Cardiac Management in the Frail Elderly Patient and the Oldest Old

Andrea Ungar
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Editors

Springer

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ISBN 978-3-319-43466-7 ISBN 978-3-319-43468-1 (eBook)
DOI 10.1007/978-3-319-43468-1

Library of Congress Control Number: 2016959471

Printed on acid-free paper

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

Foreword

When I was invited to write this foreword, I wondered whether a new book on geriatric cardiology might be useful in the present era of accessible scientific information. I came to a positive conclusion for several reasons: first of all, because of the continuous general population ageing process; in the second place, because the tremendous technological progress in the cardiology field over the last three decades provided new diagnostic and therapeutic tools, potentially helpful for cardiac disease treatment in elderly patients, where this is prevalent; and lastly because the complexity of elder cardiac patients – due to their frailty, comorbidities and disabilities – makes the clinical decision-making process particularly difficult, if we consider that life and end-of-life quality, rather than mere survival, are the outcomes to be reached.

Such complexity can be fully captured and efficiently managed only through a comprehensive geriatric assessment, a specific clinical methodology developed by geriatricians many years ago, and validated by solid evidences including several randomized trials.

The essential need for defining instruments and objectives of geriatric cardiology is reinforced by the evidence that the burden of cardiovascular disease constantly increases with ageing. More than 80% of deaths due to coronary artery disease, for example, occur nowadays in patients older than 65 years, and other common causes of cardiovascular deaths, such as congestive heart failure or valvular heart disease, follow a similar age-associated pattern. In contrast with this remarkable epidemiological paradigm, cardiology textbooks and guidelines often dedicate a very limited attention to this complex clinical scenario. As an example, it is only in the most recent edition of the popular *Braunwald's Heart Disease* textbook that geriatric cardiology gained an appropriate relevance.

Indeed, the need for specific geriatric assessment has already been taken into account by important cardiological subspecialties, such as interventional cardiology, where frailty and non-cardiac comorbidity evaluation is becoming a reliable method in risk stratification of elder candidates for invasive procedures, such as transcatheter aortic valve implantation (TAVI). It has been proven that the short-term and midterm outcomes of this new interventional procedure are largely predicted by the physical and cognitive functional status of older patients. We expect that an in-depth knowledge of those frailty and comorbidity components that maximally affect the final outcomes independently from age will improve the selection

process of older patients who will mostly benefit either from TAVI or from cardiac surgery.

Hence, I think that this book on *Cardiac Management in the Frail Elderly Patient and the Oldest Old* has the merit of focusing mainly on those areas where scientific advances in geriatrics have changed the diagnostic and therapeutic approach to older cardiac patients.

The authors belong to a team of medical professionals from the Division of Geriatric Cardiology and Medicine that has been active at the University of Florence for over 50 years; all of them are involved in managing older cardiac patients in an intensive care setting and in doing scientific research in the area of gerontology, geriatrics and, specifically, geriatric cardiology. The invitation to write this foreword is a privilege and an honour for me: having directed this same team for many years and contributed to its professional and scientific growth, it is a great satisfaction for me to see that, after my retirement, its members were able to keep up with the progress of geriatric cardiology at both national and international level.

Florence, Italy Giulio Masotti

Preface

In Western countries, cardiovascular diseases still represent the main cause of death, particularly in older patients. However, primary and secondary prevention has successfully reduced the incidence of cardiovascular events, improving life expectancy and leading to a demographic transition characterized by an increase of older and oldest old patients. Nowadays, cardiovascular diseases occur later in life and progressively increase with advancing age; as a consequence, patients referred to the cardiologist are usually old and frail subjects, presenting with several geriatric comorbidities and disabilities which influence the clinical management. This is why the geriatric expertise is needed in modern cardiology, in order to successfully manage the complexity of cardiac patients according to evidence/guidelines-based clinical practice.

In 1997, William W. Parmley, editor-in-chief of the *Journal of the American College of Cardiology*, called into question the management of old, frail patients affected by cardiovascular disease, focusing on the relationship between different specialties: "[…] Are we currently practicing geriatric cardiology? Yes and no. Yes because we care for this age group, and no because we are less well prepared to fully coordinate the care of the frail elderly […] We need to learn from the geriatricians those elements of care that will fully qualify us to practice geriatric cardiology". Twenty years later, geriatric cardiology still has not acquired the central role Parmley hoped for and it still is a matter of debate.

Guidelines-based clinical practice is limited by the absence of evidence referring to complex elderly patients; indeed, the majority of clinical trials do not include frail subjects with a high comorbidity burden and a higher risk of drug interactions and side-effects, and therefore being poorly representative of the real world. In addition, an ageist approach is so common in everyday practice that older patients are frequently excluded by diagnostic workup and treatment options, thus influencing and worsening their prognosis and quality of life. In this context, it is necessary to promote the geriatric culture, which faces the complexity of these patients through a multidimensional assessment, integrating different medical specialties and competences. Geriatric cardiology therefore aims at introducing crucial concepts of geriatric medicine – known to be the specialty of frailty and complexity – into the cardiology care system.

This book does not aim at being a comprehensive textbook of geriatric cardiology, but rather at providing clinicians with the geriatrician's awareness and point of

view, in order to favor a more appropriate decision-making in the management of the frail elderly and oldest old patients – the present and future protagonists of medicine. To this end, we focus on some crucial aspects of cardiovascular diseases in these patients and illustrate how to apply comprehensive geriatric assessment to the major topics of clinical and scientific relevance, on the basis of the experience of professional geriatricians and cardiologists.

Florence, Italy

Andrea Ungar
Niccolò Marchionni

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Introduction: The Specificity of Geriatric Cardiology

1

Niccolò Marchionni and Alessandro Boccanelli

Though atherosclerotic vascular and heart disease still represent the first cause of death in western countries, improved primary and secondary prevention of these diseases have given a substantial contribution to the remarkable prolongation of average life expectancy, which over the last two centuries has characterized the demographic transition in Western countries. In Italy, persons over 65 years of age presently represent 21 % of the whole population and will become 33 % in 20 years. The fastest growing segment is represented by individuals 80 years of age and older, whose numbers are expected to more than double over the same time period, while Italian persons over 90 years are now 600.000, while centenarians are more than 17.000, having tripled over the last 15 years.

As a consequence of the absolute and relative numeric expansion of elderly individuals, the clinical population of cardiac patients is getting older and older as well and quite commonly presents with coexisting geriatric syndromes that affect healthcare goals, outcomes, and the whole process of care. Indeed, cardiovascular diseases account for 80 and 60 % of causes of death in the population over 65 and 75 years of age, respectively. Coronary artery disease, hypertension, stroke, sustained supraventricular arrhythmias, and valvular heart disease all become more common with each decade of increasing age [1], and heart failure and atrial fibrillation are now the most frequent cause of hospitalization for medical reasons and contribute to 2 % of global healthcare economic burden. Nowadays,in current clinical practice, the average patient with acute coronary syndromes, chronic heart failure, and atrial fibrillation is

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_1

older than 70, 75, and 80 years of age, respectively [2]. As a consequence, cardiologists are facing with a broad array of comorbidities and age-associated impairments which are unfamiliar to them and may challenge the applicability of traditional evidence- and guideline-based management. Among the various comorbid conditions, for example, a certain degree of cognitive impairment is found in 10 % of persons over 65 and in more than 40 % of octogenarians and is an independent negative prognostic factor in cardiovascular diseases such as chronic heart failure [3].

Geriatric cardiology can be considered as an emerging discipline aimed at adapting the clinical management of older cardiac patients by introducing concepts of geriatric medicine into their routine cardiological care [4]. Cardiology is one of the medical specialties with the broadest recent advances in clinical and pathophysiological knowledge and high-tech diagnostic and therapeutic means. Geriatrics is, by vocation and tradition, the specialty of the clinical, functional, psycho-emotional, and socioeconomic complexity and of frailty, which are all the factors affecting the global state of health of the elderly [5].

The extraordinary technological evolution of cardiology, including a broad array of new pharmacological agents and advanced technologies for the treatment of ischemic heart disease, advanced cardiac failure, cardiac arrhythmias, or heart valve disease, increasingly challenges the clinical decision-making process that, in the face the clinical complexity characterizing the typical geriatric patient, has strong ethical and economic implications, both at the social and the individual level.

A further difficulty in making the right choices is represented by the fact that, due to frequently stringent exclusion criteria driven by concerns on feasibility and economic costs, most randomized clinical trials have recruited patients in good physical and mental conditions and, hence, poorly representative of those older, frail, and comorbid cardiac patients who are common in the real world [6]. Therefore, the generalizability of guideline recommendations based on those trials is limited, particularly for patients with complex comorbidities, which imply multiple treatments at increased risk of unpredictable interactions and untoward effects.

This limited generalizability of guideline recommendations, together with concerns on economic sustainability and on the clinical benefit of interventions with potentially harmful side effects, are all factors that contribute to the reduced utilization in older cardiac patients of diagnostic and therapeutic means of proven efficacy currently observed in real-world registries [7], whose findings suggest that, even though not deliberately chosen, an ageistic approach is operative in practice. Indeed, ageism is not a rule, but “an attitude that discriminates, separates, stigmatizes, or otherwise disadvantages older adults on the basis of chronological age” [8].

In this scenario of complexity, uncertainty, and also limited resources, the main purpose of geriatric cardiology may be regarded as a process of cultural integration between the two specialties, not to generate a novel specialty but rather to promote a new culture and sensibility toward specific problems. At the same time, a further integration process is needed with other specialties, among which general medicine is of greater relevance for its pivotal role in intercepting the unmet needs of the general older population, promoting adherence to primary and secondary preventive measures, and managing chronic illness. Such an integration process is to be focused on

sorting out the most appropriate and cost-effective solutions to the special problems of this population, by means on newly designed, real-world observational studies that should deliberately include frail and comorbid older individuals and should be provided with information needed to control outcomes for comorbidity and frailty.

1.1 Specificity of Cardiovascular Diseases in Older Adults

As a consequence of successful, large-scale primary prevention strategies, the incidence, and prevalence of atherosclerotic diseases continuously have reduced over the last two to three decades [9], and we can consider this secular epidemics nearly eradicated, as it happened with previous centuries' plagues, syphilis, and tuberculosis, each within its own reference century. As a consequence, atherosclerotic diseases occur less and later in life, and with the shortening of the "vascular" causes of heart disease, those due to aging-associated tissue degeneration, come forward.

Numerous cellular mechanisms underlie the aging of the cardiovascular system, including replicative senescence, apoptosis, protein misfolding, and low-grade inflammation [10]. Typical aging-associated anatomical modifications are represented by increased left ventricular mass, left atrial size, myocardial collagen deposition, and calcium deposition in valvular structures and coronary arteries. Large arteries are stiffened due to collagen overproduction, calcification, and endothelial dysfunction. Isolated systolic hypertension, calcific aortic stenosis, and senile cardiac amyloidosis are frequent hallmarks of the degenerative processes, along with increased prevalence of multivessel, calcific coronary atherosclerosis. All these factors contribute to explain the increasing prevalence of heart failure with preserved left ventricular ejection fraction and diastolic dysfunction, which is not linked to necrotic tissue loss secondary to coronary artery disease but rather to progressive replacement by fibrotic tissue. The same holds true for atrial fibrillation, which presents in up to 15 % of individuals above 80 years of age and is linked to degeneration of atrial tissue and to atrial enlargement secondary to ventricular diastolic dysfunction. Therefore, the present epidemiological picture is characterized by an increasing prevalence of non ST segment elevation myocardial infarction, chronic heart failure, and atrial fibrillation, all occurring in an increasingly aged population presenting with multiple problems at the level of other organs and systems.

1.2 Multimorbidity

Multimorbidity ($\geq$2 concurrent diseases) is present in the overwhelming majority of older adults and increases the likelihood of many adverse outcomes, such as hospital readmission, disability, and death [11]. Chronic kidney disease [12] and cancer are conditions to be often taken into account in many clinical scenarios, for example, because acutely worsening renal insufficiency may be precipitated by contrast medium used for coronary angiography or because reduced life expectancy due to cancer may exclude otherwise indicated interventions. Since evidence-based

medicine has been built on results gathered in younger or middle-aged population, the commonly used guidelines are of limited utility. In older adults with multimorbidity, patient's preferences, prognosis, clinical feasibility, and reasonably optimized therapies are to be taken first into account in the decision-making process, interpreting the evidence on an individual basis.

Despite this, the high cardiovascular morbidity and mortality of the elderly should deserve an aggressive and technologically advanced treatment, whenever possible. Despite trials have reported that the complication rate from early invasive procedures for acute coronary syndromes is substantially higher in patients older than 75 years [13], in registry studies [14–16] and in observational studies, aggressive treatment proved even more effective in terms of reduced number needed to treat, compared to younger adults [14]. Nonetheless, as already mentioned, registry studies report that older patients are systematically undertreated in parallel with their increasing burden of comorbidities [7]. Similar findings, which introduce the concept of a "net clinical benefit" that may increase with increasing age, has been found in other clinical areas, such as anticoagulation to prevent cardioembolic stroke in atrial fibrillation [17], where older patients are again systematically undertreated.

Cognitive impairment including deficits in memory and executive function is, among several geriatric syndromes, one of the most frequent comorbidities [18–22], with a well-established relationship with poor outcomes in several cardiovascular conditions such as chronic heart failure [3]. Urinary incontinence (18–45 %), falls (32–43 %), and frailty (14–25 %) are other geriatric syndromes with high prevalence that commonly complicate the management of chronic heart failure in older adults [23].

1.3 Frailty

Frailty, generally defined as a reduced homeostatic reserve leading to increased vulnerability to stressors, has gained attention in recent years as another geriatric syndrome associated with adverse health outcomes [24–26]. Frailty must be taken into account in clinical decision-making in elective procedures very commonly indicated in geriatric cardiac patients. For example, instruments for risk assessment in candidates to elective cardiac surgery or interventional procedures (e.g., transcatheter aortic valve implantation, TAVI), which have been built from data collected in middle-aged or young-adult populations, are inaccurately predictive when applied to older patients, and this has prompted an increasing research interest in testing the clinical utility of frailty indexes in improving the prediction of risk [27]. In the original PARTNER randomized trial, 31 % of patients died within 1 year even after immediately successful aortic valve replacement [28], an observation that underlines the need for improved identification of those older patients who might really profit long-term from TAVI. Following PARTNER, frailty has been identified as a syndrome that meaningfully predicts outcomes in older adult candidates to TAVI [29, 30].

The most widely used criteria for frailty assessment include the following five elements: slow gait speed, reduced grip strength, self-reported exhaustion, low physical activity level, and unintentional weight loss; following this approach, patients with three or more criteria are classified as frail [26]. Studies have demonstrated that frail patients are more likely to experience falls, disability, hospitalization, and death compared with those who are not frail. Beyond TAVI, frailty has been assessed in patients with recent myocardial infarction and found to be significantly associated with recurrent cardiovascular events after adjusting for traditional risk factors [31]. The individual planning of care for older adults may also be influenced by other geriatric impairments that include functional disability, falls, incontinence, and depression. The risk of traumatic bleeding linked to falls, for example, is one of the reasons for not treating atrial fibrillation with oral anticoagulants, thus increasing the probability of thromboembolism.

1.4 Geriatric Cardiology: Aims and Tasks

From what we mentioned above, a one-time consultation including with full multidimensional, comprehensive geriatric assessment (CGA) and medication review should be systematically offered to cardiac patients presenting with multiple comorbidities and age-associated impairments and limitations. An accurate evaluation of risk based on CGA prior to invasive procedures (e.g., TAVI, cardiac and noncardiac surgery) is necessary, to provide a holistic approach to management, targeted at individually tailored goals. As a further task, geriatric cardiology should offer consultation to primary care providers for a broad range of symptoms that may have an underling cardiovascular origin (i.e., falls potentially related to syncope, dizziness, weakness, and fatigue). Finally, a geriatric expertise is mandatory to define organizational models providing the continuity of care – from hospitals to rehabilitation facilities, home care, and palliative care units – which is needed for older, frail cardiac patients with heart failure or other chronic cardiac conditions.

Conclusions

A 2011 white paper in the *Journal of the American College of Cardiology* stated that "Mainstream cardiology has become, de facto, geriatric cardiology, but it still lacks a systematic approach that incorporates age-related complexities into clinical decision-making" [4]. Accordingly, the authors recommended that providers would develop "the skills needed to assess patient preferences, circumvent hazards of hospitalization, facilitate successful transitions from one care setting to the other, engage in useful risk-benefit discussions, and provide care collaboratively within a care team responsive to the needs of the oldest patients" [4]. This reinforces the idea of geriatric cardiology as a discipline which should link the knowledge and skills of cardiology with the sensibility and culture of geriatrics.

In the perspective of a further, rapid expansion of the population of older cardiac patients, there is a strong need for specific educational programs for the next

generation of cardiologists. Bell et al. recently advocated for the development of "a formalized geriatric cardiology skill set" which "would help providers who must immediately have the ability to facilitate effective care for older adults, rather than awaiting years of practice experience to develop practical gestalt" [32]. Hopefully a new generation of specialists will develop specific expertise in aging-related issues, in order to become or even to be certified as "geriatric cardiologists." The exact training for this has yet to be defined, and efforts in this direction should be made by individual academic institutions and national subspecialty societies.

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Cardiovascular Disease in the Oldest Old: A Geriatric Epidemiology Perspective

2

Mauro Di Bari and Daniela Balzi

Ageing represents a non-modifiable risk factor for the most common cardiovascular diseases (CVD), from hypertensive to coronary heart disease, atrial fibrillation, aortic stenosis and heart failure. These conditions may profoundly affect global health status (i.e. physical and cognitive functioning, quality of life and survival) of older patients. At the same time, specific aspects of ageing frequently modify presentation, clinical management, therapeutic approach and outcomes of CVD.

Aim of this chapter is to provide, within an epidemiological perspective, a general overview of the relationship between the demographic transition and global and cardiovascular health of older persons. Whereas a comprehensive description of the epidemiology of CVD in the aged is beyond its scope and can be found elsewhere [1], some pertinent examples will be succinctly reported.

2.1 Population Ageing, Global Health and Cardiovascular Health: An Overview

Worldwide, from 1990 to 2013 life expectancy at birth has increased by 6.2 years, from 65.3–71.5 years. In the same time frame, the number of deaths increased for most non-communicable diseases, but, because of changes in the age structure of the world's population, age-standardised death rates fell by 18.6 %. Interestingly,

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_2

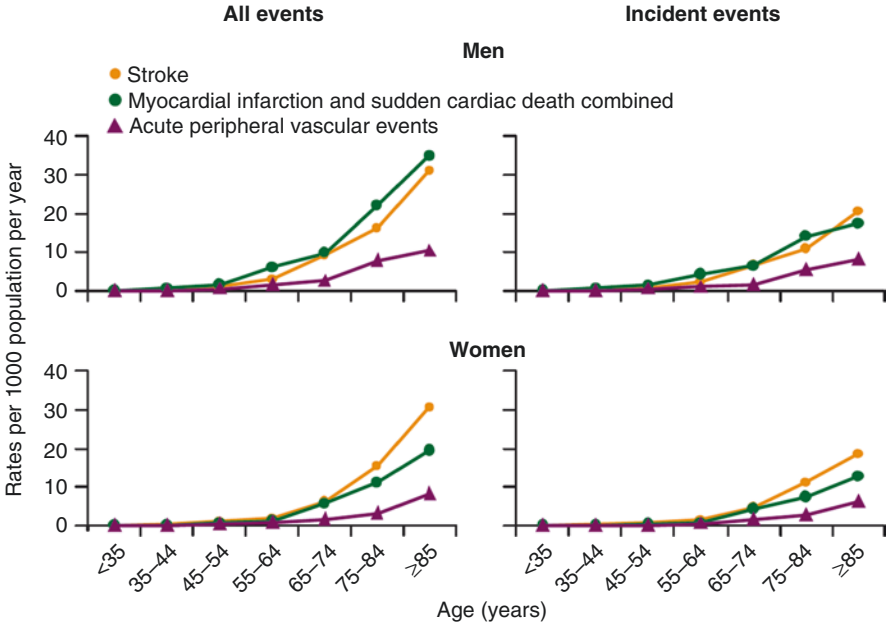

Fig. 2.1 Gender- and age-specific rates of all events and of incident events for stroke, myocardial infarction and sudden cardiac death combined and acute peripheral vascular events (Modified from Rothwell et al. [3])

the reduction in age-standardised death rate was even greater (22 %) for CVD, particularly in high-income and many middle-income countries [2]. Nevertheless, in 2013 CVD still accounted for almost a third of all deaths: ischaemic heart disease and stroke continue to cause most CVD deaths in almost all countries and significant increases (+100 % age-standardized death rates) occurred for atrial fibrillation/flutter and peripheral vascular disease [2]. Local statistics, as those collected in the Oxford Vascular Project [3], confirm these trends (Fig. 2.1).

A closer look at data from the USA and Italy, two paradigms of industrialised countries, provides further insights to understand more recent trends in the demographic revolution and, at the same time, warns towards the fragility of this revolution. Huge disparities in the extent and quality of ageing are observed across strata of the US population: in 2008, the difference in median survival between Caucasians with at least 16 years of education and African Americans with less than 12 years was 14.2 years in men and 10.3 in women, and, even more alarming, this gap was greater in 2008 than only a few years earlier [4]. At the beginning of the twentieth century, life expectancy at birth in Italy was just above 40 years in both sexes, while nowadays it is close to 80 years in men and 85 in women. For many decades, the increase in life expectancy was mainly due to decreasing mortality at a young age, whereas starting from the 1980s, the mortality decline progressively involved older subjects: from 1960 to 2007, life expectancy at birth increased only by 17 % in women and 18 % in men, compared to 61 and 55 % at the age of 80 years, to reach almost 10 and 8 years, respectively [5] (Fig. 2.2). Nevertheless, after years of progressive reduction, in 2015 the number of deaths in Italy increased markedly,

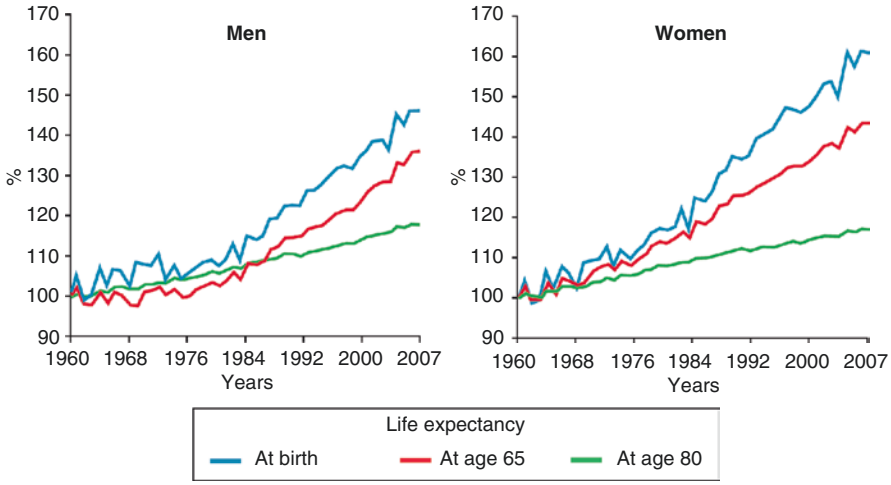

Fig. 2.2 Index numbers (1960 = 100) of life expectancy at birth, at age 65 and 80 years in Italy, 1960–2007, by gender (Modified from Bernabei et al. [5])

unexpectedly and so far inexplicably: most of these fatalities occurred in the oldest olds [6]. Both these examples indicate that achievement of an extended and healthy longevity in a population represents the final effect of the interplay of a complex, sometimes unknown series of factors: as such, it may not be granted universally and forever, and its preservation requires attention and surveillance.

