/1.73 m^2 GI: diarrhea, nausea, vomiting, abdominal pain Hematologic: B12 deficiency [10, 11] CV: potential ASCVD benefit [10]; VA-IMPACT study is expected to provide more information regarding its CV safety [28] HF: considered a reasonable option for T2DM in those with stable HF and appropriate renal function [2, 10], considered to have neutral effects on HF [10, 11], ADA recommended avoiding in hospitalized patients with HF [10], avoid for those with unstable or acute heart failure or shock [29]

(continued)

Table 12.2 (continued)

Class	Examples	Anticipated efficacy/average HbA1c reduction	Hypoglycemia risk	Potential weight effects	Anticipated cost (may vary or change)	Other select considerations
SGLT-2 inhibitor	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Intermediate ~0.5–1%	Neutral	Loss (~1.5–7.7 pounds)	Higher	Endo: FDA warning—DKA [18, 30]; not FDA-approved for use in T1DM [18, 26, 30] GU: genitourinary infections [22], genital mycotic infections [11], serious urinary tract infections [18] Renal: risk of volume depletion, see drug labels for renal considerations [10]; some have demonstrated benefits in CKD [10]; drugs in this class are expected to have limited efficacy in patients with an eGFR <45 mL/min/1.73 m^2 due to their mechanism of action [11] MS: risk of bone fracture (canagliflozin) [10, 24] noted in CANVAS Program but not CREDENCE trial [25] CV: risk of hypotension [10], some have demonstrated ASCVD benefits [10]; empagliflozin and canagliflozin have indications for CV event risk reduction [26] HF: some have HF indications (such as dapagliflozin and empagliflozin) [26]; some SGLT2i have shown demonstrated benefits in HF in CVOTs (such as empagliflozin, dapagliflozin, canagliflozin) [10]; an SGLT2i, such as dapagliflozin or empagliflozin, was recommended by the ACC's 2021 expert consensus decision pathway for those with HFrEF (EF ≤40%) with or without T2DM and NYHA class II–IV HF [27]; the 2022 AHA/ACC/HFSA HF guideline added SGLT2i as a component of GDMT and recommended SGLT2i for patients with symptomatic chronic HFrEF to reduce hospitalization for HF and CV mortality, irrespective of the presence of T2DM [22]

GLP-1 receptor agonist	Albiglutide Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Higher ~1–2%	Neutral	Loss (~2.2–8.8 pounds)	Higher	General: administration considerations—many are injected with a pen-delivery device Endocrine: Black box warning, avoid personal/family history of MTC or history of MEN2 [11] GI: nausea, vomiting; see cautions regarding pancreatitis and gastroparesis Renal: possible benefits in CKD are being examined, see drug labels for renal considerations [10] CV: may reduce the risk of major adverse cardiovascular events and mortality in the general population of patients with T2DM [2]; some have demonstrated ASCVD benefits, such as liraglutide, semaglutide, dulaglutide [10] HF: ADA categorized HF effects as neutral [10]; role in HF has been described as unclear [5], AHA/HFSA highlighted studies indicating potential for worse outcomes for patients with established HFrEF and recent decompensation [2]
DPP-4 inhibitor	Alogliptin Linagliptin Saxagliptin Sitagliptin	Intermediate ~0.5–1%	Neutral	Neutral	Higher	GI: see cautions regarding pancreatitis MS: FDA warning joint pain [19] CV: ADA noted ASCVD effects as neutral [10] HF: FDA warnings regarding potential increased HF risk with saxagliptin [2, 10, 20] and alogliptin [11, 21]; the 2022 AHA/ACC/HFSA HF guideline recommended avoiding saxagliptin and alogliptin in patients with HF [22]
Sulfonylurea	Glimepiride Glipizide Glyburide	Higher ~1–1.5%	Higher	Gain (~4.6–5.7 pounds)	Lower	CV/HF: considered to have neutral ASCVD and HF effects (second generation) [10]; CAROLINA trial expected to provide more evidence on cardiovascular safety, including effects on hospitalization for HF [2]

(continued)

Table 12.2 (continued)

Class	Examples	Anticipated efficacy/average HbA1c reduction	Hypoglycemia risk	Potential weight effects	Anticipated cost (may vary or change)	Other select considerations
TZD	Pioglitazone Rosiglitazone	Higher ~1–1.5%	Neutral	Gain (~5–6 pounds)	Lower (pioglitazone)	GU: FDA warning to avoid pioglitazone with active bladder cancer, and carefully consider caution and potential risks in those with a history [31] MS: fracture risk CV: potential ASCVD benefit with pioglitazone [11] HF: edema; black box warning regarding HF; avoid with symptomatic HF; contraindicated in NYHA Class III-IV HF [26]
Insulin	Multiple options—long, rapid, short, intermediate-acting; premixed	High	High	Gain (~2–6 pounds more than other agents) [11]	Variable	General: administration and training requirements Resp: pulmonary considerations for inhaled insulin [10] CV: considered neutral for ASCVD [10, 11] HF: potential for fluid retention [2], ADA categorized HF effects as neutral [10]

focusing on cardiovascular effects of drugs" for T2DM, and significant progress has been made as large numbers of patients (hundreds of thousands) have been included in CVOTs for newer T2DM agents with follow-up over multiple years [5, p. S13]. However, randomized controlled trials on older medications, such as insulin, sulfonylureas, and metformin, have been described as limited [5], and it can be challenging to compare cardiovascular profiles of older and newer drugs for T2DM [28].

T2DM medications have shown different cardiovascular effects, including benefits, risks, and neutral cardiovascular impact. The ADA Standards of Medical Care-2021 published a helpful table summarizing several current cardiovascular safety considerations for drug classes [10]. Additionally, our understanding of the safety of some DM medications for those with HF has evolved over time. For example, HF was previously a contraindication to metformin use due to concerns about the risk of lactic acidosis, but, in 2006, the FDA removed the warning, and several studies have suggested a survival benefit with metformin [2]. A meta-analysis revealed metformin was associated with reduced mortality and a small reduction in all-cause hospitalization in patients with HF when compared to those in the control group [2]. It is important to note that metformin should not be used for patients with unstable or acute heart failure or shock [29], and the ADA Standards of Care-2021 recommended avoiding in hospitalized patients with heart failure [10]. An ongoing trial that is due to conclude in mid-2024, the Investigation of Metformin in Prediabetes on Atherosclerotic Cardiovascular OuTcomes (VA-IMPACT), is expected to provide more information regarding the cardiovascular safety of metformin [28].

There have also been some questions and concerns over the years about the cardiovascular safety of sulfonylureas. The ADA Standards of Medical Care-2021 noted that sulfonylureas may increase cardiovascular mortality, but the document expounds that data to support this association are limited [10]. In addition, the ADA's T2DM treatment algorithm noted: (1) if a sulfonylurea is needed for a patient with ASCVD or indicators of high risk, a later generation sulfonylurea should be chosen to lower risk of hypoglycemia, and (2) glimepiride has shown similar CV safety to DPP4 inhibitors [10]. The AHA/HFSA 2019 scientific statement recommended considering an SGLT-2i or metformin before a sulfonylurea [2]. The CAROLINA trial (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes) is expected to offer important evidence on the cardiovascular safety of sulfonylurea drugs, including effects on hospitalization for HF [2].

There are warnings about use in HF for TZDs (pioglitazone and rosiglitazone) and some DPP4 inhibitors (saxagliptin and alogliptin) [2, 10, 11]. Though there is a potential ASCVD benefit for pioglitazone, there is increased risk in HF with TZDs [10], and drugs in this class should be avoided in symptomatic heart failure [2, 10, 29] and are contraindicated in New York Heart Association (NYHA) class III and IV heart failure [29]. The ADA Standards of Medical Care-2021 concluded that overall DPP-4 inhibitors are expected to have neutral ASCVD effects [10], but there are cautions about HF risks with some, such as saxagliptin [10] and alogliptin [11], as noted in Table 12.2 and discussed in the DPP-4 inhibitor section below. Potential

adverse effects of T2DM medications are also discussed in another chapter in this text: "Medications to Avoid when Treating Heart Failure."

Certain SGLT-2 inhibitors and GLP-1 RAs have been highlighted for their cardiovascular benefits. The ADA Standards of Medical Care-2021 highlighted that "There are now multiple large randomized controlled trials reporting statistically significant reductions in cardiovascular events in patients with type 2 diabetes treated with an SGLT-2 inhibitor (empagliflozin, canagliflozin, dapagliflozin) or GLP-1 RA (liraglutide, semaglutide, dulaglutide)" [10, p. S118]. At this time, canagliflozin, dapagliflozin, and empagliflozin have shown reduction in HF in CVOTs, with dapagliflozin and empagliflozin having primary heart failure outcome data [10]. An SGLT-2i or GLP-1 RA with demonstrated CV benefit is recommended as part of the treatment regimen for patients with T2DM and established ASCVD or indicators of high ASCVD risk—with consideration of patient-specific factors and independent of HbA_{1c} and metformin use [10]. The AHA/HFSA [2] scientific statement highlighted the finding that some drugs in the GLP-1 RA class "may reduce the risk of major adverse cardiovascular events and mortality in the general population of patients with DM" (p. e304). However, the current role of GLP-1 RAs among patients with heart failure has been described as unclear [5], and the AHA/HFSA [2] highlighted two small randomized control trials that suggested there is potential for worse outcomes for patients with established HFrEF and recent decompensation.

SGLT-2 inhibitors have been highlighted as a treatment option that should be considered for patients with T2DM and established HF with reduced ejection fraction (HFrEF), as well as those at high risk of HFrEF, due to their beneficial effects and potential to reduce hospitalizations [2, 4]. There may be more to learn regarding the potential mechanisms by which SGLT-2 inhibitors might reduce HF-associated risk, and research is ongoing [2]. Mechanisms that might explain the reduction in HF events (beyond glucose-lowering or diuresis) include reductions in oxidative stress, improvement in endothelial function, and anti-inflammatory effects [2]. The important role of SGLT2 inhibitors in HF is discussed further in a following section. Though type 1 diabetes mellitus (T1DM) is not as common as T2DM, there are many important cardiovascular considerations with T1DM; however, at this time, comorbid HF and T1DM has not been as extensively explored as in patients with T2DM, and further clinical investigation has been recommended [4].

12.2.4 T2DM and Kidney Disease

Some T2DM drugs may have beneficial effects for patients with CKD and DKD, but the degree of renal impairment is a critical factor that must be considered before initiating therapy, as some drugs may require dose adjustments or may need to be avoided at certain levels of renal function. The ADA [10] Standards of Medical Care-2021 recommended that "SGLT2 inhibitors and GLP-1 RAs should be considered for patients with type 2 diabetes and CKD who require another drug added to metformin to attain target A1C or cannot use or tolerate metformin" (p. S155). An SGLT-2i with evidence of reducing progression of disease may have benefits for

some with T2DM and CKD or DKD and albuminuria [10]. The ADA Standards of Medical Care-2021 highlighted that canagliflozin, empagliflozin, and dapagliflozin reduced CKD progression in CVOTs, with canagliflozin and dapagliflozin having primary renal outcome data [10]. Because of their mechanism of action, SGLT2 inhibitors are expected to have limited efficacy in patients with an eGFR <45 mL/min/1.73 m^2 [11]. Cautious use of a GLP-1 RA may be considered for some patients with T2DM and CKD, as drugs in this class may slow CKD progression, and in cardiovascular outcomes trials, some GLP-1 RAs revealed beneficial effects on indices of CKD (liraglutide, semaglutide, and dulaglutide) [10]. It is important to appropriately select and dose drugs for patients with kidney disease. A provider may consult a prescribing reference, nephrologist, or pharmacist when needed for more details or individualized recommendations. The ADA [10] Standards of Medical Care-2021 included a table that summarizes some important renal dosing/drug use considerations for many therapies for T2DM.

12.2.5 Special Considerations for Treatment of DM in Patients with HF

12.2.5.1 Individualized Glycemic Goals

There are some variations among recommendations for glycemic goals in DM. The ADA [10] Standards of Medical Care-2021 stated an HbA_{1c} level of less than 7.0%, pre-prandial glucose of 80–130 mg/dL, and peak post-prandial glucose less than 180 mg/dL (without significant hypoglycemia) are appropriate for many nonpregnant adults with DM, with a caveat that "more or less stringent glycemic goals may be appropriate for individual patients" (p. S79). Further, glycemic goals may need to be adjusted over time, as medical status and circumstances change for a patient. A less stringent HbA_{1c} goal may be considered when the harms of treatment are greater than the benefits [10]. Some factors that may prompt less stringent glycemic targets include increased risks with hypoglycemia, long-standing disease duration, limited life expectancy, severe comorbidity, severe vascular complications, limited resources and support system, and patient preference for less burdensome therapy [8, 10].

The AHA/HFSA [2] scientific statement suggested a target range of HbA_{1c} 7–8% for most patients with HF, while also acknowledging there is currently a lack of HF-specific data to guide HbA_{1c} goals in patients with DM and HF. The statement adds that "patients with short life expectancy, advanced microvascular or macrovascular complications, or any end-stage comorbidity are advised to treat to minimize symptomatic hyperglycemia and hypoglycemia, corresponding to HbA_{1c} levels 8–9%" [2, p. e298]. The recommendation expounds that for patients with advanced, stage D HF who are not pursuing mechanical circulatory support or transplantation, less stringent HbA_{1c} goals may be appropriate [2]. The AHA/HFSA statement highlighted that "Optimal glycemic targets for patients with DM and HF should be individualized to reflect comorbidity burden, including the severity of HF, and to balance the benefits likely to be achieved by lowering HbA_{1c} with the potential

risks. Potential harms of intensive treatment include hypoglycemia, polypharmacy, treatment burden, and high costs of care. Moreover, treatment decisions need to consider potential benefits and harms of individual glucose-lowering medications" [2, p. e298].

The AHA/HFSA [2] scientific statement noted:

- A meta-analysis of 8 randomized controlled trials (RCTs) that included over 35,000 patients found no significant difference in the risk of HF between intensive glycemic control and standard treatments [2].
- Observational studies suggest that moderate glycemic control may be optimal for patients with DM and HF, with the lowest mortality in patients with HbA_{1c} 7–8% [2].
- Some studies identified higher HF event rates when HbA_{1c} levels fell below 6% [2].

12.3 Pharmacotherapy for T2DM

12.3.1 General Considerations

There are a variety of pharmacologic options for T2DM. In general, metformin has been recommended by the ADA [10] as an initial first-line pharmacologic therapy for T2DM if not contraindicated and tolerated. It is also recommended that a diabetes regimen be as simple as possible to promote adherence [11]. Compelling indications that prompt prioritization of certain drugs for patients with high risk or established ASCVD, HF, CKD, or DKD should also be considered, as discussed above.

12.3.2 Metformin

Metformin is the most prescribed oral diabetes medication in the United States and worldwide [32]. Much has been learned about this drug in the many years since its clinical discovery in the 1950s [33]. Its primary site of action appears to be the liver, decreasing hepatic glucose production [8, 33]. To a lesser extent, it also reduces intestinal glucose absorption [14, 34] and enhances glucose uptake in the peripheral tissues [33, 34], decreasing insulin resistance. In addition to a robust amount of long-term safety data, metformin has a number of other attributes that have contributed to recommendations as a first-line treatment option, including low cost, efficacy (average HbA_{1c} reduction of 1–1.5%) [15], low hypoglycemia risk, and potential weight loss [10, 11] (neutral weight effects or modest loss [10], such as approximately 2 pounds [16]).

Gastrointestinal (GI) adverse effects may occur, but this might be attenuated with certain strategies, such as gradual dose titration, food intake, or extended-release formulations [8]. Metformin has been associated with reversible vitamin B12 deficiency (particularly with long-term use [29]), which can cause anemia and peripheral neuropathy [10, 11]. Lactic acidosis is a rare, but severe and lethal, potential adverse

effect of metformin; some risk factors include unstable heart failure, hypoxic states (such as acute heart failure, acute myocardial infarction, shock), renal or hepatic impairment, excessive alcohol intake, surgery, and having a radiological study with contrast [29]. Patients 65 years of age and older are also at higher risk [29]. If lactic acidosis is suspected, it is recommended to immediately discontinue metformin and receive further evaluation and treatment in a hospital setting [2, 29]. Metformin is expected to have good antihyperglycemic efficacy, and a commonly considered dose range for many adults with T2DM is 1000–2000 mg/day [11], but it is important to note renal function and other factors may affect use of this drug and dosing.

The U.S. Food and Drug Administration (FDA) revised metformin safety information in 2016 to provide further guidance for mild or moderate renal impairment [17]. They recommended a shift in renal monitoring procedures from serum creatinine to estimated glomerular filtration rate (eGFR) in order to better estimate kidney function [17]. Because metformin therapy often lasts for many years, it is important to keep these cautions in mind and adjust therapy as needed if a pertinent change in health status develops.

Additional renal recommendations for metformin therapy include [17, 29]:

- Monitor eGFR at baseline and at least annually, more frequently for those with increased risk of renal impairment.
- Avoid metformin in patients with an eGFR below 30 mL/min/1.73 m^2.
- Initiating metformin is not recommended if the eGFR is 30–45 mL/min/1.73 m^2.
- If the eGFR falls to 30–45 mL/min/1.73 m^2 during therapy, assess the benefits and risks of continuing treatment. A dose reduction [11] and close monitoring have been suggested if metformin use is continued in this lower eGFR range [29].
- There are cautions with iodinated contrast procedures. It is recommended to discontinue metformin before these procedures in patients with eGFR 30–60 mL/min/1.73 m^2, history of heart failure, liver disease, or alcoholism, or those receiving intra-arterial iodinated contrast. Re-evaluate eGFR 48 h after the procedure and resume therapy if renal function is stable. Some potential benefits and risks to be considered with metformin are highlighted in Fig.12.2.

12.3.3 SGLT-2 Inhibitors

SGLT-2 inhibitors are oral glucose-lowering medications that block glucose reabsorption by the kidney, increasing glucosuria [10]. This class boasts several desirable effects, including weight loss (such as ~1.5–7.7 pounds) [14], mild blood pressure reduction, and low hypoglycemia risk [10, 11]. A moderate average HbA_{1c} reduction (such as ~0.5–1%) may be anticipated [15]. Some potential beneficial effects of SGLT-2i for ASCVD, HF, DKD, and CKD are outlined above.

Select potential adverse effects include volume depletion [10], hypotension, mycotic genital and other genitourinary infections, and slight increases in low-density lipoprotein cholesterol (LDL) levels [11]. Bone fracture risk has been linked with canagliflozin (see Table 12.2) [10], but the AACE/ACE 2020 algorithm described the SGLT2i class as having a neutral bone effect [11]. An increased risk

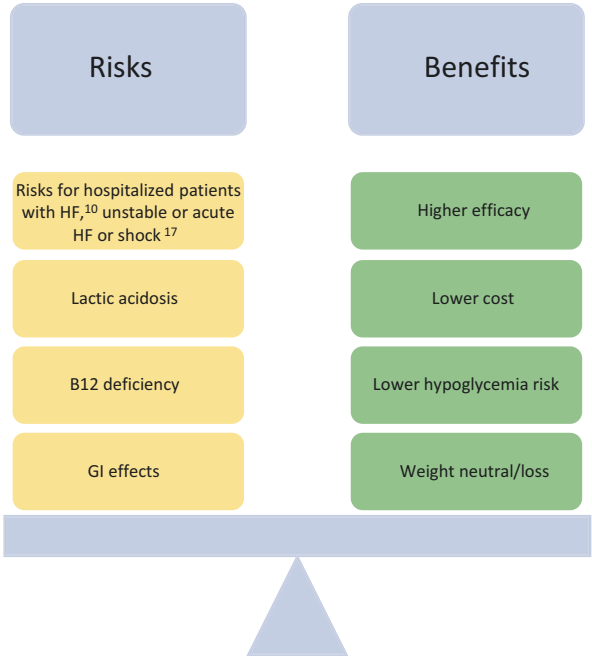

Fig. 12.2 Some potential benefits and risks for metformin [10] (individual factors and priorities can shift the weight for the final decision)

of necrotizing fasciitis of the perineum (Fournier's gangrene) has been identified as a rare but serious genital infection [10, 11].

There was a concern about a link between SGLT-2 inhibitors and acute kidney injury (AKI) due to volume depletion, particularly when combined with diuretics or other medications that reduce glomerular filtration [10]. Additionally, the FDA issued a warning about the risk of acute kidney injury with canagliflozin and dapagliflozin [35]. Several predisposing factors were identified, such as heart failure; decreased blood volume; chronic kidney insufficiency; and certain medications: diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs) [35]. However, the ADA Standards of Medical Care-2021 noted that the AKI risk of SGLT-2 inhibitors has been refuted in some randomized clinical outcome trials [10]. Further, the ADA [10] addressed the concern that SGLT2 inhibitors may promote AKI through volume depletion, particularly when combined with certain medications that reduce glomerular filtration, stating, "…this has not been found to be true in randomized clinical outcome trials of advanced kidney disease or high cardiovascular disease risk with normal kidney function" (p. S153). Monitoring renal function prior to initiation of an SGLTi and periodically thereafter is recommended [35]. Providers should weigh renal cautions in the context of individual factors when an SGLT2i is prescribed for a patient with HF; close clinic follow-up can be considered to assess volume status and monitor laboratory data as indicated.

There were also post-marketing reports of diabetic ketoacidosis (DKA) in patients with types 1 and 2 DM [18], and investigations are ongoing [11]. SGLT-2 inhibitor–associated DKA was found in 5% of 2500 patients with T1DM [11, 36]

(Of note, SGLT-2 inhibitors are not FDA-approved for use in T1DM [18, 30]), and in T2DM, the incidence rate ranged from 0.16 to 0.76 events per 1000 patient-years [10, 11, 37]. The majority of cases occurred in individuals with diabetes who were insulin deficient, including those with long-standing T2DM, T1DM, or latent autoimmune diabetes in adults (LADA) [30]. Metabolic stress was identified as a unifying theme among cases, with nearly all involving surgery, injury, acute illness, exercise, or severely reduced carbohydrate intake [30].

Some safety recommendations for SGLT-2 inhibitors to reduce the risk of ketoacidosis include:

- Avoid SGLT-2i in cases of severe illness, in patients with ketonemia or ketonuria, and during prolonged fasting and surgical procedures [10].
- SGLT-2 inhibitors should be stopped temporarily before scheduled surgeries (such as 3–4 days prior, depending on the drug) [10, 18]. For those undergoing emergency surgery or any severe stress event, the drug should be stopped immediately [30].
- SGLT-2 inhibitors should also be temporarily stopped prior to planned invasive procedures [30].
- Patients taking SGLT-2 inhibitors should avoid excess alcohol intake and very low carbohydrate/ketogenic diets [30].
- If a patient taking an SGLT-2 inhibitor presents with symptoms suggestive of DKA (such as abdominal pain, nausea, vomiting, fatigue, and dyspnea), a diagnosis of DKA should be considered and appropriate evaluation and treatment promptly initiated [30]. Some potential benefits and risks to be considered with SGLT-2 inhibitors are highlighted in Fig. 12.3.

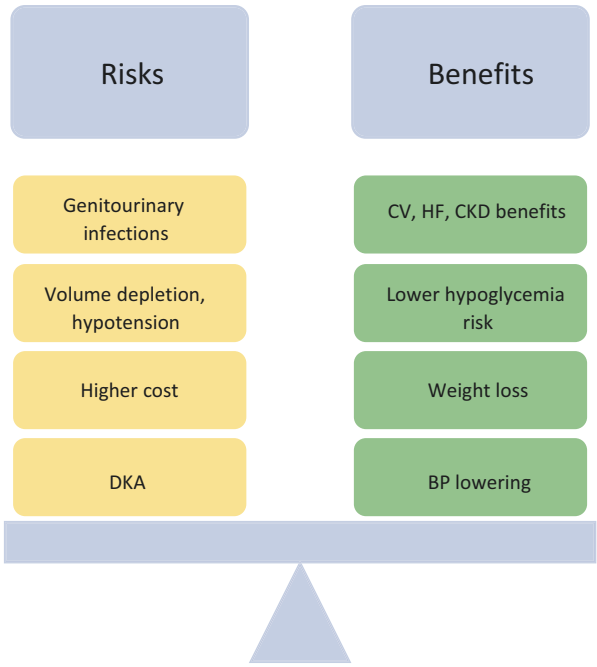

Fig. 12.3 Some potential benefits and risks for SGLT-2i [10] (individual factors and priorities can shift the weight for the final decision)

12.3.4 GLP-1 Receptor Agonists

The GLP-1 RA class continues to emerge as a valuable option for the treatment of T2DM due to its glycemic efficacy, weight loss, low hypoglycemia risk, and research highlighting cardiovascular benefits. Potential cardiovascular benefits and important considerations in ASCVD, HF, CKD, and DKD are discussed above [10]. This incretin-based therapy is expected to stimulate glucose-dependent release of insulin, decrease glucagon, delay gastric emptying, and suppress appetite [38]. Weight loss (such as about 2.2–8.8 pounds) [14] and average HbA_{1c} reduction of 1–2% may be anticipated [14, 15]. Many GLP-1 RAs are administered via subcutaneous injection, but at the time of writing, one drug in this class offers an oral option (semaglutide). GLP-1 RAs offer a variety of dosing options, such as once weekly, once daily, and twice daily.

Gastrointestinal adverse effects may occur, but these symptoms may be transient [39]. GLP-1 agonists have a black box warning to avoid use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or those with multiple endocrine neoplasia syndrome type 2 (MEN2) [11]. There are cautions for patients with a history of pancreatitis and gastroparesis [11]. Some potential benefits and risks to be considered with GLP-1 RAs are highlighted in Fig. 12.4.

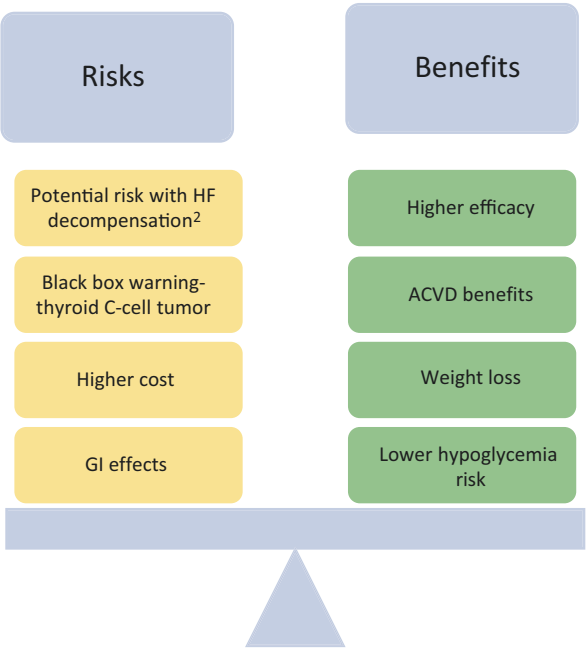

Fig. 12.4 Some potential benefits and risks for GLP-1 RA [10] (individual factors and priorities can shift the weight for the final decision)

12.3.5 DPP-4 Inhibitors

This oral incretin therapy stimulates glucose-dependent insulin secretion and suppresses glucagon [11]. DPP-4 inhibitors (DPP4i) are considered a weight neutral option that is expected to have intermediate HbA_{1c} reductions (average 0.5–1%) [15] and low hypoglycemia risk as monotherapy [10, 11]. In 2015, the FDA issued a safety alert regarding cases of severe joint pain associated with the use of DPP-4 inhibitors [19]. Providers also have been cautioned regarding use in patients with a history of pancreatitis [11].

Potential heart failure risks with some DPP-4 inhibitors have been identified [10, 11]. The increase in heart failure hospitalization with certain DPP-4 inhibitors has been described as an unexpected finding, and the reasons for discrepancies with regard to this risk unclear, but studies are ongoing [5]. There are warnings about possible increased risk of HF with saxagliptin [2, 10, 11, 20] and alogliptin [11, 21]. The FDA prescribing information for saxagliptin and alogliptin refers to findings in the SAVOR and EXAMINE trials, respectively, and contains warnings to consider the risks and benefits prior to initiating treatment in patients at risk for HF and consider discontinuation if HF develops [20, 21]. The 2022 guideline for the management of HF by the American Heart Association, American College of Cardiology, and Heart Failure Society of America (AHA/ACC/HFSA) highlighted increased risk of HF hospitalization associated with saxagliptin and alogliptin in patients with T2DM and high cardiovascular risk, and this guideline recommended these drugs be avoided in patients with HF [22]. The AHA/ACC/HFSA guideline stated it is unclear if risk of worsening HF is a class effect of DPP4i [22]. The AHA/HFSA scientific statement discussed concerning findings in some trials, and although they stated additional data is still needed, they recommended on the basis of current data, "the risk-benefit balance for most DPP-4 inhibitors does not justify their use in patients with established HF or those at high risk for HF" [2, p. e305]. Some potential benefits and risks to be considered with DPP-4 inhibitors are highlighted in Fig. 12.5.

12.3.6 Sulfonylureas

Sulfonylureas are sometimes referred to as insulin secretagogues [11], as they lower glucose by stimulating insulin secretion from the pancreas [14]. Drugs in this class usually have lower costs [10], and an average HbA_{1c} reduction of ~1–1.5% may be anticipated [15]. Some primary disadvantages include hypoglycemia and weight gain [11] (an approximate 4.6–5.7 pounds increase has been noted) [16]. Additional cardiovascular considerations for sulfonylureas are discussed above. Some potential benefits and risks to be considered with sulfonylureas are highlighted in Fig. 12.6.

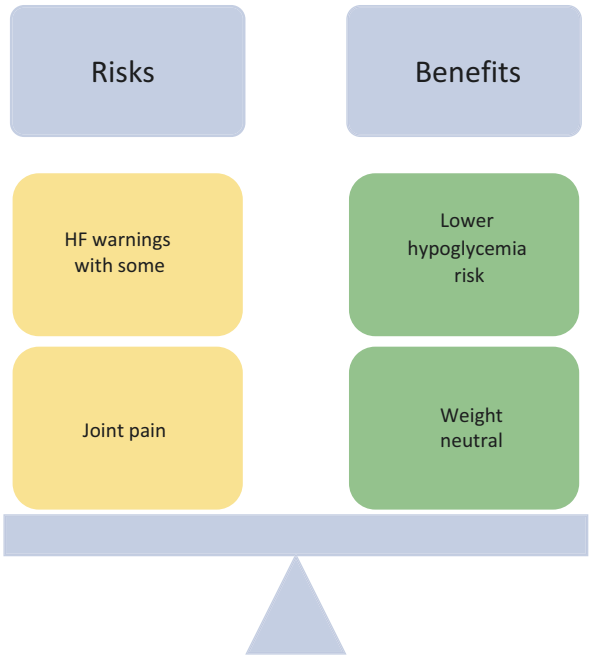

Fig. 12.5 Some potential benefits and risks for DPP-4i [10] (individual factors and priorities can shift the weight for the final decision)

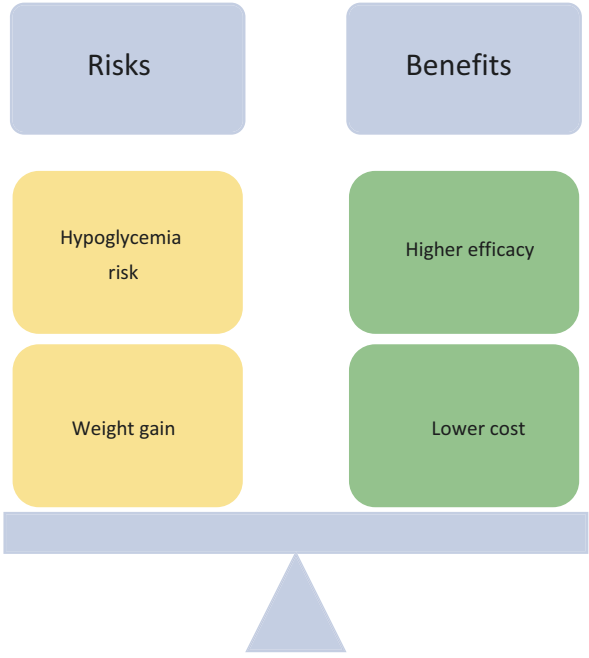

Fig. 12.6 Some potential benefits and risks for sulfonylureas [10] (individual factors and priorities can shift the weight for the final decision)

12.3.7 Thiazolidinediones

The TZDs have been found to directly reduce insulin resistance [11] and are expected to have relatively potent HbA_{1c} lowering properties (average 1–1.5% reduction) [15] and low risk of hypoglycemia [10, 11]. Pioglitazone is a lower-cost option [10] and may have some ASCVD benefits [11]. Some potential adverse effects include edema, increased bone fracture risk, and weight gain [10, 11] (an approximate 5.7 pounds increase has been noted) [16]. As discussed above, there are important HF risks with this class; the AHA/HFSA [2] scientific statement highlighted that a TZD is not recommended for patients with established HF and may increase the risk of HF in those with DM without HF. There were substantial safety cardiovascular concerns regarding rosiglitazone, but in 2013, the FDA removed rosiglitazone prescribing restrictions, and in 2015, the Risk Evaluation and Mitigation Strategy was eliminated [31, 40]. The FDA cautioned providers to carefully consider the risks and benefits before prescribing pioglitazone for individuals with a history of bladder cancer and avoid for those with active disease [23]. Some potential benefits and risks to be considered with TZDs are highlighted in Fig. 12.7.