Beyond mortality rates, world's population health status can be better described by healthy life expectancy (HALE), which represents the share of an individual's life free of significant morbidity and dependency. According to recent estimates, between 1990 and 2013, HALE increased worldwide by 5.4 years at birth, i.e. less than total life expectancy. Whether this may reflect an expansion of morbidity is controversial, whereas there is substantial agreement that the drivers of the difference between HALE and life expectancy are not CVD: conversely, years lived with disability from CVD might be decreasing [7]. Thus, even in the face of an unprecedented ageing of the population, cardiovascular health in the world and, more specifically, outcomes of CVD in older persons [8] appear to be somehow improving. Yet, these findings are only partially reassuring, because projections through 2030 suggest that, in terms of disability-adjusted life years, the burden of CVD will increase by 40.6 %, compared to 2004, throughout the world, particularly in low income countries [9].

2.2 Descriptive Epidemiology of CVD in the Elderly: Selected Examples

2.2.1 Coronary Artery Disease

According to the US National Health and Nutrition Examination Survey 2007–2010, approximately 21 % of men and 10 % of women aged 60–79 years have coronary artery disease, whereas over the age of 80, prevalence figures are close to 35

and 19 %, respectively [1]. In strata defined on the basis of gender and race, incidence varies between 4 and 14 per 1000 p-y in the 65–74 years age range and between 9 and 19 per 1000 p-y in the following decade [1].

Temporal trends show that in the US hospital, discharges for coronary artery disease, after a slow increase from 1970 to 2000, are progressively declining thereafter at a faster pace, so that 2010 values are close to those recorded in 1970 [1]. With an acceptable degree of approximation, this trend is considered to reflect changes in the incidence of the condition.

2.2.2 Aortic Valve Stenosis

Degenerative aortic valve stenosis is nowadays the most common heart valve disease of surgical interest: it is estimated that approximately 50 % of patients with severe aortic stenosis are referred for cardiothoracic surgery [1]. Occurrence of aortic stenosis consistently increases with age: in a population-based report from Norway, prevalence figures were 1.3 % in the 60–69-year cohort, 3.9 % in the 70–79-year cohort and 9.8 % in the 80–89-year cohort. Incidence rate was 4.9‰/year and average annual increase in mean transvalvular gradient 3.2 mmHg [10]. Prevalence values were similar in a more recent population-based report, conducted in Iceland with a combination of echocardiography and CT scan-detected aortic valve calcium [11].

In Scotland, age-gender-adjusted temporal trends of hospitalisations for aortic stenosis showed a dramatic increase, from 246 cases per one million population in 1997 to 365 per one million population in 2005 [12]. Remarkably different trends have been observed in Sweden: across a 20-year interval, the unadjusted incidence of aortic stenosis remained stable, whereas its age-adjusted incidence declined. Furthermore, in spite of a 4-year increase of median age at diagnosis, mortality declined markedly, similar to the trends reported, in the same and in other studies, for heart failure and acute myocardial infarction [13]. These findings suggest that degenerative aortic stenosis shares with other largely prevalent CVD a set of modifiable risk factors, whose intensive treatment can efficaciously prevent this common valvular disease, as well as coronary artery disease.

2.2.3 Atrial Fibrillation

Atrial fibrillation is the most frequent tachyarrhythmia of late life. Its incidence increases markedly with advancing age, from less than one per 1000 p-y below the age of 60 years to 25.6 per 1000 p-y in men and 23.4 in women over the age of 80 years, respectively; these values remained steady from 2000 to 2010 [14]. Prevalence of the arrhythmia in persons aged 65+ years is around 5 %; age-related trends are similar to those reported for incidence, from 4.3 % in subjects aged 66–69 years to 5.4 % above the age of 90 [15]. Long-term recordings of spontaneous heart rhythm by pacemakers and defibrillators have shown that episodes of clinically unrecognised atrial fibrillation are frequent in individuals with no documented history of the arrhythmia and may be responsible for thromboembolism [16].

Atrial fibrillation is associated with diminished survival at any age, although this excess risk is limited to the first 6 months after the diagnosis in individuals in their 80s, whereas in subjects aged 60–69 years it extends over 4 years [14]. Besides being a recognised risk factor for stroke [17], atrial fibrillation, either prevalent or incident, is associated with a 1.5–2-fold greater incidence of dementia [18], independent of stroke occurrence. Dementia is one of the most worrisome conditions associated with ageing, and its prevalence will continue to escalate in industrialised countries [19], and interventions to contrast this epidemic are eagerly searched. Thus, investigating whether optimal treatment of atrial fibrillation can prevent or postpone dementia would be a major contribution of cardiovascular medicine to healthy ageing.

2.2.4 Heart Failure

Prevalence of heart failure is 5–6 % in subjects aged 60–79 years and increases to 9–12 % in those 80+ years old [1], with good consistency across different studies [20, 21]. In the Framingham Heart Study, incidence increased from 9.2 to 4.7 per 1000 p-y in men and women aged 65–74 years to 41.9 and 32.7 per 1000 p-y after the age of 85 [22], whereas greater incidence figures have been reported in the Cardiovascular Heart Study [23]. At the age of 80, the remaining lifetime risk for onset of heart failure is still a remarkable 20 % [22].

As the common final pathway of most CVD, heart failure can be expected to become increasingly common, due to the combined effect of advancing age of the population and decreasing mortality from age-related, previously highly fatal conditions, such as acute myocardial infarction. However, recent data do not fully support this expectation. In a study from Denmark, Schmidt et al. [24] reported that, from 1983 through 2013, the rate of first-time hospitalisation for heart failure increased slightly, by an average of 1 % per year, initially through 2000, and declined markedly thereafter, by 3.5 % per year. Among heart failure patients, the proportion of those aged 80+ years increased from 34 to 44 % between 1983 and 2007 and declined to 42 % in subsequent years; conversely, a threefold increase in the proportion of patients with more severe comorbidity, from 5 to 16 %, was recorded throughout the entire study period. In spite of the more advanced age and increasing complexity, 5-year mortality rate declined, by more than 40 % overall, across the 30-year period; this decline occurred for all age, sex, comorbidity and risk status patient groups [24].

2.3 Geriatric Syndromes and Other Specific Features of the Oldest Old Patient with Cardiovascular Disease

Similar to CVD, many other chronic diseases have an age-related prevalence, from degenerative osteoarthritis [25] to diabetes, chronic bronchitis or Alzheimer's disease [26]. Each of these conditions may require long-term complex drug therapy regimens. Moreover, besides specific diseases, geriatric syndromes such as

functional impairment, falls, sensory deficits, urine incontinence and chronic pain are frequent in late life [27]. Even isolated, geriatric diseases and syndromes can deteriorate health status of aged persons and compromise their independence and quality of life. Not surprisingly, these consequences are more common and severe when these conditions coexist, as it usually occurs.

2.3.1 Comorbidity and Multimorbidity

Comorbidity is the presence of one or more additional disorders (or diseases) co-occurring with a primary disease or disorder, or the effect of such additional disorders or diseases [28]. Unlike complications, it does not have any aetiologic relationship with primary diagnosis. More recently, the concept of multimorbidity has been introduced in medical literature, as the co-occurrence of two or more chronic medical conditions in one person [29], irrespective of any index disease. Multimorbidity describes better what is commonly observed in older persons, when clinicians cannot identify any dominant disease and must deal with several coexisting conditions at the same time [30]. More than half of the persons aged 75+ years have at least three coexisting chronic diseases [27, 30, 31]; possibly because of more severe multimorbidity, women spend a longer part than men of their life as disabled [32].

Multimorbidity has a major role in public health, as it is responsible for escalating health-care costs; yet, it is also important for the practising physician, because it strongly influences the diagnostic process, the therapeutic approach, the effect of treatment and ultimately the patient's outcome, in particular increasing the risk of functional decline and mortality in older persons. For example, multimorbidity confounds the diagnostic process, because it favours atypical presentations of diseases: delirium often heralds dementia, but it may represent the onset of several clinical conditions, including acute heart failure or myocardial infarction. Multimorbidity complicates treatment, because most randomised trials that represent the foundation of evidence-based guidelines enrolled young patients free of significant associated diseases [33]. Paradoxically, rigorous application of disease-specific guidelines in typical geriatric patients may have serious adverse effects [34], mostly mediated by polypharmacy. Indeed, the risk and severity of adverse drug reactions and of drug-drug interactions increase with the number of prescriptions [35], so that polypharmacy may represent an independent risk factor for death [36]. On the other hand, abstention from appropriate therapies is also very common in complex older persons with multimorbidity and may negatively affect survival, as observed after acute myocardial infarction [37].

Several approaches have been proposed to quantify comorbidity and multimorbidity, usually based on clinical appraisal of the presence or severity of diseases [31, 38]. A simple count of chronic coexisting diseases has good predictive ability against important outcomes such as death or incident disability, although better results are provided by measures that also score disease severity, such as the Charlson Comorbidity Index [39] or the Index of Coexistent Diseases [40]. The Cumulative

Illness Rating Scale (CIRS) [41] is another very popular instrument to weigh the severity of comorbidity: in spite of its large diffusion, it should be considered as suboptimal, because it considers the functional impact of a disease to measure its severity, therefore preventing any independent assessment of the association between a given chronic disease and functional status. Analysis of therapeutic patterns offers an alternative approach to measuring comorbidity and multimorbidity [42], although its reliability and validity are lower than with clinical methods [31, 38].

2.3.2 Disability and Frailty

Functional status is a major determinant of health status and prognosis of older persons. In cardiac patients, clear evidence for this has been offered by a large study of older persons hospitalised for heart failure, whose 30-day and 5-year prognosis was strongly predicted by the presence of dementia and mobility limitations, adjusting for the severity of the underlying cardiac condition [43].

Evaluation of functional status is an essential component of comprehensive geriatric assessment, the specific technology that geriatrics applies to identify and, possibly, correct the variety of problems an older person may have [44, 45]. Traditional measures of functional status are represented by Katz's activities of daily living (ADL) [46], which evaluate the ability of an older person to manage basic tasks (bathing, dressing, transferring, using the toilet, maintaining continence and feeding) essential for indoor independence, and Lawton's instrumental activities of daily living (IADL) [47], exploring higher-level abilities (using public transportations and telephone, managing finances and drug therapy, housekeeping, shopping and preparing meals), which consent outdoor independence and social life. Consistently in most studies, approximately 10 % of persons aged 65+ and one-third of those aged 80+ are found to have ADL disability and, therefore, depend on somebody's help for their primary needs. Conversely, the prevalence of IADL disability is more variable across different settings, because IADL tasks are more sensitive to the social and cultural context.

These tools were initially proposed to standardise the process of evaluating the needs an older person might have and identifying the most appropriate level or setting of care. They were subsequently applied also to guide rehabilitation. However, with time it became clear that the level of disability represents a summary measure of the combined effect of "normal" ageing, multimorbidity, changes in cognition and mood on an older person's global health; therefore, measuring disability improves prognostic assessment, independent of specific clinical diagnoses [48].

The relationship between coexisting diseases and functional status is complex. On one hand, multimorbidity strongly increases the risk of disability, proportionately to the number and severity of coexisting diseases [31]. On the other hand, specific associations of diseases may synergistically compromise functional autonomy: for example, chronic heart failure and previous stroke combined increase the risk of disability in excess of what can be anticipated from a simple summation of the risks associated with each individual condition [49]. Therefore, functional

evaluation has gained a remarkable role within comprehensive geriatric assessment, because it conveys relevant information across the entire spectrum of conditions an older person may present, within all care settings. Mostly, functional evaluation is essential to identifying frailty.

Approximately one-third of older persons are robust, i.e. have no major diseases and free of IADL disability; on the other end, about 10 % of persons aged 70+ years have an unsteady health status, characterised by multimorbidity and a rapid deterioration of physical and cognitive abilities following apparently trivial injuries. Geriatric literature identifies these subjects as "frail" [50]. Disability and frailty must be considered as two distinct, though correlated, conditions, with similar epidemiology (age-related prevalence) and multifactorial pathophysiology. There is a general consensus that frailty represents an expression of reduced functional reserve, with impairment of mechanisms of biological homeostasis, leading to extreme vulnerability to stressors, such as an acute disease or environmental changes. As a consequence, frailty can be better identified from the assessment of complex, integrated functions and application of stimuli that challenge one's physiological reserves. The most convincing example is probably the reduction in gait speed: albeit it is observed as a universal age-related phenomenon, it occurs with a wide range of variability across individuals depending on several factors, and it is magnified in the presence of a precarious health status. Because walking is a very complex activity, slowing gait may depend on abnormalities in central or peripheral nervous system, impaired cardiopulmonary efficiency or muscular-skeletal problems. No matter how complex its pathophysiology is, in order to operationalise frailty, it is important to have measures easy to detect and strongly associated with global health status: gait speed has all these features, and its decrease is a formidable predictor of death and disability in the elderly, both in the general population [51] and in clinical settings [52].

Using data from the Cardiovascular Health Study, Fried et al. developed a model coherent with this conceptualisation of frailty and easy to operationalise [50]. According to this model, frailty is characterised by the presence of at least three of the following five measurable conditions: muscle weakness, unintentional weight loss, reduced walking speed, reduced level of habitual physical activity and fatigue (Table 2.1). More recently, the concept of sarcopenia (age-related loss

Table 2.1 Frailty phenotype according to the Cardiovascular Health Study model

1. Unintentional weight loss ≥10 lbs (4.5 kg) in prior year
2. Weakness: grip strength in the lowest quintile (by gender and body mass index)
3. Poor endurance, exhaustion (self-reported)
4. Slowness: short distance gait speed in the lowest quintile (by gender and height)
5. Low activity (self-reported): lowest quintile (males: <383 kcal/week, females: <270 kcal/week)
Frail: ≥3 criteria
Intermediate (*prefrail*): 1 or 2 criteria
Robust: 0 criteria

Modified from Fried et al. [26]

of skeletal muscle mass and strength) [53] has gained popularity as an important determinant of health status in older persons, combined with frailty. Together, these conditions may indeed lead to reduced energy production and limitation in functional activities, such as walking: this has been shown in the InCHIANTI epidemiological study on community-dwelling older persons, in whom poor nutrient intake and decreased muscle mass were associated with frailty and had negative health effects [54].

In agreement with Fried's model [50], acute and chronic diseases may favour the onset of frailty by either reducing functional reserves or as stressors that unmask previously compensated deficits. The need for tapping into functional reserves for too long or too extensively may precipitate frail older persons into disability: it should be emphasised that, unlike other models of frailty, within Fried's model disability would represent a possible consequence of frailty rather than one of its determinants.

Consistent with Fried's model and expanding the aforementioned observations on the prognostic value of disability [48], numerous studies show that a reduction in physical performance, documented through objective and quantitative tests, is a powerful predictor of mortality and, in subjects initially non-disabled, the development of disability. The short physical performance battery (SPPB) [55] combines a balance test in three positions of increasing difficulty, 4-m gait speed and a repeated chair-standing test (Fig. 2.3). By comparing the timings recorded with those obtained in a reference population, the result of each test is converted into a score, which ranges from 0 (poor performance) to 4 (optimal performance), so that the final score of the battery ranges between 0 and 12. In a large population-based study of initially non-disabled 70+ years old subjects, the risk of new ADL or mobility disability over 4 years increased with decreasing SPPB score and was more than 4

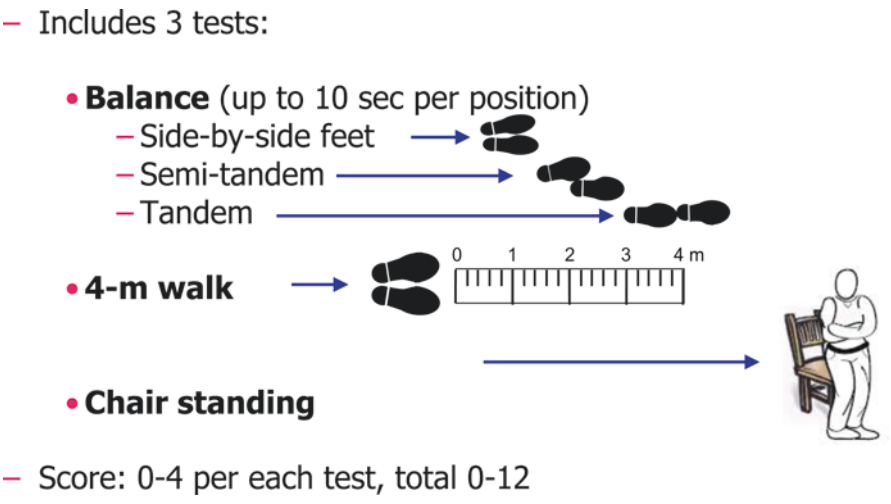

Fig. 2.3 Short physical performance battery (Modified from Bernabei et al. [5])

Table 2.2 Cox proportional hazard model predicting death in community-dwelling older persons, based on comorbidity, demographics, physical performance and cognitive status

Variables	Hazard ratio (95 % confidence interval)	*p*
Comorbidity (ICED)		0.01*
Level 1	1	_
Level 2	1.5 (0.9, 2.4)	0.10
Level 3	1.8 (1.1, 3.1)	0.02
Level 4	2.2 (1.3, 3.6)	0.002
Age (years)	1.12 (1.11, 1.15)	<0.001
Gender (F vs. M)	0.5 (0.4, 0.6)	<0.001
SPPB score	0.93 (0.88, 0.99)	0.008
MMSE score	0.98 (0.94, 0.996)	0.03

Modified from Di Bari et al. [31]
Abbreviations: *ICED* index of coexistent diseases, *MMSE* mini mental state examination, *SPPB* short physical performance battery
**p* for trend

times greater for scores between 4 and 6, compared with scores of 10–12, independent of age, sex and presence of some chronic diseases [55]. These results have been repeatedly confirmed in other populations: in particular, the SPPB emerged as a powerful predictor of disability and mortality in the elderly population of the ICARe Dicomano Study, after adjustment for age, sex, multimorbidity and cognitive status (Table 2.2) [31].

SPPB was proven as a valuable predictor of prognosis not only in population-based studies but also in clinical settings, especially in people with heart disease: in elderly hospitalised for acute exacerbation of chronic heart failure, SPPB at discharge was able to predict long-term mortality independent of left ventricular ejection fraction and New York Heart Association functional classification, both considered key tools for prognostic stratification in cardiac patients [56]. Thus, it appears that functional assessment conducted with the SPPB captures aspects of health status of an older person that are outside the restricted sphere of disease-specific measures and, possibly, represent the status of reduced homeostatic reserve inherent in the concept of frailty. Thus, non-disabled older persons with reduced physical performance, as documented from SPPB scores between 5 and 9, may be considered frail and deserve special attention and tailored interventions to reduce the risk of adverse consequences.

Conclusions

CVD is a major health issue in older individuals. Advancements in medical care and technology have decreased cardiovascular mortality more than incidence; thus, most CVD patients nowadays have outlived current evidence-based recommendations. The challenge that cardiologists must confront with when dealing with these patients is therefore threefold: (1) need for superior cardiological competences and technical skills because of more severe organ-specific diseases;

(2) ability to handle, mostly within team collaboration, geriatric issues (frailty, multimorbidity, polypharmacy, functional decline, cognitive impairment, depression, social disadvantage and end-of-life care) that affect goals, outcomes and the process of care; and (3) lack of sound clinical guidelines. The new paradigm of geriatric cardiology is thus emerging as an effective answer to overcome these complexities [57, 58].

Examples have been shown [45, 56] that assessment of functional status is an essential component of geriatricians' evaluation of their patients. Although with different technical specificities, this approach is also a central component of the cultural and professional background of the cardiologist, and it may, therefore, represent a possible meeting point between different professionals, dealing with elderly cardiac patient. In addition, numerous data demonstrate close relationships between frailty, disability and cardiovascular disease. The Cardiovascular Health Study demonstrated that subclinical cardiovascular disease is a risk factor for functional and cognitive impairment, limiting successful ageing [59]. Both global and active (i.e. disability-free) survivals are strongly conditioned by some traditional cardiovascular risk factors, such as smoking and sedentary lifestyle [60]. In agreement with these observations, experimental evidence indicates that physical activity, whose in cardiovascular prevention is undisputed, is also effective for promoting and maintaining health in older persons, even in the presence of frailty [61, 62]. Thus, cardiovascular prevention and prevention of disability in late life appear to share common targets and intervention strategies.

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Molecular Mechanisms of Cardiovascular Aging

3

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A number of functional and anatomical changes occur in the heart and vessels with age.

In human arteries, aging is characterized by structural modifications of endothelial and smooth muscle cells, forming the vascular wall. The hallmark of age-dependent endothelial dysfunction is an impaired endothelium-dependent vasodilatation. Aging is associated with reduced bioavailability of NO, due to decreased expression and activity of eNOS and deficiency of NOS substrates and cofactors [1]. Senescence is characterized also by intimal proliferation, increased arterial stiffness, and appearance of low grade, chronic inflammation [2–4].