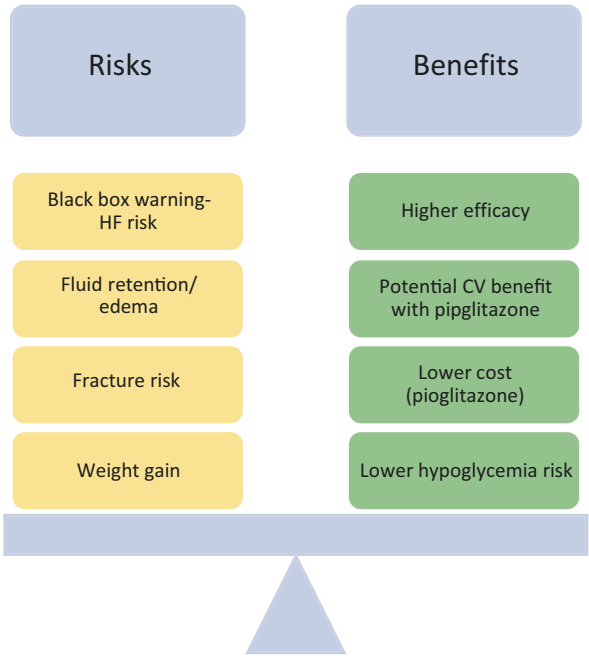

Fig. 12.7 Some potential benefits and risks for TZDs [10] (individual factors and priorities can shift the weight for the final decision)

12.3.8 Insulin

Evidence-based recommendations include insulin as an option for patients who are not achieving glycemic goals and those with severe hyperglycemia [10, 11]. Insulin is considered most potent among antihyperglycemic agents [11]. The AHA/HFSA [2] scientific statement discussed preference for other agents, such as metformin and SGLT-2i, if adequate glycemic control can be achieved without insulin. The ADA Standards of Medical Care-2021 [10] stated that a GLP-1 RA is "preferred to insulin" in T2DM when possible, and a basal insulin and GLP-1 RA can be a valuable combination (p. S113). However, there are times when insulin may be needed for certain patients with T2DM, such as for those experiencing weight loss, symptoms, and severe hyperglycemia, such as HbA_{1c} over 9–10% [5, 6] and high glucoses (>300 mg/dL) [10]. The ADA [10] Standards of Medical Care-2021 and AACE/ACE 2020 algorithm [11] both described ASCVD effects for insulin as neutral, and the ADA noted neutral HF effects. Insulin use has been associated with fluid retention [2], which is an important consideration for the patient with HF.

A variety of insulin products are available with various onsets, peaks, and duration of actions, and most are injected via a vial and syringe or insulin pen (there is one inhaled insulin option at the time of writing). There are long-acting, intermediate-acting, short-acting, and rapid-acting insulin options. Assorted types of premixed human and analog insulins (such as 70/30, 75/25, 50/50) are also available. Analog insulins are considered to offer more precise and physiologic pharmacokinetic properties (onset, peak, and duration of action) and less hypoglycemia than human insulin [11]. A basal insulin may be initially selected for some patients with T2DM. Administration of an insulin indicated for use at mealtime (such as rapid-acting insulin) for one or more meals may be considered when greater treatment intensity is indicated [11]. Insulin type and doses should be individualized and adjusted at regular intervals as needed [10].

Some potential disadvantages of insulin therapy are hypoglycemia, weight gain (described as about 2–6 pounds more than other agents) [11], and fluid retention [2]. Some patients with DM have a high degree of insulin resistance and may require high doses of insulin, and an endocrinology consult can be a very helpful resource and guide for those requiring complex insulin regimens. Some potential benefits and risks to be considered with insulin are highlighted in Fig. 12.8.

12.3.9 Combination Therapy

T2DM is progressive, and combination therapy comprised of medications with complementary actions is often necessary to address multiple pathophysiologic defects of T2DM [7] and meet glycemic goals [10, 11]. In general, the ADA [10] Standards of Medical Care-2021 recommended combining metformin with one of these six preferred treatment options: sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin; drug-specific effects and patient factors should guide drug selection. As noted in the ADA's T2DM algorithm, many diabetes medications are compatible in combination, but not all [10]. For example, combination of a

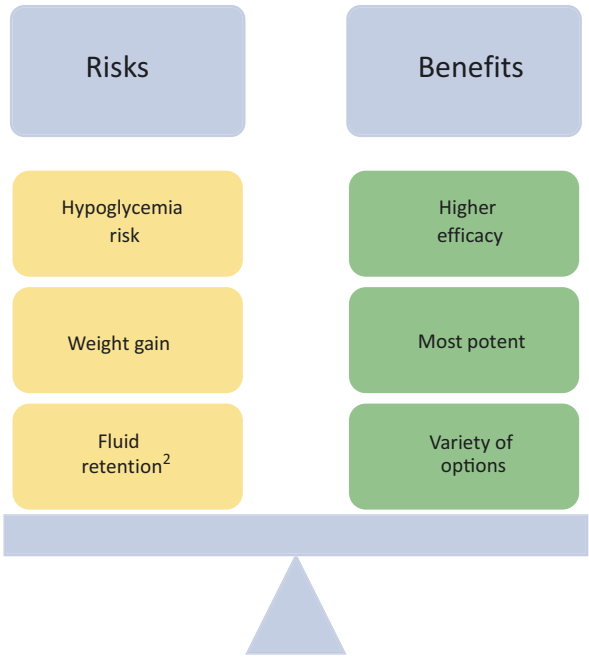

Fig. 12.8 Some potential benefits and risks for insulin [10, 11] (individual factors and priorities can shift the weight for the final decision)

DPP-4i and GLP-1 RA was not listed among recommended options in the ADA Standards of Medical Care-2021 [10]. Risk for hypoglycemia and weight gain is further increased when a sulfonylurea and insulin are combined [11]. The AACE/ACE 2020 insulin algorithm recommended providers consider discontinuing or reducing the dose of a sulfonylurea after starting basal insulin [11]. Further, even though metformin, GLP1-RA, SGLT2i, DPP4i, and TZD have lower hypoglycemia risks, if any of these are combined with insulin, the AACE/ACE recommended considering a lower dose of either drug to reduce the risk of hypoglycemia [11].

12.4 Conclusion

Individualizing pharmacotherapy and weighing risks and benefits are important steps in diabetes management. There are a variety of factors that may make one drug a better fit for a particular patient. For those with cardiovascular disease, certain drugs may have compelling indications. As discussed, GLP-1 receptor agonists and SGLT-2 inhibitors have important cardiovascular benefits for patients with T2DM [10], and SGLT-2 inhibitors should be considered for those with T2DM and HFrEF [2, 4, 10], due to their beneficial effects and potential to reduce hospitalizations [2, 4].

Though this chapter focuses on management of T2DM for those with HF, it is important to note that some SGLT-2 inhibitors, such as dapagliflozin and empagliflozin, have indications for HF, even without a diagnosis of T2DM [26, 27]. The 2022 AHA/ACC/HFSA HF guideline recommended SGLT2i for patients with symptomatic chronic HFrEF to reduce hospitalization for HF and cardiovascular

mortality, irrespective of the presence of T2DM [22]. In addition, this guideline added SGLT2i as a component of guideline-directed medical therapy (GDMT) for HFrEF [22]. The American College of Cardiology's (ACC) 2021 Expert Consensus Decision Pathway update outlined indications for an SGLT2i in HF (in conjunction with a background of GDMT), including: HfrEF (EF ≤40%) with or without T2DM and NYHA class II–IV HF [27].

The AHA/HFSA scientific statement stated, "There are many unanswered questions regarding the epidemiology, pathobiology, optimal pharmacotherapy, and co-disease management strategies for patients with DM and HF" [2, p. e313]. Further, DM and HF treatment options and recommendations are expected to change over time, as research reveals new information and new drugs are developed. Because of the dynamic nature of this content, it is important for providers to stay abreast of changes in updated, evidence-based literature and prescribing resources. There have been many exciting findings for some T2DM and HF therapies, and it will be interesting to see what new breakthroughs may be revealed in the future.

12.5 Case Study

12.5.1 Subjective

Mr. P is a 59 year-old Causcasian male with the following past medical history:
- CAD-ischemic cardiomyopathy
- HFrEF
- Hyperlipidemia
- Hypertension
- T2DM

Family history
- Mother—early onset heart disease, deceased at age 53 due to myocardial infarction
- Father—T2DM, hypertension, deceased at age 75 due to stroke
- Sibling (alive) with CAD

Social history—lives with wife, works part-time in retail, denies ETOH, tobacco, illicit drug use

Medications
- Atorvastatin 80 mg once daily
- Coreg (carvedilol) 12.5 mg twice daily
- Entresto (sacubitril/valsartan) 24/26 mg twice daily
- Furosemide 40mg once daily in the morning
- Spironolactone 25 mg daily
- Aspirin 81 mg daily
- Metformin 1,000 mg twice daily with food

Allergies: No known drug allergies

HPI
Mr. P presents to the office today for 1 week post hospital follow-up for heart failure. He has a long-standing history of T2DM and was diagnosed with HFrEF and ischemic cardiomyopathy 1 year ago. He was hospitalized last week due to acute decompensated heart failure and fluid overload. This was his first heart failure hospitalization, thought to be secondary to dietary sodium indiscretion. His hospitalization was uncomplicated. An echocardiogram was obtained and left ventricular ejection fraction was unchanged at 35%. He was diuresed and discharged home 2 days later. Discharge weight was 225 pounds. Today, he reports NYHA class II symptoms. Able to walk to mailbox without limiting dyspnea. Denies orthopnea and or PND. He is attempting to limit sodium and fluid intake, but states he often feels thirsty. He reports that his home blood sugars are usually around 180–200 mg/dL throughout the day. No chest pain, palpitations, abdominal distention or pain, nausea, diarrhea, myalgias.

12.5.2 Objective

Vital signs: BP 124/72, weight: 225, ht: 70 inches, BMI: 33

Labs:

HbA_{1c}: 8.3%

BMP: Sodium 136, Potassium 4.0, BUN 15, Creatinine 1.06, eGFR 75 mL/minute/1.73 m^2

NT-Pro BNP: 2,500 pg/mL

Physical Examination
General: no acute distress, pleasant, communicates well, obese

Neck: Supple, JVD ~5 cm

Cardiovascular: regular rate and rhythm, normal S1 and S2, no S3 or S4, no murmur

Respiratory: lungs clear to auscultation with no increased work of breathing

GI: abdomen round without tenderness, normoactive bowel sounds, no hepatosplenomegaly, negative hepatojugular reflux (HJR)

Extremities: 1+ bilateral pitting lower extremity edema, no skin breakdown, no decreased sensation with monofilament test on both feet

12.5.3 Assessment

Diagnosis
1. Acute on chronic heart failure with reduced ejection fraction
2. Uncontrolled type 2 DM
3. Hypertension
4. Hyperlipidemia

12.5.4 Plan

Pharmacologic:

- Start SGLT-2i. Take Farxiga (dapagliflozin) 10 mg once daily in the morning. (Note: the target dose for HF recommended in an ACC report was also 10 mg daily [27].) Continue current Metformin therapy for T2DM and diuretic therapy for HFrEF, Furosemide 40 mg daily, with ongoing monitoring.

Education:

- May experience increased urination, given SGLT2i mechanism of action.
- Monitor weight daily and notify provider of weight changes that are outside of recommended parameters, such as less than or greater than 5 pounds.
- Periodically monitor BG at home, which can give insight into changes in glycemic control in addition to HbA_{1c}. Both metformin and dapagliflozin have low risk for hypoglycemia [10]. One possible regimen is to test BG a few times a week at alternating times, such as fasting, before evening meal, and/or bedtime. Keep BG log; call if BG under 80 or over 200 mg/dL.
- Call if any new symptoms, such as dizziness; genitourinary infections; nausea or abdominal pain; weight change, such as rapid loss or gain of more than 5 pounds; increased swelling in legs, ankles, or feet.
- Discuss symptoms of DKA and when to seek care. It is recommended that patients avoid a low carbohydrate/ketogenic diet while taking Farxiga due to potential risks [30].

Non-pharmacologic:

- Discuss strategies to support integration of self-care and healthy behaviors for both DM and HF, such as medication adherence, dietary modification as needed, physical activity, weight and stress management [2].

Follow-up:

- Return to clinic in 2 weeks to reassess fluid status, obtain labs (BMP and NT-Pro BNP); discuss progress with new medication, Farxiga (dapagliflozin)-assess medication adherence, inquire about adverse effects, review BG logs; assess weight and review weight logs, monitor BP. Return sooner or call if needed.
- Repeat hemoglobin A_{1c} testing in 3 months. Continue routine monitoring of renal function and volume status as clinically indicated.

Referral considerations:

- A referral to cardiac rehabilitation professional may be considered for specific evaluation, recommendations, and rehabilitation sessions. An exercise specialist can also help with strategies to safely and effectively increase physical activity.
- A registered dietitian can be a valuable resource to plan and support implementation of appropriate dietary recommendations for HF and T2DM.
- Endocrinology can be a valuable resource when more complex insulin therapies are needed or a patient is not achieving glycemic goals. The AHA/HFSA [2] scientific statement stated, “Endocrinology consultation is strongly advised for patients with end-stage HF, DM, and poor glycemic control undergoing evaluation for advanced HF therapies” (p. e313).

12.6 Clinical Pearls

- The 2022 AHA/ACC/HFSA HF guideline added SGLT2i as a component of GDMT for HFrEF and recommended SGLT2i for patients with symptomatic chronic HFrEF to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of T2DM [22].
- Certain SGLT-2i have shown demonstrated benefits for patients with HFrEF and should be an initial pharmacologic consideration. Consider current research and recommendations—dapagliflozin and empagliflozin currently have HF indications [26] and were recommended by the ACC's 2021 expert consensus decision pathway for HF [27], in conjunction with a background of guideline-directed medial therapy (GDMT), for those with HFrEF (EF ≤40%) with or without T2DM and NYHA class II–IV HF [27].
- Consider safety recommendations for SGLT-2i, such as potential genitourinary infections and risk of DKA [10, 22].
- There is a risk of volume depletion and hypotension with SGLT-2 inhibitors [10]. Providers should weigh renal cautions in the context of individual factors when an SGLT2i is prescribed for a patient with HF and consider close follow-up as appropriate. Patients can also monitor BP outpatient, keep logs, and notify the provider if new symptoms (such as lightheadedness or dizziness) develop, or BP drops below recommended parameters.
- Given the drug's mechanism of action, an SGLT-2i can increase diuresis [11]. Monitor for changes in fluid status, BP, renal function, and potassium. Diuretic adjustments should be patient-specific and followed with close monitoring.
- Be mindful of thirst mechanism in hyperglycemic state with T2DM, which can lead to increased fluid intake and subsequently causing volume overload and challenging fluid balance. This has been described as a common issue seen in HF patients with diabetes that is uncontrolled.
- Metformin can be continued for many patients with T2DM and stable HF, but it is important to consider cautions, such as risk factors for lactic acidosis, and ensure renal function is appropriate for use [2]. Avoid if unstable or acute heart failure or shock [29], and it is not recommended for those with HF who are hospitalized [10].
- The AHA/HFSA scientific statement noted carvedilol could be used preferentially if a patient with HFrEF has poor glycemic control, due to more favorable effects on glycemic control than metoprolol succinate and bisoprolol [2].

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Chronic Obstructive Pulmonary Disease, Obstructive Sleep Apnea, and Heart Failure

13

J. Travis Dunlap, Melissa Glassford, and Leslie W. Hopkins

13.1 Introduction

The synergy between the cardiac and pulmonary systems is important to the human body. Healthcare technology and cardiovascular risk factor prevention have improved, and as a result, individuals who may have died as a result of myocardial infarction (MI) now have a better chance of surviving the event. However, a significant portion of these patients are still at risk for developing heart failure (HF). When an individual develops HF, the cardiopulmonary partnership is severely affected. If pulmonary comorbidities such as obstructive sleep apnea (OSA) or chronic obstructive pulmonary disease (COPD) are also present, cardiopulmonary efficiency is further reduced. Primary care providers need to understand the interaction between HF and OSA as well as HF and COPD. Successful diagnosis and management are fundamental in these vulnerable populations.

13.2 Obstructive Sleep Apnea

13.2.1 Obstructive Sleep Apnea Definition and Prevalence

Sleep-disordered breathing (SDB) is a spectrum of disorders associated with breathing impairment that occurs during sleep. These include central sleep apnea (CSA), mixed sleep apnea, and obstructive sleep apnea (OSA). Central sleep apnea is characterized by repetitive apneas, with no ventilatory effort, followed by arousal and resumption of respirations [1]. Mixed sleep apnea is a combination of both CSA and

J. T. Dunlap (✉) · M. Glassford · L. W. Hopkins
Vanderbilt University School of Nursing, Nashville, TN, USA
e-mail: travis.dunlap@vanderbilt.edu; melissa.glassford@vanderbilt.edu; leslie.hopkins@vanderbilt.edu

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_13

OSA [2]. Obstructive sleep apnea, the most common form of SDB, occurs when increased airway resistance leads to recurring upper airway collapse during sleep, which results in apneic and hypopneic episodes [3].

The American Academy of Sleep Medicine has a complex definition for OSA that requires either signs/symptoms of SDB (which are discussed later in the chapter) or associated medical or psychiatric disorder paired with "five or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or respiratory effort-related arousals, as defined by the AASM scoring manual) per hour of sleep during PSG" [PSG = polysomnogram] [1]. In the absence of SDB symptoms or associated medical or psychiatric disorders, an individual can also be diagnosed with OSA if they have ≥15 predominantly obstructive respiratory events per hour during PSG [1].

The severity of OSA is often defined in terms of the apnea-hypopnea index (AHI), which is the number of apneas and hypopneas per hour [4]. An apneic or hypopneic event is the cessation or significant reduction in respirations for at least 10 s with subsequent arousal, oxygen desaturation, or both [1]. The AHI values vary from source to source but most sources classify mild OSA as 5–15 events/h, while moderate OSA is 15–30 events/h, and severe is >30 events/h [5].

In a systematic review by Senaratna et al. [6], the authors determined the overall prevalence rate of OSA (defined as ≥5 events/h) in the general population ranged from 9% to 38%, with a higher prevalence in men than women. In an analysis of the Sleep Heart Health Study Cohort, Donovan and Kapur [3] determined that 55% of patients with HF self-reported a diagnosis of OSA, while only 4% admitted to having CSA. For this reason, OSA will be the only form of SDB discussed in this chapter.

13.2.2 Obstructive Sleep Apnea Risk Factors and Pathophysiology

Unmodifiable risk factors for OSA include any anatomical conditions that narrow any part of the airway, a family history of OSA, gender, menopause status, age, and race [7]. Modifiable risk factors for OSA include obesity and alcohol consumption [8]. Obstructive sleep apnea is characterized by upper airway collapse that occurs during sleep because of increased airway resistance. The upper airway, or pharynx, is a collapsible tube that is involved in respiration, speech, and swallowing [8]. The pharynx experiences negative pressures as the lungs inflate during inspiration, but this negative pressure is normally counteracted by the dilator muscles of the pharynx that work to maintain the patency of the upper airway [8]. Any imbalance between these two opposing influences may result in obstruction of the upper airway, which is the hallmark of OSA. This imbalance may cause transient hypoxic conditions resulting from the apneic and hypopneic events [8]. An important factor that affects the likelihood of the pharynx becoming obstructed during inspiration is the cross-sectional size of the pharynx. The pharynx can narrow as a result of excess

Table 13.1 Clinical manifestations of obstructive sleep apnea [7]

Fatigue
Observed apnea
Snoring
Excessive daytime sleepiness
Choking or gasping at night
Night sweats
Neurocognitive impairment
Heartburn
Morning headaches
Maintenance insomnia
Erectile dysfunction
Nocturia

fat deposits in the area surrounding the pharynx, as well as from tonsillar hypertrophy, hyoid bone positioning, tongue hypertrophy, or posterior positioning of the mandible (retrognathia) [8]. Please see Table 13.1 for common clinical manifestations [7].

13.2.3 Obstructive Sleep Apnea Concerns

The transient hypoxic episodes experienced in OSA can be severe and reduce oxygen saturation to ≤60% [9]. Somers et al. [9] also stated that blood pressure during an apneic occurrence can be as high as 240/130 mmHg. Together, the transient hypoxic episodes and elevated blood pressures during the apneic occurrence can promote systemic vascular inflammation and oxidative stress that result in endothelial dysfunction and may lead to atherosclerotic cardiovascular disease (ASCVD). ASCVD and HF are related, and if these transient hypoxic episodes remain untreated, HF is a highly probable outcome [10]. Obstructive sleep apnea has also been linked to increased platelet activation and increased fibrinogen levels, and this can increase the potential for forming a thrombus. These coagulation changes could lead to myocardial infarction (MI), pulmonary embolus, or embolic cerebrovascular accident [9].

Destructive neurohormonal consequences also occur during the hypoxic conditions associated with OSA. Regarding HF specifically, neurohormonal effects related to the sympathetic nervous system and the renin-angiotensin-aldosterone system cause the most significant negative remodeling [11]. As a result, individuals with OSA are at increased risk for many diseases, including type 2 diabetes mellitus (T2DM), cancer, stroke, MI, HF, and depression [12, 13]. Obstructive sleep apnea plays a factor in causing disease, and it has also been linked to exacerbating diseases including cardiovascular disease, stroke, T2DM, cognitive decline at an earlier age, and depression [14, 15]. In fact, OSA has been described as an independent risk factor for cardiovascular diseases such as stroke, hypertension, HF, dysrhythmias, and coronary heart disease as well as cancer incidence and cancer mortality [12, 15].

13.2.4 Obstructive Sleep Apnea Evaluation and Management in the Presence of Heart Failure

The STOP-Bang questionnaire is designed to assess the risk of undiagnosed OSA and is a useful tool in primary care [16]. The STOP portion of the questionnaire asks about symptoms [16]. The Bang portion of the questionnaire asks yes/no about the presence of four objective findings [16]. The STOP questions ask if a person snores loudly, tires during the daytime, has been observed not breathing while sleeping, and are they treated for high blood pressure. The BANG asks for the provider to observe if the patient has a BMI >35 kg/m^2, is older than 50 years of age, has a neck circumference >40 cm, and is male sex [16]. The person is considered high risk if the answer is "yes" to three or more questions [16]. The full questionnaire can be found at the website http://www.stopbang.ca/osa/screening.php [16].

The Epworth Sleepiness Scale (ESS) is a sleep instrument designed to measure excessive daytime sleepiness [17]. The ESS is a self-administered questionnaire that asks about the "chance of dozing" during eight low stimulation scenarios, including sitting and reading, watching TV, and sitting "in a car while stopped for a few minutes in the traffic" [17]. Scores range from "0 = would never doze" to "3 = High chance of dozing" [17]. A higher score indicates a higher level of excessive daytime sleepiness and a score of ≥11 represents increasing levels of excessive daytime sleepiness [18]. However, according to Heidenreich et al. [19], daytime sleepiness in patients with HF may not be as reliable in determining the severity of the OSA. For that reason, the decision to do a sleep study should be based on clinical judgment [19].

The physical assessment to evaluate for OSA should focus on evaluating the upper airway including neck circumference, Mallampati score, and examination of the tonsils, tongue, uvula, hard palate, and nares for any anatomic abnormalities that could potentially narrow the upper airway [20]. The Mallampati score is determined by asking the patient to open their mouth as wide as they can while emitting no sound: Class I—soft palate and entire uvula are visible; Class II—soft palate and portion of the uvula are visible; Class III—soft palate is visible; Class IV—soft palate is not visible [21].

Polysomnography (PSG) is the benchmark for monitoring sleep and evaluating sleep disorders including OSA. Data obtained during a PSG include sleep state and brain activity, head and limb movements and muscle tone, eye movement, myocardial activity using an electrocardiogram, snoring, nasal/oral airflow, nasal air pressure, thoracic and abdominal effort, oxygen saturation, and body positions including left lateral, right lateral, supine, and prone positions [22]. Instruments such as STOP-BANG find patients with a low risk of other sleep disorders and a high pretest probability of OSA that are ideal candidates for home sleep apnea testing (HSAT) [22]. Home sleep apnea testing is a cost-efficient method that monitors cardiorespiratory parameters during sleep to determine the presence or absence of OSA. However, if the HSAT is inconclusive, there are technical issues with the equipment, or if OSA is still suspected, a full PSG is recommended [22].

The goals of treating OSA are to reestablish normal breathing during sleep and to mitigate the symptoms of OSA, such as snoring and excessive daytime sleepiness [20]. Managing the symptoms of OSA requires a long-term approach. According to the Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine (AOSATF) [20], it is recommended that the patient play an active role in the decision-making process in determining the most appropriate treatment. Treatment regimens are also guided by the severity of the OSA and include behavioral modalities (e.g., sleep positioning, weight loss, and exercise), positive airway pressure (PAP), oral appliances (OAs), and surgery. The AOSATF [20] recommends that sleep positioning, weight loss, alcohol avoidance before bedtime, and sedative avoidance before bedtime be a part of any behavioral treatment for OSA. Another effective behavioral treatment that is safe and effective for improving AHI and subjective symptoms in patients with both HF and OSA is exercise, including aerobic and strength training [23].

Oral appliances first began as an alternative therapy for those patients with OSA who could not tolerate PAP treatment. The AOSATF [20] recommends OAs as first-line therapy for patients with mild-to-moderate OSA based on preference, those that are not good candidates for PAP treatment, or for patients who have failed PAP treatment. Oral appliances enlarge the upper airway space by either holding the lower jaw in a more anterior position or by preventing the tongue from collapsing into the airway [14].

There are multiple surgeries performed to alleviate or eliminate the effects of OSA. These surgeries include maxillomandibular advancement and pharyngeal surgeries, such as uvulopharyngopalatoplasty and uvulopalatoplasty [14]. These surgeries can be performed individually, simultaneously, or in phases to reduce or eliminate apneas and hypopneas. In their systematic review and meta-analysis, Zaghi et al. [24] found that maxillomandibular advancement is an effective treatment for OSA that substantially reduced the AHI. However, other surgeries including uvulopalatopharyngoplasty, partial glossectomy, and/or nasal surgery have not shown consistent reductions in AHI [24].

A newer surgical treatment uses nerve stimulation to improve the symptoms associated with OSA. The hypoglossal nerve stimulator is an implanted medical device that electrically stimulates the hypoglossal nerve, causing tongue movement, and is timed with breathing to relieve upper airway obstruction [25]. The hypoglossal nerve stimulation system is fully implanted beneath the skin and controlled with a remote [25].

The "gold" standard of OSA treatment for all severity levels has been and continues to be PAP treatment, with continuous PAP (CPAP) being the most utilized option. The AOSATF [19] recommends that CPAP be offered to every patient with OSA. Continuous positive airway pressure treatment works by administering air at a positive pressure through a mask that covers either the mouth, nose, or both, and is connected to a hose that leads to the machine responsible for generating the air pressure [25]. This treatment acts to open the airway by using positive air pressure to open the upper airway and maintain its patency [25]. Continuous positive airway

pressure treatment has been found to be an effective treatment in HF patients. For example, in a systematic review, meta-analysis, and GRADE assessment, Patil et al. [26] noted that individuals who used CPAP reduced their AHI by 86% compared to those not on CPAP therapy. The study also demonstrated that patients who were on CPAP therapy had significantly less excessive daytime sleepiness than controls, had a significantly higher sleep-related quality of life, and significantly lower blood pressure readings. One caveat to PAP use is the avoidance of adaptive servo-ventilation (ASV) in patients with HF from reduced ejection fraction and CSA since ASV has been associated with increased mortality in that population [19].

13.3 Chronic Obstructive Pulmonary Disease

13.3.1 COPD Definition and Prevalence

Comorbid chronic obstructive pulmonary disease (COPD) and HF affect a large number of patients [27]. Chronic obstructive pulmonary disease affects the lower respiratory tract and includes chronic bronchitis and emphysema. Airflow blockage and the overproduction of sputum cause a constellation of breathing-related issues. Changes to the respiratory tract from COPD are not reversible; thus appropriate management is very important [28]. The gradual development of dyspnea, chronic cough, and sputum production with a slow decline in respiratory function over time is the hallmark of COPD [29]. Smoking tobacco is the number one cause of COPD [28–30].

Chronic obstructive pulmonary disease is the fourth leading cause of death in the United States affecting approximately 15.7 million people [31]. According to the US Preventive Services Task Force [28], 14% of adults in the United States aged 40–79 have COPD. Patients with COPD are at higher risk for cardiovascular disease than those without COPD [32]. Many of the clinical manifestations of COPD can mimic symptoms of HF. The incidence of chronic obstructive pulmonary disease in HF patients ranges between 11 and 15% [33].

13.3.2 COPD Chronic Bronchitis

Chronic bronchitis (CB) is defined as a productive cough lasting 3 months and occurring in two consecutive years [34]. Active cigarette smoking is the number one cause of CB. Other causes include passive cigarette smoke, toxic fumes, and particles [31, 34]. The incidence of CB in adults in the United States ranges from 3 to 7% [34]. Chronic bronchitis develops slowly, and symptoms usually begin to present in patients 40 years of age and older [35].

13.3.3 Pathophysiology of Chronic Bronchitis

Chronic bronchitis is a disease of chronic inflammation caused by an irritant, most commonly cigarette smoke [34, 36–38]. Inflammation causes edema, which leads to an increase in the size and number of both goblet cells and mucus glands [34, 36–38]. The result is the hypersecretion of thick, viscous mucus that cannot be cleared by the cilia that line the lower respiratory tract [34, 36–38]. Early in the disease progression, only large bronchi are affected, but over time inflammation damages small bronchioles as well [34, 36–38]. Thick mucus and damage to the smooth muscles of the lower respiratory tract cause narrowing of the airways leading to irreversible obstruction ultimately, resulting in hypoxia [34, 36–38].

13.3.4 COPD Emphysema

Emphysema is commonly associated with chronic bronchitis and is included in the second subgroup of COPD. Emphysema is characterized by permanent and abnormal enlargement of the acini and distal air sacs of the lung parenchyma [39]. Destruction of alveolar elasticity leads to air trapping and narrowing of the bronchioles which increases airway resistance and collapse of the airways during expiration [39, 40]. Smoking is the most significant risk factor for the development of emphysema. In young adults or smokers under the age of 50 who develop emphysema, it can be associated with α1-Antitrypsin deficiency. Patients with emphysema represent approximately one-third of individuals in the United States with COPD [39].

13.3.5 Pathophysiology of Emphysema

Alveolar wall destruction is the hallmark of emphysema. Inhaled oxidants such as from pollution or smoking activate the inflammatory cells which release proteolytic enzymes from neutrophils and macrophages. These cells damage alveolar tissue by breaking down elastic tissue and collagen [39]. With the loss of elastic recoil, inhaled air becomes trapped, and the air sacs become distended. Over time, the increased pressure produces bullae and blebs which leads to a loss of healthy tissue for gas exchange [40]. As lung tissue is compromised, radial traction, which helps hold the airway open for exhalation, is lost. This leads to further airflow resistance and air trapping [39]. Air trapping eventually causes hyperinflation of the lungs and increases the work of breathing for the individual. Prolonged inflammation promotes hyperreactivity of the bronchi with bronchoconstriction [40].

13.3.6 COPD Clinical Manifestations

The three hallmark symptoms of COPD are dyspnea, chronic cough, and sputum production [36]. Some patients, especially in the presence of more severe disease, may also experience some or all of the following: wheezing, chest tightness, fatigue, anorexia, weight loss, lower extremity edema, muscle wasting, depression, and anxiety [30, 36].

Chronic bronchitis presents with a productive cough in patients 50% of the time [34]. The amount of sputum produced can vary, and the sputum color can range from clear to yellow, green, and may be blood-tinged [34]. Thick, purulent sputum is indicative of an increase in inflammatory mediators and is often thought to signify a bacterial infection though the evidence to support this association is weak [36].

There are key differences in the clinical manifestations of chronic bronchitis and emphysema. The hallmark barrel chest of emphysema results from air trapping, hyperinflation, use of accessory muscles, and the increased work of breathing [39]. Individuals often appear thin and cachectic due to muscle wasting and the high caloric demands associated with the increased work of breathing [39]. Patients typically present with progressive exertional dyspnea [39]. Coughing, which is a key sign of CB, is usually only present in emphysema if the patient has an acute infection [39]. Clubbing is also present [39]. See Table 13.2 for a comparison of clinical manifestations between CB and emphysema [40].

13.3.7 Heart Failure and Chronic Obstructive Pulmonary Disease Clinical Manifestations

The primary presenting symptom of both COPD and HF is dyspnea. The dyspnea of COPD is secondary to inflammation, sputum production, and air trapping that leads to progressive damage to the respiratory tract and poor oxygenation of the blood [30, 36]. This limited oxygen exchange leads to hypoxia. Dyspnea related to HF is secondary to the ineffective contractility of the heart and/or the decreased ability to fill the left ventricle causing a decrease in cardiac output [30]. Compensatory

Table 13.2 Clinical manifestations of chronic obstructive pulmonary disease [40]

Clinical manifestation	Chronic bronchitis	Emphysema
Productive cough	• Classic sign	• With infection
Dyspnea	• Late in course	• Common
Wheezing	• Intermittent	• Common
History of smoking	• Common	• Common
Barrel chest	• Occasionally	• Classic
Prolonged expiration	• Always present	• Always present
Cyanosis	• Common	• Uncommon
Chronic hypoventilation	• Common	• Late in course
Polycythemia	• Common	• Late in course
Cor pulmonale	• Common	• Late in course

mechanisms decline over time, which leads to circulatory volume overload and then hypoxia occurs, causing dyspnea [30]. It should be noted that a diagnosis of COPD places a patient at risk for the development of HF. Chronic obstructive pulmonary disease affects the systolic and diastolic function of the heart. Right-sided HF is due to the vasoconstriction caused by hypoxia secondary to COPD, which leads to pulmonary hypertension (cor pulmonale) [30]. Right-sided HF leads to left-sided HF over time [30].

13.3.8 Approach to the Management of Chronic Obstructive Pulmonary Disease and Heart Failure

When managing patients with comorbid COPD and HF, it is important to keep a few things in mind. Each disease can exacerbate the symptoms of the other, and it is often difficult to distinguish presenting symptoms specific to COPD or HF. A thorough evaluation of risk factors is key to a correct diagnosis. A history of smoking is a key component of the assessment, including a patient's pack per day history [41]. Additionally, many diagnostic tests are needed to best identify symptom causes and effective treatment options. See Tables 13.3 and 13.4 for details about diagnostic testing for COPD in HF [33].