Aging vessels show a defective capacity to repair that may be attributed to a loss in function of circulating endothelial progenitor cells (EPCs) [5]. This translates in defective re-endothelization of injured arteries [6].

In the heart, aging is identified by left ventricular hypertrophy, cardiac fibrosis, impaired ventricular compliance, progressive myocardial remodeling and deteriorated cardiac reserve. There is an increased sensitivity to stress, linked to decreased defensive mechanisms (e.g., ischemic preconditioning), resulting in heightened vulnerability to injury. The number of cardiomyocytes declines, in parallel with a progressive decline in organ regenerative capacity [7].

Intrinsic aging may be defined as the progressive structural and functional changes developed with age. However, it is a real challenge to discern the effects of aging per se from the modifications produced by the presence of cardiovascular risk factors, as "healthy" aging and "pathological" aging are deeply interrelated.

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_3

What is the molecular base of cardiac and vascular aging? The answer is complex. A multitude of pathways and signals are modified over time, all contributing to the aging phenotype. However, some senescence-related molecular mechanisms have been explored extensively and seem to give a distinct contribution to the age-related modifications detected in the cardiovascular system. Those pathways will be reviewed in this chapter.

3.1 Mitochondria and Cardiovascular Aging

Mitochondrial function is essential for the cell; mitochondria are the major source of energy, provide biosynthetic pathways, regulate differentiation and apoptosis, and control ion and redox homeostasis. Mitochondria provide energy for the cell in the form of adenosine triphosphate (ATP), by oxidative phosphorylation. Reactive oxygen species (ROS) are a natural byproduct of oxygen metabolism and the mitochondrial respiratory chain is the major source of ROS within the cell. An imbalance between production of oxidative molecules and ability of the cell to mount an appropriate antioxidant defense may result in oxidative damage to the main cellular structures.

The free radical theory of aging proposed by Harman in 1956, postulates that intracellular ROS are the major determinant of lifespan in mammals: age-related decline in organ functions could be ascribed to the detrimental effect of ROS on all major cellular components [8]. Since 90 % of cellular ROS are produced in mitochondria, Harman later hypothesized that mitochondrial ROS is mainly accountable for human aging [9]. In addition, due to the proximity of mitochondrial DNA (mtDNA) to ROS and the lack of protective histones, mtDNA is largely exposed to oxidative damage [10]. A "vicious cycle" hypothesis has been postulated which suggests that the initial ROS-induced damage to the mitochondrion increases the production of ROS that, in turn, leads to further mitochondrial damage.

However, it is well established that ROS are not purely harmful; they act as signaling molecules to modulate many intracellular pathways and their presence within the cell is crucial to build a strong response against stress (mitohormesis). Thus, while high levels of ROS are detrimental, the production of low levels of ROS may activate compensatory signaling pathways that promote longevity [11].

Several experimental evidence indicate that mitochondrial integrity declines as a function of age, resulting in an amplified leakage of ROS [12]. However, whether mitochondrial oxidative phosphorylation is impaired in senescence cells remains controversial. Some studies demonstrated a decline in oxygen consumption whereas others reported no change. This discrepancy may be due to the fact that there are two types of mitochondria: interfibrillar mitochondria exhibit a lower oxidative phosphorylation rate with age, whereas subsarcolemmal mitochondria, obtained from aged hearts, do not [13].

In the body as a whole, aging is accompanied by a decline in skeletal muscle mass and contractile function, leading to impaired mobility. However, this age-related decline in physical activity does not fully explain the decreased aerobic

metabolic capacity detected in elderly individuals, as exemplified by trained older adults and master athletes still showing a reduced muscle and whole body $VO2_{max}$. This can be attributed to an age-related, intrinsic decline in mitochondrial enzyme activity and function [14].

Among the five electron transport chain complexes, complex I includes seven of 13 mtDNA-encoded polypeptides. Therefore, complex I is likely to be the most susceptible to age-associated decline in activity and the major source of the increased ROS production with age [15]. Indeed, a recent study of aged mouse heart demonstrated an increased oxidative protein modification in complexes I and V, associated with a decline in energy-producing activity [16].

What is the evidence supporting the notion that age-related mitochondrial dysfunction contributes to cardiovascular aging?

Since the bulk of ROS production results from mitochondrial oxidative phosphorylation and myocardial activity is highly energy-dependent, the heart is particularly exposed to oxidative injury [17, 18].

The most convincing evidence that mitochondria and oxidative stress are related to cardiovascular aging originates by the study of transgenic animals. Mice overexpressing the antioxidant enzyme human catalase targeted to the mitochondrion (MCAT), exhibit a decreased level of oxidative damage and mtDNA deletions, and an increased lifespan. They also display a sharp protection from cardiac aging: compared to wild type mice, aged MCAT mice show reduced left ventricular mass index (LVMI), improved diastolic function (Ea/Aa), and reduced left atrium dilatation [19].

Mice expressing a proofreading-deficient version of mtDNA polymerase γ (PolG) accumulate a high number of mtDNA mutations and deletions in the heart and die prematurely from dilated cardiomyopathy [20]. They display early-onset morphological and functional changes to the heart, including fibrosis, cardiac enlargement, and impaired systolic and diastolic function. Cardiomyocytes of PolG mice exhibit accumulation of enlarged, irregularly shaped mitochondria, with reduced ATP production [21]. Of interest, PolG mice subjected to endurance exercise show improved mitochondrial biogenesis and mitochondrial morphology, and diminished level of apoptosis in multiple tissues and organs. Exercise also prevents premature mortality in this animal model [22]. Exercise may prove effective in mitigating age-related mitochondrial dysfunction in humans, as well.

Additional evidence of mitochondrial involvement in cardiac aging comes from mice with $p66^{Shc}$ gene mutation [23]. The $p66^{Shc}$ gene encodes a mitochondrial enzyme involved in the regulation of redox homeostasis; the mutation reduces ROS-mediated oxidative damage, modifies ROS-mediated intracellular signaling and prolongs the lifespan of mice. The mutation also increases cardiomyocyte resistance to apoptosis and prevents angiotensin II-induced LV hypertrophy [24, 25].

In the vasculature, the senescent phenotype is characterized by increased oxidative stress [26] and pro-inflammatory gene expression [2]. Generation of ROS within the vascular wall has been proposed to be the major pathophysiological mechanism of vascular aging. The production of mitochondrial ROS increases in senescence endothelial cells and VSMCs, in vitro and in vivo [27]. It has been

suggested that increased production of ROS may contribute to generate the low-grade inflammation detected in aged vascular cells. Indeed, the increased NFkB activity observed during aging can be attenuated by H_2O_2 scavengers [28]. In addition, recent evidence suggest that endothelial cells may acquire a "senescence-associated secretory phenotype" which coordinates the synthesis and release of several proteins involved in the pro-inflammatory and pro-thrombotic pathways, including Interleukin-1α, ICAM-1, PAI-1 [29].

Mitochondrial Turnover and Aging During the life of a cell, damaged mitochondria are continuously removed and replaced with newly formed organelles. This quality-control mechanism is necessary to maintain a functional mitochondrial pool. Only recently we discovered that mitochondria are fluid entities working in networks. For instance, the function of damaged mitochondria can be restored by their fusion with neighboring intact organelles [30]. If severely damaged, mitochondria are removed from the network by fission (break down into pieces of manageable size for engulfment) and eliminated by autophagy (mitophagy). Autophagy is a cytoprotective mechanism involving degradation and recycling of damaged intracellular organelles and proteins [31]. This mechanism is particularly important for the permanently differentiated cells, such as cardiomyocytes, which rely on autophagy to remove damaged cellular components. As cardiomyocytes are heavily dependent on mitochondrial oxidative metabolism for energy supply, the maintenance of a healthy pool of mitochondria is vital for the viability of these cells.

Recently, autophagy has emerged as a crucial regulator of the aging process [32]. The efficiency of autophagy seems to decrease with age [33, 34]. When mitochondrial turnover is unbalanced, the result is an accumulation of dysfunctional mitochondria which produce high levels of ROS and compromise the respiratory capacity of the cell [35].

The best indication that impaired autophagy/mitophagy is related to cardiovascular aging comes from transgenic animal studies. Autophagy impaired, Atg (autophagy-related) 5-deficient mice exhibit left ventricular dilatation, contractile dysfunction and heart failure, compared to control mice [36]. Mice with deficient autophagy/lysosome degradation mechanisms, activate an inflammatory response in cardiomyocytes when exposed to pressure overload [37]. Because cell-autonomous inflammation is a hallmark of cardiovascular aging [38], these data suggest that age-related alteration of mitochondrial autophagy may be causally linked to age-related cardiac inflammation.

Impaired mitochondrial biogenesis and reduced mitochondrial mass have been observed in senescent endothelial cells and VMSCs [39, 40]. A recent study involving older adults demonstrated that autophagy is impaired in aging human arteries and contributes to the endothelial dysfunction; enhancing autophagy reduces oxidative stress and inflammation and increases NO bioavailability, preserving a healthy endothelium [41].

Enough scientific evidence has been collected to indicate that optimization of autophagy in the aging heart may be beneficial against senescence and age-related

cardiovascular diseases. Research is currently ongoing to screen for molecules able to enhance autophagy.

3.2 Telomeres and Cardiovascular Aging

Loss of replicative competence is the hallmark of cellular senescence and has been linked to telomere shortening [42]. Telomeres, repetitive DNA sequences located at the end of chromosomes, act as protective caps, preventing erosion of genetic material and fusion with neighboring chromosomes. Each time a cell divides, telomeres shorten. When telomeres become too short, the chromosomes can no longer be replicated and the cell enters senescence. Telomerase is a reverse transcriptase enzyme able to maintain the length of telomeres by adding DNA sequence repeats at the end of chromosomes. However, telomerase is poorly express in the majority of somatic cells [43].

Is telomere shortening implicated in cardiovascular aging?

Longitudinal cohort studies have related shorter telomeres in peripheral blood leukocytes to increased incidence of atherosclerotic disease [44]. If we compare morphologically normal arteries with diseased arteries, we find a significant difference in telomere length, with diseased vessels displaying shorter telomeres [45]. Intimal cells of iliac arteries have greater rate of telomere loss than internal mammary arteries, a difference that increases with age [46]. This variance in telomere length has been attributed to a greater hemodynamic stress, inducing higher telomere attrition, in iliac compared to mammary arteries. Telomere attrition and subsequent cellular senescence have been related to the propensity of iliac arteries to develop atherosclerotic lesions [46]. However, it is difficult to prove that telomere shortening is the reason for arterial disease; indeed, atherosclerosis per se may increase the proliferative index of vascular cells, signaled by reduced telomere length. Nevertheless, the senescent endothelial phenotype of human coronary arteries may be reversed by telomerase activity [47]. Of interest, in humans, physical exercise correlates with the maintenance of telomerase activity and telomere length, in circulating leukocytes and in vascular cells [48].

The human heart has been traditionally considered a post-mitotic organ. However, we know now that stem/progenitor cells with the ability to generate new cardiomyocytes exist in adult cardiac tissues [49], together with a subpopulation of myocytes that are not terminally differentiated and are still able to enter the cell cycle and undergo division [50]. The presence of cell division in non-diseased myocardium implies a turnover, although limited, of cells during the life span of the organism. An age-associated decline in stem/progenitor cell-dependent regeneration, associated with telomere shortening, may contribute to cardiac aging. Indeed, although mitotic index and telomerase activity increase with age, they are inadequate to compensate for cardiomyocyte loss in the adult heart [51]. Studies on humans have demonstrated that terminally differentiated cardiomyocytes are characterized by dysfunctional telomeres, as well. In post-mitotic cells, telomere-mediated signaling works in ways different than proliferative arrest. Indeed, telomere dysfunction may

result in metabolic changes involving impaired mitochondrial biogenesis and electron transport chain performance, negatively affecting cardiac ATP synthesis and availability [52]. Therefore, age-associated telomerase dysfunction may instigate mitochondrial decay, which, in turn, may lead to decreased mitochondrial efficiency and increased ROS production.

In telomerase-deficient transgenic mice, telomere shortening is coupled with decreased cardiomyocyte proliferation, increased apoptosis, and cardiac remodeling resembling the phenotype of human aging heart [53]. Cardiomyocyte-specific reactivation of telomerase induces cardiac hypertrophy but not fibrosis or impaired function [54].

Taken together, these data suggest that telomere shortening may play a critical role in cardiac aging and may represent a promising target for therapy. In this regard, the demonstration that telomere dysfunctional mice can be rejuvenated by reactivation of endogenous telomerase [55], opens a scenario of possible future interventions on the aging heart.

3.3 Caloric Restriction, Sirtuins and Cardiovascular Aging

Caloric restriction (CR) is defined as a dietary regimen of limited energy intake in the absence of essential nutrients and vitamins deficiency. CR increases the median and maximal lifespan of all animal species tested, from yeast to mammals [56], including non-human primates (rhesus monkeys) [57], linking metabolism to aging.

Whether CR extends life span in humans will be never determined in randomized clinical trials for the obvious ethical implications and the limitation to follow study subjects until the end of their life. However, lower-length trials (from few months to few years) have been designed to determine the effect of CR on surrogate biomarkers of longevity. The randomized controlled trial CALERIE (Comprehensive Assessment of Long term Effects of Reducing Intake of Energy) was launched to test the health benefits of 2 years of intensive calorie restriction in human subjects [58]. However, the interpretation of the study results is controversial and there is still no conclusive indication whether or not reduced energy intake positively modulates longevity in humans.

Although there is no direct proof that CR is able to increase the mean and maximum lifespan of humans, it is widely accepted that reducing energy intake delays the aging of the cardiovascular system, through its pleiotropic effect on heart and vessels [59]. CR protects arteries from oxidative stress and fibrosis [60], prevents intima-medial thickening and inhibits the formation of atherosclerotic plaques [58]. Moreover, CR reverses vascular endothelial dysfunction by increasing the bioavailability of NO [61].

The positive effect of CR on the cardiovascular system is due, at least in part, to its effect on major cardiovascular risk factors: in human subjects exposed to reduced calorie intake total serum cholesterol, LDL cholesterol, total cholesterol/HDL cholesterol ratio, and triglycerides fall significantly; in addition, blood pressure, fasting glucose and C-reactive protein concentrations are extremely low, compared with

age and sex-matched controls [58, 62]. Interestingly, CR has been shown to reduce myocardial collagen and extracellular matrix content [63] and to prevent LV diastolic dysfunction of the aging human heart [64].

Several hypotheses have been proposed to explain the positive effect of CR on cellular senescence, on the molecular level. The most intuitive hypothesis is that it regulates the exposure of the cell to oxidative stress [65]. It is well established that CR delays the age-related deterioration of mitochondrial function, limiting the surge of ROS production by the aged mitochondrion, and preserving the enzymatic activity of the electron transport system [66].

However, the link between limited energy intake and longevity is exquisitely complex [67]. Indeed, the longevity response to CR seems to be regulated by several nutrient-sensing signaling pathways, including mammalian target of rapamycin (mTOR) [68], insulin/IGF-1, and sirtuins (SIRT). All these pathways mediate a variety of cellular metabolic responses and control mitochondrial function. Of those, the most widely studied is mTOR.

TOR is a serine-threonine protein kinase that is inhibited by rapamycin and constitutes an important nutrient sensing pathway for the cell. It has been reported that inhibition of TOR activity induces longevity in yeast [69], C. elegans [70], and D. melanogaster [71]. Inhibition of mTOR with rapamycin dramatically extends the lifespan of mice [72], as well. mTOR integrates signaling from several intracellular nutrients and nutrient-sensitive pathways, including amino acids, insulin, growth factors, energy status, stress, and hypoxia. Downregulation of mTOR induces autophagy and mitophagy, improving the quality of mitochondrial function [73]. Chronic cardiac-specific activation of Akt stimulates mTOR and inhibits autophagic activity of myocardial cells, mimicking age-specific functional changes of the heart, including hypertrophy, fibrosis, decrease contractility and compromised diastolic function [74]. As Akt activity is enhanced by age, the Akt/mTOR pathway may play an important role in human heart aging.

Many studies report that CR reduces circulating levels of IGF-1 [75]. IGF-1 mediates several growth hormone (GH) biological responses and affects multiple signaling cascades, promoting proliferation, inhibition of apoptosis and stimulation of growth in many tissues and organs. The decreased level and activity of IGF-1/insulin observed under CR, have been causally linked to the lifespan increase of calorie restricted animals [76]. However, the effect of IGF-1/insulin signaling pathway on longevity is complex and somehow controversial [67]. Ames dwarf mutant mice which lack GH and have reduced IGF-1, live longer than control mice. These animals display potentiated anti-oxidant defenses. On the contrary, animals that overexpress GH have shorter lifespan than wild type animals, and display defected anti-oxidant capacity [77]. Mitochondria from Ames dwarf mice produce less ROS whereas GH transgenic mice exhibit greater protein oxidative damage, compared to wild types [78]. These data suggest that the effect of IGF-1 signaling on longevity may be mediated, at least in part, by its effect on oxidative stress. An alternative mechanism by which IGF-1 signaling may affect lifespan is the stimulation of autophagy [79]. However, it is important to emphasize that whereas CR reduces circulating levels of IGF-1 in most animal models, this is not true in men [80].

The effect of IGF-1 on life expectancy in humans is exquisitely complex. Low IGF-1 predicts extended life expectancy in exceptionally long-lived females [81]. However, IGF-1 deficiency is associated with premature atherosclerosis and elevated cardiovascular disease mortality [82]. IGF-1 protects cardiomyocytes from apoptosis, promotes cardiac stem cell survival, and improves myocardial contractile function [83, 84]. In the vasculature, IGF-1 counteracts the age-related carotid artery intima-media thickness [85]. On the other hand, higher IFG-1 levels are positively correlated with cancer mortality [86].

To further complicate things, recent data suggest that IGF-1 axis bioactivity, rather than IGF-1 serum concentration per se, is more likely to predict the effect of this hormone on cardiovascular health and mortality [87]. Therefore, the role of IGF-1 on life expectancy in humans remains elusive.

The data supporting the involvement of sirtuins in CR-mediated effect on survival is quite strong. CR stimulates the activity of several sirtuins and overexpression of sirtuins increases longevity [88]. Knocking down any one sirtuin gene abolishes the CR-mediated phenotype, including the effect on lifespan.

SIRTs are a family of NAD+−dependent protein deacetylases with pleiotropic intracellular effects, ranging from control of metabolic homeostasis, to limitation of cellular damage, to inhibition of inflammation. The need of NAD+ for enzymatic activity links sirtuins to the energetic status of the cell, with their activity increasing when energy availability is low, i.e. under caloric restriction.

Seven mammalian orthologues (Sirt 1–7) with different subcellular localization have been described so far [89].

The most widely studied is Sirt1, a master regulator of mitochondrial integrity and metabolic homeostasis, localized in the nucleus and cytoplasm of the cell. In the heart, overexpression of Sirt1 attenuates age-dependent cardiac hypertrophy, apoptosis and fibrosis, and expression of senescence markers, in a dose-dependent manner. Moreover, Sirt1 protects the heart from oxidative stress by increasing the expression of antioxidants and decreasing the production of pro-apoptotic molecules [90, 91].

Overexpression of Sirt1 in endothelial cells prevents the appearance of the ROS-mediated senescence phenotype [92]. Sirt1 potentiates eNOS activity, through deacetylation of the enzyme, increasing endothelial nitric oxide availability [93]. Moreover, Sirt1 attenuates vascular NFkB induction, protecting endothelial cells and macrophages from pro-atherosclerotic modifications [94]. Pharmacological activation of Sirt1 reverts the senescent endothelial cell phenotype [95], whereas downregulation of Sirt1 accelerates endothelial senescence [96, 97]. Finally, Sirt1 promotes angiogenesis, through the inhibition of notch signaling pathway in endothelial cells [98].

Sirt3 may also play a role in cardiovascular aging. Sirt3 regulates mitochondrial lysine acetylation, enhancing the antioxidant defense of the cell and preserving mitochondrial function [99]. Overexpression of Sirt3 decreases cellular levels of ROS through deacetylation and activation of the ROS detoxifying enzyme, superoxide dismutase. Sirt3 was reported to prevent stress-induced mitochondrial apoptosis of mammalian cardiomyocytes, and to protect endothelial cells from oxidative

damage [100, 101]. Sirt3 deficient mice show cardiac hypertrophy and interstitial fibrosis, whereas Sirt3-overexpressing mice are protected from age-related cardiac modifications [102].

Sirt6 is a nuclear chromatin-associated deacetylase with a critical role in telomere stabilization [103]. The heart has a high expression of Sirt6, suggesting a possible involvement of this protein in myocardial physiology [104]. Cardiomyocytes overexpressing Sirt6 are protected from hypoxic injury, an effect that has been attributed, at least in part, to Sirt6-mediated inactivation of NFkB [105].

The ability of Sirt6 to interfere with NFkB intracellular signaling is of particular importance in vascular biology, where inflammation is the key regulator of atherogenesis. Sirt6 deficient endothelial cells display an increased expression of pro-inflammatory cytokines, such as interleukin 1β and NFkB, in vitro [106].

Sirt7 is the only sirtuin mainly localized in the nucleoli. Very little is known about Sirt7 biological activities and intracellular targets. However, there is evidence indicating that Sirt7 plays a major protective role in the adult myocardium. Sirt7-deficient mice develop progressive heart hypertrophy, accompanied by cardiomyocytes inflammation and decreased stress resistance, and die of inflammatory cardiomyopathy related to a multi-systemic mitochondrial dysfunction [107].

A fair amount of research is devoted to identify compounds mimicking CR positive effects, without the need to reduce calorie intake. Among them, the phytochemicals resveratrol and quercetin, and the drug rapamycin, are the most widely studied [108, 109]. Resveratrol has been shown to inhibits induction of apoptosis by oxidative stress in cultured rat arteries [110] and inflammatory gene expression in human endothelium [111], providing the first concrete pharmacological alternative to CR to preserve a healthier cardiovascular system.

3.4 Epigenetic Regulation and Cardiovascular Aging

Epigenetic changes are considered a major hallmark of aging [112]. The majority of age-related modifications observed in elderly organisms can be explained by changes in tissue-specific epigenetic background. It is widely accepted that the epigenetic trait contributes to the cardiovascular phenotype of an individual and to the pathogenesis of cardiovascular diseases.