Table 13.3 Diagnostic testing for COPD in HF [33]

Diagnostic testing	
Pulmonary function test	Classify airflow limitation; COPD more obstructive; HF more restrictive
Arterial blood gases	Evaluation of hypoxia
ECG	Negative predictive value of HF and COPD
Echocardiogram	Evaluate left ventricular hypertrophy r/t HF; cor pulmonale r/t COPD
Chest X-ray	Difficult to diagnose HF as COPD decreases the cardiopulmonary ratio
BNP	Sensitive marker for HF
Exercise stress testing	Reduced ability to perform with COPD and HF thus influences the clinical interpretation
C-reactive protein	Biomarker for low-grade systemic inflammation r/t atherosclerosis, COPD, and ischemic heart disease
Fibrinogen	Marker of COPD activity; particularly helpful in severe stages and during acute exacerbations
Troponin	Often elevated in COPD patients during exacerbation
Vascular endothelial growth factor	Biomarker for cardiovascular disease; often elevated in COPD exacerbation
Complete blood count	COPD and HF at increased risk for infections; erythrocytosis secondary to smoking
Complete metabolic panel	Evaluation for other potential comorbid conditions such as electrolyte imbalances, diabetes; kidney disease, liver disease
Thyroid panel	Hyperthyroid and hypothyroid conditions have multisystem effects and could exacerbate COPD and HF

Table 13.4 GOLD classification for airflow limitation per spirometry testing [36]

GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very severe	$FEV_1 < 30\%$ predicted

13.3.9 Pharmacological Management of Chronic Obstructive Pulmonary Disease and Heart Failure

Standards of care for COPD and HF should be followed regardless of comorbid occurrence. There is no evidence to indicate an alternative approach should be used for patients who have COPD-HF [36]. There are several considerations when comanaging COPD with comorbid HF. Ongoing monitoring for side effects and adverse reactions to pharmacotherapy agents should be considered appropriate for each patient [30].

13.3.10 Medications Used in Comorbid Chronic Obstructive Pulmonary Disease and Heart Failure

Antiplatelet therapy has been shown to dramatically reduce all-cause mortality in patients with COPD [42]. Further, multiple studies show that aspirin use is associated with fewer COPD acute exacerbations and slower progression in pathology as evidenced by radiology studies [42]. Smoking is well known to increase platelet aggregation, but the role of platelets in COPD may be even more significant than previously known. Platelets are thought to play a role in the loss of alveolar elasticity which contributes to the development of emphysema. Regular aspirin use is associated with a significant reduction in emphysema progression [43]. As platelets aggregate in the lung due to local mediators, they may have a role in pulmonary vascular remodeling. This vascular remodeling can cause pulmonary hypertension, a significant complication of COPD that is compounded with heart failure [42].

Renin-angiotensin-aldosterone system blockade is a mainstay of therapy for CHF. Angiotensin-converting enzyme is expressed primarily in the endothelium of the lung tissue and thus a common side effect of ACE inhibitors is cough. Providers and COPD patients can be reassured that ACE inhibitors do not increase the risk of bronchospasm or angioedema [30, 44].

Beta-blockers are generally underutilized in patients with COPD and heart failure. Coexisting asthma and COPD are associated with suboptimal beta-blocker prescribing [45]. This is due primarily to provider hesitancy because nonselective beta-blockers can exacerbate pulmonary disease by antagonizing beta 1 and beta 2 receptors throughout the body and cause bronchospasm [45]. While these effects can be mild and temporary, there is mixed evidence of potential harm [44, 46]. Cardioselective beta-blockers that preferentially antagonize beta-1 receptors are highly favored, and ample evidence demonstrates increased rates of survival in

patients with comorbid COPD and HF without compromising lung function [44, 45, 47]. Starting doses of cardioselective beta-blockers should be low and patients should be monitored for any bronchospasm [48].

Bronchodilators are central to the pharmacologic management of COPD. Side effects of these beta 2 agonists include tachycardia secondary to beta 2 stimulation and increased myocardial oxygen demands [44]. Evidence of harm with the use of beta-agonists in HF with comorbid COPD is mixed. Some observational studies show a potential increased risk of sinus tachycardia and possible rhythm disturbances in patients with symptomatic HF but retrospective reviews of multiple RCTs showed no long-term impact on mortality [27]. Close monitoring of HF patients starting bronchodilator therapy should be conducted on a case-by-case basis [27]. Short and long-acting beta-agonists are first-line pharmacotherapy for COPD patients to relax the smooth muscle of the airway and improve symptoms [36]. Long-acting beta-agonists have further been shown to significantly improve FEV_1 and reduce symptoms [32].

There are several other medications to consider when treating comorbid COPD-HF. Anti-muscarinic agents are used commonly in COPD and have been shown to improve lung function and reduce the need for oral steroids [36]. There has been a report of a small increase in cardiovascular events for patients with COPD regularly treated with antimuscarinic agents but this has not been borne out in larger trials looking specifically at long-term efficacy and safety [33]. Inhaled corticosteroids are also used frequently in COPD. The adverse events associated with ICS therapy are primarily related to an increased risk for infection [29]. They are not used as monotherapy in COPD and there are no specific cardiac adverse events associated with their use. In contrast, oral steroids should be reserved for only the most severe COPD exacerbations since they increase sodium and fluid retention and can aggravate heart failure [44]. This effect is dose-dependent [30]. Diuretics are frequently used in HF for treating symptoms of fluid retention but can also relieve lung congestion which can improve lung compliance and reduce the work of breathing [30, 44]. The dose of diuretic should be the lowest effective dose to preserve cardiac output, which is particularly sensitive in these patients with COPD-HF [44]. Additional considerations should be made for patients who experience COPD exacerbations that require antibiotics. Macrolides should be used with caution in patients with heart failure due to potential QT prolongation [30].

13.3.11 Nonpharmacological Management of Comorbid Chronic Obstructive Pulmonary Disease and Heart Failure

13.3.11.1 Smoking Cessation

Smoking cessation is the most significant modifiable risk factor and should be a priority in the treatment of comorbid diseases. This has the most impact on disease progression of all interventions, especially COPD [29, 49]. Patients should be evaluated for readiness to quit smoking at every visit. The World Health Organization

Table 13.5 5 As [50]. [Reprinted with permission from World Health Organization, World Health Organization. Toolkit for delivering the 5A's and 5R's brief tobacco interventions to TB patients in primary care, 2014, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6358171/, with permission from World Health Organization]

Ask	Includes any aspect of the encounter which addresses smoking. This includes diagnosis codes applied to the visit, updated smoking status in the patient's social history, or mentions of tobacco use or prevention in the text notes
Advise	Includes generic statements advising the patient to quit. This is typically indicated by imperative, directive statements by the clinician
Assess	Includes statements reflecting a patient's readiness to quit, usually indicated by phrases that invoke the patient's current intent, motivation, or effort at quitting
Assist	Includes statements addressing commitment to a method to achieve quitting. This includes ordering, planning, or provision of information relating to smoking cessation medications or nicotine replacement therapies; by a notation ordering, planning, or provision of information related to outside cessation help; an indication of aspects of counseling to quit smoking including in-office discussion of barriers, triggers, strategies, etc., related to quitting
Arrange	Includes statements documenting specific plans for follow-up with a patient's effort to quit

recommends the use of "the 5As" which are ASK, ADVISE, ASSESS, ASSIST, and ARRANGE to document smoking cessation counseling in the clinic visit progress note (Table 13.5) [50]. Nonpharmacologic interventions such as cognitive behavioral therapy, smoking cessation intervention hotlines, and individual and/or group programs may assist patients [51]. A combination of nonpharmacologic and pharmacologic treatment yields the highest chance for successful cessation in many patients. Nicotine replacement therapy assists with the withdrawal symptoms patients often experience. Oral medications such as varenicline and bupropion have proven helpful [52]. Many smokers also experience depression and/or anxiety, and antidepressants and/or anti-anxiolytics may also help with smoking cessation for these patients [52].

13.3.11.2 Cardiopulmonary Rehabilitation

Chronic obstructive pulmonary disease and HF affect patients' exercise tolerance and quality of life substantially [29, 49, 53]. Daily activity levels, most specifically walking, are significantly decreased and the intensity of symptom exacerbation is elevated in this population [53]. Avoidance of exercise and other activities of daily living that increase symptoms cause patients to avoid these activities, resulting in further deconditioning thus becoming a detrimental cycle [53, 54]. Decreases in blood oxygen levels related to limited airflow related to impairments in the respiratory system and excess circulating volume cause problematic symptoms [29, 53, 54]. Patients should be encouraged to participate in cardiopulmonary rehabilitation to increase exercise tolerance and decrease symptoms [54]. Cardiopulmonary rehabilitation has been shown to improve overall symptoms more so than pharmacological interventions alone [55]. Cardiopulmonary rehabilitation includes an assessment of the patient's baseline level of activity tolerance so an individualized plan can be developed. The goals of the plan would be to increase fitness, decrease symptoms,

reduce exacerbations, and decrease hospitalizations [54, 56]. Rehabilitation programs tend to be interdisciplinary and include such things as aerobic exercise, strength training, Tai Chi, disease education, and behavior change counseling [29, 54, 56].

13.3.11.3 Dietary Considerations

Malnutrition and weight changes may be experienced by patients for several reasons. Malnutrition is a result of decreased caloric intake with accompanying weight loss and functional decline [57, 58]. The increased metabolic demand required for breathing as well as other pathophysiologic problems can lead to unintentional weight loss and malnutrition in patients with COPD [57]. In addition, malnutrition contributes to COPD by increasing the decline of respiratory function further increasing exercise intolerance [57, 59]. Early satiety and anorexia also contribute to malnourishment. As is commonly known, sodium intake is the most frequent dietary change recommended in the treatment of heart failure. Fluid retention is directly correlated to sodium intake leading to the lower extremity and intestinal edema as well as dyspnea and overall weight gain [58, 60, 61]. Intestinal edema, such as that seen in patients with HF, often leads to early satiety resulting in decreased caloric intake [58, 61]. Referral for nutritional counseling should be considered for these patients.

13.3.11.4 Recommended Vaccinations

Immunocompromised patients, including those with COPD and HF, should stay up to date on vaccinations. Influenza, pneumococcal, and COVID-19 vaccines decrease the likelihood of hospitalizations and mortality secondary to lower respiratory tract infections. Either live attenuated or killed virus influenza vaccines may be given [29, 62]. Pneumococcal vaccines which are recommended for patients over the age of 65 are also recommended for patients with COPD regardless of age [29, 63]. Recommendations for COVID-19 vaccinations continue to evolve. As of October 2022, COVID-19 vaccinations are recommended for patients with any cardiovascular disease (including HF) and/or COPD. These patients are at high risk for adverse outcomes secondary to a COVID-19 infection [64, 65].

13.4 Case Study

Subjective: R.M. is a 65-year-old white male with a history of HFrEF (LVEF 35%), type 2 DM, hyperlipidemia, obesity, general anxiety, and depression, who presents with his wife for evaluation. According to his wife, over the past month, "he has been coughing non-stop and complains about being tired all the time." She's worried he has bronchitis and wants an antibiotic and cough medicine prescribed. In addition, he states he does not feel rested upon waking and often falls asleep watching TV or reading a book. His weight has been stable and has not noticed any LE edema. Has not required furosemide since last month. He denies chest pain, palpitations, or paroxysmal nocturnal dyspnea. He is experiencing increased dyspnea on

exertion with ADLs. He denies any worsening anxiety but endorses not enjoying activities with family and friends "like I used to."

PMH

HFrEF (LVEF 35%)
- Type 2 diabetes
- Hyperlipidemia
- Obesity (BMI = 35.7 kg/m^2)
- Generalized anxiety disorder
- Major depressive disorder (recurrent, moderate)

Medications

Metformin 1000 mg twice daily
- Dapagliflozin 10 mg daily
- Rosuvastatin 20 mg daily
- ASA 81 mg daily
- Carvedilol 25 mg twice a day
- Sacubitril/valsartan 24–26 mg twice a day
- Spironolactone 25 mg once a day
- Furosemide 40 mg once a day as needed for weight gain >3 pounds overnight
- Sertraline 100 mg daily
- Alprazolam 0.25 mg as needed for acute anxiety

Family History

His family history is unknown as he was adopted.

Social history: He and his wife have been married for 40 years and have three children, all of whom live out of state. He worked as a long-haul truck driver until his retirement earlier this year. He smoked one pack of cigarettes a day for 47 years. He quit last year after he was diagnosed with heart failure.

ROS

Constitutional: no fever, night sweats, chills, or unintended weight change

HEENT: wears glasses, no recent change in vision, no eye pain, no double vision, last eye exam 6 months ago; no ear pain, discharge, ringing, or dizziness; no change in hearing; no nasal congestion or nose bleeds; no sore throat, no hoarseness, no bleeding gums

Neck: no swollen glands, no stiffness

CV/Respiratory: shortness of breath especially with exertion, no chest pain, no palpitations, no bilateral lower extremity edema; + cough occasionally productive, stopped smoking 2 years ago

GI: decreased appetite, no nausea, vomiting, diarrhea, constipation; no abdominal pain; no rectal bleeding or melena

GU: difficulty starting a urine stream, no incontinence, no nocturia, no frequency, no dysuria

MSK: no pain or swelling of any joints, + morning stiffness in knees and hands, no history of fractures or gout

Neuro: no headaches, no seizures, no weakness, no numbness, no tremors

Heme: no history of anemia, no transfusions

Psychiatric: + anxiety and depression; no psychiatric hospitalizations, no history of suicidal ideation or attempts; no problems with memory; + sleep disturbance (daytime somnolence)

Objective

Vital Signs: T 98.6 BP 110/70 HR 88 RR 22 O^2 sat 88% RA

Physical examination is unremarkable except for crackles throughout all lung fields which clear with cough.

Testing Ordered

Concerns arise that R.M. may have undiagnosed obstructive sleep apnea and chronic obstructive pulmonary disorder. He is given the STOP-Bang questionnaire and answers "yes" to 3 of 4 STOP questions and "yes" to 3 of 4 Bang questions. In addition, his score on the ESS is 14 indicating moderate excessive daytime sleepiness.

Diagnostic testing for his dyspnea and cough includes a chest X-ray that reveals flattening of the diaphragm with destruction of the lung parenchyma. There are no findings suggestive of pneumonia. Pulmonary function tests reveal an FEV_1 of 65% placing him in GOLD category two for COPD, with moderate severity of disease. Alpha-1 antitrypsin is negative. A complete blood count reveals no evidence of anemia or infection. An echocardiogram reveals a reduced ejection fraction, 35%, which is unchanged from one done six months ago.

Assessment: *Newly diagnosed obstructive sleep apnea and chronic obstructive pulmonary disease*

HFrEF (LVEF 35%)

Type 2 diabetes

Hyperlipidemia

Obesity (BMI = 35.7 kg/m^2)

Generalized anxiety disorder

Major depressive disorder (recurrent, moderate)

Plan:

HFrEF, type 2 diabetes, hyperlipidemia, obesity, anxiety, and depression medications were refilled for 3 months without changes.

Sleep apnea: There was a minimal concern for other sleep disorders, but an HSAT was ordered and R.M. was found to have an AHI = 50 episodes/h. As a result, CPAP therapy was ordered and R.M. was able to tolerate the mask and was able to wear it for 6–7 h/night for 6 days/week. Automated reports obtained from the CPAP machine now show that R.M. is having <5 apneic or hypopneic episodes per hour.

COPD: A long-acting bronchodilator is begun at this visit. In addition, R.M. receives counseling on the importance of avoiding passive cigarette smoke and other noxious fumes. A cardiopulmonary rehabilitation referral is made to

evaluate his current physical activity level to improve it with therapy. COPD places him at increased risk for infections, and R.M. was given influenza and pneumococcal vaccines.

At a return visit, R.M. states that he is feeling more rested upon waking, has more energy throughout the day, and is not falling asleep while watching TV or reading a book. His cough has improved. His respiratory rate today is 16 and his oxygen saturation is 96% on room air. Lungs are bilaterally CTA.

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Pulmonary Hypertension in Heart Failure

14

Douglas J. Pearce

14.1 Introduction

The subject of pulmonary hypertension is complex, and the terminology is frequently confusing. Since its beginning in 1973, there have been six World Symposia on Pulmonary Hypertension (WSPH). During these symposia, experts in PH attempt to classify PH patients based on clinical characteristics and hemodynamic findings. With each symposium, there have been changes in classification and terminology. These changes are based on evolving scientific knowledge and are geared toward treatment recommendations and management protocols. However, there is recognition that the disease taxonomy lacks a clear connection to pathobiology [1]. In August of 2022, an update on pulmonary hypertension was published by a combined task force of the European Society of Cardiology and the European Respiratory Society [2]. Updates from this document have been incorporated here. Presently, patients with PH are clinically classified into five groups: each with subgroups (Table 14.1). The groups are frequently referred to as World Health Organization (WHO) Groups 1–5. It is important to understand that the term "pulmonary arterial hypertension" only refers to WHO Group 1 patients. It is not synonymous with the term "pulmonary hypertension" as a whole. Patients with "pulmonary hypertension associated with left heart disease" (PH-LHD) are categorized as WHO Group 2 [2].

D. J. Pearce (✉)
University of Tennessee Health Sciences Center, Memphis, TN, USA
e-mail: drpearce@uthsc.org

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_14

Table 14.1 Pulmonary hypertension clinical classifications from the 2022 ESC/ERS[a] guidelines for the diagnosis and treatment of pulmonary hypertension [2]

Group type	Sub group type	Associations
Group 1 PAH	1.1 Idiopathic	1.1.1 Nonresponders at vasoreactivity testing 1.1.2 Acute responders at vasoreactivity testing
	1.2 Heritable	
	1.3 Associated with drugs and toxins	
	1.4 Associated with	1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis
	1.5 PAH with features of venous/capillary (PVOD/PCH) involvement	
	1.6 Persistent PH of the newborn	
Group 2 PH associated with left heart disease	2.1 Heart failure (HF)	2.1.1 HF with preserved ejection fraction 2.1.2 HF with reduced or mildly reduced ejection fraction
	2.2 Valvular Heart Disease	
	2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH	
Group 3 PH associated with lung diseases and/or hypoxia	3.1 Obstructive lung disease or emphysema 3.2 Restrictive lung disease 3.3 Lung disease with mixed restrictive/obstructive pattern 3.4 Hypoventilation syndromes 3.5 Hypoxia without lung disease (e.g., high altitude) 3.6 Developmental lung disorders	
Group 4 PH associated with pulmonary artery obstructions	4.1 Chronic thrombo-embolic PH 4.2 Other pulmonary artery obstructions	
Group 5 PH with unclear and/or multifactorial mechanisms	5.1 Hematological disorders 5.2 Systemic disorders 5.3 Metabolic disorders 5.4 Chronic renal failure with or without hemodialysis 5.5 Pulmonary tumor thrombotic microangiopathy 5.6 Fibrosing mediastinitis	

[a]*ESC* European Society of Cardiology, *ERS* European Respiratory Society, *HF* heart failure, *HIV* human immunodeficiency virus, *PAH* pulmonary arterial hypertension, *PCH* pulmonary capillary hemangiomatous, *PH* pulmonary hypertension, *PVOD* pulmonary veno-occlusive disease

14.2 Pathophysiology

Pulmonary hypertension due to left heart disease is the largest category of PH, accounting for up to 70% of PH cases [2]. Group 2 PH has four subgroups: 2.1 PH due to heart failure with preserved left ventricular ejection fraction (HFpEF), 2.2 PH due to heart failure with reduced left ventricular ejection fraction (HFrEF), 2.3 PH due to valvular heart disease, and 2.4 congenital/acquired cardiovascular conditions leading to post-capillary PH. Patients who fall into subgroups 2.3 and 2.4 are likely to receive specialty care; in this chapter, we will focus on the diagnosis and management of the patients who would be found in subgroups 2.1 and 2.2. Of note, valvular heart disease is a common in conjunction with HFrEF. Thus many patients will present with a combination of Group 2 subgroups. It should be noted that the majority of patients diagnosed with PH-LHD have HFpEF as the underlying etiology. HFpEF is the most common cause of PH in general [2, 3].

While pulmonary artery systolic pressure can be estimated using noninvasive testing, the diagnosis of PH requires a right heart catheterization. For decades following the 1973 WSPH, PH was defined as an mPAP >25 mmHg [3]. During the sixth WSPH in 2018, using newer data, PH was re-defined as a mean pulmonary artery (mPA) pressure >20 mmHg [4]. Regardless of etiology, PH should be further characterized during an invasive hemodynamic assessment. The current terminology divides PH patients into three groups using hemodynamic status: (1) patients with pre-capillary PH, (2) patients with isolated post-capillary PH (IpcPH), and (3) patients with combined pre- and post-capillary PH (CpcPH) (Table 14.2). The overall concept is that patients with pre-capillary PH have an elevated mPAP and an increased pulmonary vascular resistance (PVR), but have a normal pulmonary artery wedge pressure (PAWP). Patients with IpcPH have an elevation in their PAWP (due

Table 14.2 Pulmonary hypertension hemodynamic parameters [2]

Type of pulmonary hypertension (PH)	Hemodynamic parameter[a]
Pre-capillary Pulmonary hypertension	mPAP = >20 mmHg PAWP = ≤15 mmHg PVR = >2 WU
Pulmonary hypertension (PH)	mPAP = >20 mmHg
Isolated post-capillary pulmonary hypertension (IpcPH)	mPAP = >20 mmHg PAWP = >15 mmHg PVR = ≤2 WU
Combined post/pre-capillary pulmonary hypertension (CpcPH)	mPAP = >20 mmHg PAWP = >15 mmHg PVR = >2 WU
Exercise pulmonary hypertension (Exercise PH)	mPAP/CO slope between rest and exercise = >3 mmHg/L/min

[a]*CO* cardiac output, *mPAP* mean pulmonary arterial pressure, *PAWP* pulmonary arterial wedge pressure, *PVR* pulmonary vascular resistance, *WU* wood units

to passive pulmonary congestion) but a normal (<2 Wood Units[1]) PVR. Finally, patients diagnosed with CpcPH have elevations of all three of the variables [2, 4].

Patients diagnosed with pre-capillary PH would fall into clinical groups: 1, 3, 4, or 5. Patients diagnosed with pulmonary hypertension due to left heart disease either have IpcPH or CpcPH (Table 14.2). It is believed that patients with PH-LHD initially have an elevation in PAP due to an increase in downstream pulmonary venous pressure because of elevated left atrial pressure. An example of this might be stenosis of the mitral valve, with volume and pressure backing up behind the diseased valve. Historically, this was a common phenomenon due to rheumatic valvular heart disease [4]. An elevation of left ventricular (LV) pressure due to LV dysfunction is common, regardless of etiology. Pulmonary circulation, however, is not meant to be a high-pressure system. The initial response to the high pressure is likely pulmonary arteriole constriction; at first reversible [4]. A significant subset of patients with PH-LHD go on to develop a vasculopathy with structural changes similar to those seen in pre-capillary pulmonary hypertension [4, 5]. The patients with PH-LHD who develop CpcPH seem to have a genetic predisposition [6]. A recent study reported an overlap of gene expression between patients with pre-capillary PH and those with CpcPH [7]. When compared with patients with IpcPH, patients with CpcPH generally are more impaired and have a poor prognosis [8].

14.3 Assessment of PH-LHD

As previously discussed, the diagnosis of PH requires the finding of an mPAP >20 mmHg on a right heart cath. However, PH is rarely initially diagnosed from invasive testing. It is more common that a history and physical examination are obtained, followed by noninvasive testing. The symptoms and signs present with PH-LHD are typically those associated with heart failure. Thus, patients in the early stages of PH will complain of dyspnea on exertion and fatigue. As their disease process progresses, they frequently develop paroxysmal nocturnal dyspnea, orthopnea, and peripheral edema. On examination, they may or may not display signs of volume overload. Signs of volume overload include elevated jugular venous pressure, hepato-jugular reflux, hepatomegaly, ascites, and edema. Unless the patient is acutely decompensated, pulmonary rales are often absent. This is thought to be due to enhanced drainage of the pulmonary lymphatics. Additionally, thickening of the pulmonary capillary basement membrane may limit the transudation of fluid into the airways [4]. Noninvasive testing includes an ECG, chest X-ray, and an echocardiogram. Frequently a cardiac MRI is also performed. The greater the number of risk factors for LHD that the patient has, coupled with abnormal cardiac test findings, the greater the likelihood that the patient's PH is PH-LHD. Findings that

[1] The term Wood Unit is in honor of Australian cardiologist, Dr. Paul H. Wood. He was an early pioneer in the field of hemodynamics and the most respected European cardiologist of his day. He died of a myocardial infarction at the age of 54 on July 13, 1962. The SI unit for vascular resistance is Dynes s cm^{-5}. It can be calculated by multiplying the WU value by 80.

strongly favor a diagnosis of PH-LHD are age >60 years, the presence of hypertension, diabetes, obesity, and coronary arteriolosclerosis. Imaging findings of valvular heart disease, left atrial enlargement, and left ventricular hypertrophy and/or dysfunction, also favor PH-LHD as the correct diagnosis [5, 9].

Echocardiography (echo) is typically the first cardiac imaging test utilized in the assessment of possible PH. Figure 14.1 addresses some findings that help in distinguishing between PH- LHD and PAH. Additionally, if the echo estimated right ventricular systolic pressure (RVSP) is >35 mmHg, the mPAP at cath will likely be >20 mmHg. However, there is much room for error in this doppler derived estimate. Attention to echo quality metrics is critical [9]. Peak tricuspid regurgitation velocity >3.4 m/s is also highly suggestive of PH [6].

Provocative testing is recommended in patients with HFpEF who have an intermediate to high likelihood of PH-LHD, but an mPAP in the normal range at rest. Exercise right heart catheterization is typically utilized but requires a complex cath lab setup [10, 11]. A fluid challenge of 500 ml NS over 5 min is easier to perform and much more common in practice [12, 13]. It should be noted that exercise pulmonary hypertension is an independent predictor of poor cardiovascular outcomes [14]. However, analysis of data derived from provocative testing is highly controversial and beyond the scope of this chapter [15].

The hemodynamic differentiation between IpcPH and CpcPH is based on pulmonary vascular resistance (Table 14.2). Both types of patients have an mPAP >20 mmHg as required for the diagnosis of PH. Both types of patients have a PAWP >15

		Likelihood of	
Echo parameter	Echo finding	PH-LHD	PAH
Ejection fraction	<50%	↑	↓
Left atrial size	LAD > 40 mm LAVI > 28 mm/m^2	↑	↓
LV wall thickness	>11 mm	↑	↓
Transmitral Doppler	Grade II/III diastolic dysfunction	↑	↓
Mitral regurgitation	Severity > 1 +	↑	↓
RV size	RV-to-LV area > 1.0	↓	↑
Interventricular septum	Systolic flattening Lateral-septal TDI disparity	↓	↑
Interatrial septum	Bowing into LA	↓	↑
RV systolic function	TAPSE <1.5 cm	↓	↑
RVOT Doppler	Notching	↓	↑

LAD, left atrial dimension; LAV1, left atrial volume index; LHD, left heart disease; LV, Left ventricular; PH, pulmonary hypertension; RV, right ventricular; RVOT, right ventricular outflow; TDI, tissue Doppler imaging.

Fig. 14.1 Distinguishing pulmonary hypertension-left heart disease from pulmonary artery hypertension using echocardiography [Reprinted from Journal of Heart and Lung Transplantation, Fang, JC, DeMarco, T., Givertz, MM, et al., World Health Organization Pulmonary Hypertension Group 2. Pulmonary hypertension due to left heart disease in the adult—a summary statement from the Pulmonary Hypertension Council of the International Society for Heart and Lung Transplantation, 913–933. Copyright (2012), with permission from Elsevier]

mmHg reflecting an elevated left atrial pressure. However, patients with CpcPH have a PVR >2 WU consistent with a pre-capillary component of their PH. Over time, this pre-capillary component can often be reversed with treatment of the pathology causing the elevated left atrial pressure. This issue is particularly important for patients being considered for heart transplantation. An irreversibly elevated PVR is a contraindication for a heart transplant. The donor right ventricle, unadapted to high vascular resistance, quickly fails [7].

Some pulmonary hypertensive specialists also incorporate diastolic pressure gradient (DPG) and trans-pulmonary pressure gradient (TPG) into their assessment. DPG = diastolic pulmonary artery pressure (dPAP) − PAWP. TPG = mPAP − PAWP. However, the calculated PVR is felt to be a more robust predictor of outcome [2]. As previously noted, CpcPH has a worse prognosis than IpcPH. Indices of right ventricular (RV) function, such as RVEF and RV longitudinal strain, are also very helpful prognosticators [16, 17]. Impaired RV function portends a poor outcome.

14.4 Case Study

Subjective: Mrs. Beverly Johnson is a 44 y/o WF referred for evaluation and treatment of difficult-to-control hypertension, and dyspnea on exertion (DOE).

Chief Compliant: "I have trouble breathing when walking; particularly on an incline. Also, my ankles are swollen at the end of the day."

History of Present Illness: We were asked to see this 44 y/o WF in consultation for evaluation and management of DOE and difficult to control HTN. The patient has been overweight since her early teens, and after two children her weight has continued to increase. Presently she weighs 244 pounds with a BMI of 43. Her blood pressure has risen with her weight. At the same time, her exercise tolerance has declined. She now has NYHA Class III dyspnea. No PND. No chest pains. She sleeps on two pillows. Her husband says that she snores and stops breathing at night. She is sleepy during the day, but only falls asleep in her Lazy Boy recliner when at home. She does not fall asleep at work. She has tried multiple antihypertensive combinations but has not achieved good BP control. She does not like amlodipine because it makes her lower extremity edema much worse. An ECG is the only cardiac testing that she has had.

Past medical history: Obesity, HTN, fatigue, daytime somnolence, pregnancy.

Past surgical history: T&A, cholecystectomy, hysterectomy for uterine bleeding, Lap Band inserted and explanted.

Social history: Married, no alcohol, tobacco, or drugs. Works at a dry cleaner drop-off site.

Family history: Father and sister are obese. No known cardiac disease.

Allergies: None. Amlodipine causes increasing lower extremity edema.

Medications: Losartan/HCTZ 100/12.5 mg q AM, metoprolol succinate 25 mg q HS, furosemide 20 mg tablet daily, as needed for edema. She doesn't take it because it makes her "run to the bathroom."

Review of Systems: Pertinent positives noted in HPI.

Objective:

General: Obese, Caucasian female, comfortable sitting on the examination table.

Vitals: P-88, BP-176/94, R-16, Oxygen saturation: 98% on room air.

Wt.-243 lbs, Ht.-63 in., BMI-43 kg/m^2.

Eyes: Non-icteric, conjunctiva not pale.

Neck: Obese, thyroid grossly normal, no obvious JVD, + HJR with the patient 45°, carotid artery pulsations 2+ without bruit.

Heart: RRR without murmur or rub. A subtle S4 is present. Lungs: Clear to auscultation and percussion.

Abdomen: Obese, no obvious organomegaly or mass. Mild RUQ tenderness.

Extremities: Upper and lower extremities are obese. There is ~ 2+ LE edema about 1/2 the way up the tibia. There is no cyanosis or clubbing.

Skin: Butterfly tattoo in right suprascapular area, mild chronic venous stasis changes bilaterally of the LE.

Musculoskeletal and neurologic exams are grossly normal.

Laboratory: CBC, CMP, and TSH were normal, except for a fasting Glu of 122. BNP- 311.

ECG: NSR. Mild changes c/w LVH.

Echocardiogram: Left ventricular hypertrophy, mild right ventricular enlargement, Grade 2 left ventricular diastolic dysfunction, mild tricuspid regurgitation, right ventricular systolic pressure (RVSP) estimated at 50 mmHg.

14.4.1 Interim Assessment and Plan

Objective assessment of this patient's vignette notes several findings contributing to likely pulmonary hypertension, including obesity, systemic arterial hypertension, physical exam findings of volume overload, as well as an elevated BNP level. An echocardiogram is consistent with HFpEF and pulmonary hypertension, given notations of diastolic dysfunction and an elevated RVSP. The diagnosis is likely hypertensive heart disease with HFpEF and subsequent WHO Group 2 PH. Sleep-disordered breathing should also be considered a comorbidity. Thus, this patient case is also consistent with a component of WHO Group 3 PH.

PH is a concern. Providers must consider possible etiology, such as IpcPH or CpcPH? Given the current data, differentiation is not known. A right heart catheterization may be helpful; however, additional conditions should be treated first as assessing hemodynamics at this point would not alter treatment plans. Managing hypertension and treating volume overload should be a priority at this point. In addition, screening for untreated sleep apnea is pertinent.

The goal for treatment of PH-LHD is to treat the underlying LHD and associated comorbidities. There is no indication at this point for a PAH-specific drug [16, 18]. Emphasis should be placed on decongesting with a loop diuretic, monitoring electrolytes, and optimizing blood pressure control. Adding spironolactone or eplerenone may be appropriate. Long-acting nitrates may also lessen dyspnea. Sacubitril/valsartan (Entresto) is now indicated for all forms of chronic heart failure in adults. It

would be reasonable to discontinue losartan/HCTZ, begin sacubitril/valsartan, and replace the HCTZ with chlorthalidone. Notably, chlorthalidone may be superior to HCTZ in this situation given its longer duration of action [19]. Next steps should be to focus on titrating sacubitril/valsartan to the maximum tolerated dose, with careful monitoring of electrolytes and renal function. Lastly, emphasis should be placed on suspected sleep apnea and likely the metabolic syndrome. Collaboration among specialty providers and primary care providers is essential given multiple complex comorbidities.

14.4.2 Follow-Up

After executing the plan, Mrs. Johnson returns in two weeks. She is feeling better. Lower extremity edema has resolved. Dyspnea has improved, now NYHA class II. Blood pressure better, now 138/77. Pulse is 80 and regular. She was seen by her primary care provider and placed on metformin. She has a sleep study pending in ten days. At this time, we will increase metoprolol succinate to 50 mg. At her subsequent 4-week follow-up with cardiology, symptoms continued to improve. Before her visit, she was placed on CPAP. Daytime somnolence has resolved. She has lost 14 pounds and can walk farther without dyspnea. P-68. BP-130/70, R-14. She was reassured that she was making good progress and advised to return to cardiology in 3 months.