The “epigenetic trait” may be defined as a “stably heritable phenotype resulting from changes in the chromosome without alterations in the DNA sequence” [113]. These traits are the result of modification in gene expression, regulated by changes in chromatin structure.

Epigenetic changes may be influenced by exogenous factors, explaining how the environment can shape the genome in defining the phenotype of an individual (gene-environment interaction) [114].

Three major types of epigenetic modifications play a role in shaping DNA accessibility by transcription factors: DNA methylation, histone post-translational modification and noncoding RNAs. However, many other mechanisms of chromatin rearrangement may exist that we still don’t know or completely understand that

interact with the major epigenetic modifications in shaping the genome. These epigenetic mechanisms confer to the cell an extraordinary ability to react to physiologic and pathologic stimuli.

DNA Methylation and Demethylation DNA methylation is a covalent modification consisting in the addition of a methyl group to the carbon 5 of a cytosine residue. In adult somatic cells, DNA methylation occurs typically in the context of a CpG dinucleotide. Methylation of DNA changes its biophysical characteristics, inhibiting the recognition of DNA by some transcription factors or allowing the binding of transcriptional repressors, impacting the overall gene transcription [115]. Together with DNA methylation, demethylation occurs but this mechanism is less understood. Demethylation plays a crucial role in modulating transcriptional responses to hormones and other stimuli, and global loss of methylation has been associated with several pathological processes, including cardiovascular diseases [116].

A study on 421 individuals (age 14–94) demonstrated that the human "methylome" is deeply modified by age [117]. Centenarians confirmed this finding revealing that their methylome exhibits dramatic changes compared to that of young subjects [118]. This gradual change in the genome methylation profile over time is defined as "DNA methylation drift".

Indeed, several evidence indicates that the overall DNA methylation of mammalian genome decreases with age. Interestingly, in a recent study on frailty, the global DNA methylation level observed in old frail individuals was lower compared to prefrail and nonfrail subjects, suggesting that relaxation of the epigenetic control may be associated with the functional decline of old age [119]. The genome hypomethylation here described could exert pro-ageing effects by promoting genomic instability [120].

However, the age-associated methylome modification is exquisitely complex. In parallel to global hypomethylation, aging seems associated with a trend towards an increase of DNA methylation for specific genomic *loci*.

Although the epigenomic landscape varies widely across different tissue types, recent studies have identified an age-dependent CpG signature that can predict age across a wide range of tissues and cell types [121]. This CpG signature, referred to as DNAm age, is based on 353 CpGs which, as a whole, identify an "epigenetic clock". Studies are ongoing to determine the correlation between DNAm age, aging and cardiovascular disease.

Histone Modifications Histones undergo a variety of post-translational modifications, including acetylation, methylation, phosphorylation, and ubiquitination, that change the chromatin structure and the gene expression profile of the cell. Different types of histone post-translational modifications induce different transcriptional profiles.

Noncoding RNA and RNA Epigenetics Noncoding RNAs can silence genes by recruitment of remodeling complexes that promote histone methylation. They can also recruit RNA-binding proteins, impairing histone deacetylation or inhibiting

transcription factor binding to promoter regions. Although less understood, methylation and demethylation of RNAs (tRNA, mRNA, and rRNA) also occur inside the cell and represent another type of epigenetics [114].

MicroRNA (miRs) have been described also that play a crucial role in modulating cellular senescence phenotypes. MiRs are small, non-coding RNA molecules with a powerful gene regulatory role [122]. A single miR can target hundreds of messenger RNAs at the same time; groups of miRs can induce regulation of definite biological processes by acting in a coordinated manner [123]. It has been proposed that a specific modulation of miRs expression with age may positively impact longevity [124]. A number of miRs have been described to play a role in modulating cellular senescence and age-related inflammation [122].

This is an area of high interest for gerontological research, and we can anticipate that more and more miRs involved in the modulation of senescence will be identified in the near future.

Epigenetic regulations appear to be essential for cardiovascular development and differentiation, as well as for the appearance of cardiovascular diseases. Epigenetic mechanisms participate in the pathogenesis of atherosclerosis. DNA methylation has been related to atheroma progression: specific DNA methylation profiles have been detected in vascular lesions that mapped to genes regulated by transcription factors involved in inflammatory and immune responses [125]. In senescent coronary endothelial cells, CD44 promoter becomes unmethylated and the protein is expressed on the cell surface making endothelial cells very adhesive to monocytes. This modification enables monocyte infiltration in the vessel wall, initiating atherosclerotic lesions [126].

Several evidence have also suggested that histone modification is involved in myocardial diseases. Chromatin remodeling plays a crucial role in adult cardiomyopathy. Modulation of histone demethylase, JMJD2, in the heart modifies H3 methylation status and alters the hypertrophic response after pressure overload [127]. Deficiency of the histone methylation enzyme Dot1L in mouse heart results in adult lethality from dilated cardiomyopathy and heart failure [128].

It has been proposed that nutritional and environmental changes during critical periods of life, such as in utero [129], may alter the epigenetic trait and the expression of genes that contribute to disease risk, later in life. This concept of a "fetal programming of cardiovascular disease", has been reinforced by the demonstration that healthy children conceived by assisted reproductive technologies, which alter the epigenetic scenario of the embryo [130], suffer from systemic endothelial dysfunction [131].

The plasticity of epigenetic modifications has encouraged to search for interventions that, acting on epigenetic regulators, could delay or revert the aging phenotype of the cardiovascular system [132]. Nutrition is one of the most promising of such interventions. Indeed, specific types of diet have been proved to alter single epigenetic traits by modifying the intracellular metabolic state or the cell. Indeed, CR could exert anti-ageing effects by reversing age-related epigenetic alterations. However, epigenetic data on the effects of CR in humans are very limited.

The epigenetics of cardiovascular aging remain largely unexplored and constitute a promising area of investigation.

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Frailty and Heart Disease

4

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4.1 Frailty

4.1.1 Definition, Models, and Assessment

Frailty, from the Latin "fragilis," meaning "easily broken," is a biological syndrome that reflects a state of decreased physiological reserve and vulnerability to stressors [1, 2]. Stressors are generally classified as acute or chronic illness, minor or major (e.g., myocardial infarction), or iatrogenic events (e.g., new drug therapies, minor surgery). When exposed to such stressors, frail patients global health state changes dramatically, and they become at risk for adverse outcomes such as procedural complications, adverse drug reactions, prolonged recovery, mobility decline, disability onset, and mortality [3]. Many models have arisen to define and operationalize frailty in a specific and standardized manner. Reliable frailty models should be assessed as predictors of both natural history and response to therapeutic interventions and based on biological principles of causality [4]. In fact, different models of frailty, underpinned by different theoretical constructs, capture basically different groups of older adults [5].

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_4

The two principal emerging models of frailty are the phenotype model [6] and the cumulative deficit model underpinning the Canadian Study of Health and Aging (CSHA) Frailty Index [7]:

- Fried and colleagues postulated frailty to be a "biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems" and defined a physical frailty phenotype in terms of five components present in a hypothesized cycle of frailty. They developed this Biologic Syndrome model of frailty in the Cardiovascular Health Study (CHS) [6], the lowest quintile values were used to define the absence/presence of the components. Frailty phenotype is defined as meeting three or more of the following five criteria, pre-frailty as one or two of these characteristics, and no frailty has having none:
  - Unintentional weight loss (≥5 % of body weight in the last year)
  - Self-reported exhaustion (positive response to questions regarding effort required for activity)
  - Weakness (decreased grip strength) according to gender and body mass index
  - Slow gait speed (>6 s for height >173 cm and >7 s for height <173 to walk 4.57 m)
  - Low energy expenditure (Kcal spent per week: males expending <383 Kcal and females <270 Kcal)
- Rockwood and colleagues developed a frailty index (FI) as a measure of deficit accumulation, that is, a measure of the cumulative burden of a number of symptoms, diseases, conditions, and disability (originally 70 variables that range from medical conditions and symptoms to functional decline). The higher the score in this index, the frailer the individual. This index is clinically attractive because it allows frailty to be considered gradable rather than present/absent. Subsequent studies showed that variables can be reduced to 30 without loss of predictive validity [7].

As a matter of fact, with the population aging, recognition of frailty in older adults becomes increasingly important [4]. Recently, a consortium of a number of international societies has suggested that all persons over 70 years of age should be screened for frailty using one from a number of simple validated questionnaires available to carry out the screening [8]. At present, frailty assessment is often embedded in the comprehensive geriatric assessment (CGA). CGA is a multidimensional, interdisciplinary diagnostic process to determine the medical, psychological, and functional capabilities of an older person in order to develop a coordinated and integrated plan for treatment and long-term follow-up. While integrating standard medical diagnostic evaluation, CGA emphasizes also problem solving, functional status, and prognosis with the aim of restoring independence and alleviating distress. It involves an interdisciplinary care team that coordinates evaluation of an older patient and develops a plan for integrated care. CGA is currently the perfect tool to detect frailty and it should be more widely employed in different settings. There is evidence that CGA improves clinical outcomes in frail older patients admitted to acute hospitals [9].

4.1.2 Epidemiology

Depending on different definitions of frailty, the inclusion/exclusion criteria between the different studies, the prevalence of frailty ranges from 4 to 59 %. When the reported rates are restricted to the studies that used the phenotype model, the weighted average frailty prevalence rate is 9.9 %, and the prevalence of pre-frailty is 44.2 % [10].

Differences in frailty prevalence have been reported according to:

- Age: frailty steadily increases with increasing age.
- Gender: it is more prevalent in women than men.
- Education: the prevalence of frailty is increased in individuals with lower education.
- Smoke: smokers are more likely to be frail.

Chronic comorbidities and disability are often associated with frailty, but there is evidence that frailty can exist independently of these factors. In the CHS, frailty and comorbidity (defined as two or more co-occurring chronic diseases) were present in 46.2 % of the population, frailty and disability (defined as the presence of restriction in at least one activity of daily living) were present in 5.7 %, and the combination of frailty, disability, and comorbidity was present in 21.5 % of the study group, but frailty was present without comorbidity or disability in 26.6 % of the study group [11].

4.1.3 Pathophysiology

Dysregulation in multiple physiologic systems, especially immune, endocrine, and neurohormonal systems, is a key feature of frailty. There is a gradual decline in physiological reserve with aging, but, in frailty, this decline is accelerated, and homeostatic mechanisms start failing. Together, these dysregulated systems create an anabolic–catabolic imbalance, leading to increased muscle catabolism, weight loss, and subclinical organ dysfunction [12].

Skeletal muscle is currently one of the organ systems best studied in the development of frailty, and sarcopenia is a key component of frailty. Wasting and weight loss are manifested by loss of muscle fibers, altering muscle composition, which in turn leads to the phenotypic weakness, slowness, and functional deterioration inherent to frailty syndrome [12]. Hormonal changes, including lower levels of insulin-like growth factor-1 (IGF-1) and dehydroepiandrosterone sulfate (DHEA-S), and higher levels of cortisol as well as low vitamin D, can contribute to decrease skeletal muscle mass. Sarcopenic and frail patients have elevated levels of inflammatory markers such as interleukin 6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor alpha (TNFα) and increased markers of oxidative stress [13]. Inflammation is associated with anorexia and catabolism of the skeletal muscle [14].

The other organ systems often evaluated in the pathophysiology study of frailty are the neurological, endocrine, and immune systems which in turn are correlated with the skeletal muscle.

A study involving 1,002 female participants investigated cumulative physiological dysfunction in six different systems (hematological, inflammatory, hormonal, adiposity, neuromuscular, and micronutrients) using 12 measures and reported a nonlinear relationship between the number of abnormal systems and frailty, independently of age and comorbidity [15]. The presence of abnormal results in three or more systems was a significant predictor of frailty. Significantly, the number of abnormal systems was more predictive than abnormalities in any particular system, providing evidence that when physiological decline reaches an aggregate critical mass, frailty becomes evident.

4.1.4 Assessment of Frailty

Entreating clinicians away from judgments based on chronological age toward the notion of frailty is very important because there is a large between-group difference for people who are frail compared to not frail. Moreover, due to the dynamicity of the process, frailty needs to be measured at different time points in order to identify different stages of frailty in the same individual during time. Geriatricians have been struggling to identify a way to operationalize the concept of frailty into measurable variables. Standardized measures of frailty have been developed, but they are better suited for research settings—not the clinic. Researchers and clinicians, therefore, require simple, valid, accurate, and reliable tools to detect frailty. Walking speed has been investigated as potential single assessments to detect frailty; it could be administered in primary care as it does not need special equipment, and it takes few minutes to be measured, and it captures much of the clinical construct of frailty [16]. A pooled analysis of nine prospective studies ($n = 34{,}485$) [17] showed that slow gait speed successfully characterized the subgroup of older people who had adverse outcomes and had similar accuracy to complex multivariate models that included itemizing chronic conditions. Survival increased across the full range of gait speeds. In the Cardiovascular Health Study, participants ≥65 years with incident heart failure (HF) were evaluated. Impairment in gait speed measured within 1 year before the diagnosis of incident HF was independently associated with mortality, adjusting for sociodemographic and clinical characteristics [18]. Beyond mortality, gait speed has been recently studied as a useful instrument for identifying which elderly adults are most at risk for the adverse effects of hypertension. In the National Health and Nutrition Examination Survey, the association between blood pressure (BP) and mortality varied by walking speed. Among faster walkers, those with elevated systolic BP had a greater adjusted risk of mortality compared with those without. Among slower walkers, neither elevated systolic nor diastolic BP was associated with mortality [19].

4.1.5 Interventions

Frailty is dynamic and its earlier stages are potentially reversible [8]. However, transition to a level of greater frailty is more common than reversion to a pre-frail status [4]. The 2013 consensus statement on frailty focused on some interventions which have shown some efficacy in the treatment of frailty. The most consistent benefit has been demonstrated with physical exercise. In a randomized trial, exercise-based rehabilitation decreased hospitalization and nursing home placement following hip fractures in frail patients [20]. Nutritional supplements or a dietary plan that includes 25–30 g of high-quality protein per meal have been proposed to slow or prevent sarcopenic muscle loss [21]. Nutritional supplements can work synergistically with the benefits of resistance exercises in older adults. Vitamin D supplements have been reported to improve muscle function, reduce falls, and fractures [22], but meta-analyses suggest calcium supplements with or without vitamin D may increase the risk of myocardial infarction [23]. Finally, polypharmacy or the use of multiple or duplicative or inappropriate medications increases the risk of drug–drug and drug–disease interactions and contributes to adverse health outcomes and should be limited especially in frail elderly which are at high risk of not recovering prestressor health status.

4.2 Frailty and Heart Failure

4.2.1 Epidemiology

Due to the aging and increasing complexity of patients affected by cardiovascular diseases (CVDs), the identification of frailty has become a high-priority topic in cardiovascular medicine [24]. The American Heart Association and the Society of Geriatric Cardiology have called for increased understanding of the role of frailty in CVD [25]. The prevalence of frailty in older adults with CVD depends on the population studied and the frailty assessment tool used but ranges from 10 to 60 % and is about 3 times more prevalent compared to older persons in the community [26]. Among all CVD, the phenotype of heart failure (HF) is one of those most rapidly increasing. In fact, due to improved management of chronic diseases such as hypertension and coronary artery disease, as well as interventions that improve survival, the HF population is aging. HF incidence doubles with each decade, starting at 5 % between ages 65 and 74 years and rises to 20 % in those over 80 years of age [27]. Prevalence of HF is high in older persons with frailty and vice versa. In the Cardiovascular Health Study (CHS), the prevalence of HF increases from 1.8 % in the non-frail, 4.6 % in the intermediate group, to 14.0 % in the frail group [28]. Similarly, participants of the women health initiative (WHI) who have HF were 6–7 folds more likely to be frail [29]. In addition to HF precipitating frailty, the reverse is also true. Frail community-dwelling elders are more likely to develop de novo HF then their non-frail counterparts [30]. The Health ABC Study followed 2,825 older

patients free of HF at baseline over a period of 11 years and found that frailty conferred a 30 % higher risk of developing new HF [30]. Excluding HF events in the first year did not alter the results, showing that frailty was not merely capturing undiagnosed/imminent cardiac dysfunction. Notably, the risk for HF-related frailty rises dramatically with age, as a 30 % prevalence has been identified in patients younger than age 70 versus a 52 % prevalence in those 70 years or older [31].

4.2.2 Pathophysiology

Whether there is an etiological distinction between the primary frailty of aging and frailty secondary to chronic disease such as HF is still unknown, but there is the need to address this distinction. Similar to that seen in primary frailty, the wasting process of HF is likely related to an anabolic–catabolic imbalance in which initially adaptive neurohormonal mechanisms and autonomic nervous system activation yield detrimental systemic effects over time. Inflammatory, metabolic, and autonomic abnormalities that are associated with frailty are frequently seen in patients with HF. Consistent evidence exists for tumor necrosis factor alpha (TNFα), interleukin-1 (IL-1), and interleukin 6 (IL-6) upregulation [32], along with abnormalities in the growth-hormone/insulin-like growth factor (GH/IGF-1) axis and cortisol regulation. Furthermore, the clustering of muscle loss, weakness, and exhaustion has been a long recognized in HF. In addition to sarcopenia and frailty, cardiac cachexia, defined as loss of 5 % of one's body weight over 6 months [33], is a third term referring to the wasting process of this population. Depending on the definition used, studies in HF find about a 20 % prevalence of sarcopenia, a 20–50 % prevalence of frailty, and 15 % prevalence of cardiac cachexia [34].

4.2.3 Frailty and Comorbidities in HF

Frailty and comorbidity are clinical manifestations of two distinct, though possibly interconnected, aging-related processes, namely, diminished functional reserve and accumulation of pathological processes. Nevertheless, frailty and comorbidity often overlap in the elderly and lead to impairment in quality of life and functional status. Morley described how disease processes (HF as well as its associated comorbidities) can accelerate functional muscle loss leading to sarcopenia, the hallmark of physical frailty [35]. The burden of comorbidities in elderly patients with HF is much higher than in those without HF [36]. Braunstein et al. studied the burden of noncardiac comorbidities in 22,630 HF patients, 65 years and older, identified in a 5 % random sample of all US Medicare beneficiaries. He found that 40 % of these patients had ≥5 comorbidities, 70 % had ≥3 comorbidities, and only 4 % had no comorbidities at all [37]. Once frailty is developed, both HF and its associated comorbidities can give rise to acute stressors which can lead to rapid functional decline resulting in disability, hospitalization, institutionalization, and eventually

death. Finally, frailty and comorbidities are two main reasons of persistent exclusion of HF patients in clinical trials [38, 39]. Frail patients are more likely to be excluded from trials based on their limited mobility and access to research facilities, their cognitive impairment that limits the ability to understand and sign informed consents, and their presumed intolerance of the intervention being studied [40]. This underrepresentation of elderly patients with HF in RCTs, especially those with frailty and multiple comorbidities, results in a paucity of evidence in this patient population and makes many aspects of their care still empirical [39].

4.2.4 Outcomes and Interventions

Patients with chronic heart failure who were frail had a higher risk of mortality at 1 year (17 % vs. 5 %), heart failure hospitalizations (21 % vs. 13 %), and impaired quality of life [31]. Chaudhry et al. [41] showed that slow gait speed was the most powerful predictor of hospitalizations, conferring a 30 % increase; weak grip strength was also predictive, conferring a 16 % increase. In a long-term study by Cacciatore et al. [42], patients with chronic heart failure who were frail had a substantially lower probability of surviving >10 years (6 % vs. 31 %). Another study showed significantly higher rate of 1-year mortality (16.9 % vs. 4.8 %; $P<0.001$) and higher rate of hospitalization (20.5 % vs. 13.3 %; $P=0.01$) in elderly patients with HF who have frailty than in those who do not [43].

Therefore, given two heart failure patients with similar chronological age and comorbidities, the presence of objectively measured frailty alerts the clinician that 1 of the 2 patients has a substantially higher risk of mortality and major morbidity.

However, the importance of screening for frailty in heart disease is not only because of its prognostic value but also because a variety of therapeutic interventions is available for the components of physical frailty, which should be implemented in the framework of a comprehensive geriatric assessment [44]. In essence, frail older patients with HF should necessarily undergo comprehensive geriatric assessment followed by a personalized health plan.

Furthermore, the frail patient faces a higher risk from invasive procedures but also a potential benefit from interventions such as cardiac rehabilitation to counteract the physical weakness characteristic of frailty.

A key therapeutic intervention for frailty is exercise training. Exercise improves not only cardiac aerobic capacity and reverses the sarcopenic aspects of frailty and heart disease [45, 46] but also the energetic reflex in the muscle resulting in a decrease in fatigue [47]. Enrolment in cardiac rehabilitation improves outcomes of patients with CVD, but this intervention remains underutilized [48].

At present, evidence that interventions designed to improve frailty result in better outcomes in elderly patients with CVD is still limited and controversial. Large randomized clinical trials are needed to evaluate the optimal management of these patients and if interventions should target different groups of cardiovascular patients according to frailty [49].

4.3 Frailty and Coronary Artery Disease

4.3.1 Epidemiology

Coronary artery disease (CAD) is common in older adults, representing the first cause of death also in this segment of the population. Older subjects account for 80 % of deaths for CAD. The most recent data estimated that almost one in five men and one in ten women in the age group 60–79 years have CAD, while the percentage rises to over 30 % in men and 19 % in women older than 80 years [50, 51]. The improvement of available treatments and their implementation in health care caused a progressive decline in mortality due to this condition, also in older patients, with a relevant contribution to the increase of life expectancy that occurred during the last part of the twentieth century [52]. CAD is also a leading cause of morbidity, disability, and health-care utilization in older subjects.

Frailty is common in older patients with CAD. The prevalence of frailty is reported to be up to 20 % of patients aged ≥65 years undergoing percutaneous coronary intervention (PCI) [53] and 27 % in patients aged ≥70 years with significant coronary artery disease at cardiac catheterization [54]. As in other cardiovascular conditions, the presence of frailty implies a worse prognosis, in terms of morbidity, disability, and mortality [53–56]. In 628 patients ≥65 years who underwent PCI at the Mayo Clinic, 3-year mortality was 28 % for frail patients defined according to the Fried criteria compared with 6 % for non-frail patients. Furthermore, the addition of frailty, comorbidity, and QOL significantly improves the prognostic ability of the Mayo Clinic risk score, a model based on traditionally assessed cardiovascular risk factors, for long-term mortality [53]. In other studies frailty was a better predictor of adverse outcome, particularly mortality, than other geriatric conditions, such as disability, cognitive impairment, or comorbidity in older patients with acute coronary syndromes [56]. In 4671 patients aged ≥65 years with an acute coronary syndrome managed medically who participated in the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial, 25 % were pre-frail (one to two items) and 5 % frail (≥3 items) according to a questionnaire based on the Fried frailty score. Frail participants were more likely to reach the composite primary endpoint (cardiovascular death, myocardial infarction, or stroke) over a period of 30 months even after adjustment for baseline variables and the Global Registry of Acute Coronary Events (GRACE) score [57].