Following 90 days of heart failure guideline-directed medical therapy, she has lost another six pounds, is compliant with her CPAP, and says that her HbA1C is "normal." However, she continues to have NYHA class II symptoms. She can walk down to the mailbox without trouble, but if she pushes herself at all she becomes dyspneic. No chest pain or other symptoms. She is euvolemic by exam. Her pulse is 66; BP-132/70. Current medications: Entresto 97/103 mg bid, chlorthalidone 25 mg q AM, spironolactone 25 mg q AM, torsemide 20 mg q AM, metoprolol succinate 50 mg q HS, metformin 500 mg bid, and atorvastatin 40 mg q HS. At this point, we consider checking another BNP. Now that she is on sacubitril, an NT-ProBNP level is ordered. Results indicated NT-ProBNP level of 350. Given ongoing NYHA class II dyspnea and lack of evidence of volume overload by exam, we elect to proceed with a right heart catheterization. Results of right heart catheterization at rest are as follows: mPAP = 19 mmHg, PAWP = 9 mmHg, C.O.= 6.09 l/m, C.I. = 3 l/m/m^2. PVR = 2 WU (160 Dynes s cm^{-5}). These results are in the normal range. So, why does she have DOE and impaired exercise tolerance? Factors may include: obesity (BMI-39.5), diagnosis of sleep-disordered breathing (albeit using CPAP), BP level is suboptimal, and she surely still has a "stiff heart" with impaired function. Thus, she still has HFpEF. While her hemodynamics are normal at rest, her pulmonary artery pressures almost certainly increase with exercise, resulting in PH. Would a provocative test confirm this suspicion? Possibly, but it will not likely change the current management. Continuing to emphasize treating the causes of LHD should be the goal. In February 2022, the indications for implantation of the CardioMEMS™ HF System were expanded to include patients with NYHA functional class II heart failure (www.abbot.com). The CardioMEMS™ device is a small (about the size of

a paperclip), permanently implanted, pulmonary artery pressure and heart rate monitor. In the GUIDE-HF trial, the CardioMEMS™ system was used to guide heart failure therapy based on pulmonary artery pressures. Results demonstrated significant reductions in hospitalization, emergency visits, and death [20].

The above case report depicts an example of how patients typically present with PH-LHD. Consider the following: what if her right heart hemodynamics were concerning for CpcPH? Hemodynamically, we can encounter this situation in two possible scenarios. The first is that the PAWP is >15 mmHg c/w volume overload and the PVR is >2 WU indicating pre- and post-capillary components to the elevated pulmonary pressures. In this case, we would treat the post-capillary components and then reassess the hemodynamics. Often reversing the pulmonary congestion will correct the pre-capillary component over time. However, what if on right heart catheterization, Mrs. Johnson had these findings: mPAP = 30 mmHg, PAWP = 9 mmHg, C.O. = 6.09 l/m, C.I. = 3 l/m/m2, and PVR = 3.5 WU (280 Dynes s cm^{-5}). Under these circumstances, we would presume she had HFpEF with CpcPH and that we have corrected the post-capillary component, but we are left with a residual pre-capillary component. When we encounter this situation, it is very tempting to try a PAH-specific drug to treat the pre-capillary component of the CpcPH. Several studies using PAH-targeted medications have been undertaken in patients with PH-LHD. Drugs including sildenafil, bosentan, epoprostenol, and riociguat have been tested [4, 6]. Results have largely been neutral or negative; however, most of these studies did specifically study patients with CpcPH [4]. Subjects could have had either IpcPH or CpcPH when randomized. A recent retrospective study specifically looked at 50 patients with CpcPH treated with PAH therapies. No improvement in symptoms, exercise capacity, or echocardiographic parameters was seen [18]. Nevertheless, some centers will cautiously try PDE-5 inhibitors in selected patients [6]. Interestingly, a study published in May 2021 randomized 37 prespecified patients with PH-HFpEF to a once-per-week infusion of levosimendan vs placebo for six weeks. They observed a statically significant improvement in PAWP and 6 MWD [21]. Of note, levosimendan is a calcium sensitizer that increases cardiac inotropy and vasodilation. It is administered intravenously. Levosimendan was invented in Finland in the 1990s. It is available in over 60 countries but not in North America [22]. We know that some patients with CpcPH will normalize pulmonary pressures with the treatment of LHD and a persistent reduction of left atrial pressure; however, many do not. In the future, hopefully, advancements in research will uncover a group of CpcPH patients who will respond favorably to specific PAH or other novel therapies.

14.5 Conclusions/Practice Pearls

- PH is common in patients with heart failure due to left heart disease, regardless of etiology.
- Among all types of PH, HFpEF is the most common etiology.

- In HFpEF patients, elevated pulmonary artery pressure and impaired chronotropic reserve, coupled with impaired peripheral oxygen extraction, result in a substantial decline in exercise tolerance.
- PH-LHD (WHO Group 2) patients can be further categorized as having IpcPH or CpcPH.
- Of the two, patients with CpcPH have a worse prognosis [7, 23].
- The management of PH-LHD is to treat the etiology of the LHD and the surrounding comorbidities.
- Even when resting pulmonary pressures are normal in PH-LHD, they frequently increase during exercise resulting in substantial morbidity.
- Presently, there is no convincing data that PAH-specific therapies are beneficial in PH-LHD. The strong recommendation of the sixth WSPH, as well as the 2022 ESC/ERS guidelines is not to use them.
- Research continues in hopes of finding new therapies for PH-LHD, by far the most common category of PH patients.
- The CardioMEMS™ HF System allows us to monitor PAP and heart rate remotely resulting in decreased morbidity and mortality in this patient population.

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Liver Disease and Heart Failure

15

Mary Lauren Pfieffer and Julie Hannah

15.1 Introduction

Liver disease prevalence and mortality has increased worldwide since 2000 [1] with an estimated 1.5 billion people living with liver disease [1]. There are an estimated 26 million people worldwide living with heart failure [2]. Awareness of the increased prevalence and knowledge of cardiohepatic interactions is important for primary care providers when providing care to patients. More specifically, cardiomyopathy can lead to or worsen liver disease and vice versa; liver disease can cause or worsen heart failure.

Hepatologists and cardiologists are not the only providers that need awareness of these coinciding conditions. Primary care providers are often the first provider a patient encounters when dealing with health complaints. Time until diagnosis can be lengthy, and quality of life can be poor for patients diagnosed with coinciding liver disease and heart disease [2]. Therefore, it is important for primary care providers to be well educated on the cardiohepatic interactions to identify symptomology promptly for overall improved patient care.

M. L. Pfieffer (✉)
Vanderbilt University, Nashville, TN, USA
e-mail: mary.pfieffer@vanderbilt.edu

J. Hannah
Main Street Health, Nashville, TN, USA
e-mail: jhannah@mainstreetruralhealth.com

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_15

15.2 Liver Disease Related to Heart Failure

Liver disease occurs with heart failure related to the circulatory connection. The liver receives 25% of cardiac output. The liver receives blood flow from the hepatic portal vein and the hepatic artery [3]. Receiving perfusion from these two sources ultimately protects the liver as the other perfusion source can compensate if necessary. The hepatic vein carries the blood through the inferior vena cava which leads to the right side of the heart [4]. When the heart cannot tolerate an increased venous return, it can cause a hepatojugular reflux. This occurs with an increase in jugular venous pressure and can be a noninvasive physical exam finding that can aid in diagnosis.

15.2.1 Liver Diseases and Conditions That Exacerbate Heart Failure

Specific liver diseases and conditions are seen when there is acute or chronic decrease in perfusion. Liver hypoperfusion and hepatic congestion are two major triggers for this [4]. These liver diseases and conditions then lead to or exacerbate heart failure. Liver diseases and conditions that will be discussed in further detail in their role with heart failure are cirrhotic cardiomyopathy, nonalcoholic fatty liver disease, and post-liver transplantation complications.

15.2.1.1 Cirrhotic Cardiomyopathy

Cirrhotic cardiomyopathy (CCM) has been discussed in the literature since the 1960s but was originally thought to arise from alcoholism [5]. CCM is seen in patients with the absence of other heart diseases [5]. CCM is a condition related to heart failure and electrolyte abnormalities that leads to a decrease in cardiac output with an overall impaired cardiac function [6]. In advanced stages, CCM may lead to a hyperdynamic state and increased cardiac output. CCM is seen in 50 percent of patients with cirrhosis [7]. It generally has a delayed diagnosis related to its initial presenting symptoms [5]. Most patients with cirrhosis have left ventricular diastolic dysfunction with usual systolic function, but not all go on to have CCM [6].

There are three things that occur with CCM: systolic dysfunction, decreased diastolic function, and electrophysiological disturbances [4]. Cardiac dysfunction originates from splanchnic arterial vasodilation that occurs in patients with cirrhosis [6]. Systolic dysfunction relates to the impaired responsiveness to stress which leads to decreased contractility [5]. Diastolic dysfunction occurs in early stages of CCM and causes increase in filling pressures and decrease in ventricular relaxation [5]. Finally, patients with CCM experience electrophysiological disturbances. Patients with cirrhosis have prolonged QT intervals, but patients with CCM have more electrophysiological changes [5]. CCM patients have additional instances of electromechanical desynchrony and chronotropic incompetence [6]. Chronotropic incompetence is the inability of the sinus node to increase HR after exercise, leading to fatigue and exercise intolerance. QT prolongation makes these patients more

susceptible to ventricular arrhythmias. These circulatory abnormalities also relate to liver toxicity causing arterial dilation and hyperdynamic circulation [8].

Patients with CCM are often asymptomatic or experience very vague symptoms—fatigue and exercise intolerance [6]. Patients with CCM have peripheral dilation which masks many heart failure symptoms [6]. The diagnosis is typically made based on cardiac labs and diagnostics more so than patient presentation.

Prognosis of CCM is not encouraging for patients. Some treatments are contraindicated in cirrhosis but would be useful in the presence of heart failure, such as beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) [4]. Beta blockers are potentially contraindicated in the case of refractory ascites or infection. Liver transplantation is a possibility for these patients if their cardiomyopathy is well managed before transplantation [4]. There are risks to liver transplantation on the heart as well which will be described in later sections. It is important for health care providers to be able to differentiate CCM from cardiac cirrhosis. In CCM, the liver affects the heart and in cardiac cirrhosis the heart affect the liver.

15.2.1.2 Nonalcoholic Fatty Liver Disease

Nonalcoholic fatty liver disease (NAFLD) increases the risk of heart disease and heart failure in many ways [9]. NAFLD is a metabolic disorder that correlates with increased adipose tissue on the liver [9]. While NAFLD is most connected to coronary artery disease and buildup of coronary plaque, there are heart failure characteristics also seen—left ventricular diastolic dysfunction, morphological and valvular heart abnormalities, and cardiac rhythm disturbances [9].

As the obesity rates continue to rise in the United States, so does the prevalence of NAFLD. It is the most prevalent liver disease worldwide [5]. It is seen in an estimated 30% of healthy patients and 50–90% of patients with increased metabolic risks such as type 2 diabetes and dyslipidemia [5]. Both NAFLD and cardiovascular disease are seen in patients with metabolic syndrome; however, not all patients with NAFLD and cardiovascular disease will progress to heart failure.

There are many factors that trigger NAFLD to increase cardiac risk. Endothelial dysfunction causes greater atherosclerosis development that can affect heart function [9]. NAFLD leads to altered lipogenesis [9]. Thirdly, NAFLD increases systemic inflammatory markers [9]. NAFLD also can lead to insulin resistance [9]. Lastly, NAFLD causes greater oxidative stress in the body which increases cardiometabolic risk [5, 9]. These six pathophysiological mechanisms cause NAFLD to increase cardiovascular disease.

Patients need to meet four criteria to be diagnosed with NAFLD. They first need to have hepatic steatosis seen on imaging or from biopsy [9]. Secondly patients with NAFLD need to demonstrate they do not overconsume alcohol [9]. Thirdly, patients cannot meet criteria for other diagnoses for hepatic steatosis [9]. Lastly patients with NAFLD cannot have other causes of chronic liver disease [9]. Once all four of these criteria are met, patients can receive the official NAFLD diagnosis. Clinical manifestations vary depending on the level of fibrosis and the amount of cardiometabolic diagnoses—diabetes, hypertension, dyslipidemia, and obesity severity [5].

NAFLD can lead to hepatocellular carcinoma (HCC) and cirrhosis [10]. NAFLD is the third leading cause of HCC [10]. Patients with the combination of NAFLD and HCC are at increased risk for death related to other cardiometabolic factors attributing to NAFLD [10].

15.2.1.3 Heart Failure Following Liver Transplant

Roughly 12% of patients will have early onset heart failure after liver transplant [11]. Twenty-two percent of patients will have heart failure within 6 months of liver transplant [11]. The risk of heart failure goes down to 11% six months and beyond after liver transplant [11]. Increased heart failure risk is seen in older patients that are non-Hispanic and had poorer functional status prior to transplantation [12].

Heart failure after liver transplant can occur early or late after transplant. Early heart failure occurs within the first 30 days after transplant and late heart failure is greater than 30 days after transplant [4]. Close follow-up post-transplantation is necessary to ensure identification of symptoms immediately.

Heart failure in the early stages of liver transplantation relates to the post-operation cardiac stress and all the hemodynamic changes from surgery [13]. Early heart failure also can be related to decreased myocardial function of the heart [13]. Research shows that late heart failure from liver transplantation is most likely connected to other cardiovascular and metabolic risk factors [13].

The major cardiac adverse events that occur after liver transplantation are atrial fibrillation, heart failure, pulmonary embolism, stroke, myocardial infarction, and cardiac death [12]. Clinical manifestations depend on the presenting cardiac condition and can vary greatly. Also, presenting symptoms depend on the cardiac function of the patient pre-liver transplant.

Heart failure after liver transplant is associated with a high mortality [12]. Patients with the largest risk of heart failure and death are those that had prior history of atrial fibrillation and those with increased stroke risk factors [12].

15.3 The Role of Heart Failure in Liver Disease

Every condition that affects the right ventricle of the heart can cause burden on the liver related to backwards circulatory blood flow [3]. Reduction of right ventricular blood flow triggers liver congestion [3]. Many acute injuries to the heart can cause injury to the liver. Examples include myocardial infarction, acute decompensation of chronic heart failure, infection/sepsis, or pulmonary embolism [14]. Chronic heart issues can also lead to liver injury/disease, and the liver damage is related to chronic perfusion issues [14]. Examples of these chronic heart diseases that can lead to liver disease are heart failure, congenital heart disease, cor pulmonale, and several others [14]. One of the major risks of chronic right-sided heart failure is congestive hepatopathy. With acute heart failure, patients may experience cardiogenic ischemic hepatitis.

15.3.1 Congestive Hepatopathy

Congestive hepatopathy is a condition related to progressive liver dysfunction and a slow progression of liver damage [14], which leads to congestion of liver parenchyma [15]. Congestive hepatopathy occurs in up to 65% of patients with heart failure [16, 17] and is most often seen in those with severe heart failure, left ventricular assist devices (LVAD), congenital heart disease, and patients with Fontan circulation [4, 18].

There are three things that trigger congestive hepatopathy: blood inflow, blood outflow, and decreased oxygenation to the liver. Chronic decrease in hepatic blood inflow and outflow leads to congestion in the liver and volume overload [4, 5]. The deoxygenation leads to hypoxia of the liver and eventual liver failure [4, 5].

Patients suffering from congestive hepatopathy may complain of jaundice, right upper quadrant pain, early satiety, weight loss, and malaise [5, 19]. Physical exam findings most often include peripheral edema, ascites, jugular venous distension, hepatomegaly, and hepatojugular reflux [5, 19]. Hepatomegaly is seen in 90–95% of patients with congestive hepatopathy and can be as clinically significant as >5 cm below right costal margin [3]. Occasionally patients with congestive hepatopathy have a pulsatile liver related to increased blood volume in right side of the heart [3].

After surgical repair to resolve cardiac dysfunction, there is potential for chronic hepatopathy to lead to benign regenerative nodules, focal nodular hyperplasia (FNH), and/or malignant hepatocellular carcinoma (HCC) [14, 20]. Deciphering nodules versus normal enhancement on computed tomography (CT) is difficult for radiologists related to the chronic cardiac and liver dysfunction [20]. Therefore, close follow-up is imperative to ensure proper management and treatment for these patients.

15.3.2 Cardiogenic Ischemic Hepatitis

Cardiogenic ischemic hepatitis is a condition that occurs often in patients presenting with heart failure. There are many names in the literature surrounding this condition—cardiogenic ischemic hepatitis, acute cardiogenic liver injury (ACLI), hypoxic hepatitis, ischemic hepatitis, and shock liver. For the purposes of this chapter, the term cardiogenic ischemic hepatitis will be used.

Cardiogenic ischemic hepatitis occurs in roughly 20–30% of patients with acute heart failure [21]. This is seen most often following acute coronary events, cardiac arrythmias, and acute, severe hypotension and cardiogenic shock [4, 5].

The cause of cardiogenic ischemic hepatitis is the decrease in hepatic blood flow related to impaired cardiac output. Decreased hepatic perfusion can lead to hepatocellular dysfunction and necrosis of the liver [22]. Hepatic congestion and liver hypoperfusion are both needed to confirm this diagnosis.

Cardiogenic ischemic hepatitis is typically asymptomatic [4]. These patients occasionally will have acute hepatitis symptoms like nausea, vomiting, decreased

appetite, fatigue, and right upper quadrant abdominal pain [3, 23]. Increased symptom duration can lead to jaundice and decreased urinary output, potentially leading to a flapping tremor and/or hepatic coma [3, 5, 19, 23]. The flapping tremor in these patients is related to decreased hepatic function leading to inability to filter toxins. Ultrasound exam may show dilation of the inferior vena cava and suprahepatic veins resulting in liver congestion [5]. This condition, like many other liver conditions, may lead to issues with bleeding related to lack of liver coagulability [3, 4].

Mortality remains high for this condition related to the acuity and its effects on the entire patient [4]. Quick identification of the condition and perfusion restoration can improve patient outcomes [4]. Management will be discussed later in this chapter.

15.4 Approach to the Management of Liver Disease and Heart Failure

When managing patients with comorbid heart failure and liver disease, it is important to keep in mind the additive effects of the two disease states. Early recognition of each disease is important due to the complex interplay between the two. The severity of heart disease and fatty liver disease is worse in patients who have both disease states, and there is a higher prevalence of fatty liver disease in patients with heart failure compared with the general population [24]. One study demonstrated that patients with comorbid heart failure with reduced ejection fraction and nonalcoholic fatty liver disease (NAFLD) were younger, had higher body mass indexes (BMIs), and had more left ventricular changes compared to patients with normal liver morphology [25]. Additionally, patients with liver disease and heart failure are more likely to have a poorer prognosis and are at higher risk when undergoing cardiac surgeries [26]. Both pharmacological and nonpharmacological management techniques are needed to prevent the more severe disease progression that can be seen in patients with these two comorbidities.

15.4.1 Pharmacologic Management

There are a few general principles of drug metabolism that are important to consider when treating co-occurring liver disease and heart failure. The efficiency of hepatic metabolism is multifactorial, comprised of the functionality of the hepatocytes themselves, the blood supply to the liver, and the availability of plasma proteins capable of binding drugs [27]. Therefore, there are multiple mechanisms by which disease processes can impair hepatic metabolism. Liver function test abnormalities do not always correspond with alterations in metabolism, making it difficult to predict to what degree drug metabolism will be affected [27]. However, it has generally been found that mild to moderate liver disease does not impair metabolism significantly, and it is not until a patient is cirrhotic that medication doses need to be adjusted [27]. In cirrhosis, shunting of blood reduces drug elimination during the

first pass effect and cytochrome activity can be decreased; both can lead to increased serum concentrations of drugs [27]. Heart failure can additionally damage the liver due to venous congestion and decreased perfusion, which ultimately causes liver hypoxia and impacts hepatic metabolism of drugs [27]. Specific medication considerations as they pertain to liver disease and heart failure treatment will be discussed further below.

15.4.1.1 Nonalcoholic Fatty Liver Disease (NAFLD)

There are currently no approved medications specifically for the treatment of NAFLD. High-dose vitamin E can be used in more advanced fibrosis [28]. There are several other current or emerging drug therapies that are being studied for use in NAFLD. Diabetes medications, including pioglitazone, metformin, GLP1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors, are all being studied due to observed positive benefits in liver fibrosis or steatosis [28, 29]. In patients with comorbid heart failure, SGLT2 inhibitors could have the added benefit of reducing heart failure-associated risks. Conversely, though pioglitazone shows promise in treating NAFLD patients, it would be contraindicated in those with comorbid heart failure due to its risks of swelling and heart failure exacerbation [29]. There is additionally early research to suggest that use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) could slow progression of hepatic fibrosis [29], which would be advantageous in heart failure patients given that treatment with ACE inhibitors or ARBs is already part of the standard of care.

15.4.1.2 Heart Failure

The standard therapeutic agents used to treat heart failure with reduced ejection fraction include ACE inhibitors, ARBs, ARNIs, beta blockers, diuretics, SGLT2is, and aldosterone antagonists. Specific considerations for each will be discussed separately below.

ACE Inhibitors

ACE inhibitors are largely excreted by the kidneys and are not expected to be affected much by hepatic dysfunction [26]. However, many are prodrugs which require metabolism in the liver to form active metabolites. These include enalapril, ramipril, fosinopril, trandolapril, quinapril, benazepril, and moexipril [26, 27]. Hepatic impairment may decrease the bioavailability of the active metabolite and increase the prodrug concentration in the blood stream. Therefore, it is advised to start at the initial dose but titrate slowly in cirrhotic patients when administering the aforementioned prodrugs, with the exception of moexipril and trandolapril which require a dose reduction [27].

ARBs

Candesartan, losartan, and valsartan are currently the three ARBs with an approved indication for use in heart failure patients [30]. Of these, candesartan and losartan are both prodrugs and require a lower starting dose in cirrhosis [25, 26]. Telmisartan also requires a lower starting dose and slower titration [27].

ARNIs

Sacubitril/valsartan is now recommended in place of ACEs or ARBs for all HFrEF patients who can tolerate it due to its superior ability to reduce hospitalizations and mortality [31]. It requires a dose reduction for patients with moderate liver disease and is contraindicated for those with severe more advanced liver disease.

Beta Blockers

Bisoprolol, metoprolol succinate, and carvedilol are the three FDA-approved beta blockers for heart failure treatment. All of these are lipophilic beta blockers, which are predominantly metabolized by the liver and require a dose reduction in the setting of cirrhosis [26, 27]. Other commonly used lipophilic beta blockers requiring dose reduction include propranolol, timolol, and nebivolol [26, 27]. Nonselective beta blockers (such as nadolol, propranolol, timolol, and carvedilol) can further be of benefit in liver disease patients as the preferred treatment for portal hypertension and prevention of variceal bleeding [32]. There have been concerns raised about the use of nonselective beta blockers in cirrhotic patients with refractory ascites due to concerns for increased mortality. However, current evidence still supports their use in heart failure and in cirrhotic patients with portal hypertension, but it is recommended to start at a very low dose and titrate slowly, every 1–2 weeks [32]. Close monitoring to watch for signs of decreased organ perfusion and hypotension is advised [32]. Beta blockers may need to be temporarily discontinued in heart failure patients in the setting of ischemic hepatitis, as treatment focuses on restoration of blood flow to the liver typically through removal of negative inotropes and blood pressure reducing medications [5].

Diuretics

Use of diuretics in heart failure can be mutually beneficial in liver diseases by improving jaundice, ascites, and liver congestion [19]. Thiazide diuretics can be utilized in mild heart failure, though loop diuretics are typically the mainstay of therapy in heart failure patients. Thiazide diuretics may also be used for ascites management. Diuretics are typically excreted renally so there is no dose reduction in advanced liver disease. However, dehydration can cause hepatic encephalopathy in cirrhosis, so close monitoring of volume status is required to avoid diuretic-induced dehydration [27].

SGLT2 Inhibitors

The most recent heart failure guidelines have a new addition of SGLT2 inhibitors to the treatment regimen of patients with symptomatic chronic heart failure, even if they do not have comorbid diabetes [31]. There are no dose adjustments required for patients with comorbid liver disease, and in fact SGLT2 inhibitors show promise in improving liver fibrosis or steatosis [28, 29].

Aldosterone Antagonists

Spironolactone and eplerenone are common adjunct therapies in heart failure, especially in diuretic-resistant patients. Spironolactone is also highly effective for the treatment of ascites in liver disease [33]. However, the doses for these two

conditions may differ. Adjunct therapy in heart failure often involves spironolactone doses of 25–50 mg daily, whereas ascites treatment may require up to 400 mg daily for adequate diuresis [33].

Lipid-Lowering Agents

Patients with heart failure as well as liver disease commonly have comorbid hyperlipidemia. Pharmacological treatment with statins and ezetimibe is recommended to reduce the risk of cardiovascular events in these patients, though there is no known benefit in improving liver disease itself [29]. However, both classes of medications are contraindicated in severe hepatic disease and dose reduction may be required for more mild hepatic impairment [27]. Although not typically first-line agents, fibric acid derivatives may also commonly be used for adjunct lipid lowering therapy, but again would be contraindicated in severe liver disease [27].

Anticoagulant/Antiplatelet Therapy

Anticoagulant or antiplatelet therapy may be indicated in many patients with heart failure due to common comorbidities such as atrial fibrillation, coronary artery disease, or prior stroke. However, both heart failure and hepatic dysfunction are associated with elevated prothrombin levels leading to increased clotting times [19]. Furthermore, patients with cirrhosis have an increased risk of hemorrhage due to the high prevalence of esophageal varices [1]. Therefore, use of anticoagulants in these patients can be controversial, particularly with newer agents such as rivaroxaban or apixaban which are contraindicated in more advanced hepatic disease [19]. There is also concern for possible liver toxicity in all newer oral anticoagulants [3]. Warfarin is still commonly used in patients with heart failure and hepatic dysfunction requiring anticoagulation [19] though frequent INR monitoring is advised.

15.4.1.3 Congestive Hepatopathy

The primary treatment of congestive hepatopathy involves correcting the underlying heart disease which in turn alleviates the hepatic congestion. It is predominantly treated with diuretics to reduce fluid overload, which corrects the associated liver congestion, ascites, and jaundice [19]. ACE inhibitors and B blockers are also recommended as they are indicated in the treatment of symptomatic heart failure [5].

15.4.1.4 Cardiogenic Ischemic Hepatitis

Pharmacological management of cardiogenic ischemic hepatitis typically involves removing medications that contribute to decreased perfusion, predominantly negative inotropes such as B blockers [5]. Patients may also require the use of positive inotropes or vasopressors to return perfusion to the liver, such as milrinone or digoxin [5, 19]. Inotropic and vasopressor medications can generally be used without dose adjustment in the setting of hepatic impairment [27].

15.4.1.5 Post-Liver Transplant

Immunosuppressive therapies used after liver transplantation may have cardiac side effects. Tacrolimus has been shown to cause significant myocardial hypertrophy in some patients [3]. Corticosteroids such as prednisone can cause edema and heart

failure exacerbations. On the other hand, cyclosporine, sirolimus, and mycophenolate mofetil do not appear to cause significant cardiac issues [3].

15.4.2 Nonpharmacologic Management

15.4.2.1 Lifestyle Modifications

Lifestyle modifications are currently the mainstay of NAFLD. These modifications include diet, weight loss, exercise, smoking cessation, and alcohol reduction [28, 29]. Given that fatty liver disease tends to have many of the same risk factors as heart failure, including type 2 diabetes, obesity, hypertension, hyperlipidemia, and metabolic syndrome, the lifestyle modifications aimed at reducing liver disease tend to improve heart failure, as well [29].

Diet

Current evidence suggests that the Mediterranean diet or a low-glycemic index diet containing high fiber, few saturated fats, and few simple sugars are the best diets for improving hepatic steatosis [28, 29]. The Mediterranean diet has also repeatedly been shown to improve cardiovascular outcomes [34].

Exercise

Exercise regimens should include 150 min weekly of resistance training and moderate to high intensity aerobic exercise. This not only improves hepatic steatosis but also assists with weight loss, reduces insulin resistance, and improves lipid profiles, all of which improve cardiovascular outcomes [28, 29]. Aerobic exercise also improves exercise tolerance in heart failure patients [24].

Weight Loss

Patients with fatty liver disease are typically advised to lose 5–10% of total body weight to see improvements in NAFLD. There are times even more weight loss may be advised based on the degree of aminotransferase elevation or severity of histological change [28, 29]. Weight loss can help prevent the development of heart failure or improve exercise tolerance and reduce symptoms in those with preexisting heart failure [24, 35]. However, in patients with preexisting heart failure, there is a well-established obesity paradox in which obesity seems to provide a protective mechanism on heart failure outcomes. Obese patients have better prognoses and higher survival rates than those heart failure patients who lose weight or have lower BMI [29, 35]. There are currently unclear guidelines about weight loss recommendations for heart failure patients, which poses a challenge when trying to advise those with comorbid fatty liver disease. More research is needed in this area. In the interim, for those patients with preexisting heart failure, it is best to focus on dietary improvements rather than a specific weight reduction goal itself. If patients are more severely obese, a modest amount of weight reduction may be advisable for the sake of reducing heart failure-associated symptoms and improving quality of life [35].

15.5 Laboratory Monitoring and Diagnostics for Hepatic Complications in Heart Failure

15.5.1 Liver Function Tests

The pattern of liver function test elevations can be an important indicator of heart failure status and severity. Elevations in cholestatic markers including alkaline phosphatase, ϒ-glutamyl transpeptidase (GGT), and bilirubin are indicative of congestive hepatopathy, the venous liver congestion that results from poor right ventricular function [3, 19, 26]. These changes are more likely to be seen in chronic heart failure, and the degree of elevation corresponds to the severity of heart failure [3]. Sharp increases in aminotransferases (AST, ALT) and lactate dehydrogenase are more indicative of an abrupt decrease in cardiac output resulting in ischemic hepatitis. This is more likely due to acute decompensated heart failure, and levels typically improve within 7–10 days [10]. In the setting of acute heart failure with acute cardiogenic liver injury, elevated liver function tests at baseline are associated with higher mortality rates over the next 6 months [3]. Elevated bilirubin in particular is a strong predictor of cardiovascular death in heart failure patients [19].

15.5.2 Synthetic Function Tests

Liver synthetic function tests can also be affected in the setting of heart failure. Congestive hepatopathy can impair the liver's production of both clotting factors and albumin [26]. Prothrombin time may be increased, an important consideration prior to surgery or other medical procedures that carry a risk of bleeding. Albumin production may be decreased [19, 26]. Hypoalbuminemia is associated with poorer outcomes in heart failure patients, likely due to low albumin causing increased edema, platelet aggregation, inflammation, and oxidative stress [36].

15.5.3 Metabolic Markers

It is important to screen for underlying diabetes and dyslipidemia. These are commonly seen in both liver disease and cardiovascular disease, including heart failure. Many patients with NAFLD meet criteria for metabolic syndrome, which increases cardiovascular disease risk. Insulin resistance, diabetes, and dyslipidemia are all associated with more advanced disease and poorer outcomes in both liver and heart disease [29]. The typical lipid profile in NAFLD includes high triglycerides, high low-density lipoproteins, high very-low-density lipoprotein, and low high-density lipoproteins.

15.5.4 EKG

Fatty liver disease is commonly associated with several EKG disturbances, including atrial fibrillation, QT prolongation, or ventricular arrhythmias, which could lead to sudden cardiac death [3, 5]. Routine EKGs could be beneficial in determining those experiencing a prolonged QT interval, as this could impact dosing and selection of medications used to treat heart failure.

15.5.5 Echocardiogram

Fatty liver disease is commonly associated with several structural and functional changes on echocardiogram, including increased left ventricular mass, interatrial thickness, left atrial stiffness, and left ventricular diastolic dysfunction [29]. It is also common to find calcifications of the aortic and mitral valves in patients with fatty liver disease [29].

15.5.6 Risk Scores

There are a few different scoring systems that can be beneficial in clinical decision making and risk stratification for patients with coinciding heart failure and liver disease. All of these are noninvasive and utilize common laboratory values that the clinician could readily have available.

15.5.7 Fibrosis Score

The fibrosis score is used to estimate the amount of scarring on the liver. Although typically used to determine presence of advanced fibrosis, it can also predict cardiovascular risk [5]. A higher fibrosis score correlates to more frequent cardiovascular events and more advanced heart failure stages [37].

15.5.8 Model for End-Stage Liver Disease (MELD)

The MELD score and its affiliates (MELD-Na and MELD-XI) are risk calculators used to assess the severity of liver disease especially for transplant planning purposes. However, it can also be clinically useful in risk stratification when assessing mortality or disease progression in heart failure patients [26]. The MELD score is the most used clinical score among advanced heart failure patients and is an accurate predictor of mortality rates, bleeding risk, and high-risk surgical candidates [3].

15.5.9 Child-Pugh Score

The Child-Pugh score has historically been used to determine the prognosis of patients with advanced liver disease. It is calculated similarly to the MELD score and the two are often used in conjunction when determining candidates for liver transplantation. The Child-Pugh score has been subject to criticism due to its use of subjective data (ascites and encephalopathy). Nevertheless, it can be useful to calculate since hepatic dosing guidelines for medications often reference the Child-Pugh class, including medications used in heart failure treatment [38]. For example, Ivabradine, a newer medication used to treat symptomatic heart failure with reduced ejection fraction, is contraindicated in those with severe hepatic dysfunction falling into Child-Pugh Class C [26]. Entresto, which falls in the ARNI class of medications, also carries a contraindication for Child-Pugh Class C and dose reduction for Class B.

15.6 Case Study: Putting It All Together

15.6.1 Subjective

15.6.1.1 History of Presenting Illness (HPI)

JM is a 58-year-old male patient presenting to primary care provider with a chief complaint of progressive, right upper quadrant pain that has been occurring for 2 months. Pain is 6/10 on the pain scale, dull and tender to touch. Associated symptoms include: weight loss (5%), fatigue, decreased appetite. Over the past week, he noted progressive worsening of bilateral lower extremity edema and decreased exercise tolerance. Experiencing dyspnea and fatigue when performing activities of daily living (ADLs) such as bathing and brushing teeth. Describes orthopnea the past two nights. Noted changes in chronic conditions since last visit:

15.6.1.2 Chronic Conditions Changes Since Last Visit

- *Heart Failure with Reduced Ejection Fraction*—Seen by cardiology 4 months ago. Echocardiogram noting LVEF 35%, LVIDD 6.7 cm, right ventricle moderately dilated. Stable, NYHA class II symptoms at that time. Entresto was increased.
- *Dyslipidemia*—Managed by primary care provider. Total cholesterol and LDL drawn 3 months ago and within goal. Continuing diet modifications and exercise.
- *Hypertension*—Managed by cardiologist—compliant with medications. Patient does not check BP at home but denies chest pain, headaches, and dizziness. Reports shortness of breath over the past 4 months.
- *Type 2 Diabetes Mellitus, controlled, non-insulin dependent*—Managed by primary care provider—Hemoglobin A1c 3 months ago was 7.1. Complaint with medications. Checks glucose BID and numbers are within goal. Continues with dietary modifications and exercise.

- *Depression*—Managed by primary care provider—stable on current medications. Medications provide relief of depressive symptoms. Denies suicidal/homicidal ideation.

15.6.1.3 Past Medical History/Problem List

- Heart Failure with reduced ejection fraction (diagnosed in 2010)
- Dyslipidemia (Diagnosed 2006)
- Hypertension (Diagnosed 2006)
- Type 2 Diabetes Mellitus, controlled, non-insulin dependent (Diagnosed 2008)
- Obesity
- Depression (Diagnosed in 2008)
- *Surgeries*: Appendectomy at age 28, tonsillectomy at age 20
- *Immunizations*: Received two COVID vaccines (Pfizer)—last one 5 months ago

15.6.1.4 Family History

- *Father*—Deceased at age 65—Hypertension, dyslipidemia, myocardial infarction
- *Mother*—Deceased at age 68—Hypertension, stroke
- *Sister*—Alive—Hypertension, obese, history of breast cancer
- *Brother*—Deceased at age 50—Hypertension and fatal myocardial infarction at age 50
- *Son*—Alive—Obese, hypertension, depression

15.6.1.5 Social History

Patient lives with partner of 20 years in an apartment downtown. Patient is unemployed, on medical disability. Receives Medicaid. Has one child. Patient smokes cigarettes and has a 20-year pack/day tobacco history. Drinks alcohol four times a week, and totals 16–20 drinks/week. Denies illicit drug use. Drinks 2 cups of coffee/day.

15.6.1.6 Medications/Allergies

- Furosemide 80 mg bid
- Sacubitril/Valsartan 97 mg/103 mg BID
- Metoprolol succinate 100 mg QD
- Spironolactone 25 mg QD
- Sertraline 100 mg QD
- Bupropion XL 150 mg QD
- Metformin ER 1000mg BID
- Empagliflozin 10 mg by mouth daily
- Patient has no known drug allergies (NKDA)

15.6.1.7 Review of Systems (ROS)

Constitutional: Positive for fatigue and weight loss, Negative for fever, lightheadedness, and syncope.

Cardiovascular: Positive for chest tightness, swelling of legs and joint stiffness. Negative for chest pain and palpitations.

Respiratory: Positive for shortness of breath with exertion. Negative for cough and difficulty breathing.

Abdomen: Positive for upper quadrant abdominal pain, weight loss, and decreased appetite. Negative for vomiting, diarrhea, constipation, and blood in the stool.

15.6.2 Objective

Vital Signs Blood pressure 132/90, Heart rate 100, Respiratory Rate 22, Temperature 98.4 °F, Height 68 inches, Weight 235 pounds (down 12 pounds since last visit), BMI 35.7.

15.6.2.1 Physical Examination

General statement: JM is a 58-year-old African American male alert and oriented x3, cooperative and obese.

Neck: JVD elevated to 16 cm with head of bed elevated to 45°. Hepatojugular reflux is positive with moderate palpation of the liver.

Cardiovascular: Apical heart rate 100, rhythm regular. No murmurs, heaves, lifts or thrills present. 2+ bilateral edema in shin, ankles, and feet.

Respiratory: Tachypneic at rest, increased work of breathing, expiratory wheezes present bilaterally.

Abdomen: Normoactive bowel sounds in all four quadrants. Abdomen is distended with ascites and there is right upper quadrant pain to palpation. Murphy's sign is negative. Hepatomegaly noted. Pulsation is palpated in liver during exam.

15.6.2.2 Labs and Risk Scores

- *Comprehensive Metabolic Panel (CMP)*—serum alkaline phosphatase level 200 (elevated), aspartate aminotransferase 120 (elevated), alanine aminotransferase 125 (elevated)
- *Bilirubin*—2.7 (elevated)
- *Serum gamma-glutamyl transpeptidase (GGT)*—75 (elevated)
- *Albumin*—2.7 (decreased)
- *Prothrombin time*—20 seconds (elevated)
- Pro-B-type natriuretic peptide (BNP)—1200
- New York Heart Association (NYHA) Functional Classification III-IV
- *Child-Pugh* Score—Child-Pugh Class B
- *Fibrosis Score*—2 (Moderate Fibrosis)
- *Model for End State Liver Disease (MELD) Score*—12

15.6.3 Assessment

Differentials Diagnoses: Acute on Chronic Decompensated Heart Failure, Budd-Chiari syndrome, acute or chronic hepatitis, biliary obstruction, constrictive pericarditis, congestive hepatopathy, hepatic infiltrative disorders, and drug toxicity causing liver failure.

Final Diagnosis: Acute decompensated heart failure with hepatic congestion.

15.6.3.1 Plan

Mr. JM is experiencing NHYA Class III-IV symptoms in the setting of volume overload. Hospital admission is recommended for intravenous diuretics, possible hemodynamic monitoring, and further treatment and evaluation of concomitant heart failure and liver congestion.

15.6.3.2 Nonpharmacology

Labs ordered: Hepatitis panel including autoimmune hepatitis, iron and total iron binding capacity (to rule out hemochromatosis), alpha-1 antitrypsin, celiac panel, prothrombin time/international normalized ratio and thyroid-stimulating hormone.

Imaging: Right upper quadrant ultrasonography with Doppler studies of the portal and hepatic veins and hepatic artery, electrocardiogram, and echocardiography.

Diagnostic testing: Histologic examination of the liver is sometimes performed to look at level of liver fibrosis. It is crucial to weigh risks of this related to elevation in prothrombin time and potential to cause more harm [4].

Patient Education: JM should be educated on monitoring signs and symptoms of fluid volume overload in an effort to prevent acute decompensation in the future. This is particularly important as cardiac dysfunction causing congestive hepatopathy of the liver can lead to benign regenerative nodules, focal nodular hyperplasia (FNH), and/or malignant hepatocellular carcinoma (HCC). Referral to hepatologist should be considered. Additionally, the patient should prepare for potential diagnostic paracentesis looking for an increase in protein count in peritoneal fluid. Extensive education regarding the importance of refraining from alcohol should be advised given its cardio and liver toxic effects.

15.7 Clinical Pearls

Labs help to identify patients with congestive hepatopathy as there is generally mild hyperbilirubinemia with coinciding mild increase in alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase [5]. Patients with congestive hepatopathy may also have mild decrease in albumin levels. Hepatomegaly is seen in almost 99% of patients with congestive hepatopathy but only 25% of these patients will have ascites [3]. If a paracentesis is performed, seeing protein in ascitic fluid helps to differentiate congestive hepatology from other causes of cirrhosis [3]. Underlying heart failure needs to be corrected for patients to have symptomatic improvement. This may result in assessment of acute decompensated heart failure with likely invasive hemodynamic evaluation. In extreme cases it can include surgery, temporary left ventricular assistive device support (LVADs), or cardiac transplantation depending on the levels of severity of heart failure [5]. Therefore, it is imperative that the patient is safely diuresed and managed in the hospital acutely related to decompensation. They may need swift inpatient inotropic support if diuresed with no symptom improvement [4]. Prognosis is worse in patients with increased liver biomarkers with hypoalbuminemia [4]. If liver function does not

improve with heart failure management, patients are typically not a candidate for heart transplantation unless a combined liver and heart transplant is considered [4]. Lastly, heart failure patients who are volume overloaded with notable passive hepatic congestion may present with a chief complaint of "right upper quadrant pain," therefore, mimicking concerns for cholecystitis. After decongestion, the pain most often subsides. It is important to consider acute decompensated heart failure as a differential for a chief complaint of right upper quadrant pain.

15.8 Conclusion

Managing heart failure and liver disease is challenging related to all the cardiohepatic interactions [4]. Interprofessional management of these patients including primary care providers, hepatologists, and cardiologists is important for improved care and quality of life. Diagnosis and treatment of these conditions is generally related to the complexity of identification of the triggers of illness. Therefore, it is imperative that primary care providers have knowledge of the cardiohepatic interactions so patients can receive swifter diagnosis and improved care.

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Substance Abuse and Heart Failure

16

Amy Howard and Linda Howerton

16.1 Alcoholic Cardiomyopathy

16.1.1 Overview of Alcoholic Cardiomyopathy

The leading cause of non-ischemic dilated cardiomyopathy in the United States among all races and in both sexes is long-term heavy alcohol consumption which is referred to as alcoholic cardiomyopathy [1, 2]. Alcoholic cardiomyopathy is characterized by a dilated left ventricle (LV), normal or reduced LV wall thickness, increased LV mass, and a reduced LV ejection fraction (<40%) in advanced stages [3]. Alcoholic cardiomyopathy is related to several adverse changes within the myocardium, including histological, cellular, and structural [3]. The pathology of these changes has several proposed mechanisms: oxidative stress, apoptosis leading to cellular loss and remodeling, impaired mitochondrial bioenergetics resulting in changes in mitochondrial ultrastructure and function, altered fatty acid metabolism and transport, and decreased myocardial protein synthesis leading to accelerated protein catabolism. Although there are multiple theories surrounding etiology, the pathology of alcoholic cardiomyopathy is not fully understood [2]. With early diagnosis, proper management, and cessation (or reduction) of alcohol intake, complete recovery of cardiac function can occur [2, 4].

A. Howard (✉) · L. Howerton
Vanderbilt Heart and Vascular Institute, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: amy.howard@vumc.org; ginlin@comcast.net

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_16

16.1.2 Prevalence of Alcoholic Cardiomyopathy

Approximately 1–2% of heavy alcohol users develop alcoholic cardiomyopathy, and it is estimated that 21–36% of all non-ischemic cardiomyopathies are later determined to be related to alcohol [1, 2]. Alcoholic cardiomyopathy most commonly affects men aged 30–55 years with a history of heavy alcohol use (defined as more than 90 grams per day, or approximately 7–8 standard drinks) for greater than 5 years. According to the Center for Disease Control, 1 standard drink is equal to 14.0 grams (0.6 ounces) of pure alcohol. This is generally found in 12 ounces of beer (5% alcohol content), 8 ounces of malt liquor (7% alcohol content), 5 ounces of wine (12% alcohol content), and 1.5 ounces or a "shot" of 80-proof (40% alcohol content) distilled spirits or liquor (gin, rum, vodka, whiskey, etc.) [5]. Table 16.1 displays the percentage of alcohol content per fluid ounce in each type of drink.

Although women represent a smaller number of alcoholic cardiomyopathy cases, it is speculated that they may be more vulnerable to developing this with less alcohol consumption over their lifetime [4]. Men have a greater proportion of body water and women have a larger proportion of body fat. The larger proportion of body fat can result in consistently higher blood alcohol concentrations with similar levels of consumption due to the slower distribution of alcohol from the blood. Women are also known to have fewer alcohol-metabolizing enzymes, which predisposes women to the development of alcoholic cardiomyopathy despite a lower lifetime dose of alcohol when compared to men [6].

Alcoholic cardiomyopathy presents as either systolic or diastolic dysfunction and may be asymptomatic (preclinical) or symptomatic (presenting with signs and symptoms of heart failure). The exact point at which alcohol-induced changes to the myocardium occur is not well established. No specific relationship between alcohol dose-response and myocardial injury has been determined. There is some data to suggest that longer durations of alcohol consumption and individual genetic susceptibility are often associated with symptomatic alcoholic cardiomyopathy [3, 4].

The exact prevalence of alcoholic cardiomyopathy is difficult to determine since this is dependent on how patients are classified using the International Classification of Diseases (ICD) codes. Patients with alcoholic cardiomyopathy may be classified as idiopathic dilated cardiomyopathy or other nonspecific, broader diagnostic category, which would result in difficulty capturing the true number of patients affected [3].

Table 16.1 Percentage of alcohol content per ounce of drink [5]

Type of drink	Size (fluid ounces)	Percentage of alcohol content (%)
Beer	12	5
Malt liquor	8	7
Wine	5	12
"Shot" of 80-proof distilled spirits or liquor (gin, rum, vodka, whiskey, etc.)	1.5	40

16.1.3 Pathophysiology of Alcoholic Cardiomyopathy

The pathology of alcoholic cardiomyopathy is not fully understood [2]. There is evidence to suggest that alcoholic cardiomyopathy is the result of defects in heart mitochondrial function, oxidative stress, and apoptosis. It has been established that alcohol changes mitochondrial structure by producing mitochondria enlargement and degeneration of inner mitochondria membrane folds, impairing mitochondrial function [7]. Dysfunctional mitochondria are not as bioenergetically efficient and can also generate increased amounts of reactive oxidative species, which are more likely to initiate apoptosis (cell death) [3]. Apoptosis has been well established as a contributing factor to cardiovascular disease in general since it results in the loss of myocytes. The loss of myocytes leads to organ dysfunction, pathology, and adverse remodeling at the cellular level [2, 3, 8]. Oxidative stress within the myocardium may occur with long-term alcohol exposure either directly by stimulating the generation of free radicals or indirectly by activating another system such as the renin-angiotensin system [2, 3]. It has also been suggested that fatty acid metabolism and transport may be altered contributing to myocardial dysfunction. Long-term alcohol use also accelerates protein catabolism and autophagy and decreases myocardial protein synthesis [2]. Additionally, there is some evidence to suggest genetic factors may predispose certain individuals to alcoholic cardiomyopathy [7].

16.2 Clinical Presentation and Diagnostic Testing for Alcoholic Cardiomyopathy

16.2.1 History and Physical

The diagnosis of alcoholic cardiomyopathy is typically one of exclusion in individuals with no identified etiology for cardiac dysfunction and a history of heavy alcohol abuse; thus quantifying the amount of alcohol consumed regularly is a key factor [9]. Patients with alcoholic cardiomyopathy most often present with a clinical picture like other forms of heart failure or dilated cardiomyopathy of any etiology [2]. Symptoms may develop insidiously or may be acute, and typically include dyspnea, orthopnea, paroxysmal nocturnal disease, and edema [2]. Syncopal events and palpitations may also be reported since they can occur with tachyarrhythmias associated with alcoholic cardiomyopathy [10]. Physical exam findings often include elevated jugular venous pressure, S3-S4 heart sounds, pulmonary rales, peripheral edema, and abdominal distention or ascites [1]. Measurement of jugular venous pressure may be important in determining if ascites is due to alcoholic cardiomyopathy or cirrhosis as jugular venous pressure is typically normal or low-normal in cirrhosis except in the setting of tense ascites, as this can increase intrathoracic pressure. An elevated jugular venous pressure is highly suggestive of cardiac dysfunction, at the very least, being a contributing factor [2]. Signs of liver disease may also be present, including folate deficiency, higher risk for bleeding, malnutrition, peripheral neuropathy, and neurological conditions, including Wernicke-Korsakoff syndrome [1].

16.2.2 Diagnostic Testing

Initial testing when alcoholic cardiomyopathy is suspected should include imaging and testing for new heart failure diagnosis as outlined in the previous chapter of this book. This includes laboratory testing for brain natriuretic peptide (BNP) or pro-brain natriuretic peptide (NT-proBNP). If either of these are elevated, this would suggest a component of heart failure contributing to presenting symptoms. Other lab testing would include a complete metabolic panel and a complete blood count. Higher values for mean red cell corpuscular volume and hemoglobin, mild thrombocytopenia, and elevated liver function tests may be suggestive of alcohol abuse [2]. If alcohol abuse is suspected or reported, a blood alcohol level could also be obtained.

An electrocardiogram should be included in the initial evaluation, although findings are often nonspecific. Patients with alcoholic cardiomyopathy do, however, have similar rates of atrial and ventricular arrhythmias as those with other forms of dilated cardiomyopathy. Chronic alcoholism can result in hypomagnesemia and hypokalemia, which may contribute to the mild prolongation of QTc interval, which is a risk factor for ventricular arrhythmias [2].

Chest imaging is often obtained for further evaluation of reported dyspnea and may reveal cardiomegaly; however, this has limited specificity and sensitivity for left ventricular dilation. Chest radiographs may also be helpful to identify signs of pulmonary edema and exclude other etiologies for dyspnea [2].

An echocardiogram is the gold standard diagnostic test when the diagnosis of heart failure is suspected. Alcoholic cardiomyopathy is characterized by pronounced left ventricular or biventricular dilation, increased left ventricular mass, diastolic dysfunction, systolic impairment, and thin (or normal thickness) left ventricular walls. Around one-half of asymptomatic alcoholic subjects have a mild increase in left ventricular wall thickness without echocardiographic evidence of depressed myocardial contractility. Depressed myocardial contractility could be indicated by decreased ejection fraction, wall excursion, decreased velocity, and circumferential fiber shortening. Diastolic dysfunction often precedes systolic dysfunction, and once systolic impairment becomes apparent, diastolic dysfunction occurs more frequently [2].

As with any new diagnosis of heart failure and/or dilated cardiomyopathy, patients should undergo evaluation for coronary disease. Noninvasive stress testing would be a reasonable first step; however coronary angiography should be considered in patients with other risk factors or suspicion of ischemia [2].

Cardiac magnetic resonance imaging should also be considered if available to differentiate alcoholic cardiomyopathy from other types of cardiomyopathy. There are no distinctive features to identify alcoholic cardiomyopathy with CMR; however, this will also assess for ischemic heart disease and infiltrative diseases such as amyloid and iron overload [2]. Endomyocardial biopsy is not generally recommended as the histologic changes in alcoholic cardiomyopathy are similar to those present in idiopathic dilated cardiomyopathy [2].

As previously discussed, alcoholic cardiomyopathy is a diagnosis of exclusion and requires a very thorough history from the patient and family. If all other causes for cardiomyopathy are ruled out (hypertensive, valvular, ischemic, and other inherited/systemic causes) and the patient has a history of heavy alcohol use, it can be assumed that the etiology of cardiomyopathy is alcohol-related [2].

16.3 Management of Alcoholic Cardiomyopathy

A top priority for managing patients with alcoholic cardiomyopathy is encouraging them to completely abstain from further alcohol use. Complete recovery of LV function has been reported after cessation of drinking alcohol and even if LV dysfunction persists, the symptoms and signs of heart failure tend to improve with abstinence [4]. Supporting patients as needed (including referrals to an alcohol support group or mental health provider) and close clinic follow-up with frequent telephone contacts/visits for accountability are crucial. Patients should be provided with education regarding a balanced diet, and nutritional deficiencies should be addressed and corrected when deficiencies are noted. Vitamin B12, vitamin B6, and folate are important adjunctive therapy when a history of sustained heavy alcohol is noted. Potassium and magnesium levels should be closely monitored and corrected as well [2].

Pharmacologic therapy to treat alcoholic cardiomyopathy is the same as other forms of dilated cardiomyopathy and includes a combination of a beta-blocker (carvedilol, bisoprolol, or metoprolol succinate), angiotensin II receptor blocker/angiotensin-converting enzyme inhibitor/angiotensin blocker-neprilysin inhibitor, mineralocorticoid receptor antagonist, SGLT-2, and combination of hydrazine and isosorbide dinitrate when indicated [11].

As with other forms of dilated cardiomyopathy, alcoholic cardiomyopathy is mainly characterized by dilation of the left ventricle and loss of cardiac function. This often results in systolic and diastolic dysfunction and predisposes to ventricular arrhythmias and sudden cardiac death [12]. Refer to the previous chapter of this book for specific criteria regarding the potential need for an implantable cardiac defibrillator or other device therapy (biventricular pacing).

16.4 Prognosis of Alcoholic Cardiomyopathy

Although patients with alcoholic cardiomyopathy can completely recover cardiac function with early diagnosis, proper management, and cessation (or at least reduction) of alcohol intake, a subset of patients will continue to progress and develop persistently severe symptoms despite full optimization of guideline-directed medical therapy [2, 4]. Advanced therapies (mechanical circulatory support and cardiac transplantation) are beneficial in carefully selected patients and require complete abstinence from alcohol per International Society of Heart and Lung Transplantation (ISHLT) guidelines. Data is very limited regarding transplant outcomes in alcoholic

cardiomyopathy; however, medication adherence and relapse are common concerns for patients with a history of substance abuse [13].

Overall prognosis is often adversely influenced by comorbidities such as liver disease, drug abuse, smoking, depression, and pulmonary disease [2]. Genetic testing may play an important role in identifying patients with an increased vulnerability to developing alcoholic cardiomyopathy; however, this is not yet considered a standard of care [8].

16.5 Additional Considerations for Alcoholic Cardiomyopathy

Patients with heart failure often have many other underlying conditions which can be exacerbated by alcohol use, including hypertension and hyperlipidemia. Alcohol use can result in a pressor effect, which contributes to hypertension and an increase in left ventricular mass. Heavy alcohol use can result in a substantial increase in blood pressure. Alcohol consumption also often results in deficiencies in magnesium, potassium, phosphorus, and thiamine and can in turn further exacerbate dysfunction. Alcohol consumption can elevate triglyceride levels, causing an increase in both total cholesterol and low-density lipoprotein concentration [14].

16.6 Case Study: Alcoholic Cardiomyopathy

Name: J.A.

Age/Sex: 43-year-old, Caucasian male

Past Medical History/Problem List:

Hypertension

GERD

Alcohol Abuse

Tobacco Abuse

Family History: Significant family history of CAD (mother—MI in 2002), Diabetes (father)

Social History: 8–10 beers per day, smokes 1 pack of cigarettes per day, lives with his wife who has multiple sclerosis and he is the primary caregiver for her

Medications: Ibuprofen (occasionally), ranitidine OTC 1 tablet twice per day

Allergies/Intolerances: Codeine

Case Scenario: 43-year-old Caucasian male who presents with new onset chest pain and dyspnea, in the setting of heavy alcohol use

Subjective: Presented with chest pain for 3 days and dyspnea associated with a dry cough, most noticeable when "throwing darts." The dyspnea had progressed over the past few days and was reported as "severe" at times. Reported orthopnea (3 pillows) as well as occasional PND. No prior cardiac history. Had not been evaluated by his primary care provider in nearly 4 years and off all anti-hypertensives since that time.

Objective:

Vital signs: BP 92/58; HR 83; Oxygen Saturation 98% on room air. Weight: 180 pounds

Physical exam: JVD 12 cm. Positive HJR. Positive S3. 2 + bilateral lower extremity pitting edema, cachectic

Labs: BNP >3000, Troponin 0.02, Creatinine 1.19, AST 53, ALT 53, Total bilirubin 1.5, Peth >20 ng/dL

EKG: LVH, QRS 140 ms, PVCs

Assessment: J.A. has a history of alcoholism. After being lost to follow-up for the past 4 years, he now presents with signs and symptoms concerning for heart failure based on symptoms, labs, and EKG changes.

Plan: He is significantly hypervolemic per exam, though does have a normal renal function and oxygen saturation is 98% on room air. Would be reasonable to start him on furosemide with a referral to Cardiology and an echo ordered to be completed as soon as possible. If his oxygen saturation were to be low (<90%), blood pressure significantly low (systolic blood pressure less than 90), or he was to be noticeably dyspneic with minimal activity would recommend admission to the hospital for further evaluation and management. Emphasize the importance of abstaining from alcohol and start thiamine and multivitamin.

Clinical Pearls: This patient would need very close monitoring of his response to the addition of diuretics with frequent phone calls and clinic visits. In addition to adequately managing his volume status once heart failure is diagnosed, he would also need to start on guideline-directed medical therapy with plans for titration every 2 weeks if tolerated. Patients with alcoholic cardiomyopathy seem to respond better with frequent contacts for accountability as alcohol use should be addressed at each encounter.

16.7 Cocaine- and Methamphetamine-Induced Cardiomyopathy

16.7.1 Overview of Cocaine and Methamphetamine Use

Cocaine abuse is a major public health challenge with millions of Americans affected. Its use has continued to escalate in the United States and worldwide. Estimates of emergency room (ER) visits in the United States related to cocaine abuse account for over 500,000 visits per year, which presents a significant burden on our healthcare system [15, 16]. These visits are usually related to cardiovascular complaints such as chest pain, palpitations, and severe hypertension which are caused by increased inotropic and chronotropic effects and increased peripheral vasoconstriction [15, 16]. Cocaine abuse is also a major source of morbidity and mortality that causes long-term cognitive impairment and often leads to early death [16–20].

Cocaine and methamphetamine are both highly addictive and have similar actions; they are both cardiac stimulants that lead to euphoria and cardiovascular

complications [21]. Amphetamines are often used to treat attention deficit hyperactivity disorder and are the second most widely used illicit drug in the United States, second only to cannabis [20]. Chronic cocaine and methamphetamine abuse can lead to coronary artery disease (CAD), acute myocardial infarction (AMI), ischemic cardiomyopathy, severe palpitations, aortic dissection, malignant hypertension, methamphetamine-associated cardiomyopathy (MACM), dysrhythmias, and sudden cardiac death (SCD) [20]. Acute ischemia with subsequent myocardial infarction is generally related to coronary artery vasospasm and tachyarrhythmias [21]. The number of cocaine users in the United States in 1985 was estimated at 5.8 million, but by 2016, the total number of cocaine users had increased to an estimated 18.2 million worldwide [18].

Cocaine is a powerfully addictive stimulant that is a naturally occurring alkaloid extracted from the leaves of *Erythroxylum coca,* first isolated in 1860 [15]. The effect of cocaine on the cardiac muscle and coronary blood vessels remains poorly understood [22]. Cocaine affects endothelial cells by stimulating the release of endothelin-1, a potent vasoconstrictor, and inhibiting the production of nitric oxide, a major vasodilator [23]. Cocaine also blocks sodium and potassium channels across the cell membrane during depolarization and causes local anesthesia leading to abnormal, depressed cardiovascular profiles [22, 24]. Concurrent abuse of cocaine and alcohol significantly increases cocaine levels in the blood [24]. Cocaine and methamphetamine are both highly addictive and have similar actions in that they are both cardiac stimulants that lead to euphoria and cardiovascular complications. Chronic cocaine and methamphetamine abuse can lead to coronary artery disease (CAD), acute myocardial infarction (AMI), ischemic cardiomyopathy, severe palpitations, aortic dissection, malignant hypertension, methamphetamine-associated cardiomyopathy (MACM), dysrhythmias, and sudden cardiac death (SCD) [18, 20].

Cocaine can be either ingested orally, by inhalation, injection, rectally or vaginally. The inhalation route has a more rapid onset and a shorter duration of action compared with ingestion. Its half-life is variable depending on its route of administration and varies from 1 min to up to 2 h. Cocaine is excreted primarily by urination and can remain in the urine or bloodstream for up to 72 h [15, 24, 25].

16.8 Clinical Presentation and Diagnostic Testing in Setting of Cocaine and Methamphetamine Use

Given the severity of symptoms, patients often present for urgent evaluation. There are various reasons for Emergency Room visits regarding ongoing cocaine use and addiction, but the most common presentation is acute coronary syndrome. Other presentations are noted below [15, 19, 22].

- Unstable angina.
- Severe hypertension.

- Pulmonary hypertension.
- Aortic dissection.
- Myocarditis.
- Stroke—endothelial dysfunction, vascular injury, prothrombotic state, impaired cerebral blood flow, cerebral artery vasoconstriction induced by cocaine's sodium-blocking effect.
- Arrhythmia.
- Vasculitis.
- HIV from contaminated IV needles.

A detailed medication history is extremely important since multiple cocaine-related drug-drug interactions potentiate the toxicities and adverse reactions related to cocaine abuse [25]. Cocaine-related drug-drug interactions are outlined in Table 16.2.

Initial diagnostic testing for cocaine use/abuse should include:

1. EKG to rule out ischemia, tachycardia, or other pertinent arrhythmias.
2. PA/Lateral chest X-ray to evaluate general heart size and for pneumonia and/or cardiac or pulmonary effusions.
3. CBC, CMP, BNP or NT-proBNP, TSH/FT4, and toxicology screen.
4. Transthoracic Echocardiogram is the gold standard to evaluate left ventricular function and for the presence of valvular dysfunction.
5. Right and left heart catheterization, if ischemia is suspected based on EKG and symptoms.
6. Pregnancy test for females.

Table 16.2 Cocaine-related drug-drug interactions [Reprinted from US Pharmacist, 40(2), Barnes, KA, Fasanmi, EO, Iwuorie, OP, Simon, PS, Hylick EV. Cocaine-Induced Cardiomyopathy, HS11-HS15, copyright (2015) with permission from US Pharmacist]

Drug	Interaction
Ethanol	Increases toxicity of cocaine; increases morbidity and mortality
Opiate/opoid medications	Enhance toxicity of cocaine; cocaine enhances opiate/opioid toxicity
Heroin	Enhances toxicity of cocaine and increases risk of death; enhances toxicity of heroin
Anitdepressants/ antipsychotics	Increase toxicity of cocaine and risk of cardiac dysrhythmias; combined use with MAOIs may lead to hypertensive crisis
Antihistamines	Increase toxicity of cocaine
Cannabionoids	Increase adverse effects of cocaine
Methamphetamine	Increases seizure risk
Nicotine	Increases cardiovascular risks and enhances incidence of myocardial dysfunction

16.9 Methamphetamine-Induced Cardiomyopathy

16.9.1 Prevalence

A review of the 2017 National Survey on Drug Use and Health (NSDUH) notes that approximately 1.6 million people (0.6% of the population) reported using methamphetamine (MA) in the past year, and 774,000 (0.3%) reported using it in the past month. The average age of new MA users in 2016 was 23.3 years old. In North America, MA abusers are predominately in their 30s and 40s, but use has also been reported in adolescents because of the lower cost and longer duration of action than cocaine. An estimated 964,000 people aged 12 or older (about 0.4% of the population) had a MA use disorder in 2017 with clinically significant impairment, including health problems, disability, and failure to meet responsibilities at work, school, or home as a result of their drug use. This number is significantly higher than the 684,000 people who reported having methamphetamine use disorder in 2016. A 2009 report from the RAND Corporation noted that methamphetamine misuse cost the nation approximately $23.4 billion in 2005. Most of the MA abused in the United States is produced in superlabs that are located in Mexico; however, it is also relatively easy and inexpensive to produce on a small scale [19].

16.9.2 Pathophysiology of Methamphetamine-Induced Cardiomyopathy

Methamphetamine (MA) is a powerful, highly addictive stimulant related to amphetamine that affects the central nervous system. It generally increases energy levels, false sense of well-being, and often makes users hyperactive. These effects often last for about 8–20 h, depending on urine pH, recent use, and recent dosage. Eventually, there is a significant crash which often leads to depression, severe mood swings, agitation, and strong cravings for more methamphetamine. It is available in powder and crystalline forms and can be taken orally, intravenously, snorted, or smoked. The smokable form of methamphetamine produces an immediate euphoria similar to crack cocaine but the effects may last much longer [19].

16.9.3 Clinical Presentation and Diagnostic Testing

Acute MA overdose can result in sympathetic overdrive, intracranial hemorrhage, cardiovascular collapse, rhabdomyolysis, ventricular tachyarrhythmias, and death [19]. Acute presentation to the Emergency Department (ED) may include chest pain, aortic dissection, myocardial ischemia and/or infarction, hypertension, palpitations, tachyarrhythmias, dyspnea, and edema. They may demonstrate agitation, violent behavior, new onset seizures, psychosis, paranoia, headache, abdominal pain, or obstructions. These patients should be sent to the ED.

Initial diagnostic testing is similar to the section on cocaine abuse with the addition of CT of the head if clinically indicated, and low-dose CT abdominal imaging if body-packers, body-stuffers, or parachuters are suspected [19]. Immediate management is focused on treating the presenting symptoms (ACS, chest pain, arrhythmias, agitation).

16.10 Additional Considerations for the Primary Care Provider for Methamphetamine-Induced Cardiomyopathy

Patients with cocaine-induced or methamphetamine-induced cardiomyopathy most often present to the emergency room given the severity of acute to chronic symptoms. Longitudinal follow-up after initial diagnosis is extremely important to improve prognosis and outcomes. Treating underlying addiction along with a comprehensive assessment of psychosocial factors is imperative.

16.11 Case Study: Methamphetamine-Induced Cardiomyopathy

Name: JB

Age/Sex: 56 y/o AAM.

Past Medical History/Problem List:

Cocaine abuse, in remission for 2–3 months before the initial visit.

Dilated cardiomyopathy with hypotension that prevented maximizing Guideline-Directed medical therapy (GDMT)

Hypertension was diagnosed 8–10 years ago.

Osteoarthritis of both knees.

Hyperlipidemia, newly diagnosed.

No insurance.

Family History: Negative for CAD and heart failure

Social History: Single, lives alone, works as a driver for a local church. Non-smoker, no alcohol currently. No significant caffeine intake.

Medications:

Lisinopril 2.5 mg po daily.

Metoprolol tartrate 25 mg po bid.

Furosemide 80 mg po bid.

ASA EC 81 mg po daily.

Atorvastatin 80 mg daily at bedtime.

Allergies/Intolerances: No known allergies.

Subjective: Six-minute walk 450 feet. Tired, no energy.

Objective:

Vital signs: BP 128/68, Pulse 88, Respirations 18. SaO2 98% on room air.

Weight 157 lbs. Height 5 feet 7 inches. BMI 24.9.

Physical exam: JVD 12 cm. Positive HJR. Positive S3. 2 + bilateral lower extremity pitting edema, cachectic.

Labs:

CBC—Hemoglobin 12.8. Hematocrit 35%. Normal platelet count.

CMP—WNL. BUN 19. sCr 1.2.

BNP was elevated at 1500. Normal less than 100.

TS/FT4—WNL.

Lipid profile—at goal with current statin.

Anemia profile—WNL.

EKG: Normal sinus rhythm with ventricular range 88 bpm.

Echo: Left ventricular ejection fractions (LVEF) 10–15% with very dilated left ventricle (7.6 cm). Normal right ventricular size and function. Unchanged from previous outside echo.

Right and Left Heart Catheterization: No significant obstructive coronary artery disease but notable for elevated right heart filling pressures, completed several months before the initial visit with the new provider.

Assessment/Plan: Over the next few months, Guideline-Directed Medical Therapy for Heart Failure was initiated, and doses were up-titrated. Metoprolol tartrate was changed to carvedilol and was up-titrated to 25 mg twice daily. Lisinopril was discontinued. The patient was advised to begin sacubitril/valsartan (Entresto) 49/51 mg twice daily after a 36-h lisinopril washout period. Spironolactone 25 mg PO daily was initiated, and follow-up labs were normal, specifically potassium and creatinine. BNP decreased to 96 (normal). Furosemide dose was decreased to 40 mg daily and eventually was able to use only as needed. He was encouraged to completely refrain from using cocaine again, which he adhered to at subsequent visits. All repeat urine drug screens were negative. A repeat echocardiogram was completed around 6 months after GDMT was maximized and his LVEF improved to 55–60% and LVIDd decreased to 4.9 cm. Weight 170 lbs. Blood pressure 128/70 with a pulse of 69. His exercise capacity improved with 6 MWT of 1500 feet.