There is some evidence of a bidirectional relationship between CAD and frailty. In the Health ABC study, older adults with frailty had increased risk to develop CAD events during the follow-up [58]. Furthermore, slow gait speed as well as impaired mobility predicted cardiovascular mortality and CAD-related mortality [59–61]. On the other hand, older women who suffered from CAD had a more than twofold higher probability to develop incident frailty during a 3-year follow-up in the Women Health Initiative study [29].

4.3.2 Frailty and the Management of Coronary Artery Disease

Although older patients usually have a higher degree of severity of CAD as well as more coexisting diseases and therefore a worse prognosis, medical treatment as well as invasive procedures, such as revascularization, has been associated with clinical benefits also in this population [49, 62–66]. However, older patients have also a higher probability of having multimorbidity and occurrence of complications [67, 68], and therefore they should be properly evaluated in order to identify those where the risk to benefit ratio might not be favorable. Unfortunately, chronological age alone is not a good criterion to predict the risk of adverse events. Frailty is a more suitable construct to capture the degree of vulnerability of the individual since it is closer to the biological age [49]. Nevertheless, while the prognostic importance to measure frailty in older subjects with CAD is well established, the implication that the diagnosis of frailty should have in the management of CAD in the individual patient is currently unclear [24]. A major determinant of current uncertainty is the fact that older patients with CAD have been usually excluded by clinical trials, particularly when very old, frail, and clinically complex due to the coexistence of multimorbidity and polypharmacy [69–71]. Gurwitz was the first to report that while an increasing proportion of patients with acute myocardial infarction were older subjects, the patients included in randomized trials were much younger and more often males than females [70]. A decade later, Lee and colleagues performed a reevaluation of the topic and confirmed these findings [71]. Moreover, older patients who are included in trials are highly selected and hence not representative of the population treated in clinical practice [25].

On this premise it is not surprising that older subjects in general, and particularly frail ones, with ACS are frequently undertreated in clinical practice [68, 72]. Several authors showed that effective drugs, such as ace inhibitors and beta-blockers, are less commonly prescribed to frail older patients, who are also less likely to be admitted to coronary care units and to undergo cardiac revascularization or coronary artery bypass surgery [54, 55]. Moreover, older patients are less likely to receive cardiologist specialist care [73].

Recent observational data suggest that optimal medical therapy in older men with ischemic heart disease is associated with better survival and lower probability of institutionalization independent of the presence of frailty; therefore frailty seems not to prevent the possibility to obtain the benefits of medical treatment of CAD [74]. On the other hand, it is still controversial how to choose invasive procedures, i.e., PCI versus CABG, for CAD in the presence of frailty. In this respect very interesting findings have been reported in the Acute Myocardial Infarction in Florence 2 registry study, including all acute coronary syndromes hospitalized in 1 year in the area of Florence (Italy), patients older than 75 years were selected and classified according to the Silver Code (SC), a validated tool to predict mortality based upon administrative data. In this sample for each point increase in SC score, the odds for use of PCI decreased by 11 %, whereas the hazard of 1-year mortality increased by 10 %, adjusting for predictors. On the other hand, PCI reduced 1-year mortality

progressively more with increasing SC, showing that the highest risk patients were those who could benefit more from the application of invasive procedures [75].

Knowing that the patient is frail should lead to an individualized approach, in order to identify the more appropriate therapeutic strategy in each individual patient. Moreover, the frail older patient with CAD might be referred to a geriatric consultation to perform a comprehensive geriatric assessment that can allow an adequate evaluation and treatment of his or her multiple complex conditions [76].

4.4 Frailty and Atrial Fibrillation

4.4.1 Epidemiology

Atrial fibrillation (AF) is an arrhythmia characterized by disorganized atrial activation, with consequent deterioration of the mechanical function of the atrium.

AF is the most common arrhythmia in older subjects: the prevalence of this condition increases with the age and ranges from 5 to 6 % in people older than 65 years reaching up to 20 % in patients aged ≥80 years [77–79]. Almost two thirds of patents are older than 75 years [77]. The prevalence of this condition is increasing in recent decades [80]. The risk of thromboembolic complications (stroke and systemic embolism) is high in AF, progressively increasing with advancing age: AF is associated with a four- to fivefold increased risk of embolic stroke with an estimated increased stroke risk of 1.45-fold per decade [81–83]. Moreover, ischemic strokes due to AF tend to be more severe, and patients suffering them are more likely to become chronically disabled, bedridden, and requiring constant nursing care [84, 85]. Recent studies found that atrial fibrillation is an independent risk factor for cognitive decline, dementia, and disability in older subjects, even in the absence of overt stroke [86, 87]. Finally, AF in older subjects increases the occurrence of hospitalization, adverse drug events, and mortality [88–90].

The prevalence of frailty is high in older patients with AF. Although there is preliminary evidence that frailty is more prevalence in older subjects suffering from atrial fibrillation [91], further studies are needed to confirm this association. Other authors suggested that AF may be a risk factor for increased vulnerability, i.e., frailty, but did not use any standardized criteria for frailty assessment [92].

Whether the presence of atrial fibrillation increases the risk to become frail or the other way around, it is currently unknown. More research is needed in this area to better define the relationship between AF and frailty.

4.4.2 Impact of Frailty on the Management of AF

The treatment of AF has several aims: first of all stroke prevention with antithrombotic therapy, then symptom reduction, and also management of associated medical conditions, such as cardiovascular and kidney disease [93, 94]. In particular, antithrombotic therapy in patients with AF has been shown to reduce the

frequency, severity, and mortality from stroke [94]. The benefit is higher in older patients, although they do not only have a higher risk of thromboembolic events but also of bleeding [95, 96]. Vitamin K antagonists (VKAs) are more effective than aspirin. Recently novel oral anticoagulants (NOACs) have demonstrated similar or even higher efficacy with lower bleeding risk compared to VKAs and are therefore recommended as first choice, unless renal function is severely compromised [97]. Nevertheless, despite the benefits of anticoagulants in preventing stroke, several studies have shown that anticoagulants are underused in older patients with AF [98–100].

The relationship of frailty with the anticoagulant prescription is conflicting: some studies showed that frailty and geriatric syndromes are independently associated with nonprescription of anticoagulants [101], while others did not confirm this finding [102–104]. Frailty by itself should not contraindicate the use of anticoagulants, but particular caution should be taken in this population, when the decision to prescribe anticoagulants should always been taken on an individual basis, after careful assessment of the balance between benefits (in terms of reduction of embolic risk) and risks (in terms of bleeding risk) [95]. This is particularly true for NOACs, since frail older patients are underrepresented in clinical trials, and real practice data are needed to understand their effectiveness and safety in this specific population.

Currently the ACC/AHA/HRS AF guidelines do not provide specific recommendations on usage of anticoagulant therapy in frail elderly patients [102]. In the recently released recommendations on the use of antithrombotic therapy in the elderly by the ESC, frailty is not considered an independent factor in the decision to prescribe antithrombotic drugs [97].

Concerning the symptoms of AF, rate control strategy is recommended as the first choice in older patients, as compared with rhythm control [94].

The management of older AF patients with frailty requires a multidisciplinary approach based on sound comprehensive geriatric assessment, due to the multimorbidity, in particular the frequent presence of kidney disease and dementia, the high fall risk, and the polypharmacy that are common in these patients [94].

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Evidence-Based Versus Evidence-Biased Medicine in Geriatric Cardiology: From Trials to Real World

5

Matteo Monami and Mauro Di Bari

Elderly people are now the most rapidly growing part of the patient population worldwide, thanks to more focus on primary prevention of diseases and improvements in healthcare for the younger ill patient. Aging is often accompanied by chronic (multiple) diseases, comorbidity, disability, frailty, and social isolation. As a consequence, elderly persons are more likely to receive a high number of drugs; this phenomenon is called "polypharmacy" and is a problem affecting advanced decades and may lead to an increased risk of inappropriate drug use, underuse of effective treatments, medication errors, poor adherence, drug–drug and drug–disease interactions, and, most importantly, adverse drug reactions [1]. Moreover, the lack of well-designed clinical studies recruiting elderly limits the availability of evidence-based information on the effect of drugs on clinically relevant outcomes such as functional and cognitive decline, quality of life, adverse events, and mortality. This is a real problem for the majority of chronic conditions, particularly for cardiac diseases, which are predominant in elderly persons.

In order to limit this problem, in 1989 the US Food and Drug Administration (FDA) published, referring to pharmaceutical industry, guidelines for studying the most used drugs in elderly [2]. These recommendations have been revised and strengthened in 1994, in a document compiled by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH; http://www.ich.org), an organization that gathers drugs regulatory agencies of the United States (FDA), Europe (European Medicines Agency,

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_5

EMA), and Japan, underlining the importance of including in randomized clinical trials (RCT) patients representative of the population in which the drug will be prescribed, in particular, including people over 75, without age limits and "unnecessary exclusion criteria for comorbidity" during recruitment [3].

Despite this, elderly are still usually excluded from RCT. A systematic review of RCT's eligibility criteria in 2007 shows that comorbidities and predefined age limits were the main reasons for elderly exclusion [4]. Women, children, and elderly were the most frequently excluded categories in the majority of clinical studies [4].

The reasons for this attitude are quite easy to understand; in fact, the need of enrolling homogeneous study population, lowering the risk of dropout, and reducing compliance and pharmacological interactions are all important issues when designing a clinical trial.

There's the perception that advanced age is a vulnerable condition per se and that enrolling elderly in RCTs could increase direct and indirect costs; moreover, the exclusion of this population from RCT is not perceived as a major problem, erroneously transferring results obtained in younger to older people individuals [5].

The European multicentric study PREDICT (Increasing the PaRticipation of the ElDerly In Clinical Trials), published in 2011 [6], involved eight European countries and Israel and was aimed to investigate attitudes in recruiting older persons in RCTs, in order to understand reasons of their systematic exclusion. The results of this project were not encouraging. In fact, despite the recommendations offered by the Helsinki Declaration of the World Medical Association and by several national and international regulatory agencies (e.g., US Food and Drug Administration, European Medicines Agency, and International Conference on Harmonization) and the best efforts of several opinion leaders in the field, the exclusion of older individuals in CTs continued to be widespread in pharmacologic and nonpharmacologic trials. This is particularly true for some chronic conditions, as for example, chronic heart failure [6].

Informations about RCT in chronic heart failure have been collected in a dedicated WHO's register, the WHO International Clinical Trials Registry Platform (WHO-ICTRP) (www.who.int./trialsearch/AdvSearch.aspx), aimed at facilitating the public accessibility of all ongoing trials and their protocols. Interestingly, by searching this dataset, until December 1, 2008, there were 378 registered trials recruiting patients with heart failure. A total of 127 studies were excluded: 79 because of their observational design, 40 because HF was not the main target condition, 6 because they investigated the physiopathology of HF without proposing any treatment, 1 because it was registered twice, and 1 because it involved children. Among the remaining 251 CTs, 64 CTs (25.5 %) directly excluded patients by an upper age limit. In addition, in the majority of the remaining trials, high rates of other exclusion criteria, such as the presence of comorbidity, cognitive impairment, physical disabilities, polypharmacy, communication barriers, or visual or hearing deficits, indirectly limited the inclusion of older individuals. Moreover, 91 trials (36.3 % ($n=91$) didn't recruit patients with short life expectancy, while 32 (12.5 %) excluded patients with cognitive impairment (only in few cases justified by educational or behavioral purposes). Other exclusion criteria were physical disability

(13.9 %) and general disability (2 %) [6]. In conclusion, the PREDICT study [6] clearly showed that available evidence-based information on the management of heart failure was based on RCT poorly representative of advanced decades; this is quite paradoxical, due to the fact that the incidence and prevalence of heart failure is particularly high in older subjects.

A further PREDICT working group collected and analyzed a survey of health-related professionals who participated in the PREDICT study in order to identify and examine their opinion between on the inclusion of older patients in clinical trials.

There was agreement that exclusion from clinical trials on age grounds alone was unjustified (87 %) and that underrepresentation of older people in trials caused difficulties for prescribers (79 %) and patients (73 %). As possible solutions they proposed that drug agencies should develop clear regulations that allow drugs to be tested in the populations that will use them before they are widely used in clinical practice; moreover, organizations that fund research should emphasize research that avoids underrepresentation of older individuals, as they actively do for sex and race. In addition, ethical committees should include considerations about age discrimination before approving protocols for clinical trials [7]. Finally, a third PREDICT working group started to organize meetings with old patients and their family members to know their point of view on this issues. Results from this project clearly showed that older subjects wish to take part to clinical studies asking for appropriate adjustments of trial protocols in order to respect their characteristics, preferences, and needs [8].

The PREDICT project and its working groups used all these findings to draft a charter for the rights of elderly people in clinical trials [8] trying to obtain more attention to this problem from scientific societies of cardiology guidelines. This should be particularly important, because the evidence on which clinical guidelines are based usually stems from randomized clinical trials or meta-analyses, which are often biased by the exclusion or underrepresentation of elderly people, especially those affected by multimorbidity and receiving polypharmacy.

It is particularly interesting comparing the European Society of Cardiology (ESC) guidelines published on 2008 [9] with that of published on 2012. In fact, 2008 ESC guidelines reported, for heart failure, only 5 paragraphs referring to elderly patients on a total of 55 pages. Unfortunately, there were no significant improvement in 2012 ESC guidelines [10]: in fact, there were only 10 quotations of the word “elder.”

So nowadays, cardiological guidelines are evidence based, but these evidences are strongly biased. In 1995 Sir John Grimley Evans, past president of the British Geriatric Society, defined this aspect introducing a new term “evidence-biased medicine” [11].

However something is changing; in fact, the most important regulatory authorities have recently created some geriatric task forces and expert groups [12] in order to create informative national networks collecting information about drugs utilization, prescription appropriateness etc., and containing data on frailty, comorbidity, and disability. These data can be of help in personalizing diagnostic and therapeutic

approaches for elderly persons and avoiding ageism in creating evidence-based medicine.

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Polypharmacy

6

Nicola Ferrara, Graziamaria Corbi, Klara Komici, and Giuseppe Rengo

6.1 Introduction

Polypharmacy has been defined by the World Health Organization as "the administration of many drugs at the same time or the administration of an excessive number of drugs" [1]. Even if the use of more drugs in many cases has been justified by concomitant diseases and complex medical situations, it is not rare, especially in old patients, the prescription of more inappropriate drugs increasing the risk of iatrogenesis defined as adverse health effects caused by medical practices or drugs prescribed by doctors for the health of the patients at the usual way or doses.

It is well known that population ageing is inducing (a) an increased prevalence of chronic diseases, in particular cardiovascular chronic diseases as congestive heart failure [2, 3]; (b) a significant increase of comorbidities, defined as the simultaneous presence of several chronic diseases, with at least one main pathology associated to disability [4–11]; (c) an increase in physical and cognitive functional decline; and (d) an increased iatrogenic risk. We need to clarify that the terms polytherapy and polypharmacy are little bit different. Polytherapy means the use of multiple prescribed medications or their excessive administration, while polypharmacy means the use of multiple, also not prescribed, drugs not strictly necessary to an

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_6

appropriate treatment [12]. Both are directly related to demographic and epidemiological ageing trends and represent the most important risk factors for onset of adverse drug reactions (ADRs), poor quality of life, rehospitalizations, increased costs and mortality [13–16].

It is important to highlight that elderly patients receive an average of 6–7 prescribed drugs. Around 90 % of these patients assume more than one drug and about 50 % of them from 2 to 4 over-the-counter (OTC) drugs [12]. In addition, around 47–59 % of elderly patients take vitamins or minerals and 11–14 % herbal remedies [12]. For example, hepatotoxicity of herbal remedies has been well defined [18], and we have demonstrated in elderly people affected by congestive heart failure (CHF) a significant relationship between the use of laxatives/antacids and the presence of hypermagnesaemia, as well as an increased mortality risk at 3 years of follow-up [14]. Interestingly, only 58 % of patients communicates to the doctors the use of OTC drugs [12], thus leading to possible interactions between OTC and regularly prescribed medications.

Drugs, even if widely indicated by clinical guidelines and best medical practice, have several potential ADRs that are related to an increased risk of hospitalization and mortality. For example, in a cohort of heart failure outpatients with a mean age >72 years and treated with spironolactone [19], it has been observed an increased prevalence of renal failure and hyperkalemia, compared to data derived from clinical trials. Of interest, there is also a great debate on the use of ACE inhibitors in patients with CHF and renal failure. In the analysis of 12 randomized controlled trials [20] enrolling patients with pre-existing chronic kidneys disease (serum creatinine >1.4 mg/dL), it has been estimated a risk of hyperkalemia that was five times higher compared to patients with normal renal function. Moreover, elevated circulating levels of digoxin, associated with clinical toxicity, are a common example of adverse reactions in the elderly population with CHF [21], initial impairment of renal function and low body weight.

The overall analysis of these data suggests that in elderly patients, it is particularly important to have a continuous supervision of the renal function, liver function, body weight and electrolyte levels in order to minimize the risk of iatrogenic injury, and the overall assessment of the elderly patient, with particular attention to comorbidities, is of great help also to identify the best individually tailored therapy. In 2011 Düngen et al. published a study comparing the tolerability and clinical effects of two proven beta-blockers in elderly patients with heart failure showing that the pattern of intolerance was different between these two beta-blockers: bradycardia occurred more often in the bisoprolol group, whereas pulmonary adverse events occurred more often in the carvedilol group [22].

6.2 Polytherapy and Polypharmacy as a Risk Factor for Adverse Drug Reactions

Epidemiological studies conducted in the elderly population have identified polypharmacy and polytherapy as a risk factor of mortality and morbidity. The combination of polypharmacy/polytherapy and the presence of multiple comorbidities

are associated with a high probability of drug-drug or drug-disease interactions. In elderly population, it is particularly frequent to observe the exacerbation of a drug-induced disease or the interaction between two or more drugs. Multidrug interactions are one of the main components of ADR, although there are several difficulties in their identification and quantification. It has been estimated that around 10–15 % of patients receiving a therapy with multiple drugs show relevant drug interactions, and these data are probably underestimated since the interactions are not always identified or reported [23, 24].

In addition, the increased use of herbal and homoeopathic medications poses the additional problem of possible interactions of these medications and other conventional drugs. The interactions between multiple co-administered drugs can be simplified into two main categories: pharmacokinetic and pharmacodynamic interactions. The higher is the number of drugs used in polytherapy, the more possible and frequent are the interactions. Based on the formula: number of interactions = [(number of drugs × number of drugs)−1/2], with eight co-administered drugs, there are 30 possible interactions. The clinical manifestations of multidrug interactions could be mild, without clinical symptoms, or severe and are always related to the dose and to the exposure time. Most frequently, drug interactions occur at the beginning of the administration during drug absorption, distribution, metabolism or excretion. Pharmacodynamic interactions, which are related to the additive, synergistic or antagonistic effects of specific compounds, are generally more predictable. Frequently, medications interact with multiple mechanisms, although generally only one mechanism is predominant.

The incidence and frequency of adverse events caused by improper use of a polytherapy/pharmacy and their possible interactions are more common nowadays than in the past. The rise in the median age of the population, the increased possibility to face multiple coexisting diseases, the management of patient therapies by several physicians, the use of self-prescribed OTC drugs and the frequent introduction of new medications are some of the causes in the increased occurrence of drug interactions. Moreover, it has to be mentioned that the identification of ADR is complicated by the difficulty to distinguish signs and symptoms derived from adverse drug effects and from those related to pre-existing comorbidities.

For all these reasons, the identification of safe and effective therapies is essential in the modern medicine, especially in the elderly population where comorbidities and polytherapies are associated with reduced physiological reserve of organ systems [25], which strongly affect drug metabolism, pharmacokinetics and pharmacodynamics. Finally, within the complex relationship between comorbidity and polypharmacy, the possible mistakes in the medication process have to be mentioned. These mistakes can be realized at any time of the medication process, including the choice of the most appropriate medication, the prescription (the process of manually prescription of medical drugs) and the delivery of drugs to patients and their administration. Lindley et al., investigating the relationship between inappropriate drug use and the occurrence of ADR, have observed that around 50 % of the ADR was related to the use of unnecessary medications that exhibited absolute contraindications in individual cases [26].

6.3 Adverse Drug Reactions (ADRs) and Hospitalizations

About one third of hospitalizations and half of the deaths related to drug use occur in over 70-year-old subjects. Among the drugs most frequently implicated in the phenomenon, an important role is covered by neurological and non-steroidal anti-inflammatory, as well as by cardiovascular molecules such as warfarin, heparin, diuretics at higher doses, majority of anti-arrhythmics, β-blockers, digitalis and antihypertensives in general [26–30]. Many of these drugs, in addition to the known phenomena of direct toxicity, can aggravate and exacerbate chronic diseases (e.g. the prostatism by anticholinergic drugs, postural hypotension by diuretics or antihypertensives, negative inotropism and chronotropism by β-blockers).

Interestingly in hospitals and nursing homes, many elders receive routine drugs that are not essential (e.g. sedatives, hypnotics, H2 receptor blockers, laxatives, antibiotics are not strictly necessary), which can cause ADR, directly or through complex interactions [32–35]. In confirmation of these allegations, the Italian Group of Pharmacovigilance in the Elderly (GIFA) of the Italian Society of Gerontology and Geriatrics found that at least one ADR occurred in 5.8 % of the elderly during hospitalization [36]. Gray et al. also established an ADRs' incidence of 14.8 % in hospitalized elderly patients [37].

Significant differences are observed in ADR rate in relation to care settings and, within the same setting, in relation to the detection method and the characteristics of the study population.