16.12 Clinical Pearls for Alcohol- and Cocaine-Induced Cardiomyopathy

- Drug- or alcohol-induced cardiomyopathy is one of the few types of cardiomyopathies that the heart function (ejection fraction) can normalize with total abstinence.
- Accountability is key for substance abuse whether it is alcohol, cocaine, or methamphetamines.
- Treat the "whole patient," and provide resources needed to help with substance abuse cessation. This includes referrals to Heart Failure Clinics, dietitians, PharmD, Social workers, and Mental Health.
- Family members should be included when appropriate and possible.
- Cocaine use is more often associated with acute rather than chronic cardiovascular illness.

- Casual use of cocaine may be associated with acute or chronic cardiovascular toxicity.
- Cocaine is excreted primarily by urination and can remain in the urine or bloodstream for up to 72 h.
- Methamphetamine addiction can be treated with behavioral therapies. There are currently no government-approved medications to treat methamphetamine addiction.

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Human Immunodeficiency Virus and Heart Failure

17

Courtney J. Pitts

17.1 Case Study

A 57-year-old male presents to reestablish care for HIV management. He reports adhering to his antiretroviral therapy regimen, abacavir-dolutegravir-lamivudine (Triumeq®), and is virologically suppressed. His previous provider switched him from efavirenz-emtricitabine-tenofovir (Atripla®) to Triumeq® about 2 years ago. His most recent labs from his provider indicated that his CD4 count was 854 with a percentage of 38.8% and his HIV viral load was less than 40 copies/mL. He denies missing any doses of medication since transitioning back to the area. He has a past medical history of hepatitis C virus infection, hypertension, diabetes, depressive symptoms, alcohol and drug dependence. He had been "clean" for 2 years prior to his return to the city until he had a one-time drug use during a social event. The drug of choice was cocaine. He was seeing a psychiatrist and wishes to transition those services to the clinic. His review of systems was unremarkable with the exception of mild swelling in the lower extremities. In addition to ART, he is also prescribed bupropion XL 300 mg tablet once daily by mouth at bedtime, hydroxyzine 100 mg capsule once daily by mouth, trazodone 300 mg tablet once daily by mouth at bedtime, ziprasidone 40 mg capsule twice daily by mouth, and lisinopril 40 mg tablet once daily by mouth. He states that he manages his diabetes with exercise. On physical exam, his BP was 138/82, pulse of 67, and respiration rate of 16. His temperature was 97.3 with a SpO2 of 98% on room air. He is 5 ft 7 in. tall and weighs 220 pounds. He is in no acute distress. Assessment with normal findings with the exception of bilateral 2+ pitting edema.

C. J. Pitts (✉)
Vanderbilt University School of Nursing, Nashville, TN, USA
e-mail: courtney.j.pitts@vanderbilt.edu

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_17

17.2 Background

The human immunodeficiency virus (HIV) works to suppress the immune system by dismantling its defenses against many infections and cancers that would not typically threaten a healthy immune system [1]. Immunodeficiency occurs as the virus impairs the function of the immune cells. When untreated over a period of time, HIV develops into acquired immunodeficiency syndrome (AIDS). This syndrome often entails the development of severe long-term clinical manifestations.

More than 79 million people have acquired HIV since the start of the epidemic in the 1980s, with an estimated 46% of them having succumbed to AIDS-related illnesses [2]. As of 2020, approximately 38 million people were living with HIV globally with an estimated 1.5 million new infections being reported that year [1, 2]. Of these individuals, approximately 95% are adults and 53% being women and girls [2]. An estimated two-thirds of these individuals reside in the Sub-Saharan region of Africa [2]. In 2020, approximately 18% of people living with HIV (PLWH) succumbed to AIDS-related illnesses [2].

Fortunately, three decades of enhanced technology and research has resulted in the development of safe and effective antiretroviral therapy (ART). The use of ART has resulted in HIV transitioning from a highly infectious disease to a chronic disease. By the end of 2020, more than 27 million PLWH were accessing antiretroviral therapy [1, 2]. This means that around 73% of PLWH that were at least 13 years or older were receiving treatment for HIV [1].

17.3 HIV and Heart Failure

PLWH have an increased life expectancy due to the implementation of ART [3]. This is especially evident in regions in which there is widespread ART accessibility [4]. As this population now ages, they are more susceptible to the long-term effects often associated with chronic diseases, such as cardiovascular disease and heart failure [5–7]. The risk of cardiovascular disease is reported to be 61% higher compared to the general population [6]. With this increased life expectancy, PLWH are more likely to develop cardiomyopathy and experience related morbidity and mortality with onset at two to three decades younger than that of the general population [5].

It is projected that by 2030, approximately 73% of PLWH globally will be 50 years of age or older with about 78% of them having a cardiovascular disease comorbidity, especially in high resource regions [3, 7, 8]. Globally, HIV-associated cardiomyopathy has tripled over the past 2 years with the greatest impact in Asia-Pacific and Sub-Saharan Africa regions [9]. The literature suggests that PLWH have a twofold increased risk of having heart failure compared to their uninfected counterparts which portends a poor prognosis [4, 8–10]. The 5-year mortality rate for heart failure among PLWH approaches 50% [8].

During the earlier decades of the HIV endemic, the leading causes of HIV-associated heart failure were due to direct viral effects, severe immunosuppression,

primary and secondary myocarditis, opportunistic infections, cell and humoral immunity dysregulation, and nutritional deficiencies [7, 11, 12]. This often resulted in the infection of heart muscle leading to the development of myocarditis. In the contemporary ART era, the causes are now multifactorial that include earlier causes in addition to ART effects, increased prevalence of traditional cardiovascular disease risk factors, endemic comorbidities, high-risk behaviors, and underlying genetics [3, 4, 6, 7]. The risk for heart failure is further increased due to disparities in treatment of PLWH who have heart failure secondary to harmful effects of ART [6]. However, ART access has reduced the proportion of heart failure that is secondary to infective myocarditis [12]. Unfortunately, the differences in more developed regions versus more resource-limited regions present two different pictures of the relationship between HIV and heart failure.

17.4 Pathophysiology and Clinical Presentation

Heart failure and myocardial dysfunction have been complications of HIV since the reporting of early cases in the 1980s [9]. The leading causes of HIV-associated heart failure play a significant role in its pathophysiology though the exact etiology is unclear [11]. Overall, PLWH are at increased risk for each of the heart failure phenotypes: heart failure reduced ejection fraction (HFrEF), heart failure preserved ejection fraction (HFpEF) and borderline HFpEF [9]. The heart failure phenotype HFrEF is the most common that occurs in PLWH as it is 40% of the cases [9]. This phenotype is followed by HFpEF, borderline HFpEF, and phenotype unknown at 30%, 15%, and 15%, respectively [9].

The literature suggests that myocarditis, vascular inflammation, chronic low-grade inflammation, immune dysregulation, myocardial fibrosis, metabolic dysregulation, and the harmful effects of ART are potential vascular mechanisms that result in cardiac injury [4, 5]. Myocarditis and systolic dysfunction are a direct effect of the damage inflicted on the heart by HIV [7]. The development of myocarditis, as well as the presence of opportunistic infections, results in severe, dilated cardiomyopathy [7]. PLWH are also more likely to have myocardial inflammation and interstitial fibrosis—focal and diffuse [7]. Increased levels of inflammatory markers are associated with increased risk of cardiovascular disease [5]. Vascular and myocardial pathology have been linked to arterial inflammation [4]. Cardiac injury may also occur due to the increased presence of cardiac-specific autoantibodies in PLWH, especially in the presence of myocardial disease [7, 11].

Immunity dysregulation is a result of the ability of cardiotropic viruses to alter surface antigens resulting in autoimmune reactions to endogenous epitopes. These autoantibodies are more common among PLWH, especially in the presence of a cardiac comorbidity [7]. Additionally, T cell activation in PLWH has been linked to diastolic dysfunction due to the development of arterial stiffness [7]. Myocardial fibrosis and steatosis are more prevalent in PLWH compared to their HIV negative counterparts and are associated with mechanical dysfunction and myocardial injury [7, 9]. More specifically, myocardial fibrosis results in systolic and diastolic

dysfunction [7]. Nutritional deficiencies that result in diarrheic syndromes and malabsorption are a more common cause of HIV-associated heart failure in developing countries as the primary deficiency is selenium [7]. There is a strong association between a form of cardiomyopathy and selenium [7].

Substance use has been classified as a nonvascular mechanism of heart failure in PLWH, though it is not the primary driver [9]. The use of alcohol, methamphetamine, and cocaine is more prevalent in PLWH, increasing the likelihood of cardiomyopathy and heart failure development [9]. Despite the potential yet unclear etiologies mentioned, the pathophysiology of heart failure in PLWH differs based on widespread access to ART.

17.4.1 Pre-ART Era or Limited ART Access

The pre-ART era is primarily characterized by AIDS-associated cardiomyopathy marked with progressive, uncontrolled viral replication, immune dysregulation, opportunistic infections, and systolic dysfunction with myocarditis [7, 9, 11, 12]. HIV-associated heart failure manifested as rapidly progressive systolic dysfunction and a dilated left ventricle [5]. This resulted in a median survival of approximately 100 days after initial diagnosis of cardiomyopathy [5].

17.4.2 Contemporary ART Era

In the presence of ART, heart failure has become multifactorial with proposed causes including traditional and nontraditional factors that manifest as diastolic dysfunction [3, 5, 7]. Diastolic dysfunction and heart failure are more common among PLWH who are adherent to their ART regimen compared to the general population [9]. The development of diastolic dysfunction among ART treated PLWH may be attributed to the pathologic processes associated with myocardial fibrosis and steatosis [8].

17.4.3 Clinical Implications

Clinically, PLWH with heart failure exacerbation may present with signs of volume overload. This includes, but is not limited to, peripheral edema, shortness of breath, orthopnea, weight gain, lethargy, jugular venous distension, and fatigue or lethargy.

Heart failure in PLWH is associated with increased cardiovascular mortality due to residual virally mediated inflammation and traditional risk factors [4]. This risk increases if virologic suppression or immune system reconstitution has not been achieved [3].

Studies suggest increased 30-day heart failure admission rates and higher mortality rates compared to the general population [4]. Drug and alcohol use were predictors of heart failure-related admissions [4].

17.5 Risk Factors

Risk factors for the development of heart failure in PLWH can be categorized as traditional risk factors and nontraditional risk factors (see Table 17.1). The risk factors may increase the likelihood of heart failure development and its subtypes depending on some of these risk factors.

17.5.1 Traditional Risk Factors

Age is a significant heart failure risk factor due to there being an increased prevalence of chronic diseases (e.g., hypertension, dyslipidemia, diabetes, etc.) as people chronologically age [10]. Excess rates of heart failure risk exist more among PLWH who are 40 years of age or older [12]. The risk of heart failure increases by sex as it disproportionately affects women more than men [4, 9, 11]. Women living with HIV are more likely to experience higher rates of heart failure-related hospitalizations, longer stays, and higher rates of mortality compared to their uninfected counterparts [4, 8]. This is likely due to increased myocardial fibrosis and decreased diastolic function as a result of high level systemic immune activation [4]. Cigarette use is associated with a twofold to threefold increased risk of heart failure in PLWH compared to the general population [11]. The risk is lower in PLWH who have never smoked compared to those who are current or former smokers [11]. It should be understood that there is some intersectionality among traditional risk factors. For example, metabolic syndrome, cigarette smoking, and hypertension are more prevalent in PLWH resulting in higher 10-year Framingham risk scores [7].

17.5.2 Nontraditional Risk Factors

Viral replication and immunosuppression are significant heart failure risk factors for adverse outcomes among PLWH, regardless of the subtype [3]. The literature suggests that PLWH who have viral loads of >500 copies/mL and are moderately immune compromised (CD4 count <500 cells/mm^3) are at higher risk for HF [9].

Table 17.1 Traditional versus nontraditional risk factors [4, 8, 11, 12]

Traditional	Nontraditional
Age	Viral replication
Sex	Immunosuppression
Race	Opportunistic infections
Body mass index	ART regimens
Presence of hypertension	Liver fibrosis
Metabolic syndrome	Depression
Smoking	
Alcohol or drug use	
History of myocardial infarction	

CD4 counts <200 cells/mm^3 increases the risk of heart failure twofold and increases the likelihood or worse outcomes—mortality and 30-day hospital admission [4, 12]. High viral loads and CD4 counts <200 cells/mm^3 are associated with HFrEF while ART use and CD4 < 200 are associated with HFpEF [11]. However, it should be noted that viral suppression (<40 copies/mL) does not eliminate risk [7]. It is not completely understood how viral replication and immunosuppression increase heart failure risk, but it is possible that immune system activation and persistent inflammation related to the virus itself play a role [4]. This suggests that ART may be protective against adverse outcomes associated with heart failure [4].

ART adherence is very effective in virologic suppression and immune system reconstitution. However, its use induces the onset of some nontraditional risk factors (e.g., metabolic syndrome). The use of ART increases the likelihood that PLWH will develop diabetes and at younger ages and body mass index (BMI) of the general population (Sinha and Feinsten, 2020). The integrase inhibitor (INSTIs) drug class of ART is typically well tolerated with a safer profile though they have the potential to increase the risk of insulin resistance and diabetes onset [11]. The INSTI and the protease inhibitor (PI) drug classes also increase central and peripheral fat deposits [11]. In geographical areas where ART access is limited, the pattern of HIV-associated heart failure mirrors the pre-ART era etiology [9].

There is also intersectionality among traditional and nontraditional risk factors. It is well known that age, hypertension, and smoking are risk factors in the general population. However, these factors heighten the risk of heart failure in the presence of immunosuppression and ART [11]. The risk of HFpEF in PLWH increases in those who are ART adherent, older, and female [8].

17.6 Antiretroviral Therapy and HF

During the pre-ART era, the inflammatory process of HIV, presence of opportunistic infections, nutritional deficiencies, or severe immunosuppression led to the development of HIV-associated cardiomyopathy [13]. The introduction of ART has been beneficial in the abatement of heart failure risk, though some regimens have the potential to exert cardiotoxic effects [8]. Since the introduction of ART, HIV has shifted from being a condition with a poor prognosis and inevitable mortality to a manageable chronic disease [5]. ART adherence among PLWH results in a decrease in heart failure risk as the length of adherence increases [11]. However, the protective benefits of ART are still up for debate.

The use of ART reduces the presence of opportunistic infections that would lead to the development of myocarditis [5]. This allows the course of heart failure to be a more chronic, progressive condition compared to the much shorter course (weeks or months) experienced by those who do not have access to ART [5, 10]. In children, ART seems to be more protective and a deterrent to heart failure onset as the cardiovascular system of a child is still developing [7]. Studies have demonstrated that perinatal exposure of ART results in near normal changes in left ventricle mass and dimension and septal wall thickness [7]. The drug tenofovir disoproxil fumarate is

associated with lowering the risk of heart failure as its mechanism reduces inflammation or assists in lowering lipid levels [10].

Though it has its protective effects, ART has the ability to also induce HIV-associated cardiomyopathy and heart failure in the long term [4, 7, 9]. It is highly effective in achieving virologic suppression while it simultaneously fails to mitigate arterial inflammation and systemic immune activation [4, 7, 8]. The literature suggests that this is likely due to residual viral replication, microbial translocation, and gut mucosal injury as they drive myocardial fibrosis [7, 8, 12]. Older ART regimens that included drugs such as stavudine, didanosine, and zidovudine are associated with mitochondrial toxicity, central and peripheral lipodystrophy, and direct impairment of left ventricular function [4, 5, 7–10]. Abacavir continues to be a controversial drug when considering cardiovascular risk, though the data has been inconsistent [9]. Boosted PIs (ritonavir boosted PIs) have been associated with the development of such comorbidities as type II diabetes, dyslipidemia, coronary artery disease, elevated pulmonary artery systolic pressure, and reduced left ventricular ejection fraction [5]. This drug class has also been associated with worse outcomes for PLWH who become hospitalized as there is a twofold increased risk of 30-day readmission and cardiovascular-related mortality [7, 8].

Despite their safer profiles and tolerability, newer ART regimens cause weight gain, excess adiposity, and ectopic fat deposits leading to the development of additional heart failure risk factors such as hypertension and metabolic syndrome [4, 7, 8, 10]. Regardless of the controversy, it is clear that the benefits of ART outweigh the development and management of heart failure physically and potentially economically [5, 9]. Overall, the newer regimens have safer profiles and have the ability to prevent heart failure subtypes associated with the pre-ART era [5, 8].

17.7 Evaluation and Management of HIV and Heart Failure

To date, there are no HIV-specific guidelines or risk prediction models due to the unclear mechanisms involved in heart failure and limited long-term data in the modern ART era in this population [5, 9]. Past studies that addressed heart evaluation and management in PLWH have resulted in risk models (e.g., Framingham) that underestimated cardiovascular disease risk though more recent studies have attempted to confirm that work [9, 12]. Recommendations for treatment are based on clinical trials that addressed heart failure management in the general population [7, 10].

The American Heart Association (AHA) does provide some guidance that addresses evaluation and management of risk factors and any comorbidities, promoting behavior and lifestyle modifications, and prescription management [5]. Management of risk factors focuses on optimizing medical management of comorbidities such as diabetes, hypertension, and dyslipidemia [5]. The reduction of chronic inflammation can be targeted through the use of pharmacologic agents with the appropriate mechanisms. For examples, statins are effective in decreasing markers of cardiac fibrosis via their anti-inflammatory and immunomodulatory

properties [5]. The renin-angiotensin-aldosterone system (RAAS) may be inhibited through the use of angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEs) which can be considered first-line therapy [5]. Aldosterone antagonists and beta blockers may also be options though data is limited on their effectiveness [5, 7, 10].

Behavior and lifestyle modifications should be assessed at each clinical visit. This may include encouraging smoking cessation, an active lifestyle, nutrition counseling, and conducting alcohol abuse screening [5]. More importantly, it is of utter importance that PLWH with heart failure are on adequate pharmacological therapy that includes antiplatelet therapy and statins [5]. The literature suggests that PLWH are less likely to be placed on ACEs, ARBs, and beta blockers prior to a heart failure-related hospital admission and were more likely to experience mortality at 6 months [7].

17.7.1 Diagnostic Testing and Advanced Therapy

The shift of HIV to a chronic disease limits risk assessment due to the lack of long-term data in the presence of ART [7, 9]. The utility of diagnostic testing for screening asymptomatic individuals is debatable despite studies that highlight echocardiographic abnormalities [7, 10]. For example, PLWH are more likely to have uncalcified plaque, compared to the general population that is easily identifiable with computed tomography (CT) [9]. However, CT scans are not recommended for screening in asymptomatic individuals [9]. Cardiovascular magnetic imaging (CMR) may also be beneficial to the evaluation and management of heart failure in PLWH as it provides information on the degree of myocardial fibrosis or inflammation and HFpEF resulting in the reduction of cardiomyopathy and subsequent heart failure [5]. With limited guidance on the use of diagnostic imaging and biomarker levels, it is recommended that clinicians use the 2018 ACC/AHA cholesterol clinical practice guidelines to identify risk enhancers in PLWH [9]. The only risk enhancer that should not be considered is triglycerides due to its sensitivity in the presence of ART [9].

Historically, a positive HIV status has served as a contraindication for cardiac transplantation due to poor survival and concerns related to further immunosuppression [7]. The misbelief of limited life expectancy or increased likelihood of HIV-related complications has resulted in PLWH not having access to such advanced therapy even when medically warranted [7]. More recent studies suggest that this is not true, as recipients who are HIV+ have similar outcomes to recipients of the general population without developing HIV-related events [7]. The immunosuppressant medications prescribed post-transplant have enhanced ART efficacy in viral suppression without causing rejection or worsening the HIV status [7]. To date, there is limited data on the outcomes of PLWH and mechanical circulatory support devices, though there are case series that document reasonable outcomes supporting use of advanced therapies in those living with HIV [7].

Increased risk factors, behavior and lifestyle, and prescription management of heart failure in PLWH should guide the clinician to at least order noninvasive diagnostic testing, and consider advanced therapy, if necessary. Life expectancy and HIV-related complications should not limit clinicians in their consideration of advanced therapy for PLWH with heart failure.

17.7.2 Prognosis

The prognosis of PLWH has improved from its grim state during the pre-ART [7, 9, 10]. In the presence of poorly controlled HIV, heart failure hospitalization rates and mortality among women with HIV remain high as heart failure symptoms and evidence of cardiomyopathy increase the risk of death [7, 9, 10]. Due to the structural and functional abnormalities due to the presence of HIV, sudden cardiac death is 4.5 times more likely to occur in PLWH [7]. Though the presence of ART has improved, the overall prognosis of heart failure in this population, the prognosis remains the same for those living in geographic areas with limited access to ART [7, 9, 10].

17.8 Disparities in Care

The health of PLWH with heart failure is often impacted by their positive status. Living with a strongly stigmatized condition negatively impacts their ability to seek adequate health care services. Systemic barriers, structural and economic, often perpetuate disparities in health care delivery among this vulnerable population [9]. PLWH often engage in fewer clinical visits due to factors that worsen their vulnerability (see Table 17.2). Such factors affect adherence to pharmacological therapies that could control viral replication and slow the progression of heart failure in this population [9]. Studies suggest that blacks experience poorer pharmacological

Table 17.2 Factors that increase vulnerability among PLWH [9]

Level of education
Home location
Housing, if applicable
Health literacy
Cognitive deficiency
History of drug or alcohol use
Stigma, internalized or anticipated
Social isolation
Physical impairment
Frailty
Mental health

management for traditional risk factors such as hypertension, diabetes, and cholesterol, compared to their white counterparts. This is due to the lack or ART prescribing and management of other comorbidities (e.g., hypertension and diabetes) among this group [11]. Of the most commonly reported racial/ethnic groups, blacks and Hispanics have the highest estimated 10-year ASCVD risk due to the disparity of statin prescribing in these groups [9, 11]. PLWH are also less likely to receive advanced therapy or invasive management [12]. Geographical location is important as well, especially if PLWH reside in an area with limited access to ART due to HIV prevalence and lack of infrastructure for non-AIDS comorbidity management [9, 12].

Possible solutions to these issues mostly address economic and infrastructure factors. For example, to implement team-based care that includes clinicians, pharmacists, and referral specialists, health insurance access and coverage must be addressed [9]. Additionally, clinical settings must take into consideration that the management of HIV and additional comorbidities require longer visit times, more coordination, and interdisciplinary teams [9]. Though progress has been made in these areas, it is essential to the health of PLWH that these processes be improved through policy in order to reduce the barriers that negatively impact their health.

17.9 Heart Failure Prevention

Clinical management of underlying risk factors are key to heart failure prevention in PLWH [4, 11]. The lack of HIV-specific guidelines or heart failure risk prediction tools serves as a barrier to early detection of heart failure [11, 12]. However, medication management of risk factors is a starting point, taking into account the disparities in prescribing among health care providers [9, 11, 12]. Immediate and continuous ART prescribed by an infectious disease provider for PLWH will reduce the detrimental effects of uncontrolled HIV and associated conditions that affect the heart muscle (see Table 17.3) [4, 8]. Another option is the use of statins to target inflammatory markers associated with HIV and to reduce lipid levels [4, 9]. There are currently no recommendations for PLWH who have diabetes and hypertension other than those recommended for the general population [9, 11]. In the presence of nutritional deficiencies, supplementation is an option [7].

Behavior and lifestyle risk factors should be addressed as primary and secondary prevention strategies. This includes discussing diet, sedentary lifestyle, drug and alcohol use, cigarette use, and any additional nonpharmacological strategies associated with comorbidities (i.e., hypertension, diabetes, etc.) [4, 8, 9].

Table 17.3 Antiretroviral medications and classification

Nucleoside reverse transcriptase inhibitors (NRTI or NUKES)	Protease inhibitors
Abacavir (Ziagen) ABC *Need HLA B 5701 drawn; must be negative*	Amprenavir (APV)
Didanosine (Videx) ddl *(No longer used)*	Atazanavir (ATV)
Emtricitabine (Emtriva) FTC	Darunavir (DRV)
Lamivudine (Epivir) 3TC	Fosamprenavir (FPV)
Stavudine (Zerit) d4T *(No longer used)*	Indinavir (IDV)
Tenofovir (Viread) TDF	Lopinavir/ritonavir (LPV/r)
Zidovudine (Retrovir) AZT	Nelfinavir (NFV)
Zalcitabine (Hivid) ddC *(No longer used)*	Ritonavir (RTV) *(PI not given alone. Used as a booster)*
Combination NUKES	Saquinavir (SQV)
Combivir (AZT/3TC)	Tipranavir (TPV)
Cimduo (3TC/TDF)	*Boosted PI combinations*
Descovy (TAF/FTC)	Evotaz (ATV + Cobi)
Epzicom (ABC/3TC)	Prezcobix (DRV + Cobi)
Temixys (TDF/3TC)	
Trizivir (AZT/3TC/ABC) *Need HLA B 5701 drawn; must be negative*	**Fusion inhibitors**
Truvada (TDF/FTC)	Enfuvirtide (Fuzeon)
	Ibalizumab (Trogarzo)
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	Maraviroc Selzentry (MVC)
Delavirdine (Rescriptor)	Rash, N/V, HA, fatigue
Doravirine (Pifeltro)	*Monoclonal antibodies*
Efavirenz (Sustiva) EFV	Ibalizumab (Trogarzo)
Etravirine (Intelence) ETV	
Nevirapine (Viramune and Viramune XR) NVP	**Integrase inhibitors**
Rilpivirine (Edurant) RPV	Cabotegravir (vocabria)
	Raltegravir (RAL)
Combination therapy	Dolutegravir (DTG)
Atripla (FTC/TDF/EFV)	Elvitegravir (EVG)
Biktarvy (Bictegravir/TAF/FTC)	
Cabenuva (cabotegravir + rilpivirine)	**Cobisistat (cobi)**—Acts as a booster for PIs
Complera (FTC/TDF/RPV)—*viral load could not have ever been greater than 100,000*	
Delstrigo (Doravirine/TAF/3TC)	
Dovato (DTG/3TC)	
Genvoya (TAF/FTC/Cobi/EVG)	
Juluca (DTG/RPV)	
Odefsy (FTC/TAF/RPV)—Viral load could not have ever been greater than 100,000 copies	
Stribild (TDF/FTC/Cobicistat/EVG)	
Symfi and Symfi Lo (EFV/3TC/TDF)	
Symtuza (DRV/cobi/FTC/TAF)	
Triumeq (EPZ/DVG)—*Need HLA B 5701 drawn; must be negative*	

17.10 Case Study Discussion

It is evident based on the case study that was presented that the patient presenting to the clinic is at increased risk of developing heart failure. In addition to a positive HIV status, the patient has other risk factors and clinical manifestations that support the need for preventive therapy. Traditional risk factors included his age, the presence of comorbidities, and past and current drug use. Nontraditional risk factors include the presence of depressive symptoms and adherence to an ART regimen that contains a drug with conflicting data about its relation to cardiovascular disease. Pharmacological and nonpharmacological intervention to prevent the development of heart failure would be of benefit to this patient.

17.11 Conclusion

Though the prognosis of heart failure in PLWH has improved, there continue to be barriers to effective evaluation and management in this population. The shift from pre-ART era to the contemporary ART era is a barrier to care due to the limited data available that focuses on HIV as a chronic disease. In a population that now has a longer life expectancy, heart failure will be a significant contributor to their morbidity and mortality. With limited knowledge about the etiology and associated risk factors, the rates of prevalence, incidence, morbidity, and mortality will continue to rise before a decline is seen. The role of ART seems to have a dual role in heart failure progression as it is protective and harmful. However, the benefits clearly outweigh the risks. More importantly, clinicians should be diligent in ensuring that PLWH are adequately evaluated and managed similar to that of the general population to reduce the disparities often experienced by this population.

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Medications to Avoid When Treating Heart Failure

18

Zachary L. Cox

18.1 Case Example

A 64-year-old man presents to your primary care clinic with a 1-week history of worsening shortness of breath, lower extremity edema, and 8-kilogram weight gain. Past medical history is significant for heart failure with reduced ejection fraction, type 2 diabetes, and hypertension. Home medications include nifedipine XL 60 mg once daily, valsartan 80 mg twice daily, sitagliptin 100 mg once daily, metformin 500 mg twice daily, spironolactone 50 mg once daily, and furosemide 80 mg twice daily. The patient reports compliance with dietary sodium restrictions and medications. Upon questioning, he does report taking nonprescription naproxen (1–2 tablets/day most days of the week) and melatonin as needed for sleep. Vital signs are significant for a heart rate of 94 bpm, blood pressure of 149/85 mmHg, respiratory rate of 18 bpm, and oxygen saturation of 98% on room air. On physical exam the patient is in no acute distress, and you appreciate a jugular venous pressure of 15 mmHg sitting upright at 90 degrees and 2+ bilateral lower extremity edema to the knees. Laboratory values are notable for a serum sodium of 139 mEq/L, blood urea nitrogen of 22 mg/dl, serum creatinine of 1.5 mg/dl from a baseline of 1.1 mg/dl, and b-type natriuretic peptide of 3230 pg/ml. Your diagnosis is warm and wet acute decompensated heart failure. You direct the patient to the local emergency department in anticipation of admission for intravenous diuresis and heart failure optimization.

Z. L. Cox (✉)
Department of Pharmacy Practice, Lipscomb University College of Pharmacy, Nashville, TN, USA

Department of Pharmacy, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: zachary.l.cox@vumc.org

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_18

18.2 Case Discussion

Nifedipine and naproxen can both be contributors to worsening HF in this case. Nifedipine has negative inotropic properties that can exacerbate HFrEF. Nifedipine should be discontinued. In place of nifedipine, his hypertension and HF could be better treated by changing valsartan to sacubitril/valsartan. Naproxen should also be discontinued, and the patient should be counseled on avoidance of all NSAIDs. Once the source of his chronic pain is identified, alternative therapies can be recommended. Metformin is appropriate, will not cause worsening HF, and can be restarted after hospital discharge. Unlike saxagliptin, sitagliptin has neutral effects on HF, but changing to either dapagliflozin or empagliflozin could provide benefits in HF as well.

18.3 Introduction

Given the high prevalence of multimorbidity and polypharmacy, patients with heart failure (HF) are at elevated risk of medication-induced HF exacerbations and harm. Causality of medication-induced harm in HF is difficult to definitively establish due to the high baseline rate of disease exacerbations, multiple potential precipitants of HF exacerbation, and the high rate of nonprescription medication ingestion that is unreported by patients. Medications with a potential to worsen HF may have substantial benefit for a comorbid condition that outweighs the potential risk in patient-specific scenarios. Therefore, a careful evaluation and characterization of a medication's potential for cardiovascular harm is needed. Evaluation should be multifaceted, considering the mechanism of harm relative to the patient's cardiomyopathy and HF classifications, relative benefits and risks of the medication in question for the patient as a whole, evidence supporting potential harm, and the magnitude of the potential harm. Herein, medications with potential for harm in HF will be classified across these and other categories with review of the supporting literature and known mechanism(s).

18.4 Potential for Medication-Induced Worsening HF

The average patient with HF takes more than 10 prescription medications chronically and has on average 4–5 comorbid conditions [1–3]. Medicare beneficiaries see on average 15 different providers annually, further raising the risk of medication-induced harm [4, 5]. In addition to prescription volume and specialized prescribers, 88% of patients with HF take at least one nonprescription medication and more than one-third use herbal supplements [6]. Cumulatively, these circumstances provide significant risk of a medication-induced adverse HF event.

Quantification of medication-induced worsening HF is difficult, as more than 80% of HF hospitalizations have more than 1 potential precipitant [7]. While not quantified, medications are listed as common factors contributing to HF hospitalization in the American College of Cardiology/American Heart Association Guidelines for the management of HF and the American College of Cardiology Expert Consensus statement on patients hospitalized with HF [8, 9]. Analysis of a national prospective cohort study found 41% of patients admitted with acute HF (AHF) had medications that may cause or exacerbate HF on their home medication list, and 36% were advised to continue the medication at discharge [10]. A total of 323 HF hospitalizations in a randomized prospective study of patients with heart failure with reduced ejection fraction (HFrEF) were prospectively adjudicated by study investigators for the primary and secondary causes of worsening HF [11]. Although never categorized as the primary cause, medications contributed to decompensation in a significant percentage of hospitalizations: calcium channel blockers (15%), anti-arrhythmics (13%), beta blockers (9%), and nonsteroidal anti-inflammatory drugs (NSAIDS) (4%). In response to this growing problem, the American Heart Association has published a Scientific Statement addressing medications that may cause or exacerbate heart failure [6].

18.5 Evaluation of a Medication's Potential for Harm

A comprehensive approach should be utilized when evaluating a medication's potential to worsen or cause HF and weighing the risk to HF against the benefit to a comorbid condition. Key considerations for evaluation are presented in Table 18.1. Some medications possess the ability to cause de novo HF, while others can only worsen or exacerbate chronic HF. This distinction should be considered when evaluating medications as an etiology of de novo HF or a change in HF severity/functional status. Similarly, the mechanism by which a medication can induce harm is vital. Medications that cause sodium and water retention could explain an episode of hypervolemic decompensated AHF but are unlikely to explain a significant decrease in ejection fraction or new valvular dysfunction. Consideration of the mechanism in the context of the HF classification is also important. Medications with negative inotropic properties can cause significant harm in HFrEF, but may be well tolerated by patients with HF with preserved ejection fraction (HFpEF). Similar differences can exist among various etiologies of cardiomyopathies (e.g., infiltrative, valvular). When weighing the potential risk, the clinician should also consider the level of evidence and magnitude of the potential harm. Several grading systems aid in judging the risk: benefit ratio (Table 18.1). Lastly, the onset of harm and the reversibility of harm should be considered both when adjudicating a medication's contribution to a current exacerbation or considering a trial of medication with potential harm.

Table 18.1 Evaluating medications with potential harm in heart failure

Consideration	Description
Direct cardiac toxicity	Medications with ability to cause new cardiomyopathy by direct damage to cardiac myocytes and/or valves
Exacerbation of existing cardiomyopathy	Medications with ability to exacerbate underlying chronic heart failure and create a decompensated heart failure state
Mechanism of harm	Mechanisms may include but are limited to: Negative inotropy, sodium/water retention, increased systemic vascular resistance, valvular injury, interaction with guideline-directed medical therapy, proarrhythmic, direct myocyte toxicity, myocarditis, and/or infiltrative cardiomyopathy
	Mechanisms are intrinsically linked to other considerations such as differences by HF subtypes, direct toxicity, and onset of effect. Mechanism may not be known or multiple mechanisms may exist
Differences between HF subtypes	Medications with harm in specific HF subtypes may be appropriate to use in other HF subtypes
	HF subtypes include degree of LVEF dysfunction, left versus right ventricular dysfunction, differences in cardiomyopathy etiologies such as ischemic versus non-ischemic
Level of evidence[a]	**A:** ≥ 1 randomized, controlled clinical trial or meta-analyses
	B: 1 randomized, controlled clinical trial or nonrandomized studies, observational studies, case-control studies, or retrospective studies
	C: Case reports, case series, expert opinion
Magnitude of harm[a]	**Major:** Effects are life threatening or lead to urgent HF visit
	Moderate: Effects cause worsening NYHA functional class, change in cardiac function or cardiovascular disease, or symptoms that warrant permanent change in chronic medical therapy
	Minor: Effects cause transient increase in symptoms and transient change in medical therapy
Onset of effect[a]	**Immediate:** Effect begins in the first week after medication initiation
	Intermediate: Effect begins weeks–months after medication initiation
	Delayed: Effect is more than 1 year from medication initiation
Reversibility	Effects quickly reversible with medication discontinuation

HF heart failure, *LVEF* left ventricular ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *NYHA* New York Heart Association
[a]Grading systems utilized by the American Heart Association and textbook of Drug-Induced Diseases [6, 12]

18.6 Prescription Medications That May Cause De Novo HF

Prescription medications with the potential to cause new-onset HF are listed in Table 18.2, which almost exclusively cause HFrEF. These medications should also be avoided in patients with chronic HF, as they have the ability to exacerbate HF as well. Any medication has the theoretical potential to cause myocarditis secondary to a hypersensitivity reaction while others are only cardiotoxic if serum concentrations significantly exceed the therapeutic window. Acknowledging these possibilities, the discussion below emphasizes medications with evidence of inducing de novo HF

Table 18.2 Prescription medications that may cause de novo HF

Medication class or medication	Mechanism	Magnitude of harm[a]	Level of evidence[a]	Onset[a]
Anticancer agents				
Anthracyclines	Oxidative stress	Major	A	Intermediate to delayed
Alkylating agents	Oxidative stress	Major–moderate	B	Immediate
Antimetabolites	Coronary vasospasm; others	Major–moderate	B	Immediate
Taxanes	Potentiation of anthracycline-mediated toxicity in combination	Moderate	B	Intermediate
Biologic agents				
Bevacizumab	VEGFA	Major–moderate	A	Intermediate
Imatinib	PDGFR, Abl	Moderate	B	Intermediate
Interferon	Unknown	Major–moderate	C	Immediate
Lapatinib	ErbB2	Major–moderate	A	Intermediate
Pertuzumab	ErbB2	Major–moderate	C	Intermediate
Sorafenib	VEGFR, PDGFR	Minor	B	Intermediate
Sunitinib	VEGFR, PDGFR	Major	B	Intermediate
Trastuzumab	ErbB2	Major–moderate	A	Intermediate
Medication classes				
TNF-α inhibitors	Cytokine-mediated myocardial toxicity	Major	A	Intermediate
Sympathomimetic stimulants	Adrenergic-mediated tachycardia and hypertension	Minor	B	Unknown
Medications				
Amphotericin B	Unknown	Major–moderate	C	Intermediate
Anagrelide	PDE IV inhibition	Major	A	Immediate to delayed
Bromocriptine	Serotonin excess causing valvular disease	Major	B	Intermediate to delayed
Pramipexole	Unknown	Major	A	Intermediate to delayed
Ergotamine	Serotonin excess causing valvular disease	Major	C	Delayed
Lithium	Direct myofibrillar degeneration	Major	C	Intermediate to delayed

(continued)

Table 18.2 (continued)

Medication class or medication	Mechanism	Magnitude of harm[a]	Level of evidence[a]	Onset[a]
Hydroxychloroquine	Intracellular inhibition of lysosomal enzymes	Major	C	Intermediate to delayed

ErbB2 epidermal growth factor receptor 2, *VEGFA* vascular endothelial growth factor A-ligand, *PDGFR* platelet-derived growth factor receptor, *PDE* phosphodiesterase, *Abl* Abelson murine leukemia viral oncogene, *TNF-α* tumor necrosis factor-alpha

[a]Grading systems utilized by the American Heart Association and textbook of Drug-Induced Diseases [6, 12]

when used as directed. Several agents in Table 18.2 including amphotericin B [13, 14], interferon [15, 16], and lithium [17, 18] have case-level evidence of causing de novo HF but the limited evidence prohibits further characterization.

18.6.1 Anticancer Medications

Anthracycline agents, such as doxorubicin, serve as one of the classic examples of medication-induced de novo HF with a strong base of evidence linking exposure and increased risk of developing HF. Although dependent on the patients' baseline cardiovascular risk and cumulative dose of anthracycline received, the incidence of developing HF is 2–5% [19, 20]. This risk increases with the cumulative dose per body surface area, from 5% at 400 mg/m^2 to 26% at 550 mg/m^2, but subclinical myocardial injury is present even at low cumulative doses [20, 21]. The majority of de novo HF occurs within the first year, yet late-onset HF is possible years after exposure [22]. While avoidance may not be possible, careful monitoring of natriuretic peptides, serial echocardiography, and preventative strategies can decrease the risk of HF [6]. Liposomal formulation of anthracyclines may limit myocardial exposure and have demonstrated a lower rate of HF in clinical trials [23]. Dexrazoxane is a metal-chelating agent demonstrating cardioprotective properties by inhibiting anthracycline-mediated topoisomerase 2 interactions when administered to patients receiving anthracyclines [21, 23]. Yet this mechanism of protection is theorized to also diminish antitumor activity, producing recommendations to limit dexrazoxane to patients with metastatic cancer and further anthracycline doses that will exceed a cumulative dose of 300 mg/m^2 [24]. Empiric treatment with metoprolol and/or enalapril during anthracycline therapy for breast cancer did not reduce the incidence of HFrEF at 2 years, suggesting preventative treatment may not be beneficial in an undifferentiated population [25]. Even with early detection and treatment with guideline-directed medical therapy for HFrEF, 45% of patients have irreversible HF [26].

18.6.2 Alkylating Agents

Cyclophosphamide, Ifosfamide, and Mitomycin C exert antitumor effects by alkylating tumor DNA. Approximately 15–20% of patients exposed to these agents develop HF [6]. The onset of HF is immediate, within the first 10 days of treatment, and is often reversible with time and treatment [27].

18.6.3 Antimetabolites

Fluorouracil and its oral prodrug capecitabine cause ischemic cardiomyopathies with reduced ejection fraction secondary to coronary vasospasm. The incidence of new HF is approximately 5% and may be greater with IV fluorouracil than oral capecitabine [28]. Additional associations include Takotsubo cardiomyopathy [29].

18.6.4 Biologic Agents

Several biologic agents targeting tumors through epidermal growth factor receptor 2 (ErbB2), vascular endothelial growth factor A-ligand (VEGFA), and platelet-derived growth factor receptor (PDGFR) have been associated with increased risk of de novo HF.

Trastuzumab significantly increases the survival rate of women with breast cancer expressing human epidermal growth factor receptor 2 (HER2) receptors, but increases the risk of de novo HF approximately threefold compared to anthracycline monotherapy [30]. However, trastuzumab differs from anthracyclines in that the cardiac effects are a temporary decrease in contractility and ejection fraction in the absence of myocardial cell damage [31]. Thus, the effects are reversible, with more than 80% of patients demonstrating recovery at a median of 6 months [32]. Patients with existing HF were excluded from these studies, and the magnitude and reversibility of impairment in patients with established HF is unknown. The cardiac effects of trastuzumab are diminished when the administration is delayed following anthracycline therapy, which may be a strategy in some patients [21]. Pertuzumab and Lapatinib exhibit effects on the same antitumor pathway and have similar concerns as Trastuzumab.

Tyrosine kinase inhibitors, (e.g., Sunitinib, Sorafenib, Imatinib) inhibit several different growth factor kinases responsible for tumor progression. Sunitinib's association with de novo HF and hypertension is well established [33]. Sunitinib causes HFrEF via increased afterload and direct myocyte toxicity that is incompletely understood [6]. HF is less common with Sorafenib and Imatinib.

18.6.5 TNF-α Inihibitors

Infliximab, Etanercept, and Adalimumab are pivotal mediations in treating rheumatoid arthritis and inflammatory bowel disease. TNF-α inhibitors have been associated with both de novo HF in post-marketing surveillance and have warnings for new-onset HF in their package labeling [34]. Several large randomized, controlled trials of TNF-α inhibitors in patients with established HF have been conducted. Infliximab increased the risk of HF hospitalizations and death at doses of 10 mg/kg compared to lower doses of 5 mg/kg [35]. Trials of etanercept in HF were terminated early due to lack of benefit and signals of harm [36, 37]. The risk of HF exacerbations may be greatest in patients older than 65 years with chronic HF treated with TNF-α inhibitors [38]. Because of this evidence, the American College of Rheumatology recommends TNF-α inhibitors only be considered in patients with HF if there are no other reasonable treatment options [39].

18.6.6 Sympathomimetic Stimulants

Stimulant medications include any central nervous system stimulants (e.g., amphetamine, dextroamphetamine, methylphenidate), pseudoephedrine, and illicit drugs. Excluding illicit use of stimulants which is clearly associated with cardiomyopathy (Chap. 20), use of prescription stimulants is associated with minor increases in heart rate and systolic blood pressure at the population level [40]. Epidemiologic studies found no increased risk of myocardial infarction, stroke, sudden cardiac death, or new-onset cardiomyopathy with stimulant medications [41–43]. However, given the propensity of tachycardia to induce de novo HF, heart rate monitoring and individualized treatment decisions are warranted [8]. Likewise, these medications should be avoided when possible in patients with chronic HF given the strong negative association between increased heart rate and outcomes in HFrEF.

18.6.7 Anagrelide and Cilostazol

In addition to decreasing platelets for the treatment of thrombocytosis disorders, anagrelide also increases cardiac output via inhibition of phosphodiesterase type-IV. Counterintuitively, this can lead to high-output heart failure in 2–3% of patients, which presents with similar signs and symptoms as other HF etiologies [44, 45]. Cilostazol is a phosphodiesterase type-III inhibitor which is contraindicated in HF of any severity [46]. Although never studied in patients with HF, cilostazol is contraindicated in patients with HF according to the FDA package labeling. Cilostazol is considered potentially harmful because oral milrinone, sharing the same mechanism of action, increased the risk of death in HF, presumably due to increased ventricular arrhythmias [47].

18.6.8 Bromocriptine, Pramipexole, and Ergotamine

Fenfluramine, dexfenfluramine, and pergolide were removed from the US market after association with valvular regurgitation leading to valvular cardiomyopathy [6]. The mechanism of valvular dysfunction was secondary to serotoninergic effects via the 2B receptor on cardiac valves, which raise concern for several similar medications currently available for prescription use. Ergotamine is an ergot-derivative with serotoninergic agonism properties that is associated with irreversible valvular lesions and valvular heart failure [48]. Ergotamine should be replaced by the triptan medication class to treat migraines, which has good efficacy and a better safety profile [6]. Bromocriptine, like pergolide, is an ergot-derivative possessing dopamine agonism but only partial serotoninergic agonism at the 2B receptor. Although structurally dissimilar and lacking significant serotoninergic properties, pramipexole has been compared with bromocriptine for cardiovascular adverse events as both treat Parkinson's disease. Both bromocriptine and pramipexole have been associated with an increased risk of HF is epidemiologic studies [49–51]. Yet conclusions are not definitive due to conflicting results with other observational cohorts, small number of cases, and the association with only acute but not chronic use of pramipexole. The FDA released a safety communication in 2012 of a possible increased risk of HF with pramipexole [52].

18.6.9 Hydroxychloroquine

Cardiotoxicity has been widely reported with both chloroquine and hydroxychloroquine since the 1970s during their treatment for malaria [53, 54]. Hydroxychloroquine is now commonly used in the treatment of systemic lupus erythematous and rheumatoid arthritis. Hydroxychloroquine concentrates in the myocardium, resulting in an "acquired" lysosomal storage cardiomyopathy from accumulating within cardiac myocyte lysosomes [6, 55]. Risk factors for hydroxychloroquine cardiomyopathy are predominantly related to an increased cumulative dose, including daily dose, duration of use, and older age. Although cases exist of early HF, the mean duration of hydroxychloroquine exposure is approximately 10 years before symptom onset [6, 54]. Hydroxychloroquine can cause either a dilated or restrictive cardiomyopathy, often complicated by atrioventricular block or bundle branch blocks. Endomyocardial biopsy can aid a definitive diagnosis. Congruent with the hypothesized cardiotoxic mechanism, histology is notable for vacuolated cells and the presence of curvilinear bodies, indicative of myocyte infiltration [6, 54]. Although prognoses range widely, reversal of symptoms has been reported following hydroxychloroquine discontinuation [55].

18.7 Prescription Medications That May Exacerbate Chronic HF

Prescription medications with the potential to exacerbate underlying HF are listed in Table 18.3. These medications have not demonstrated the ability to cause de novo HF, but can worsen chronic HF through a variety of mechanisms. Careful attention should be paid to the mechanism of exacerbation when known, as the mechanism may not worsen all types of HF. For example, medications with negative inotropy can significantly worsen HFrEF but are typically well tolerated in HFpEF where systolic function is preserved. Similarly, circumstances may exist where the potential benefit for another disease state outweighs the potential risk of HF for a given mechanism.

Table 18.3 Prescription medications that may exacerbate chronic HF

Medication class or medication	Mechanism	Magnitude of harm[a]	Level of evidence[a]	Onset[a]
Anesthetics, inhaled				
Desflurane	Myocardial depression, vasodilation, decreased sympathetic activity	Major	B	Immediate
Enflurane				
Halothane				
Isoflurane				
Sevoflurane				
Anesthetics, intravenous				
Dexmedetomidine	α_2-adrenergic agonism	Moderate	B	Immediate
Etomidate	Adrenal insufficiency	Moderate	B	Immediate
Ketamine	Negative inotropy	Major	B	Immediate
Propofol	Negative inotropy, vasodilation	Moderate	B	Immediate
Antidiabetic medications				
Pioglitazone Rosiglitazone	Sodium and water retention	Major	A	Intermediate
Saxagliptin	Unknown	Major	B	Intermediate to delayed
Antiarrhythmics				
Disopyramide	Negative inotropy, proarrhythmic	Major	B	Immediate to intermediate
Flecainide		Major	B	
Sotalol		Major	B	
Dronedarone		Major	A	
Calcium channel blockers				
Diltiazem	Negative inotropy	Major	B	Immediate to intermediate
Nifedipine		Moderate	C	
Verapamil		Major	B	
Mineralocorticoids				
Fludrocortisone, hydrocortisone	Sodium and water retention	Major	B	Immediate

Table 18.3 (continued)

Medication class or medication	Mechanism	Magnitude of harm[a]	Level of evidence[a]	Onset[a]
NSAIDS and COX-2 inhibitors				
NSAIDS and COX-2 inhibitors	Sodium and water retention; interference with diuretics; increased blood pressure	Major	B	Immediate
Pulmonary hypertension				
Endothelin-1 receptor antagonists (Bosentan, Macitentan)	Unknown	Major	A	Delayed
Epoprostenol	Unknown	Major	A	Immediate
Tricyclic antidepressants				
Tricyclic antidepressants (in higher doses)	Negative inotropy, proarrhythmic	Moderate	C	Intermediate to delayed
Medications				
Carbamazepine	Negative inotropy and chronotropy, inhibition of SA and AV nodal conduction	Major	C	Intermediate
Cilostazol	PDE III inhibition	Major	A	Unknown
Citalopram	Proarrhythmic via dose-dependent QT prolongation	Major	A	Intermediate
Itraconazole	Negative inotropy	Major	C	Immediate to intermediate
Minoxidil	Unknown	Moderate	C	Intermediate
Pregabalin	Calcium channel blockade	Minor	C	Immediate to intermediate

[a]Grading systems utilized by the American Heart Association and textbook of Drug-Induced Diseases [6, 12]

In addition to the active ingredient, medications can contain sodium, either in the medication formulation or as an intravenous administration fluid, which warrants discussion as a potential exacerbation mechanism. The relationship between sodium intake and outcomes in HF is complex and beyond the scope of this chapter. In AHF, the use of IV sodium-containing fluids, such as normal saline, is associated with worse outcomes in observational reports, although this association is confounded by indication [56]. Randomized trials of intense dietary sodium and fluid restrictions in AHF have not improved outcomes compared to liberal restrictions, and administration of hypertonic saline with high-dose IV loop diuretics improved diuretic response in patients with diuretic resistance [57, 58]. Sodium restriction is equally complex in chronic HF, but a sodium intake of 2-3 g/day is recommended for most patients [8]. With these uncertainties and clear need for individualizing sodium

intake goals, hidden sodium within medications can worsen HF in some patients. Although not an exhaustive list, nafcillin (77 mg of Na^+ per gram = 462 mg of Na^+ at the recommended daily dose), piperacillin/tazobactam (65 mg of Na^+ per gram = 877 mg of Na^+ at the recommended daily dose), penicillin G (24 mg of Na^+ per million units = 564 mg of Na^+ at the recommended daily dose) all contain significant quantities of sodium in their IV salt forms. Sodium bicarbonate and sodium citrate solutions used to treat metabolic acidosis in chronic kidney disease also contain high quantities of sodium in their formulations and are contraindicated in patients on sodium-restricted diets per the package labeling, although this is not an absolute contraindication.

18.7.1 Anti-Arrhythmic Medications

Disopyramide is a potent negative inotrope that should be avoided in HF. Flecainide has been associated with increased mortality due to proarrhythmic effects in patients with structural heart disease [59]. Dronedarone has a black box warning to avoid use in patients with HF complicated by recent hospitalization or New York Heart Association III or IV functional class. Dronedarone was associated with increased mortality from HF in multiple randomized trials and should be avoided in all patients with HF [60, 61]. Sotalol is relatively contraindicated in HF. Sotalol is commercially available as a racemic mixture of the *d-isomer* (potassium channel antagonist) and *l*-isomer (beta receptor antagonist). The *d-isomer* of sotalol alone has been associated with increased mortality in patients with systolic dysfunction after myocardial infarction [62]. It remains unclear how these results should be extrapolated to the racemic mixture of sotalol. However, the racemic mixture can worsen HF via negative inotropic effects from beta receptor antagonism in some patients. For the treatment of atrial fibrillation, sotalol is not recommended in patients with HF [63].

18.7.2 Antidepressants

Tricyclic antidepressants (e.g., amitriptyline, impramine, doxepin) at doses of 100–200 mg/day did not worsen HF or left ventricular function in short-term studies [64, 65]. However, these moderate to high doses can cause sinus tachycardia, hypotension, and multiple conduction atrioventricular disorders [6]. In contemporary practice, tricyclic antidepressants are mostly utilized in lower doses for neuropathy, which are likely safe in HF and better tolerated. Selective serotonin reuptake inhibitors have a proven safety profile in HF, with the exception of high-dose citalopram. Citalopram doses greater than 40 mg/day are not recommended in patients with HF due to dose-dependent increases in QT prolongation and potential Torsade de pointes.

18.7.3 Antidiabetes Medications

Extensive retrospective data exist associating thiazolidinediones (i.e., rosiglitazone, pioglitazone) with worsening HF events [6, 66]. The American Diabetes Association now recommends against the use of these medications in patients with HF [67]. Dipeptidyl peptidase-4 (DPP-4) inhibitors appear to neither improve nor worsen HF events in cardiovascular safety trials to date with the exception of saxagliptin [67]. Saxagliptin is associated with worsening HF and should be avoided in patients with HF [68]. Although historically contraindicated in HF from concerns of increased lactic acidosis risk, metformin is considered to be "neutral" in chronic HF by the American Diabetes Association and no longer has labeling warning to avoid use in chronic HF [6, 67]. Metformin is best avoided in hospitalized patients, including those hospitalized with AHF, to avoid use during a time of heightened acute kidney injury risk.

18.7.4 Calcium Channel Blockers

Diltiazem and verapamil (non-dihydropyridine calcium channel blockers) are contraindicated in HFrEF due to potent negative inotropic effects. Dihydropyridine calcium channel blockers have varying degrees of vasodilatory and negative inotropic effects. Nifedipine has a greater degree of negative inotropic properties relative to its vasodilator effects and has consistently been associated with worsening HF in small randomized trials [69]. Amlodipine did not worsen mortality in large randomized controlled trials of HFrEF, but did have higher rates of peripheral and pulmonary edema than placebo [70]. Calcium channel blocker-induced peripheral edema is very common, does not indicate hypervolemia, and is not responsive to diuretic therapy [71]. Therefore, use of calcium channel blockers can complicate the volume assessment and treatment of patients with HF. In HFrEF, calcium channel blockers should be avoided. Patient scenarios can exist in HFpEF where the benefits of calcium channel blockers outweigh the risks of edema.

18.7.5 Mineralocorticoids

Glucocorticoids do not worsen HF and can be used when indicated for concomitant medical conditions in patients with HF. Previously it was thought some corticosteroids may cause worsening HF due to sodium and water retention, yet recent evidence has disproven this assumption [72]. Each corticosteroid has a spectrum of glucocorticoid and mineralocorticoid properties [73]. Only those agents with the most potent mineralocorticoid effects (fludrocortisone, hydrocortisone) would be expected to cause sodium and water retention through aldosterone-receptor

agonism [73]. In contrast, potent glucocorticoids (e.g., dexamethasone, methylprednisolone, betamethasone) have insignificant mineralocorticoid action and are unlikely to cause sodium and water retention. Prednisone has mild mineralocorticoid properties which are negated by its glucocorticoid effects on the natriuretic peptide system. Glucocorticoids activate natriuretic peptide receptor A gene expression, increasing responsiveness to natriuretic peptides and inducing greater natriuresis [74]. Randomized, controlled trials combining prednisone 60 mg daily with loop diuretics in patients with chronic and acute HF have consistently demonstrated increased urine volume, sodium excretion, and weight loss relative to loop diuretics alone [74–76]. Analysis of over 11,000 acute HF admissions receiving corticosteroids for concomitant conditions found no increase in all-cause mortality or HF readmission after adjustment for covariates [77].

18.7.6 NSAIDs

By inhibiting prostaglandin synthesis, NSAIDs diminish diuretic response, increase systemic vascular resistance, and increase sodium and water retention. Collectively, these effects worsen HF and increase the risk of HF hospitalization between twofold and tenfold in observational studies of patients with chronic HF [78, 79]. Importantly, these negative effects occur even with short-term use. Since one-third of patients take nonprescription medications, providers should actively inquire about nonprescription NSAID use in patients with HF [6]. Alternative treatment options to NSAIDS for chronic pain control should be recommended. There is no consensus on the safety of selective cyclooxygenase-2 inhibitors such as celecoxib in HF, but avoidance of these medications is advised in patients with HF [6, 80]. Celecoxib may be less likely to exacerbate HF at low doses [80, 81]. Topical diclofenac is efficacious with minimal systemic NSAID exposure, but whether the lower plasma concentrations result in a better cardiovascular safety profile is unknown [82, 83].

18.7.7 Pulmonary Hypertension Medications

Pulmonary hypertension and HF are commonly comorbid conditions, and the choice of pulmonary hypertension therapy is strongly influenced by concomitant HF. Endothelin-1 receptor antagonists have consistently been associated with immediate risk of worsening HF from hypervolemia in multiple large clinical trials. Bosentan increased the risk of HF hospitalization in 2 prospective trials of pulmonary hypertension and chronic HF [84, 85]. Macitentan also worsened HF due to hypervolemia in a randomized controlled trial of patients with HF complicated by pulmonary hypertension [86]. Prostacyclins have also been associated with serious adverse HF events in randomized trials. Intravenous epoprostenol increased the risk of mortality in patients with HF and is subsequently contraindicated in HFrEF [87]. No pulmonary hypertension-specific medications are recommended to treat pulmonary hypertension secondary to left heart disease [88].

18.7.8 Carbamazepine

Carbamazepine is strongly associated with bradycardia and atrioventricular blockade. It is difficult to separate potential symptoms of HF from symptoms of conduction adverse events in the limited number of case report evidence [89, 90]. Carbamazepine can be safely used in most patients with HF at therapeutic concentrations, but new conduction abnormalities warrant investigation for drug-induced adverse events.

18.7.9 Itraconazole

Itraconazole is a negative inotrope that can exacerbate HF [91]. The FDA recommends avoiding itraconazole in patients with HF or systolic dysfunction due to the risk of HF exacerbation.

18.7.10 Minoxidil

Minoxidil has been associated with worsening peripheral edema and pericardial effusion in the general population. In a small, randomized controlled trial, minoxidil caused more worsening HF events than placebo [92, 93]. Minoxidil is best avoided in all types of HF.

18.7.11 Pregabalin

Pregabalin has been associated with a slightly higher rate of peripheral edema than placebo in clinical trials of patients without HF, and case reports have associated pregabalin with worsening HF events [94]. A national observational cohort study did not find an increased risk of worsening HF in patients taking pregabalin relative to gabapentin or duloxetine [95]. Although the mechanism of harm is not completely understood, edema may arise from calcium channel antagonism. The FDA package label advises caution and monitoring if used in patients with HF. Pregabalin could be used to treat neuropathic pain in patients with HF if the benefits are greater than the potential risk of edema.

18.7.12 Alpha-Adrenergic Antagonists

Historically, alpha-1 receptor antagonists (e.g., prazosin, tamsulosin) were associated with an increased risk of worsening HF based on increased incidence of HF in the doxazosin treatment arm of the ALLHAT hypertension trial [6, 96]. Subsequent investigations have refuted this extrapolation of harm, finding no increased risk of HF hospitalization in patients with HF receiving alpha-1 receptor blockers [97]. Thus, alpha-1 receptor antagonists can be used in patients with HF without concern.

18.8 Conclusion

Many medications indicated for concomitant illness may worsen chronic HF or cause new-onset HF. In patients with chronic HF, providers should evaluate the patient's medication list for medications that can worsen HF at each visit. Careful examination of each medication's potential harm in the patient's specific cardiomyopathy can inform the provider on the benefit-to-risk ratio and guide treatment decisions.

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Part V

Heart Failure Case Studies

Chapter 19 provides eight case studies exemplifying complex heart failure patient vignettes and provides practical guidance for the primary care provider, highlighting HF guideline-directed medical therapy.

Heart Failure Case Studies

19

Nicole R. Dellise and K. Melissa Smith Hayes

19.1 Case Study 1

19.1.1 Diuretic Resistance and Asymptomatic Hyperuricemia in HFpEF

Name: Suzan Smith

Age/Sex: 72-year-old female

Past Medical History/Problem List: HFpEF; Hypertension, CKD stage 3, HLD

Family History: Mother passed away at age 70 of stroke. Father passed away at age 87 of MI.

Psychosocial History: Retired school teacher. Widowed. Has two children and three grandchildren, all healthy. Lives independently. Does not drive. Children assist with obtaining groceries. Limits dietary sodium intake. Drinks three cups of coffee per day. Never smoked. Denies illicit drugs.

Medications

- ASA 81 mg daily
- Atorvastatin 80 mg QHS
- Sacubitril/valsartan 97/103 mg BID
- Furosemide 80 mg daily
- Spironolactone 25 mg QAM

Allergies: No known drug allergies

N. R. Dellise (✉)
Centennial Heart, Nashville, TN, USA
e-mail: nicole.r.dellise@vanderbilt.edu

K. M. S. Hayes
Vanderbilt University School of Nursing, Nashville, TN, USA
e-mail: k.melissa.hayes@vanderbilt.edu

K. M. S. Hayes, N. R. Dellise (eds.), *Managing Heart Failure in Primary Care: A Case Study Approach*, https://doi.org/10.1007/978-3-031-20193-6_19

Case Scenario: Ms. Smith presents to primary care office with complaints of increased dyspnea on exertion, lower extremity edema, and poor appetite. She was seen by her cardiologist two weeks ago with similar complaints. At that time, Furosemide was increased from 40 mg daily to 80 mg daily. Despite diuretic escalation, Ms. Smith notes no change in urine output, symptoms persist, and weight is unchanged. Ms. Smith reports dyspnea when getting dressed and when making meals (NYHA class III). Denies orthopnea, bendopnea, PND, chest pain or pressure, palpitations, lightheadedness, dizziness, or syncope. Endorses fatigue with minimal activity. She has had two HF hospitalizations this year. Confirms she is limiting sodium and fluid intake as advised. Review of home blood pressure log notable for systolic blood pressure ranging from 115 to 130 mmHg and diastolic blood pressure ranging from 60 to 70 mmHg.

Objective: Vital signs: BP 135/65 mm Hg; HR 79; Oxygen Saturation 98% on room air; Temp 98.7°. Weight 210 pounds. BMI 37.1. Physical exam: Fine bibasilar crackles. JVD 16 cm at a 45-degree angle, Positive HJR. Regular rate and rhythm. Positive S3. 2+ bilateral lower extremity pitting edema.

Diagnostic Reports

- Last Echocardiogram (1 month ago): LVEF 50%, grade 3 diastolic dysfunction
- Last ischemic evaluation (1 month ago): Stress test negative for ischemia
- EKG today: Normal Sinus Rhythm
- Labs results from cardiology visit two weeks ago: Sodium 131; Potassium 3.8; BUN 44; Creatinine 1.6; eGFR 38, BNP 675, Uric Acid 11.1
- Lab results today: Sodium 130; Potassium 4.1; BUN 42; Creatinine 1.7; eGFR 36, BNP 700; Uric Acid 11.4

Assessment: Ms. Smith presents to clinic volume overloaded with NYHA class III, acute on chronic HFpEF exacerbation and is demonstrating diuretic resistance. She has had little to no response after increasing Furosemide to 80 mg once a day. Compliance with fluid and dietary sodium restriction confirmed. Blood pressure is controlled. In review of labs, serum uric acid level is elevated but denies signs or symptoms of gout. Denies diet high in purine foods.

Plan

1. Acute on Chronic HFpEF
   Etiology: Hypertension
   NYHA Class: III
   Hemodynamic Status: Warm and Wet
   HF Devices: None
   Plan:
   - Discontinue Furosemide 80 mg once a day due to diuretic resistance.
   - Begin Torsemide 40 mg BID.
   - Begin Dapagliflozin 10 mg daily.
   - Continue Spironolactone 25 mg daily.
   - Continue Sacubitril/valsartan 97/103 mg BID.

- Recommend daily weight monitoring. Patient to contact clinic for 5-pound weight loss or 2-3-pound weight gain.
- Contact patient via phone in two to three days to assess response to diuretic adjustment and addition of SGLT2 Inhibitor.
- Return to clinic in one week for repeat labs to assess kidney function and potassium level and reassessment of fluid status.
- Consider Ambulatory Pulmonary Artery Pressure Monitoring as a possible HF treatment option.

2. Asymptomatic Hyperuricemia
   - Ms. Smith denies all signs and symptoms of gout.
   - Labs indicated uric acid level is high.
   - Begin Allopurinol 100 mg daily for gout prophylaxis.
   - Repeat uric acid level in two weeks.
3. CKD, Stage 3
   - Kidney function stable per review of labs today.
   - Close monitoring of kidney function with escalation of diuretics.
   - Addition of SGLT2i may offer some degree of renal protection.
   - Repeat BMP in one week.
4. Hypertension
   - Blood pressure 135/65 mmHg in office today. Presumed slightly elevated in setting of fluid volume overload.
   - Continue Sacubitril/valsartan 97/103 mg BID.
   - Advise to continue home blood pressure log.

Clinical Pearls

- When switching loop diuretics, consider dose equivalents. Based on the equivalent table below, the adjustments made for Ms. Smith (Furosemide 80 mg once a day to Torsemide 40 mg twice a day) represents a nonequivalent adjustment and an *increase* in diuretic therapy [1, 2]. Table 19.1 displays the dose equivalents for loop diuretics [1].
- Discuss patient education regarding Torsemide. Patient may experience increased urination throughout the day given the extended half-life of Torsemide. Torsemide should be taken early in the morning upon waking, then the second dose six h after in an effort to avoid nocturnal urination and increase patient compliance. Table 19.2 depicts the loop diuretic half-life along with duration of effect [2].
- For patients who require adjustments in diuretic therapy, potassium levels should be carefully monitored. Some patients on mineralocorticoid receptor antagonists (spironolactone or eplerenone) may have adequate potassium levels given its

Table 19.1 Loop diuretic equivocal doses [1]

Diuretic	Equivalent dose (mg)
Furosemide	40
Torsemide	20
Bumetanide	1

Table 19.2 Properties of loop diuretics· [Reprinted from J Am Coll Cardiol 59 (34), Felker GM, Mentz RJ, Diuretics and ultrafiltration in acute decompensated heart failure, 2145–53, 2012 with permission from Elsevier] [2]

	Furosemide	Torsemide	Bumetanide
Relative intravenous potency (mg)	40	20	1
Oral: Intravenous dosing	1: 2	1: 1	1: 1
Bioavailability (%)	10–100	80–100	80–100
Drug half-life in hours (h)	1.5–2.0	3–4	1.0–1.5
Duration of effect in hours (h)	6–8	6–16	4–6

potassium sparing mechanism. However, some patients may require additional potassium supplement. Typical potassium chloride replacement is 10 meq for every 40 mg of Furosemide/20 mg Torsemide/1 mg of Bumetanide. It is also important to consider dietary intake of potassium. Note, many HF patients may use salt substitutes that may contain high amounts of dietary potassium.

- SGLT2 inhibitors have been shown to reduce heart failure hospitalizations and slow the progression of chronic kidney disease and should be considered for patients with HF and CKD, with careful monitoring labs and fluid status [3, 4].
- Blood pressure may be slightly elevated in a hypervolemic state. If blood pressure is not significantly elevated (<140 mmHg systolic), emphasis should first be placed on volume removal, followed by reassessment of blood pressure trends.
- Allopurinol may be considered for treatment of asymptomatic hyperuricemia [5].
- Based on the 2022 ACC/AHA/HFSA guidelines, sacubitril/valsartan is class IIb recommendation for patients with HFpEF [4].
- CardioMEMS™ heart sensor (Abbott Laboratories, Illinois, USA) is a remote pulmonary artery pressure monitor and has shown to have a clear benefit in reducing HF readmissions [6]. For patients whose volume status is challenging to manage, remote pulmonary artery pressure monitoring may be beneficial and should be considered.