Recently by using an ADR database of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (2007–2009) for the estimation of the frequency and rate of hospitalization in the emergency department, Budnitz et al. [27] rated the contribution of specific medicines, including those identified as high risk and potentially inappropriate. They conclude that the majority of hospitalizations for recognized ADRs in elderly derives from the use of the most common drugs such as warfarin and insulin and that the improvement of antithrombotic and antidiabetic drugs management is potentially capable of reducing hospitalization rate by ADR in the elderly.

6.4 Adherence to Therapy in Elderly

The proper treatment of coexisting chronic conditions in elderly is essential to slow the progression, to prevent the development of further diseases and to reduce the risk of duplicate, inconsistent or even in conflict treatments that can negatively change the outcome. The key point in the treatment of chronic conditions is the overall accuracy of the drug prescription. In particular, the effectiveness of treatments and their long-term benefits can also depend on the adherence to the instructions of the prescriber [38].

Adherence refers to the perseverance with which the patient follows the instructions given in prescribing treatment. Proper adherence to therapy cannot be separated from sharing of choices through intense relationship between the doctor,

patient and caregiver. In general, significant positive predictors of adherence include (a) simple and short therapeutic regimens, (b) therapeutic classes that meet in favour of consumers, (c) understanding of the disease severity from patients and their families and (d) high symptom score.

The 30–60 % of patients are considered poorly adherent to pharmacological prescriptions. The main reasons for non-adherence of the elderly are represented by the potential side effects, poor education, cognitive impairment or psycho-affective disorders such as depression, but also by having difficulty paying for medications, the disagreement about the need for treatment and the relationship difficulties between the patient and professional staff in charge of care. Other reasons for non-adherence include pathological conditions silent in terms of symptoms (such as hyperlipidaemia, hypertension and osteoporosis), cultural factors and inadequate social support.

In a study of Karousel-Wood et al., predictors of adherence to antihypertensive therapy were investigated in a cohort of elderly subjects [38], identifying in women and being married characteristics favourable to a better adherence and depression a condition significantly unfavourable to a proper therapeutic adherence. Based on these considerations, interventions aimed at improving adherence to treatment of elderly patients with comorbidity are essential, also through the implementation of research oriented to identify the most appropriate strategies to this objective. Such approaches must certainly include psychosocial interventions involving both patients and caregivers in order to improve outcomes for complex diseases.

In addition, it has been reported, from both an experimental [39–43] and clinical [44–46] point of view, that physical exercise is able, even in elderly patients with CHF, to condition many pharmacokinetic parameters, modifying the effectiveness [47] and suggesting, therefore, a possible role of this important tool in the optimisation of drug therapy.

6.5 Inappropriate Prescriptions in Elderly

Several studies have documented that potentially inappropriate prescriptions are common in elderly patients, particularly in the outpatient setting, in nursing homes and in emergency departments and that exposure to inappropriate therapy is associated with an increase in terms of adverse events, morbidity, mortality and use of resources [48].

Inappropriate medications can be defined as “medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available” [49]. The prevalence of inappropriateness increases with the age reaching a 70 % in a geriatric hospital setting [50].

The optimisation of drug prescription is therefore becoming an objective necessity for health systems. The therapy should be guided by the appropriateness that is accomplished through the evaluation of the risk/benefit ratio, essentially when the potential benefits of a drug outweigh the potential risks. Many studies based on the use of educative interventions demonstrated their efficacy in reducing the

inappropriate prescriptions. In particular, Corbi et al. recently showed that the use of an educative/informative instrument was able to significantly reduce the number of inappropriate prescriptions, and the length of hospitalization, suggesting as this tool could be very helpful especially in complicated patients with several comorbidities and drugs [51].

Starting from the consideration that the problems related to taking the drug include factors due to the patient (emotional factors, simple forgetfulness, lack of training/information) and the doctor (lack of information to the patient, complex therapies, bad doctor/patient relationship), in conclusion it is necessary to develop strategies involving patients, family members, caregivers and family doctors who play a vital role in the proper use of medicines, in reducing iatrogenic damage and in increasing adherence [52–60].

Elderly patients should be encouraged to discuss the medicine-related problems with their doctors and their caregivers, including through the use of simple diaries of all drugs and their changes at every doctor's visit. Physicians should exercise caution in reviewing and updating the treatment of their patients. Controlled studies, articulated through the use of electronic means, should be planned to give a correct answer to the increasing need of prescription appropriateness in elderly patients *with comorbidity and* tak*ing several* different drug treatments.

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Syncope and Unexplained Falls in the Elderly

7

Martina Rafanelli, Michele Brignole, and Rose Anne Kenny

7.1 Epidemiology and Healthcare Costs

Syncope, defined as a transient loss of consciousness (TLoC) due to a transient global cerebral hypoperfusion with a rapid onset, a short duration, and a spontaneous recovery [1], is a common clinical condition, but the estimation of its true incidence is challenging because different definitions were used in the few existing population epidemiological studies, and the incidence derived from specific clinical settings is probably an underestimate because most syncopal patients do not seek medical assistance.

In the first Framingham cohort, a first syncope episode was reported in 3 % of men and 3.5 % of women over a 26-year follow-up period (mean age 30–62 years) [2]. In the latest report of the Framingham offspring study, with a 17-year follow-up period, 10 % of the 7814 participants (mean age 51, range 20–96 years) reported at least one syncope. The incidence rate of the first syncope was 6.2 per 1000 person years, with a sharp increase after 70 years from 5.7 events per 1000 person years in men aged 60–69 to 11.1 in men aged 70–79 – equivalent to an estimated 10-year cumulative incidence of 6 % (Fig. 7.1) [3].

In an emergency department (ED) study [4], the mean age of patients referred with syncope was 71 years, with 60 % of patients being older than 65 years. Similarly, in a cross-sectional study on patients with syncope identified from the US

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_7

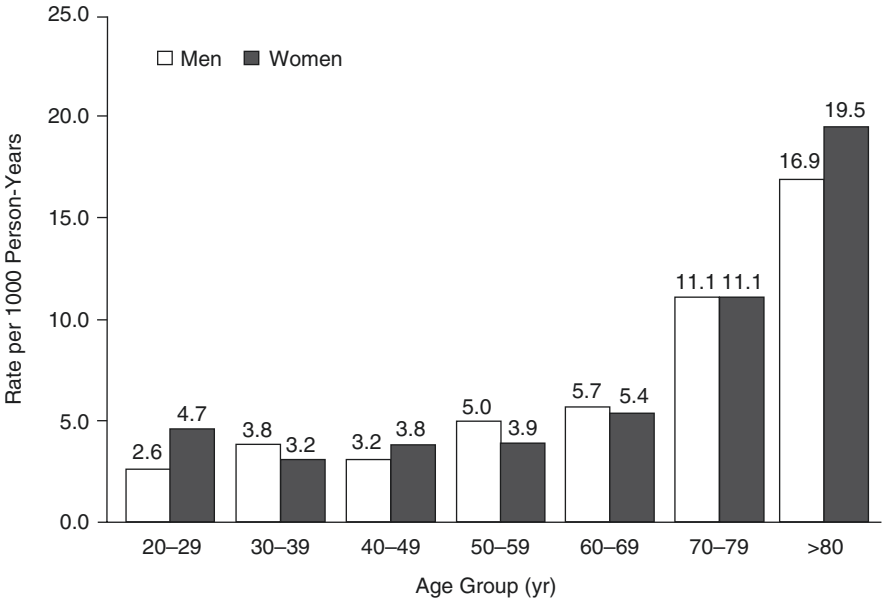

Fig. 7.1 Incidence rates of syncope according to age and sex (Reproduced with permission from Soteriades ES et al. [3])

National Inpatient Sample (NIS) database for the years 2000–2005, the mean age was 69 years; only 7.7 % of patients below the age of 40 suffered from syncope [5].

Underestimation of the problem, particularly important in the elderly, may be due to the overlap between syncope and other presentations such as falls. The incidence of syncope in older patients is thus likely to be considerably higher than current estimates, with attendant cost implications. Annual healthcare costs of syncope episodes in the United States have been estimated at $2.4 billion, with a mean cost of $5400 per hospitalization [6].

In 1999, falls accounted for 647.721 attendances at the UK accident and emergency departments and 204.424 hospital admissions in people aged 60 years and over, with cost implications approaching 1 billion pounds, the majority of which related to funding inpatient admissions [7]. Falling is indeed another major geriatric syndrome, with an age-related prevalence as for syncope (Fig. 7.2) [8], affecting mortality, morbidity, and institutionalization [9]. 34% of community-dwelling patients older than 65 years old and 50 % of octogenarians fall at least once a year [10]. 10% of hospital admissions are due to fall-related trauma [11]; 5–10 % of older patients experience fractures, concussions, and injuries [12]; and in about 1 % a hip fracture occurs, with a 20–30 % 1-year mortality and up to 50% loss of functional capacity [13]. In 30–70 % of fallers, a depressive syndrome develops, due to fear of falling and consequent disability [14].

Falls, which are not accidental, not related to a clear medical condition, or not drug induced, are defined as “unexplained” [15] and represent a relevant cause of hospital admission and increased healthcare costs [7]. Especially in older adults in whom the circumstances of a fall event cannot always be established, because of the

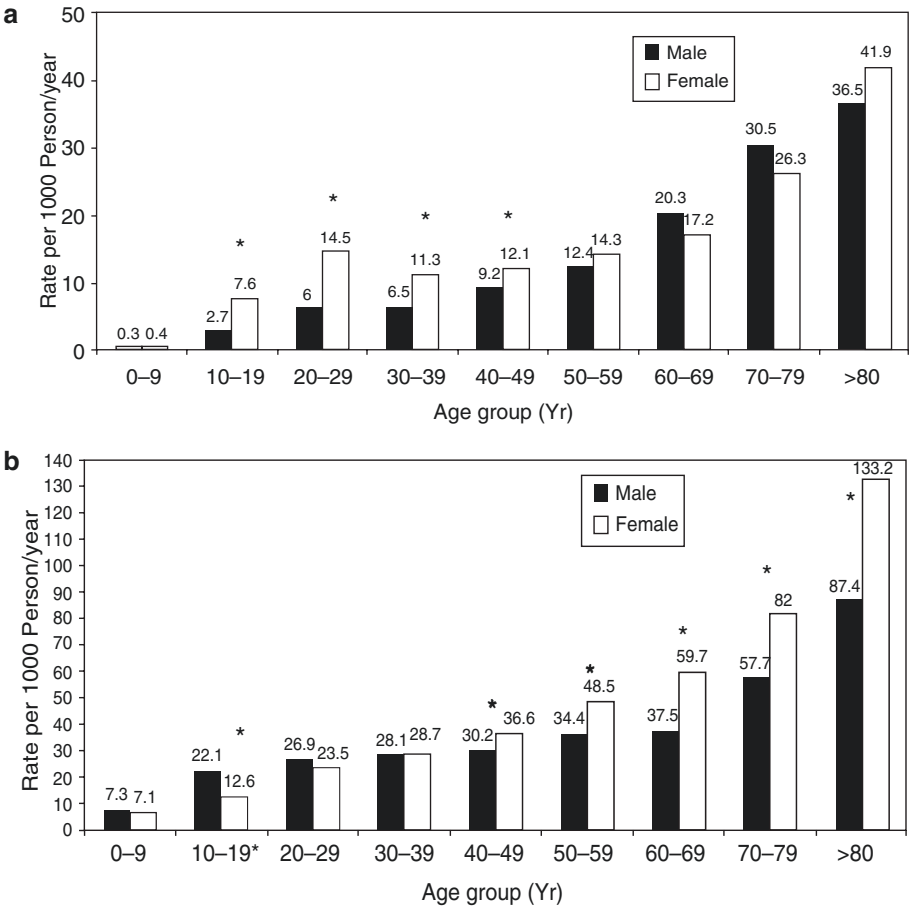

Fig. 7.2 (**a**) Prevalence of faints according to age; * indicates $P<0.01$; (**b**) Prevalence of falls according to age; * indicates $P<0.01$ (Reproduced with permission from Malasana G et al. [8])

lack of witnesses and amnesia for the episode, misdiagnosed syncope may underlie an unexplained fall. About 20 % of cardiovascular syncope in patients older than 70 years old presents as a fall, especially in patients with carotid sinus syndrome (CSS) and orthostatic hypotension (OH); more than 20 % of older patients with CSS complain of falls as well as syncope [16]. In a study of patients older than 60 years old admitted to the hospital because of a fall or syncope, fallers who had CSS during carotid sinus massage (CSM) showed retrograde amnesia for the loss of consciousness more frequently than patients with syncope [17]. Furthermore, over one third of fall events in patients in orthopedic wards are unexplained, particularly in those with depressive symptoms and syncopal spells [18], underscoring the importance of a comprehensive history and assessment at the very beginning of the medical pathway. In a recent systematic review of cardiovascular disorders and falls, positive associations were evident for low blood pressure, heart failure, cardiac arrhythmias, CSH, VVS and post prandial hypotension [19].

7.2 Pathophysiology

Syncope is caused by an inadequate supply of oxygen (<3 mLO_2/100 g tissue/min) and metabolic substrates to the brain, due to global and transient cerebral hypoperfusion [20]. Global cerebral hypoperfusion differentiates syncope from the other conditions which can mimic syncope, but without underlying cerebral hypoperfusion; such as epilepsy, hypoglycemia, transient ischemic attacks (TIA) in the vertebro-basilar region, intoxication, and episodes of apparent loss of consciousness, i.e., falls, drop attacks [1]. The functional integrity of the cerebral tissue strictly depends on oxygen supply, and in healthy subjects, cerebral autoregulation maintains a constant blood flow within a fairly wide range of pressures [systolic blood pressure (SBP) between 60 and 190 mmHg]. When SBP decreases below this threshold, brain perfusion decreases slowly and progressively, and if this hemodynamic status lasts for 8–15 s, ischemia and ultimately loss of consciousness will follow [1, 21].

Older adults are particularly exposed to syncope, because several factors differentiate them from younger adults. The effects of age-related pathophysiological changes have to be considered, such as reduced left ventricular compliance (which increases the susceptibility of cardiac output to preload and atrial contraction), altered control of blood volume, and decreased sensitivity of the baroreceptors. Moreover, diseases such as heart failure, diabetes, and chronic obstructive lung disease increase the risk of cerebral hypoperfusion. Finally, the differences in blood pressure (BP) adjustments during orthostasis between the young, which rely essentially on an increase in the heart rate (HR) and myocardial contractility, and the elderly, which rely more on an increase in peripheral resistance [22], can explain the attributable role of vasoactive drugs as precipitating factors for syncope in older patients [23]. The pathophysiological role of altered cerebral autoregulation in the elderly as a predisposing factor to syncope is debated. Serrador JM et al. [22] demonstrated that cerebral autoregulation is intact in elderly hypertensive subjects suggesting that otherwise healthy hypertensive elderly patients can safely undergo BP reduction, without concern for cerebral hypoperfusion. In older patients with syncope, there is evidence that cerebral blood flow velocity was lower than in younger subjects. However, autoregulatory indexes reflecting dynamic cerebral autoregulatory function were similar, either at supine rest or during tilt test (TT) [24]. Giese AE et al. [25] showed that in healthy individuals, age and baseline BP have only a minor effect on the lower limit of BP necessary to maintain consciousness. Higher baseline BP provides older individuals a greater BP "reserve" to maintain the consciousness compared to younger subjects. Further studies of unselected older populations are necessary to better understand the implications of cerebral blood flow, hypertension, orthostatic hypotension, and antihypertensive treatments. However, it is the case that age-related physiologic impairments of heart rate, blood pressure, and cerebral blood flow, in combination with comorbid conditions, concurrent medications, and neurohumoral adjustments, contribute to the increased susceptibility of older adults to syncope.

7.3 Etiology and Clinical Features

Neurally mediated disorders such as vasovagal (VVS), situational syncope, and CSS are the commonest cause of syncope in all age groups. Structural and arrhythmic cardiac syncope, as well as OH, increase with advancing age (Fig. 7.3) [4].

7.3.1 Vasovagal Syncope

VVS is commonly induced by triggers such as fear, pain, and instrumentation or is induced by orthostatic stress or hot environment. In older patients the presentation is often atypical. Syncope can also occur with uncertain stimuli or even apparently without triggers. Moreover, prodromes may be short and loss of consciousness starts abruptly, leading to falls and injuries [26]. However, more than 70 % of older patients with syncope complain of at least one symptom before loss of consciousness, with nausea, blurred vision, and diaphoresis being the most common in VVS, whereas dyspnea is more predictive of cardiac syncope [27]. The frequency of prodromes due to global cerebral hypoperfusion or to autonomic activation is lower in subjects >60. In one study during the syncopal phase, myoclonic movements were rarely observed in older subjects and absent in those >74 years [28]. A possible explanation is the less frequent occurrence of asystole in the elderly or slower reduction in SBP. Even during the recovery phase, the frequency of autonomic symptoms is lower in older subjects; thus, in the elderly the clinical features of VVS are very similar to those of cardiac syncope [28].

If VVS occurs when the patient is upright, he/she will fall thereby rendering clinical findings of syncope and falls very similar. In this context, retrograde amnesia has been demonstrated in patients with syncope induced in the laboratory; indeed, about 25 % of patients fail to recall their prodrome and TLoC during tilt-induced syncope [29].

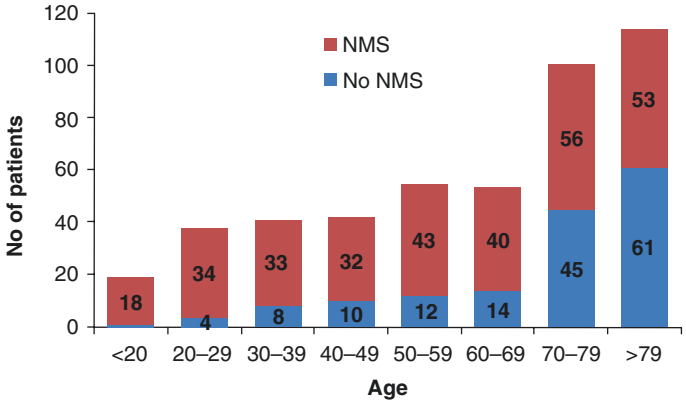

Fig. 7.3 Age distribution of neurally mediated syncope and other causes of syncope [4]. *NMS* neurally mediated syncope, *No NMS* no neurally mediated syncope

7.3.2 Orthostatic Hypotension

OH is traditionally defined as a fall in SBP from a baseline value ≥20 mmHg or diastolic BP (DBP) ≥10 mmHg or a decrease in SBP to <90 mmHg within 3 min of orthostatic position [1]. Since the magnitude of blood pressure drop also depends on baseline values, it was suggested that a drop of 30 mmHg may be a more appropriate criterion for OH in patients with supine hypertension [30]. The rate of OH increases with advancing age, reaching 24.3 % in the eighth decade and 30.9 % in the ninth decade, as recently confirmed [31], [32]. In a study conducted on patients older than 65 years old consecutively referred to the ED for a TLoC, the prevalence of syncope related to OH was 12.4 % [33].

Initial OH is represented by a drop in SBP during the first 30 s of standing with quick and spontaneous recovery, which is detectable by beat-to-beat BP monitoring. This form of OH may have implications in older adults, particularly those on medications impacting cardiovascular control [34]. A recent study has found that 15 % of long-term care residents fall after rising to standing [35]. This represents a high-risk activity for older adults, and initial OH could potentially exacerbate this falling risk, although a recent population study suggests that initial OH is more benign than other subtypes [36].

C*lassic* OH is diagnosed with the active standing test within 3 min of orthostatic position. *Delayed* OH is characterized by a slow and progressive decrease of SBP on assuming the standing position. In this syndrome, hypotension can manifest clinically up to 30 min after the achievement of the upright position, and passive TT is necessary for the diagnosis [1].

Pharmacotherapy is the most common cause of OH in older individuals; alpha-receptor blockers, nitrates, or benzodiazepines and antidepressants [37], frequently used in older people, were found to be predictors of OH and associated with syncope and falls [31]. Other causes of OH are represented by primary autonomic failure (e.g., idiopathic Parkinson's disease and multiple system atrophy), secondary autonomic failure (e.g., diabetic and alcoholic autonomic neuropathy), and dehydration. Occasionally OH may be the presenting manifestation of malignancy or anemia, which should be considered in patients with OH and particularly in the older population [38].

Postural blood pressure decreases could cause a falling event. It has been suggested that 2–10 % of falls in older adults may occur secondary to impaired hemodynamic responses, and loss of consciousness is estimated to result in as many as 10 % of falls [39]. OH could also be linked to falls through indirect mechanisms. In many cases loss of consciousness is avoided, but increased fall's susceptibility remains through pre-syncope and associated physiological impairments [40]. Older adults with Parkinson's disease or diabetes mellitus and OH have poorer balance scores in comparison to those without OH [41, 42], and as poor balance is a known risk factor for falls, it has been suggested to increase this risk threefold [10].

Blood pressure impairments including OH, hypertension, and acute and chronic cerebral hypoperfusion are associated with impaired cognitive performance in older adults [43, 44]. This association has been recently confirmed in a large sample of the general population, where patients with OH showed a worse cognitive performance in the domains of memory, attention, and executive functions [45]. Frewen J et al. [46]

have shown an independent association between early OH and cognitive decline in patients with supine hypertension. A possible explanation is that high long-term BP levels, which are per se related to cognitive impairment, could be associated with OH, which in turn aggravates cognition. This latter is also a risk factor for falls [47]. Multivariable analyses suggest cognitive deficits increase falling risk threefold. Therefore, cognitive functioning could serve as an intermediary mechanism between BP impairment and falling risk in older adults [39].

7.3.3 Carotid Sinus Hypersensitivity and Syndrome

Carotid sinus hypersensitivity (CSH) can manifest as cardioinhibitory (CI-CSH) (asystole ≥ 3 s during CSM) or vasodepressor (VD-CSH) (a fall in SBP ≥ 50 mmHg during CSM) or mixed (M-CSH) and represents a positive response to CSM in an asymptomatic patient. CSH could indicate an abnormal reflex, which may have a role in predisposing to unexplained falls; in this condition syncope has to be taken into account, even if the clear dynamic of the event could not be recalled due to retrograde amnesia. Maggi R. et al. [48] have showed that CI-CSH in patients with a clinical diagnosis of suspected neurally mediated syncope was related to a long asystolic reflex detected by an implantable loop recorder (ILR) at the time of the spontaneous syncope.