19.2 Case Study 2

19.2.1 HFrEF Optimization Considerations in the Setting of Volume Depletion

Name: Bill Frye

Age/Sex: 64-year-old male

Past Medical History/Problem List: HFrEF; Nonischemic Cardiomyopathy; Hypertension, Hypothyroidism.

Family History: Mother alive at age 85, history of diabetes. Father passed away age 81 of stroke. No siblings.

Psychosocial History: Married. Retired real-estate agent. Has two children, both healthy. Never smoked. Denies illicit drugs. Enjoys golfing when he feels well.

Medications
- Metoprolol Succinate 25 mg QHS
- Sacubitril/valsartan 49/51 mg BID
- Furosemide 40 mg daily
- Dapagliflozin 10 mg daily
- Spironolactone 12.5 mg daily
- Digoxin 0.125 mg daily
- Levothyroxine 75 mcg daily

Allergies: No Known Drug Allergies

Case Scenario: Mr. Frye presents to clinic as an add on after contacting his cardiologist due to lightheadedness and dizziness. His cardiologist recommended follow-up today with PCP for further evaluation and lab work. Of note, Mr. Frye was admitted to nearest urban hospital (two h away) three months prior and diagnosed with new-onset HFrEF. He has done well for several months, taking all medications as prescribed and adhering to dietary sodium and fluid restrictions. Recently, he started golfing again as his energy level has improved. Today, he is reporting lightheadedness and dizziness upon standing, increased fatigue, and general weakness. Able to perform ADLs. Home blood pressure log reveals blood pressure is consistently 88–90 mmHg systolic and 40–45 mmHg diastolic. Weights trending down from 162 pounds to 152 pounds. He denies syncope and/or presyncope. No chest pain, palpitations, orthopnea, dyspnea, PND, lower extremity edema, or abdominal bloating. He is scheduled to see his cardiologist next month for a repeat echocardiogram to assess his left ventricular ejection fraction and to determine if he qualifies for an implantable cardiac defibrillator.

Objective: Vital signs: BP 100/45 mmHg; HR 80; Oxygen Saturation 98% on room air; Temp 98.7°. Weight 150 pounds. Physical exam: Lungs clear, JVD not elevated, regular rate and rhythm, no murmur, no edema. Poor skin turgor. Extremities are warm. Orthostatic blood pressures checked in office and positive (lying 100/45 mmHg, sitting 85/40 mmHg, standing, 80/42 mmHg).

Diagnostic Reports
- Labs results: Sodium 140; Potassium 4.0; BUN 40; Creatinine 1.7; (eGFR 35), BNP 200
- Last Echo (3 months ago): LVEF 25%, LVIDD 6.0 cm, no valvular abnormalities

Assessment: Mr. Frye presents to office today exhibiting signs and symptoms of volume depletion, likely secondary to ongoing diuretic use in combination with secondary fluid loss due to time spent outdoors in the heat (golfing). Signs of volume depletion include poor skin turgor and positive orthostasis. Labs today also reveal slight increase in BUN and Creatinine and normal BNP. Note that a normal pulse pressure, normal heart rate, and warm extremities are reassuring that Mr. Frye is not in a low output state.

Plan

1. **Chronic Heart Failure with Reduced Ejection Fraction**
   Etiology: Nonischemic, Dilated Cardiomyopathy
   NYHA Class: II
   Hemodynamic Status: Warm and Dry
   HF Devices: None (repeat echo scheduled to reassess needs for ICD)
   Plan:
   - Discontinue Digoxin.
   - Discontinue Furosemide 40 mg daily.
   - Increase fluid restriction to 2.5 liters per day.
   - Continue current HF GDMT: metoprolol succinate 25 mg QHS, sacubitril/valsartan 49/51 mg BID, dapagliflozin 10 mg daily, spironolactone 12.5 mg daily.
   - Continue home blood pressure log and monitoring daily weights.
   - Return to clinic in one week to reassess fluid status and blood pressure log. Anticipate increasing beta-blocker once euvolemic.
   - Educate patient to call clinic if he experiences any change in symptoms.
   - Follow up with cardiologist as scheduled in one month for repeat echocardiogram.

Clinical Pearls

- Volume depletion can be associated with passive loss of fluid through perspiration and increased time spent outdoors in hot temperatures. Educate patient to monitor for signs and symptoms of dehydration.
- Patients should also monitor for dehydration (volume depletion) when first started on SGLT2i medications especially in combination with loop diuretics.
- Digoxin toxicity can present acutely in the setting of acute kidney injury [7]. Providers should thoroughly assess for symptoms of digoxin toxicity in the setting of acute kidney injury and consider stopping or holding digoxin.
- Escalation of HF GDMT should not occur in the setting of volume depletion or volume overload. Close follow-up is recommended to reassess fluid status and to determine if additional medication titration can be made.
- Obtaining orthostatic blood pressures in clinic can be a useful tool to help identify volume depletion.

19.3 Case Study 3

19.3.1 HFrEF Optimization Considerations in the Setting of Volume Overload

Name: Samuel Jones

Age/Sex: 56-year-old male

Past Medical History/Problem List: HFrEF (LVEF 25%), Ischemic Cardiomyopathy, Single Chamber Implanted Cardiac Defibrillator, HTN, CAD (history of CABG 10 years ago), Hyperlipidemia, CKD Stage 2.

Family History: Mother died at age 68 of lung cancer. Father died at age 48 of MI. Has one brother with history of stroke and two healthy adult children.

Psychosocial History: Married. Has two adult children. Works full time as a banker. No history of tobacco use or illicit drugs.

Medications/Allergies

- Sacubitril/valsartan 49/51 mg BID
- Carvedilol 12.5 mg BID
- Spironolactone 25 mg daily
- Dapagliflozin 10 mg daily
- Furosemide 40 mg daily
- Atorvastatin 80 mg QHS
- ASA 81 mg daily

Allergies: No Known Drug Allergies

Case Scenario: Mr. Jones presents to primary care office with a chief complaint of swelling in feet and ankles. He was recently seen by his cardiologist last month and was told his left ventricular ejection fraction had fallen from 35% to 25%. Recent stress test did not reveal any new ischemia and Mr. Jones' decline in ejection fraction was felt to be due to uncontrolled hypertension. Carvedilol was increased from 6.25 mg BID to 12.5 mg BID last month. In review of home blood pressure log, blood pressure remains elevated ranging from 144/90 mmHg to 160/92 mmHg. Home weight trends also elevated 10 pounds above dry weight goal. Mr. Jones states he recently returned from a weekend vacation and ate out several times, consuming food high in sodium. He is concerned about increased swelling in his feet and ankles, abdominal distention, and shortness of breath walking to his mailbox. Denies orthopnea, PND, bendopnea, chest pain, palpitations, or ICD shocks.

Objective: Vital signs: BP 148/84 mmHg left arm, 150/80 mmHg right arm; HR 80; Oxygen Saturation 98% on room air; Temp 98.7°. Weight 250 pounds. Physical exam: Lungs clear, JVD elevated ~12 cm with exam table at 45°, heart rate and rhythm regular, positive S3, no murmur. 1+ bilateral pedal edema. Extremities are warm. Capillary refill less than 3 s.

Diagnostic Reports

- Labs results: Sodium 140; Potassium 4.0; BUN 28; Creatinine 1.4; (eGFR 50), Pro BNP 2000
- Echocardiogram (1 month ago): LVEF 25%, LVIDD 6.2 cm, no valvular abnormalities
- Echocardiogram (1 year ago): LVEF 35%, LVIDD 5.5 cm, no valvular abnormalities

Assessment: Mr. Jones presents to clinic with acute on chronic heart failure exacerbation, exhibiting signs and symptoms of fluid volume overload, likely secondary to increased dietary sodium intake. Also concerning is a recent drop in left ventricular ejection fraction and further dilation of his left ventricle (LVIDD of

6.2 cm, up from previous 5.5 cm). Heart failure progression felt to be due to uncontrolled hypertension.

Plan

1. Acute on Chronic HFrEF
   Etiology: Ischemic, Dilated Cardiomyopathy
   NYHA Class: III
   Hemodynamic Status: Warm and wet
   Devices: Single Chamber ICD
   Plan:
   - Increase Furosemide to 40 mg BID × 3 days, then back to maintenance dose of 40 mg daily.
   - Continue Sacubitril/Valsartan 49/51 mg BID, Carvedilol 12.5 mg BID, Spironolactone 25 mg daily, Dapagliflozin 10 mg daily.
   - Return to clinic in one week to reassess fluid status, obtain labs, and consider escalation of HF GDMT.

One Week Follow-Up

Mr. Jones returns to clinic in one week. He is now back to his dry weight of 240 pounds and notes resolution of symptoms. On exam, JVD is not elevated, and lower extremity edema resolved. Home blood pressure log reviewed, and blood pressure remains elevated, 134/88 mmHg to 140/90 mmHg. Clinic blood pressure in left arm is 140/84 mmHg. HR is 78 bpm.

Repeat labs at follow-up notable for decrease in Pro BNP, down to 700. Kidney function is stable, Creatinine 1.3, BUN 55. Potassium level 4.3.

Follow-Up Plan

1. Chronic HFrEF
   NYHA Class: I
   Hemodynamic status: Warm and euvolemic
   - Increase Carvedilol to 18.75 mg BID (12.5 mg tablets taking one and a half tablet) for two weeks then increase further to 25 mg BID.
   - Continue Sacubitril/Valsartan 49/51 mg BID, Spironolactone 25 mg daily, and Dapagliflozin 10 mg daily.
   - Continue Furosemide 40 mg daily.
   - Prescribe rescue diuretic plan—if patient experiences 2–3 pound weight gain overnight, or 5 pounds in one week, increase Furosemide 40 mg BID for one day, then back to maintenance dose. Not to exceed more than one extra dose per week without notifying provider. Patient verbalized understanding of instruction and when to notify clinic.

Clinical Pearls

- Any decline in cardiac function warrants further investigation to determine the cause. In the case of Mr. Jones, ischemic evaluation was negative. The decline in heart function was likely due to uncontrolled hypertension.

- Escalation of HF GDMT should be consistently evaluated until maximum tolerated doses are achieved [4].
- In the setting of fluid volume overload, patients should be decongested prior to escalating GDMT, especially beta-blockers [4].
- Close follow-up following outpatient diuresis is important to assure response to treatment and consider GDMT escalation.
- Establishing a rescue diuretic regimen can be helpful in preventing extreme fluid overload. Careful education and ensuring patient understanding of instructions is important prior to prescribing.
- To help patients better tolerate up-titration of beta-blockers, doses can be half stepped upwards as demonstrated in this case.
- HFrEF patients can expect to feel mildly fatigued and have a small amount of fluid gain with up-titration of beta-blockers, which can be managed with a rescue diuretic regimen if needed. These symptoms typically improve quickly.
- Mr. Jones' Pro BNP level went down from 2000 to 700. Although 700 is still elevated by normal value criteria, heart failure patients with dilated cardiomyopathy may have a chronic BNP elevation. Assessing trends and determining baseline is important to avoid over- or under-diuresis.

19.4 Case Study 4

19.4.1 Valvular Heart Failure

Name: Martha White

Age/Sex: 82-year-old female

Past Medical History/Problem List: HTN, Arthritis, Depression, Anxiety.

Family History: Mother died at age 90 of stroke. Father died at age 80 of sepsis.

Psychosocial History: Widowed. Lives at assisted living facility. Has three healthy adult children. Enjoys playing cards. Denies history of smoking or illicit drugs. Occasional alcohol, less than one drink per month.

Medications

- Losartan 50 mg daily
- Citalopram 20 mg daily

Allergies: Penicillin

Case Scenario: Ms. White presents to primary care clinic today to establish care as her PCP just retired. Her son is concerned because he has noticed she has been less active over the past 6 months. No longer going to play cards with her friends and napping most of the day. Ms. White reports increased fatigue. She notes it is hard for her to walk down the hall of her assisted living facility because after walking 50 feet she feels weak, short of breath, and her chest is tight. Her symptoms resolve with rest. Denies orthopnea, PND, edema, palpitations, or syncope. She checks her blood pressure daily and states it is "good" and the "top number is 120." Notes her appetite the past few weeks has been poor. No recent illnesses.

Objective: Vital signs: BP 128/64 left arm, HR 70; Oxygen Saturation 98% on room air; Temp 98.7°. Weight 110 pounds. Physical exam: Lungs clear, JVD elevated ~8 cm with exam table at 45°, heart rate and rhythm regular, harsh 3/6 systolic murmur heard loudest over right upper sternal border. 1+ bilateral lower extremity edema. Extremities are warm. Capillary refill less than 3 s.

Diagnostic Reports
- EKG: Normal Sinus Rhythm, no acute ST-T changes
- Labs: Sodium 140, Potassium 3.7, Creatinine 1.2, BUN 58, BNP 670, hemoglobin 10.0, hematocrit 32

Assessment
1. **Stable chest pain concerning for cardiac etiology**
2. **Systolic murmur, new finding**
3. **Lower extremity edema**

Ms. White presents to clinic with symptoms shortness of breath, fatigue, and occasional chest pain on exertion which is relieved at rest. Although her chest pain is "stable chest pain", it is concerning due to age, risk factors, and the new finding of a harsh systolic murmur auscultated upon physical exam. She also has lower extremity edema. EKG in the office today without evidence of acute ischemic changes. No prior cardiac testing obtained per review of patient's medical chart and Ms. White confirms she has no prior cardiac diagnosis, except for hypertension. At this time, further testing is warranted to determine the cause of her symptoms.

Plan
- Refer to cardiology. Obtain echocardiogram. Advise Ms. White to proceed to the emergency room should she experience any further chest pain episodes.
- Start Furosemide 20 mg daily for 3 days for mild volume overload, then stop.

Follow-Up Plan: Ms. White's echocardiogram was obtained the day after her office visit. The report indicates severe aortic stenosis, a normal left ventricular ejection fraction of 60%, and stage 2 diastolic dysfunction. After contacting Ms. White to discuss findings, she is agreeable to follow up with cardiology to discuss treatment options. A referral to a Structural Heart Specialty clinic was placed.

After seeing the structural heart team, Ms. White was deemed a high-risk candidate for cardiovascular surgery and an appropriate candidate for a transcatheter aortic valve replacement (TAVR). As part of her preprocedural testing, a left heart catheterization was obtained and demonstrated mild coronary artery disease. She was placed on low-dose statin. A cardiac CT scan and a bilateral carotid ultrasound were also obtained as part of her evaluation. The CT scan was unremarkable. The bilateral carotid ultrasound demonstrated non-hemodynamically significant carotid artery disease. Ms. White underwent the TAVR procedure without any complications and was discharged home the following day. She was placed on dual antiplatelet medications, aspirin and clopidogrel, for 3 to 6 months, to be continued pending future cardiology recommendations. She was also advised she will need life-long

antibiotic prophylaxis prior to any dental procedures given the presence of her artificial heart valve.

Ms. White returns to primary care clinic for two-week post TAVR follow-up. She reports more energy. No longer experiencing chest pain or shortness of breath. On exam, she does continue to have trace lower extremity edema. Furosemide 20 mg daily was resumed, noting Ms. White likely has chronic HFpEF and will need close monitoring of fluid status. She will return to see cardiology for a 1 month, post TAVR follow-up and repeat echo.

Clinical Pearls

- Aortic stenosis typically is associated with a harsh systolic murmur, heard loudest over the right sternal border. Louder aortic stenosis murmurs may radiate to the carotid arteries and can be mistaken for carotid bruits. Patients may note the following symptoms: chest pain, shortness of breath, lightheadedness, dizziness, swelling, fatigue on exertion, or palpitations [8].
- Prompt evaluation is important as mortality rates for untreated severe aortic stenosis are high [8].
- A thorough health history is important, especially to determine symptom severity and facilitate prompt referral to a structural heart specialty center.
- Dual antiplatelet therapy (aspirin and clopidogrel) is prescribed post TAVR and should be continued at the discretion of a cardiologist [9].
- Within the first 30 days post TAVR, patients are at an increased risk for heart block and arrythmias. Any reported symptoms should be assessed promptly [9].

19.5 Case Study 5

19.5.1 Anemia in the Setting of HFrEF

Name: Janice Joppe

Age/Sex: 71-year-old female

Past Medical History/Problem List: Ischemic cardiomyopathy, HFrEF, single chamber ICD, Hypertension, hypothyroidism, GERD, gastrointestinal bleeding felt to be secondary to arteriovenous malformations (AVMs).

Family History: Mother alive at age 93, history of hypertension and diabetes. Father died at age 78 of stroke.

Psychosocial History: Ms. Joppe lives at home independently. Has four adult children, all healthy and three grandchildren. Retired seamstress.

Medications

- Metoprolol succinate 100 mg daily
- Sacubitril/valsartan 49/51 mg BID
- Spironolactone 25 mg daily
- Furosemide 40 mg daily
- Empagliflozin 10 mg daily

- Levothyroxine 75 mcg daily
- Ferrous sulfate 100 mg TID
- Docusate 100 mg BID
- Pantoprazole 20 mg daily
- Atorvastatin 80 mg QHS

Allergies: No Known Drug Allergies

Case Scenario: Ms. Joppe presents to primary care clinic complaining of fatigue and increased shortness of breath with ADLs, NYHA class III symptoms. She notes this is a change from 6 months ago when she was walking one mile per day. Recently seen by her cardiologist. Echocardiogram noted her ejection fraction was unchanged at 35% and stress test did not reveal ischemia. Labs indicated a slight drop in hemoglobin (9.8) and hematocrit (29). She was evaluated by her gastroenterologist and was found to have small AVMs, felt to be the cause of chronic blood loss. Cardiology discontinued her aspirin. Ms. Joppe is concerned because she continues to feel poorly and her quality of life is not what it used to be. Today, she is denying dark tarry stools. Notes some mild constipation, possibly due to her oral iron supplements.

Objective: Vital signs: BP 111/56 mmHg left arm, HR 68; Oxygen Saturation 98% on room air; Temp 98.7°. Weight 134 pounds. Physical exam: Conjunctive pale, lungs clear, JVD not elevated with exam table at 45°, heart rate and rhythm regular, no murmur. Extremities warm, no edema. Capillary refill less than 3 s. Skin slightly pale.

Diagnostic Reports

- Labs available for review: sodium 134, potassium 3.9, BUN 15, creatinine 1.0, hemoglobin 9.8, hematocrit 29, MCV 70, serum iron 24, TIBC 400, ferritin 30, transferrin saturation 10%

Assessment: Ms. Joppe presents to clinic with NYHA class III symptoms. Her heart failure appears stable by exam and recent diagnostics. She is on maximum doses of HF GDMT with adequate heart rate and blood pressure. Labs indicated iron deficiency anemia, likely the contributing factor to her increased fatigue and shortness of breath.

Plan

1. Chronic HFrEF
   Etiology: Ischemic Cardiomyopathy
   NYHA class: III
   Hemodynamic status: warm and euvolemic
   HF Devices: Single Chamber ICD
   Plan:
   Continue current HF GDMT:
   - Metoprolol succinate 100 mg daily
   - Sacubitril/valsartan 49/51 mg BID
   - Spironolactone 25 mg daily

- Furosemide 40 mg daily
- Empagliflozin 10 mg daily
- Treat iron deficiency anemia per 2022 AHA/ACC/HFSA Heart Failure Guideline

2. Iron Deficiency Anemia
   - Likely due to chronic blood loss and/or anemia of chronic disease.
   - Labs indicated serum iron of 24, ferritin 30, and transferrin saturation of 10%.
   - Currently on oral iron replacement, likely not being absorbed. Discontinue ferrous sulfate.
   - Arrange outpatient intravenous iron infusion.

Clinical Pearls
- Intravenous iron infusions have been shown to increase exercise capacity and improve quality of life for HF patients with concomitant iron deficiency anemia [4].
- Studies have shown oral iron may not be well absorbed and is inadequate in repleting iron stores in patients with heart failure [4].

19.6 Case Study 6

19.6.1 Heart Failure and Social Determinants of Health

Name: Edward Hall

Age/Sex: 60-year-old male

Past Medical History/Problem List: HFrEF (LVEF 15%), Ischemic Cardiomyopathy, Single Chamber Implanted Cardiac Defibrillator, HTN, CAD (history of CABG 2 years ago), Hyperlipidemia, Bilateral Carotid Artery Stenosis, Uncontrolled-Type 2 Diabetes, Right Below the Knee Amputation.

Family History: Mother alive, history of stroke. Father died at age 28 in motor vehicle accident. Has one brother who had a history of stroke.

Psychosocial History: Divorced. No children. Previously worked as a mail carrier, now disabled due to poor health. Receives meals from local meal service. Neighbors and elderly mother are his support system. He no longer drives and does not own a car. Continues to smoke one pack of cigarettes per day, which he has done for the past 20 years. Consumes three beers per day. No illicit drugs. Receives health insurance through Medicaid although often does not have money for medication co-pays.

Medications
- Sacubitril/valsartan 49/51 mg BID
- Carvedilol 12.5 mg BID
- Spironolactone 25 mg daily
- Furosemide 20 mg daily
- Atorvastatin 80 mg QSH

- ASA 81 mg daily
- Sertraline 50 mg daily
- Insulin Glargine 80 units/day
- Insulin Aspart sliding scale TID before meals

Allergies: No Known Drug Allergies

Case Scenario: Mr. Hall presents to clinic today for routine follow-up. He missed his last three appointments due to lack of transportation. After his missed appointments, the clinic nurse contacted Mr. Hall and provided information to him on how to arrange transportation to and from his office visits through the Medicaid transportation services, which he used today. He brought all of his medication bottles to the clinic visit. Upon medication review, it is noted that several pill bottles are empty. Mr. Hall noted he was not able to pick up his medications from the pharmacy and has been out of Furosemide and Carvedilol for three days. He was receiving sacubitril/valsartan (Entresto) though patient assistance before he qualified for disability and has a few more months of this service. He knows that insurance will pay for sacubitril/valsartan but worried about the higher co-pay for brand name medications. He reports increased swelling in his feet and shortness of breath walking 100 feet. Feels thirsty throughout the day and has been drinking Gatorade. Blood glucose elevated per home log, ranging from 275 to 350.

Objective: Vital signs: BP 130/80 mmHg, HR 90; Oxygen Saturation 98% on room air; Temp 98.7°. Weight 250 pounds. Physical exam: Lungs clear, JVD elevated ~12 cm with exam table at 45°, heart rate and rhythm regular, positive S3, no murmur. 1+ bilateral pedal edema. Extremities are warm. Capillary refill less than 3 s.

Diagnostic Reports

- Labs results: Sodium 130; Potassium 4.0; BUN 28; Creatinine 1.2; glucose 220, Pro BNP 2700
- Echocardiogram (5 months ago): LVEF 15%, LVIDD 6.7 cm, no valvular abnormalities

Assessment: Mr. Hall presents today after missing several office visits due to lack of transportation. He is now set up with Medicaid transportation services to travel to and from his office visits. However, access to medications is a barrier to his care. Most of his medications have a low co-pay but he often has trouble finding transportation to pick up his prescriptions in a timely manner and sometimes does not have the money for co-pays. He has a limited support system, only able to receive assistance from his neighbors when available. Receives meals through a local meal service, which are pre-prepared and high in sodium. Today, he is exhibiting signs and symptoms of fluid overload and needs medication adjustments. In addition, he should be counseled on avoiding alcohol and smoking cessation. Mr. Hall reports drinking Gatorade because his neighbor gets it for free and share it with him. His diabetes remains uncontrolled, and he is a fall risk due to right BKA.

Plan

1. Acute on Chronic HFrEF
   Etiology: Ischemic Cardiomyopathy
   NYHA Class: III
   Hemodynamic Status: Warm and wet
   HF Devices: Single Chamber ICD
   Plan:
   - Mr. Hall will need to resume Furosemide and Carvedilol, which he has been out of the past 3 days. To improve access to medications, a 90 prescription for all cardiac mediations was called into his pharmacy. The clinic nurse will also research if his Medicaid plan has mail services for medication delivery.
   - Mr. Hall qualifies for home health for heart failure disease management given that he is homebound. Recommend ordering home health for intermittent, skilled nursing care for heart failure disease management.
   - Education provided on avoiding Gatorade due to the sodium content as well as refraining from alcohol, as both are contributing to fluid retention and elevated blood glucose levels.
   - Limiting dietary sodium intake is challenging due to limited access to fresh foods as Mr. Hall is reliant on meal services. Additional education provided to Mr. Hall on monitoring for signs and symptoms of fluid overload and the need to call provider if any occur.
   - Optimize blood glucose control as elevated blood sugars are likely contributing to thirst mechanisms and increased fluid consumption.
   - With his current hyperglycemia he is likely experiencing some auto-diuresis and once blood glucose is better controlled his diuretics may need to be increased if he has more volume overload (no further auto-diuresis). Volume status will need to be monitored closely.
   - Return to clinic in one week to assess response to treatment, making sure to discuss his transportation options for return.
   - Before prescribing an SGLT2i medication, query which SGLT2i is on the pharmacy formulary for his insurance plan. Also, find out if a prior approval is needed, and the amount of co-pay required. If he cannot afford the co-pay, there may be assistance from the pharmaceutical company.
   - If he is unable to afford the co-pay to continue sacubitril/valsartan 49/51 mg twice a day, consider discontinuing and starting an angiotensin receptor blocker (ARB) such as Losartan or Valsartan (depending on his insurance formulary) at a mid-range dose.
   - Consider referral to heart failure disease management program.
   - Mr. Hall should have his device (ICD) interrogated every six months by an electrophysiologist and/or a heart failure cardiologist.

Clinical Pearls

- Several socioeconomical factors affect HF patient outcomes. Lack of caregiver support, low income, social isolation, and older age are associated with an increase in HF mortality and lower quality of life [4].

- Provider knowledge of community resources is essential to help mitigate factors that limit access to health care. Chapter 8 of this book highlights community resources to explore.
- Knowledge of insurance formularies, prior approval processes, patient assistant programs, and co-pay requirements is imperative for providing the heart failure patient their best options for affordable GDMT.
- Changing from sacubitril/valsartan to an ARB does not require a 36-h "wash-out" period, although if changing to an ace inhibitor a 36-h "wash-out" period is needed.
- Medicaid transportation may be an option for some patients to travel to and from office visits [10].
- Home health care for intermittent skilled nursing visits for heart failure disease monitoring and management is an option for heart failure patients who are unable to drive and considered home bound [11].
- Shared decision making between patients and providers is important to ensure compliance with the overall heart failure care plan. Despite best efforts by the care team, patients often remain confused about their treatment plan and require repetitive and comprehensive education [12].

19.7 Case Study 7

19.7.1 Heart Failure with Improved Ejection Fraction

19.7.1.1 HFimpEF

Name: Jasmine Bell

Age/Sex: 44-year-old female

Past Medical History/Problem List: HFimpEF, Idiopathic Cardiomyopathy, Hypertension, Depression.

Family History: Mother with history of diabetes. Father with history of hypertension. No siblings. 1 healthy adult child.

Psychosocial History: Married. Works as an accountant. Has one adult son in college. Denies history of tobacco use, alcohol, or illicit drugs. Enjoys playing golf and swimming. Eats fresh fruits and vegetables. Limited caffeine, drinks one cup of coffee per day.

Medications

- Sacubitril/valsartan 97/103 mg BID
- Carvedilol 12.5 mg BID
- Spironolactone 25 mg daily
- Dapagliflozin 10 mg daily

Allergies: No Known Drug Allergies

Case Scenario: Ms. Bell presents to primary care office for an annual checkup. Overall, she is doing well. Reports increased exercise over the past 6 months, now swimming at the YMCA two times per week and playing in a golf league. In reviewing her health history, she was diagnosed with idiopathic cardiomyopathy 3 years ago. Initially, her left ventricular ejection fraction was 20%. After 3 months of HF GDMT, her ejection fraction improved to 55%; thus, she did not require an ICD. She has now been on HF GDMT for the past 3 years. Now that she feels well, she is wanting to know if she can stop taking her heart failure mediations.

Objective: Vital signs: BP 110/65 mmHg, HR 70; Oxygen Saturation 100% on room air; Temperature 98.7°. Weight 150 pounds. Physical exam: Unremarkable.

Diagnostic Reports

- Labs results: Sodium 140, Potassium 4.5, Creatinine 0.9, BUN 15, eGFR 65, pro BNP 150. Hemoglobin 12, Hematocrit 38
- EKG: Normal Sinus rhythm. HR 70. QRS 90 ms

Assessment: Ms. Bell presents to clinic today for her annual checkup. She is doing well, exercising, and maintaining a healthy diet. No hospitalizations or heart failure exacerbations. She was diagnosed with idiopathic cardiomyopathy 3 years ago, with an initial LVEF of 20%. Her cardiac function normalized on HF GDMT. Now that she is feeling better and her heart function is back to normal, she is questioning if she can stop taking her medications.

Plan

1. Chronic Heart Failure with Improved Ejection Fraction (HFimpEF)
   Etiology: Idiopathic
   NYHA Class: I
   Hemodynamic Status: warm and euvolemic
   HF Devices: None
   Plan:
   Continue current HF GDMT:
   - Sacubitril/valsartan 97/103 mg BID
   - Carvedilol 12.5 mg BID
   - Spironolactone 25 mg daily
   - Dapagliflozin 10 mg daily
   - Educate Ms. Bell that ALL medications need to be continued to prevent relapse of heart failure and prevent LV remodeling

Clinical Pearls

- HF GDMT should be continued in patients who experience improvement and recovery of cardiac function to prevent relapse of heart failure. Studies have shown that LVEF can decrease after discontinuation of GDMT in patients who have improvement in LVEF, despite the absence of symptoms [4, 13].

19.8 Case Study 8

19.8.1 Advanced Decompensated Heart Failure

Name: James Johnson

Age/Sex: 61-year-old male

Past Medical History/Problem List: HFrEF, Ischemic Cardiomyopathy, Cardiac Resynchronization Therapy-Defibrillator (CRT-D), history of one ICD shock due to Ventricular Tachycardia, Coronary Artery Disease with a history of myocardial infarction 2 years ago, status post drug eluting stent to left anterior descending artery, Mitral Regurgitation (Functional), Hyperlipidemia, and Hypertension.

Family History: Mother alive, history of heart failure. Father alive, history of diabetes and atrial fibrillation.

Psychosocial History: Retired farmer, married, has two adult children (both healthy). Denies history of tobacco products. Denies alcohol or illicit drugs. Hobbies include woodworking and painting.

Medications

- ASA 81 mg daily
- Clopidogrel 75 mg daily
- Atorvastatin 80 mg QHS
- Carvedilol 3.125 mg BID
- Sacubitril/valsartan 24/26 mg BID
- Furosemide 80 mg BID
- Spironolactone 25 mg QAM
- Digoxin 0.125 mg daily
- Dapagliflozin 10 mg daily

Allergies: No Known Drug Allergies

Case Scenario: Mr. Johnson presents to primary care office with complaints of increased dyspnea with mild exertion when performing ADLs, lower extremity edema, lightheadedness and dizziness upon standing, poor appetite, and feeling "cold" all the time. He has little to no energy. He was seen by his cardiologist 2 weeks ago and his carvedilol was decreased from 6.25 mg BID to 3.125 mg BID due to symptomatic low blood pressure readings. Mr. Johnson was told by his cardiologist that his heart function is declining and may need to consider advanced heart failure therapies. He now feels worse than before and is beginning to retain fluid. Despite decreasing his carvedilol a few weeks ago, his blood pressure remains low, 80 mmHg systolic. He now has orthopnea and is sleeping in the recliner at night. His wife notes Mr. Johnson is becoming "forgetful" and at times confused.

Objective: Vital signs: BP 82/57 mmHg, HR 80, Oxygen 90% on room air, respiratory rate 20. Temp 97.7°. Weight 184 pounds. Physical exam: Lungs with faint bibasilar crackles, JVD elevated to angle of the jaw with exam table at 45°,

positive HJR, heart rhythm regular, apical heart rate 110, 2/6 murmur. Extremities cool to touch, 2+ bilateral lower extremity edema, capillary refill greater than 3 s.

Diagnostic Reports

- Last Echocardiogram (1 month ago): LVEF 20%, LVIDD 7.6 cm, bi-atrial enlargement, severe functional mitral regurgitation
- EKG today: Atrial and ventricular pacing, premature ventricular contractions. HR 80
- Lab results (3 months ago): Sodium 130, Potassium 3.9, BUN 20, Creatinine 1.1, Pro BNP 1000. LFTs normal
- Lab results today: Sodium 126; Potassium 4.1; BUN 42; Creatinine 1.7; Pro BNP 7000; AST 153, ALT 159

Assessment: Mr. Johnson presents to clinic exhibiting signs and symptoms of acute decompensated heart failure. The following subjective and objective signs are concerning for a low output state: recent need to de-escalate beta-blocker, increased fatigue, decreased mentation (forgetfulness), low blood pressure, narrow pulse pressure, cold extremities, increased BUN/Creatinine, and evidence of liver congestion (elevated LFTs). Note, he has a CRT-D and is paced at a rate of 80; therefore, his heart rate will remain the same in setting of decompensation.

Plan

1. Acute Decompensated Heart Failure with Reduced Ejection Fraction
   Etiology: Ischemic, Dilated Cardiomyopathy
   NYHA Class: IIIb
   Hemodynamic Status: cold and wet
   HF Devices: CRT-D
   Plan:
   - Mr. Johnson will need admission to the hospital for further management and treatment of Acute Decompensated Heart Failure.

Clinical Pearls

- The I-NEED-HELP [14] acronym can be helpful in identifying heart failure patients in a decompensated state and encourage prompt referral to an advanced heart failure specialist. The I-NEED-HELP acronym stands for: I: IV Inotropes; N: NYHA IIIb/IV or persistently elevated natriuretic peptides; E: End-organ dysfunction; D: Defibrillator shocks; H: Hospitalization >1; E: Edema despite escalation of diuretics; L: Low blood pressure, high heart rate; P: Prognostic medication: progressive intolerance or down-titration of GDMT [14].
- Depending on the patient's compensatory mechanisms, signs and symptoms of worsening heart failure may be severe or subtle such as a new report of mental "fogginess."
- Transcatheter mitral valve repair is an option for the treatment of secondary mitral regurgitation. However, in the case of Mr. Johnson, cardiac anatomy and degree of left ventricular dilation—over 7 cm, may prohibit his candidacy for

transcatheter edge to edge repair. He will likely need evaluation for more advanced heart failure therapy options such as left ventricular assist device (LVAD) or cardiac transplantation. Thus, referral to an advanced heart failure center is warranted.

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