When associated with syncope, CSH is defined as CSS [1]. The prevalence of CSS has been estimated to range from <4 % in patients <40 years to 41 % in those >80 years attending a specialized syncope facility [49]. CSS is frequent in older males with a mean age of 75 years and often evidence of cardiovascular disease; the related syncope has often little or no prodrome, with a consequent increased risk of traumatic fall. Syncope recurrence is common and is reported to be 50 % in 2 years. There is also a high mortality, which is considered to be related to comorbidities and age rather than CSS itself. When monitored, in CI-CSH patients the most frequently detected arrhythmia is sinus arrest without escape rhythm in 72 %. There is an association with sinus node disease in 21–56 % of the cases and with atrioventricular block in 21–37 % of the cases [49].

The most recent ESC guidelines on pacing [50] have proposed a 6 s cutoff for the CSM-induced asystole, because this latter, which causes symptoms in CI-CSH and M-CSH, is generally much longer than the historical 3 s cutoff value. On average, the duration of asystole to induce symptoms is 7.6 ± 2.2 s and the fall in BP is 63 ± 24 mmHg [51, 52].

7.3.4 Cardiac Syncope

Cardiac causes of syncope are highly represented in the older population (Fig. 7.3) [4].

Arrhythmias, structural heart disease, and pulmonary embolism are much more prevalent in older patients. In the Framingham study, cardiac syncope doubled the risk of death from any cause and increased the risk of nonfatal and fatal cardiovascular events, compared to those without syncope [3]. Short-lived syncope of abrupt

Table 7.1 EGSYS score. Point scores for the diagnosis of cardiac syncope [48]

Palpitations preceding syncope	4
Heart disease or abnormal ECG or both	3
Syncope during effort	3
Syncope while supine	2
Precipitating or predisposing factors or both[a]	−1
Autonomic prodromes[b]	−1

[a]Warm-crowded place/prolonged orthostasis/fear-pain-emotion
[b]Nausea/vomiting

onset and recovery, supine, during (rather than after) exercise or associated with palpitations or chest pain should be considered cardiac until proven otherwise. A past history of heart disease is an independent predictor of cardiac syncope with a sensitivity of 95 % and specificity of 45 % [53]. Cardiac syncope must be excluded in patients with known or suspected left ventricular systolic dysfunction (LVSD), valvular disease, and left ventricular outflow tract (LVOT) obstruction, in those with an abnormal surface electrocardiogram (ECG) and where the clinical context and concomitant investigations suggest pulmonary embolism. Neurally mediated cause of symptoms must not be assumed in any patient with these clinical and diagnostic features until a cardiac cause has been effectively excluded. The EGSYS score is a diagnostic score to identify cardiac syncope. Abnormal ECG and/or heart disease, palpitations before syncope, syncope during effort or in supine position, the absence of autonomic prodromes, and the absence of predisposing and/or precipitating factors were found to be predictors of cardiac syncope. To each variable a score from +4 to −1 was assigned according to the magnitude of regression coefficient (Table 7.1, [54]). A score >3 identified cardiac syncope with a sensitivity of 95 %/92 % and a specificity of 61 %/69 % [54].

7.4 Evaluation of the Older Patients with Syncope and Unexplained Fall

The diagnostic protocol proposed by the ESC guidelines on syncope [1] is well enforceable in older patients, and when applied, the rate of unexplained syncope decreases to 10.4 % [55].

7.4.1 Initial Evaluation

The initial assessment in older patients is aimed at considering, excluding, or identifying a cardiac cause of symptoms, given the high morbidity and mortality associated with these disorders in this age group.

The clinical history regarding the episodes should be pursued by a witness's account, for the relevant presence of retrograde amnesia in the elderly. Particular attention should be paid to the time of the day, season, relationship with meals,

nocturnal micturition, supine or upright position, drugs, duration of treatment, and time relationship between drug consumption and appearance of adverse effects. The clinical history should include the collection of systemic diseases, physical frailty, and locomotor disabilities. Details of cognitive status, social circumstances, injuries, impact of the event on confidence, and ability to carry out basal/instrumental activities of daily living independently should also be recorded [1].

However, the medical history has a limited value in the differential diagnosis between cardiac and neurally mediated cause of syncope in older patients [27]; thus, TT and CSM become essential in the diagnostic pathway.

The 12-lead ECG can be considered diagnostic and permits no further evaluation and institution of treatment, in cases of persistent sinus bradycardia <40 bpm in awake or repetitive sinus-atrial block or sinus pauses >3 s; Mobitz II second or third degree atrioventricular block, alternating left and right bundle branch block, ventricular tachycardia (VT), or rapid paroxysmal supraventricular tachycardia; non-sustained episodes of polymorphic VT and long or short QT interval; and evidence of acute ischemia with or without myocardial infarction [1].

The physical examination should include cardiovascular and neurological assessment, evidence of Parkinson's disease or other neurodegenerative conditions related to autonomic dysfunction. A careful observation of gait and standing balance is useful in the evaluation of the locomotor system and the consequent risk of falling.

The active standing test, which consists of the measurement of BP in the supine position and then immediately after changing from the supine to the upright position and after 1 and 3 min of orthostatic position, is a relevant diagnostic step, especially in older patients. OH is not always reproducible in older adults, especially when it is related to drugs or predisposing conditions; therefore, active standing tests should be repeated, preferably in the morning and/or "promptly" after the syncope [1].

Alpha-receptor blockers, nitrates, or benzodiazepines, frequently used in older people, were found to be predictors of OH; therefore, attention should be paid on the reevaluation of drug regimens in the presence of OH, in order to reduce the syncope recurrence [31].

The ESC guidelines on syncope [1] propose the execution of CSM during the first-line evaluation, because of the high prevalence of CSS as a cause of syncope and unexplained falls in the elderly.

The test is performed in a TT laboratory under continuous heart rate (HR) and beat-to-beat BP monitoring. CSM is conducted for 10 s, bilaterally, first in the supine and then in the upright position, on TT at an angle of 60°. The added diagnostic value of repeating CSM in the upright position has been well documented [56]. In order to assess the contribution of the VD component, CSM may be repeated after intravenous administration of 0.02 mg/kg of atropine, which eliminates vagally induced asystole, thereby unmasking the VD phenomenon [57]. This quantification of the VD component is clinically relevant, because it has been shown that pacemaker therapy is less effective when the VD effect is large, compared with predominant cardio-inhibition [58]. Transient ischemic attack or stroke

during the 3 months beforehand or critical carotid artery stenosis on Doppler ultrasounds performed in the presence of carotid bruits represents relative contraindications to CSM [59]. In such situation, a careful risk/benefit assessment must be undergone.

7.4.2 Second-Level Evaluation

7.4.2.1 Tilt Testing

TT is the best validated test for the clinical assessment of neurally mediated reflexes, has been validated in older subjects using the Italian protocol (300–400 mcg of sublingual nitroglycerine), is well tolerated, and has a similar positivity rate and specificity both in young and in older patients [60].

The test should be performed in the morning, in fasting state, and in a quiet and dimly lighted place. Briefly the test consists of 20 min of passive orthostatic position at an angle of 60° that is potentiated, if syncope does not occur, on administration of sublingual nitroglycerine (300–400 μg) with a further 15 min of observation at the same angle. The test is considered positive if symptoms reproducing those reported by the patient during spontaneous syncope are associated with hypotension, bradycardia, or both [61]. A recent meta-analysis [62] demonstrated that TT has a good overall ability to discriminate between symptomatic patients and asymptomatic control subjects, with a high specificity in most of the protocols investigated and a widely variable sensitivity. Pharmacological protocols have higher sensitivity and lower specificity than passive protocols. Moreover, nitroglycerine-stimulated TT has greater diagnostic capability in comparison to isoproterenol-stimulated TT [62]. However, Ungar A. et al. [63] showed that TT was unable to discriminate between cardiac and presumed neurally mediated syncope with the exception of an asystolic response which was highly specific. The test was indeed diagnostic in 56 % of presumed neurally mediated syncope and in 43 % of non-neurally mediated syncope patients and in 45–47 % of those with true cardiac arrhythmic syncope. A possible explanation of this discrepancy comes from a recent reinterpretation of TT, according to which the test could reveal a susceptibility to vertical posture stress as a "hypotensive susceptibility," which could cause syncope irrespective of the etiology and the mechanism of syncope itself [64]. The identification of hypotensive susceptibility makes TT a risk stratification tool, rather than a diagnostic one, for patients with recurrent, traumatic syncope and ECG documentation of spontaneous asystolic reflex syncope, as showed in the ISSUE 3 study [65], who could greatly benefit from pacing, especially when TT is negative, because of a pure asystolic mechanism [66].

TT can also be useful in guiding the differential diagnosis between syncope and unexplained falls, as recently confirmed that the positivity prevalence of TT and CSM was similar in patients who presented with these two conditions, suggesting that neuro-autonomic evaluation, through the standing test, TT, and CSM, should be routinely performed in older patients with unexplained falls [67].

7.4.2.2 Implantable Loop Recorder

ILR has been developed to provide ECG documentation of events that occur sporadically, as other technologies (ambulatory ECG and external event recorder) have a low rate of diagnosis due to the infrequent nature of events, such as syncope. The device is placed subcutaneously and has a retrospective (loop) memory which continuously records and deletes the patient's ECG, including a patient's activated function, through which the patient can activate the ECG storage as a result of symptoms and an automatic feature, which allows the capture of arrhythmic events without relying on patient's compliance or perception of symptoms. In pooled data from a consensus document [68], ILR provided an ECG-syncope correlation in about 35 % of patients during the lifetime of the device. Of these, 56 % had asystole or severe bradycardia. Similar findings were observed when ILR was inserted in patients with suspected neurally mediated syncope in an early phase after the initial evaluation or in unexplained syncope at the end of the conventional work-up.

Older patients are more likely to receive an ILR implantation than younger patients, because of the need for a precise diagnosis in case of structural heart disease or bundle branch block, which is almost exclusively present in patients ≥65 years, because of the limited value of the clinical history in the diagnosis of the causes of syncope, and finally because in the elderly the onset of syncope is sudden abrupt with little or no prodromes, justifying the need for ILR to detect the underlying mechanism and start a specific treatment [69]. ILR also has a high diagnostic value in conditions in which an initial diagnosis is only suspected, and the demonstration of an arrhythmic mechanism could definitively guide the therapy. Maggi R. et al. [70] showed that in highly selected older patients with an initial diagnosis of either likely epilepsy or unexplained falls, ILR gave a documentation of a relapse of their index attack and that, in about one-fourth of the patients, the final diagnosis was arrhythmic syncope. Moreover, ILR monitoring definitely excluded an arrhythmic cause, when the arrhythmia was not documented at the time of a spontaneous attack.

Different neurally mediated mechanisms can coexist especially in older people and be responsible for the genesis of syncope. In a population of 873 consecutive patients older than 65 years old, the rate of "complex diagnosis," namely, the presence of more than one diagnosis on standing test, TT, and CSM, was 23 %, and the most frequent association was between OH and VVS on TT in the 15.8 % of the cases [31]. It is therefore useful to run a comprehensive evaluation in every subject, without stopping at the apparently first etiological diagnosis.

7.5 Treatment

The treatment is based on risk stratification and identification of specific mechanisms leading to global cerebral hypoperfusion. An arrhythmic syncope may benefit from cardiac pacing, implantable cardioverter-defibrillators, and/or catheter ablation as well as, in the case of structural cardiac or cardiopulmonary disease, treatment directed at amelioration of the specific structural lesion or its consequences.

7.5.1 Neurally Mediated Syncope

Physical counterpressure maneuvers such as leg crossing, hand grip, or arm tensing can induce a significant BP increase during impending reflex syncope, but given the frequent absence or brief prodromes, particularly in older adults, these maneuvers are difficult to apply to this age group. Education and reassurance, modification or discontinuation of antihypertensive drugs, diuretics, nitrates, benzodiazepines, and alpha-receptor blockers, which are likely to be related to hypotension and falls, and avoidance of triggering situations are cornerstones of behavioral strategies. Disappointing results have been obtained by the use of various drugs in the context of neurally mediated syncope.

Cardiac pacing should be considered in patients with CI-CSS (class 2a, level B in the ESC syncope guidelines [1]). The ISSUE 3 study has demonstrated that pacing was effective in reducing the recurrence of syncope in patients ≥40 years with severe asystolic neurally mediated syncope, previously documented by an ILR [65]. Nevertheless 25 % of the patients had syncopal recurrence after 2 years, despite pacemaker therapy. The benefit of pacemaker therapy was not substantial in patients with a positive TT, speculating a hypotensive mechanism that cannot be prevented by cardiac pacing [66].

In a recent pragmatic study [71], a guideline-based diagnostic algorithm was proposed and the efficacy of cardiac pacing was assessed. Patients aged >40 years, affected by severe unpredictable recurrent reflex syncope, underwent CSM, followed by TT if CSM was negative, followed by implantation of an ILR if TT was negative. Those who had an asystolic response to one of these tests received a dual-chamber pacemaker.

The recurrence rate was similar in CSM+, TT+, and ILR+ patients and highly reduced in the year following implantation compared to the year before. The recurrence rate was also significantly lower than that observed in the group of patients with non-diagnostic test who had received an ILR, instead of a pacemaker. The guideline-based diagnostic algorithm proposed proved a clinical utility for the selection of candidates to cardiac pacing in everyday clinical practice.

7.5.2 Orthostatic Hypotension

Antihypertensive drug withdrawal (particularly beta blockers), extracellular volume expansion, and salt and water intake in the absence of hypertension are the principal treatment strategies. Elevating the head of the bed helps reducing nocturnal hypertension, with a more favorable distribution of body fluids and prevention of nocturnal micturition. Abdominal binders or compression stockings are useful against gravitational venous pooling [1]. Pharmacological interventions may become necessary when non-pharmacological measures fail to attenuate symptoms. Nevertheless, supine hypertension has to be considered as an adverse effect of pharmacological treatment.

Volume expansion may be achieved with 9-α-fluorohydrocortison, a synthetic mineralocorticoid, which increases plasma volume by renal sodium retention.

Peripheral vascular resistance is the limiting factor of 9-α-fluorohydrocortison treatment, resulting in dose-dependent supine hypertension. The alpha-agonist midodrine has been used, achieving a proper vasoconstriction of the peripheral vessels; nevertheless, its limitation is represented by a short half-life, which requires frequent dosing and limits a long-term compliance. Furthermore its use is related to adverse effects on urinary outflow, which requires special caution in older males [72].

Pyridostigmine is a cholinesterase inhibitor, which improves ganglionic transmission and vascular adrenergic tone in primarily upright position, mediating a slight increase in diastolic blood pressure during standing without worsening supine hypertension [73].

Droxidopa is an orally administered artificial amino acid converted both peripherally and centrally into norepinephrine. The enzyme responsible for the conversion, aromatic amino acid decarboxylase, is widely expressed, and so the administration of droxidopa increases norepinephrine even if postganglionic sympathetic neurons are not intact. The drug has received accelerated Food and Drug Administration (FDA) approval for the treatment of symptomatic OH, particularly in Parkinson's Disease. It has been recently demonstrated that droxidopa improved symptoms and symptom impact on daily activities, with an associated increase in standing SBP in patients with symptomatic OH due to different orthostatic intolerance syndromes, without worsening supine hypertension [74].

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Hypertension in the Oldest Old, Beyond Guidelines

8

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8.1 Introduction

The importance of blood pressure (BP) assessment among oldest old is highlighted by several reasons. The most obvious one is represented by the steep increase of old age population share since 1960 and the even steeper increase forecasted during the next 30 years all over the world [1]. This increase will be multiplicative in the subgroup of subjects aged 80+, with an expected triplication by 2050 in Spain, Germany, and Japan and a seven-time increase in Korea and China [2]. The second reason of the importance and peculiarity of this population is linked to the incidence and prevalence of comorbidities, frailty, and loss of autonomy, which greatly increase among subjects aged 80+ [3]. Finally and most important, subjects in this age stratum have both highest cardiovascular risk and potentially severe adverse effects from BP treatment, with limited evidence from randomized clinical trials regarding risk and benefits of antihypertensive treatment.

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_8

In fact, while the prevalence of high BP and the risk of vascular diseases are clearly associated with old age, the risk of syncope, falls, and fractures also increases with age, with low BP representing a major risk factor [4]. Orthostatic hypotension in particular seems to be associated both with antihypertensive treatment and with an increased fall risk [5] and was also found to increase the risk for mortality and cardiovascular events in a recent meta-analysis [6]. Of notice, in a large population-based study, older subjects showed a significant increase in hospitalizations for hip fracture over the 45 days after initiation of antihypertensive drug treatment [7]. Moreover hypotension-related events in old age are likely to be more common in real life than in clinical trials in which treatment is delivered by expert physicians, and patients are followed closely. Therefore, both the benefits (including preserving autonomy) and the risks of antihypertensive therapy should be considered before starting treatment in frail older population.

Finally, the data from randomized clinical trials seem somehow at an odd with observational studies, showing that in the very old population low BP values represent a risk factor for morbidity and mortality, at least as strong as high BP [8–10]. Although the possibility of reverse causality (i.e., more severe clinical conditions in subjects with lower BP) has been advocated for these data, a pathophysiologically founded hypothesis is that in frail very old subjects an impairment of the mechanisms preserving perfusion might critically decrease blood flow to vital organs (the heart, brain, kidney) [11]. Therefore the choice of most appropriate BP target in these subjects is still a matter of debate.

8.2 Epidemiology

Arterial hypertension (AH) represents the leading risk factor for global disease burden due to its great prevalence and deep impact on morbidity and mortality [12]. Overall the prevalence of AH appears to be around 30–45 % of the general population, presenting higher values in Europe (44 %) than in the United States (28 %) [13].

Although rise of BP values is not a normal part of aging, the prevalence of AH increases progressively with age, and thus most older subjects are hypertensive [14]. Data from the Framingham Heart Study in men and women free of AH at 55 years of age indicate that the remaining lifetime risks for development of AH until the age of 80 are 93 % and 91 %, respectively [15]. In other words, more than 90 % of individuals who are free of AH at 55 years of age will develop it during their remaining life-span. Several epidemiological surveys conducted in the United States and Europe conclude that AH prevalence in the elderly ranges between 53 and 72 % [16].

From the epidemiological standpoint, there are important subgroups with distinctive characteristics. AH prevalence is less in women than in men until 45 years of age, is similar in both genders from 45 to 64 years of age, and is much higher in women than men >65 years of age. Age-adjusted AH prevalence, both diagnosed and undiagnosed, from 1999 to 2002, was 78 % for older women and only 64 % for older men [17]. Both the prevalence and severity of AH increase markedly with advancing age in women, so that, after age 60 years, a majority of women (age 60–79 years: 48.8 %; age ≥80 years: 63 %) have stage 2 AH (BP ≥160/100 mmHg) or receive antihypertensive treatment [18]. Furthermore, BP control is difficult to achieve in elderly hypertensives [19]. Thus, although older patients with AH are

more likely to be aware of their condition and receiving treatment than middle-aged patients, BP control rates are lower in the elderly, especially after age 80 years [14].

AH in old age is commonly characterized by elevated systolic blood pressure (SBP), with often normal or even low diastolic blood pressure (DBP), which reflects a progressive increase in aortic stiffness during aging, in part related to increased collagen with cross-linking and degradation of elastin fibers [19]. Typically SBP rises gradually throughout adult life, while DBP peaks and plateaus in late middle age, declining slightly thereafter. The widened pulse pressure is a reflection of increased arterial stiffness [19]. Therefore, the proportion of hypertensive patients with isolated systolic hypertension increases with age, with this condition affecting 65 % of patients with AH >60 years of age and over 90 % >70 years of age [20]. The prevalence of isolated systolic hypertension is higher in women than in men, whereas the proportion of AH attributable to solely elevated SBP in older adults is similar across racial and ethnic groups [14].

White coat hypertension, a term reserved for those not on antihypertensive medications but with persistently elevated office BP (≥140/90 mmHg) together with a normal home BP or daytime ambulatory BP (≤135/85 mmHg), is also more common in the elderly and is more frequent among centenarians [21]. Masked hypertension, defined as normal office BP associated with high BP at home, is also frequent in the elderly and is associated with a high vascular risk profile [22]. Contrary to white coat hypertension, masked hypertension has been shown to be associated with an increased risk of cardiovascular events [23]. The frequency of non-dipping – defined as a nocturnal BP drop <10 % of daytime values – also increases with age [19]. As discussed below, these data should support the usefulness of home BP monitoring in elderly hypertensives.

In regard to treatment efficacy, resistant hypertension – defined as BP that remains above goal in spite of the concurrent use of three drugs at optimal dose amounts, one of whom should be a diuretic – has a substantial prevalence across all ages but is more frequent among older subjects [24].

AH is the most important risk factor for cardiovascular diseases in the elderly population, with estimates that 69 % of patients with incident myocardial infarction, 77 % with incident stroke, and 74 % with incident heart failure have antecedent AH. In addition, AH is a major risk factor for incident diabetes mellitus, as well as for atrial fibrillation and chronic kidney disease [14].

Therefore, the positive association of high BP with cardiovascular risk and mortality is maintained at higher age, although this association seems to loosen or even be reverted among very old, frail subjects [11]. Thus, despite the large body of evidence in middle-aged populations, the predictive value of high BP in the rapidly growing population of oldest old is still debated, as is the question of whether AH should be treated and if so, how intensively.

8.3 Clinical Assessment of BP in Older Subjects

8.3.1 Peculiar Aspects of BP Measurement

Recent guidelines reaffirm the need to obtain the BP measure in sitting position after 3–5 min of rest, repeating the measurement at least twice 1–2 min apart and

obtaining the measure on both sides at the first visit [13]. Specific aspects of BP measurement should be cared of in aged subjects. First, the age-associated increase of arterial stiffness, apart from being a main determinant on increased SBP values in old age, may affect the risk of *pseudohypertension*, which is quite common in old age and is defined as a falsely heightened SBP in comparison with the intra-arterial measurement [25]. This phenomenon is explained by the increased cuff insufflation pressure needed to obtain the collapse of brachial artery walls, due to the increased rigidity of the tunica media. The presence of pseudohypertension can be suspected with the Osler's maneuver, which is performed by assessing the palpability of the pulseless radial or brachial artery distal to the point of occlusion of the artery by cuff pressure [26]. While the Osler's maneuver is positive in about 10 % of older subjects, its ability to detect pseudohypertension has been questioned, and the measure of upper limb pulse wave velocity has been proposed as a more appropriate way of screening for this condition [27].

With a similar mechanism, arterial stiffness may be the cause of *auscultatory gap* phenomenon, which is defined by decrease or disappearance of Korotkoff sounds during BP measurement. The improper interpretation of this gap may lead to BP monitoring errors, namely, an underestimation of SBP and/or an overestimation of DBP. In order to correct for an auscultatory gap, the radial pulse should be monitored by palpation. Moreover, the examiner can avoid being confused by an auscultatory gap by always inflating a BP cuff to 20–40 mmHg higher than the pressure required to occlude the brachial pulse. The presence of an auscultatory gap has been associated with carotid atherosclerosis and increased arterial stiffness in hypertensive patients, independently of age, thus suggesting that it may have a prognostic relevance [28].

Among older subjects, BP should be measured in the sitting position, immediately after reaching the standing position, and again twice, when this position has been maintained for 1 and 3 min. Thus it is possible to detect orthostatic hypotension, defined as a decline of at least 20 mmHg of SBP and/or 10 mmHg of DBP in standing vs. the sitting position [13]. The detection of this condition is particularly important in older subjects, as it is particularly frequent and has been associated with falls, cardiovascular events, and total mortality [5, 6]. Therefore the choice of antihypertensive treatment should be based on orthostatic together with sitting BP values.

A critical point regarding BP measure in old age is represented by the discrepancy between office and out-of-office BP measures, including both home BP monitoring and 24-h ambulatory blood pressure monitoring (ABPM). In fact a meta-analysis of available studies shows that this discrepancy is age dependent, with office BP values increasing more steeply with age in comparison with daytime ABPM measures. In particular, office BP values tend to be higher than daytime ABPM ones after the age of 50 years for SBP and after the age of 45 years for DBP, while the reverse is true at younger ages [29]. This results in age-associated increases of "white coat hypertension" risk. This condition is defined as having elevated office BP without elevated daytime BP (or alternatively non-elevated 24-h BP) on ABPM in individuals not taking antihypertensive medication. White coat hypertension may

also refer to individuals taking antihypertensive medication. However, the preferred terms for this subset of patients is "treated white coat hypertension" or "white coat uncontrolled hypertension" [30].

The majority of studies regarding white coat hypertension have observed no increased cardiovascular risk for this condition in comparison with normotension. This has been confirmed in particular among older subjects with a clinical diagnosis of isolated systolic hypertension at clinical measurement and normal BP values at ABPM, whose 10-year risk of cardiovascular morbidity and mortality was similar to subjects with persistently normal BP values, both among treated and non-treated subjects [31]. Moreover, the phenomenon is highly prevalent among older disabled subjects: in a sample of older nursing home patients undergoing ABPM, it was detected in 33 % of the whole sample and in 70 % of those with high BP at office assessment [32].

The suspect of white coat hypertension is the first indication for ABPM cited in European guidelines [33]. Other indications include the suspect of masked hypertension, the detection of abnormal BP circadian rhythm (including "non-dipping" status, postprandial hypotension, and "morning surge"), and the assessment of response to treatment in complex cases (e.g., high BP variability and resistant hypertension). For all these reasons, ABPM is frequently useful among very old subjects. The superior prognostic ability of ABPM values compared with clinical ones in predicting the risk of mortality and cardiovascular events [34] represents a further reason to perform the assessment in conditions where prognostication is particularly challenging, such as complex geriatric patients. Although ABPM assessment is sometimes considered difficult to perform and poorly tolerated in older patients with cognitive impairment, this was found not to be the case for the vast majority of dementia patients in a memory clinic, with the only exception of those with severe behavioral disorders [35]. However, when ABPM is deemed as non-feasible, home BP measurements seem to be a reliable alternative [34].

8.3.2 The Role of Cognitive and Functional Status

Limitations in activities of daily living and cognitive impairment frequently occur during old age. Several longitudinal data have associated high BP with risk of disability onset [36]. This effect appears at least partly mediated by increased stroke risk [37], although higher BP has been associated with increased risk of motor impairment also in a cohort of older stroke-free subjects [38]. This association appears to be mediated by cognitive impairment onset and might be at least partly explained by the onset of microvascular cerebral lesions, such as white matter lesions, without acute cerebrovascular events [39]. Of notice, the extent of brain microvascular changes has been associated with extra-cerebral end-organ damages in AH, including chronic kidney damage [40], increased left ventricular mass [41], and retinal microvascular changes [42].

Moreover high BP at midlife has been associated with cognitive impairment and dementia in old age in several cohort studies [43]. Data are less consistent

regarding the effect of BP on risk of cognitive impairment among older subjects. In fact, while some studies have confirmed this association among older subjects [44], other studies could not confirm it and have observed just the opposite [45]. On the whole it seems that, while high BP is still associate d with increased risk of cognitive decline 10 years later among "young old" (age range 65–74), it might have a neutral effect between 75 and 84 and even act as a preventive factor among subjects aged 85+ [46]. On the other hand, it has repeatedly been shown that, while long-lasting high BP values are associated with increased dementia risk, dementia onset is associated with subsequent decline of BP values, possibly caused by an altered vascular control due to brain damage [47].

Finally, a poorer self-reported physical and mental health has been associated with lower BP values, not only among older subjects but also among younger adults with history of vascular disorders [48]. Therefore it is not surprising that lower BP is associated with lower grip strength, an objective measure of physical performance, among subjects aged 85 [49] and, similarly, with a worse cognitive and physical performance in centenarians [50].

Therefore, the assessment of cognitive and functional status in older hypertensives subjects has two different aims:

1. To have an indirect, easy obtainable estimate of brain end-organ damage associated with high BP.
2. To assess the prognostic role of BP values in the context of the biological age of the single subject. As it will be discussed below, target BP values might differ in old age according to "frailty status," which in turn can be estimated by validated and reproducible measures of cognitive and functional status.

Several short measures of cognitive status among older subjects exist and can be used in clinical practice. Among such measures, Mini Mental State Examination (MMSE) [51] is one of the best known and probably represents a "gold standard" for brief cognitive assessment, due to its widespread use both in clinical and in research setting all over the world, the ability to reliably identify dementia and stage its severity, and the possibility to follow up patients over time [52]. The administration of the test is 5–10 min long, depending on patient's cognitive status, and includes items testing orientation to space and time, memory, attention and calculation, word finding, phrase repetition, comprehension of spoken and written language, and constructional praxis. The total score is included between 0 and 30, with 24 being the most widely adopted cutoff for dementia. Locally validated rules exist to adjust the score for age and education. While this instrument is widely adopted in geriatric facilities, it will be probably felt as too time-consuming in a typical hypertension clinic. A suitable, less time-consuming alternative for cognitive screening is the Mini-Cog [53], which requests only a 2-min assessment, including the recall of the three words, similar to the MMSE, and the drawing of a clock. The scoring of the test is straightforward, as shown in Fig. 8.1.

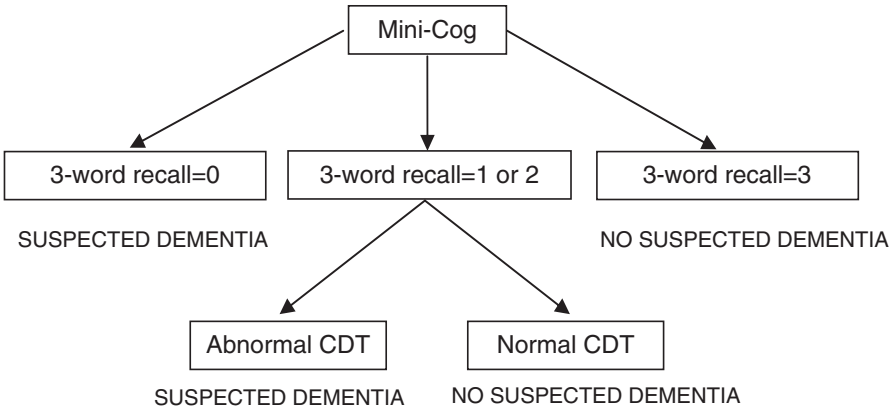

Fig. 8.1 Mini-Cog test (Borson et al. [53]): administration and scoring
- Ask the patient to repeat three semantically unrelated words.
- Ask the patient to draw a clock.
  - Draw a circle.
  - Add the numbers.
  - Set the time on 11:10.
- Ask the patient to recall the previously repeated words.

Clock Drawing Test (CDT) is normal if all numbers are present in the right sequence and position and clock's hands are in the right position.
Test is scored according to the following algorithm

To reduce the risk of false positives, it is recommended to corroborate the suspect of dementia, as resulting from Mini-Cog, with:

1. Report of cognitive impairment by the patient himself and/or relatives, according to accepted criteria for dementia and mild cognitive impairment [54]
2. Impairment in instrumental activities of daily living, especially use of telephone, handling medications, and finances, which appears to be fairly specific for dementia [55]

Lower extremity function measures are widely used in geriatric medicine as a measure of physical frailty, and several of them are usable as brief screener. The most validated single measure is represented by gait speed on a 4-m corridor, with speed <0.8 m/s (i.e., time to walk through 4 m >5 s) being a sensitive measure of physical frailty [56]. Gait speed is also included in more comprehensive physical performance tests, such as the short physical performance battery [57], which includes a balance test (measuring the ability to stand side by side, in semi-tandem, and in tandem), the abovementioned gait speed test, and the chair stand test, measuring the time needed to stand up for five times from a chair without using arms. Each subtest is scored from 0 to 4, with a total score ranging from 0 to 12 and values <10 indicating reduced physical performance and being associated with worse outcome, including higher risk of mortality, disability onset and progression,

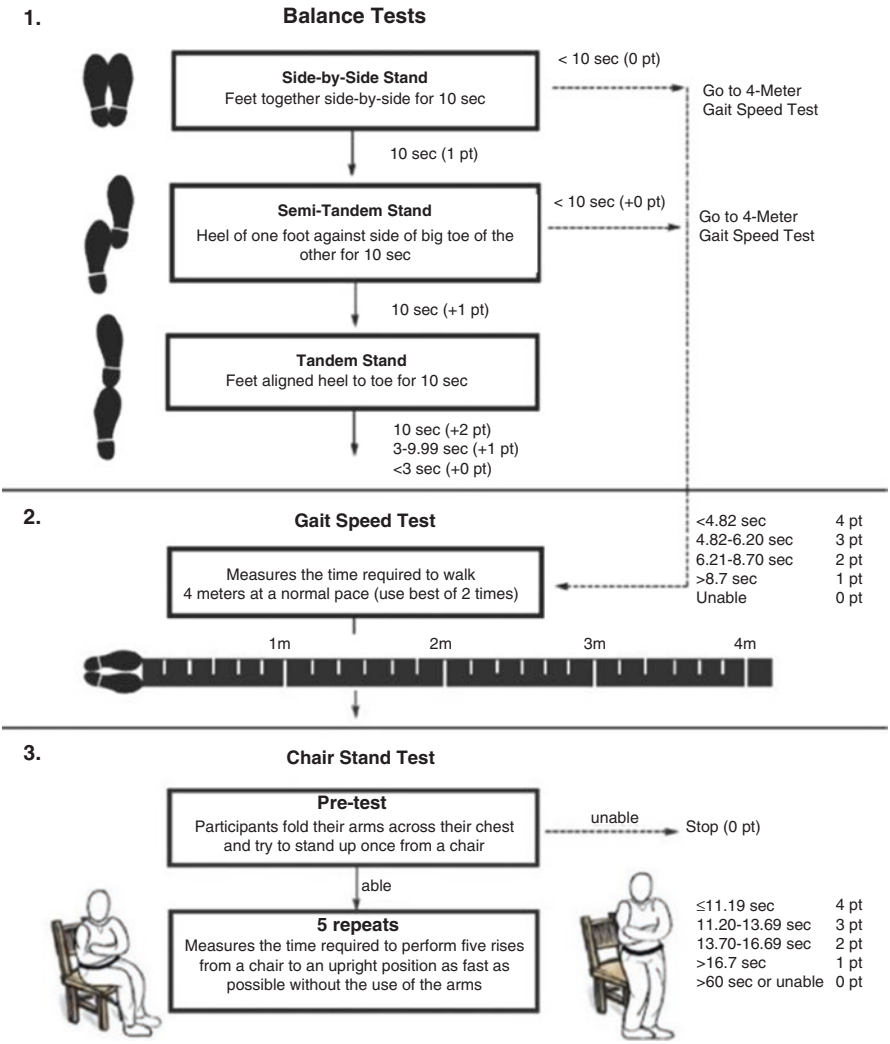

Fig. 8.2 Short physical performance battery: scoring sheet (Guralnik JM, Assesing Physical Performance in the Older Patient, National Institute on Aging)

hospitalization, and institutionalization [58, 59]. While this assessment is more comprehensive in comparison with gait speed only, as it includes measures of balance and lower extremity muscle strength, the predictive values of gait speed alone seem to be similar to the complete performance test [60] (Fig. 8.2).

Finally, the presence of overt disability in basic activities of daily living (ADL: washing, dressing, going to the toilet, transferring, eating) has to be identified in older subjects with AH, as it appears to have a strong prognostic role beyond the presence of associated comorbid conditions, including high BP [61]. This is evident for nursing homes patients, in whom the prognostic role of BP has been found

almost irrelevant in comparison with the presence of ADL disability and behavioral disorders [32], and possible beneficial effects of antihypertensive drugs have to be weighted carefully against the risk of brain hypoperfusion, falls, and fractures [7]. To screen for the presence of ADL disability, the single question regarding the ability to dress and undress oneself has been found to possess satisfactory accuracy to detect a significant impairment [62].

8.4 Treatment

8.4.1 Guidelines and Clinical Trials in the Oldest Old

Randomized clinical trials performed during last 20 years have clearly shown that the benefit of antihypertensive treatments on cardiovascular events is not significantly different at ages above rather than below 65 years, with a greater absolute benefit in the elderly because of the higher cardiovascular risk characterizing old age [63]. These results have been extended to very old age with Hypertension in the Very Elderly Trial (HYVET), which was prematurely terminated after the demonstration of a clear benefit of antihypertensive treatment in reducing total mortality, heart failure, and stroke in subjects aged 80+ [64].

Yet some points have not been clarified yet, one of the first being the effect of age on the cutoff and the target for antihypertensive treatment. Since 2013, European [13] and US [65] guidelines have acknowledged different cutoffs and target values for antihypertensive drugs treatment in old age (Table 8.1). This was mainly based on the critical reappraisal of previous guidelines, which clearly indicated that the treatment of grade I AH and the previously indicated cutoff of 140/90 mmHg were not evidence-based in the elderly [66]. In fact all randomized clinical trials including only subjects 65+ had SBP ≥160 mmHg as inclusion criterion, enrolled subjects showed a mean baseline SBP included between 166 and 196 mmHg, and generally did not attained a mean SBP <140 mmHg in the actively treated group. This is particularly true for subjects enrolled in HYVET, who were over 80, with no severe comorbidity, had mean BP values 173/91 mmHg at baseline and attained BP values of 144 and 159 mmHg at follow-up in active treatment and placebo group, respectively [64].

Only few intervention studies have addressed the issue of different BP targets among older subjects, with somehow conflicting results. In a subgroup analysis of the FEVER study, 3179 older Chinese patients randomized to more intense treatment (low-dose hydrochlorothiazide plus felodipine, achieved SBP 138 mmHg) had a lower risk of stroke, cardiovascular events, and total mortality compared to the ones randomized to less intense treatment (low-dose hydrochlorothiazide plus placebo, achieved SBP 142 mmHg) [67]. Yet it has to be acknowledged that this was a subgroup analysis and that "older subjects" group was 65+, with a mean age 69.5. Two other Japanese studies have specifically focused on different treatment targets for older subjects [68, 69]. In the VALISH study, 3260 patients aged 70–84 (mean age 76) were randomized to strict BP control (target SBP < 140 mmHg, achieved

SBP 137 mmHg) vs. moderate control (target SBP 140–150 mmHg, achieved SBP 142 mmHg). After 3 years the two groups did not differ for the primary composite end point neither for any of the secondary end points, including stroke, cardiac events, cardiovascular mortality, total mortality, and for incidence of adverse events [69]. Moreover, in the JATOS study, 4418 patients aged 65–85 (42 % over 75) were randomized to strict BP control (target SBP < 140 mmHg, achieved SBP 136 mmHg) vs. moderate control (target SBP 140–160 mmHg, achieved SBP 146 mmHg). After 2 years the two groups did not differ for the combined primary end point (stroke, cardiac events, renal failure) neither for total mortality nor for incidence of adverse events. Yet an interaction between age and treatment group was associated with primary end point, with the highest risk in the subgroup aged 75+ undergoing more strict control [68].

The abovementioned data are consistent with the results of a meta-analysis of data pertaining to subjects aged 80+ enrolled in different RCTs. In those subjects a significant effect of active treatment was confirmed for stroke, cardiovascular events, and heart failure, while no effect was observed for cardiovascular death and total mortality. In a meta-regression analysis, mortality risk was reduced in the treatment arm of trials that adopted a lower-intensity treatment and achieved the least BP reduction [70].

Moreover in observational studies of subjects aged 85+, SBP <140 mmHg has repeatedly been associated with higher mortality risk [8–10]. Yet this association might differ according to antihypertensive treatment status, as shown in an international study of home BP monitoring in older subjects aged 80+, aimed at identifying optimal BP targets in regard to mortality risk over a 5.5-year follow-up. In fact, cardiovascular mortality and morbidity showed a direct association with SBP among subjects non-treated with antihypertensives, with highest risk at values >152 mmHg, while it showed a curvilinear association with SBP in the subgroup receiving antihypertensive drugs, with an increased cardiovascular risk for SBP <127 mmHg [71]. Moreover the risk associated with low BP in old age appears to be greater among subjects with a history of AH at midlife, in regard both to survival [8] and to brain atrophy and cognitive decline [72].

On the whole the cited data raise a caveat for excessive SBP lowering among actively treated subjects in very old age, with a cutoff for increased risk around the age of 80, especially for those with a long-standing history of AH. On a pathophysiological ground, the observed epidemiological and clinical data might be explained by a small reduction of perfusion of vital organs coupled with an altered vascular autoregulation associated with chronic AH, possibly leading to critical hypoperfusion if associated with decreased BP [72]. This hypothesis has not been proven yet, as a recent study of the association between BP and cerebral blood flow of very old subjects with mild cognitive impairment was not able to show any correlation between lower BP values and cerebral hypoperfusion [73]. Moreover it should be remembered that low BP is often associated with more severe clinical, and especially cardiovascular, conditions and that at least part of the observed association might be confounded by comorbidities. For these and other reasons,

Table 8.1 Antihypertensive treatment in the elderly: synopsis of European and US guidelines and open issues

	ESH 2013 [13]	JNC VIII [65]	Open issues
General cutoff for treatment	SBP ≥160 mmHg	BP ≥150/90 mmHg	
Treatment target	140–150 mmHg	<150/90 mmHg	
Subgroups		Not specified	
Fit aged <80	Treat if SBP ≥ 140 mmHg and AHDs are well tolerated	–	*Is there a chronological age cutoff for different BP targets?*
Fit aged 80+	Treat if SBP ≥ 160 mmHg and AHDs are well tolerated	–	
Frail	Individualized choice, monitor AHDs effects	–	*Frailty indicators? Specific BP targets?*
AHDs discontinuation	Not advised after age 80 if well tolerated	Not advised for SBP < 140 mmHg if well tolerated	*Is there a lower limit to BP lowering?*

the so-called J-curve phenomenon regarding the prognostic role of BP has been widely debated [74].

The Systolic Blood Pressure Intervention Trial (SPRINT) [75] has strengthened the position of those supporting the preventive efficacy of aggressive BP treatment also among older subjects. In patients at high cardiovascular risk and already using antihypertensive drugs, a treatment strategy targeting a systolic BP of 120 mmHg resulted in lower incidence of major cardiovascular events and death from any cause compared to a less strict approach targeting a systolic BP of 140 mmHg; this result was also statistically significant in the subgroup (28 % of the entire sample, n=2636) of patients more than 75 years old. Yet, it has to be pointed out that patients with severe disability, living in nursing, affected by dementia, decompensated heart failure, previous stroke, or diabetes were excluded from the study. Conversely included subjects had a mean 20 % 10-year Framingham cardiovascular risk score and a mean BMI of 30. On the whole SPRINT results add relevant information regarding antihypertensive treatment of a significant part of the older population but seem to apply to high vascular risk patients without disability and abovementioned diseases, and therefore may not be unconditionally applied to the oldest old.

8.4.2 Frailty Detection and Antihypertensive Treatment Choices

Apart from chronological age, several studies in most recent years have pointed out at a role for "frailty" in increasing the risk associated with antihypertensive treatment among elderly subjects [11].

In geriatric research frailty is conceptualized as a physiological syndrome characterized by decreased functional reserve and diminished resistance to stressors, causing vulnerability to adverse health outcomes, including disability and death

[76]. While frailty should be reliably identified with a comprehensive geriatric assessment, identifying multiple physical, mental, and social impairments whose accumulation may ultimately lead to the increased vulnerability status [77], rapid screener for this condition is often needed in clinical practice due to time and resource constraints. Therefore simple clinical tools have been operationalized to detect frailty with sufficient sensitivity and specificity [56], instruments based on lower extremity performance being among the most useful for this purpose [59].

An analysis from the National Health and Nutrition Examination Survey (NHANES) supports a role for motor performance as a powerful modulator of BP-associated risk. In fact, in a cohort of 2340 older subjects (mean age 74), the association between BP and a 7-year mortality varied markedly among subjects, according to their ability to walk 6 m as fast walkers (≥0.8 m/s), slow walkers (<0.8 m/s), or unable to complete the task. In fact, while high SBP was associated with increased mortality among fast walkers, the association disappeared among slow walkers and was reverted among subjects unable to walk, who had a greater risk associated with low values of SBP and DBP [78].

In keeping with these data, a condition of overt disability in activities of daily living associated with low BP has been identified as a condition with a negative prognostic outcome among oldest old (age 85+), in terms of both increased risk of cognitive decline [45] and increased risk for stroke [79]. Moreover, in the vast group of disabled nursing home subjects, BP was found as unrelated to a 1-year mortality risk in one study [32] and inversely associated with increased 2-year mortality risk in another one [80]. Of notice, in the latter study the increased risk for mortality was restricted to subjects with SBP < 130 mmHg in combination with 2+ antihypertensive drugs, thus supporting the need of less intensive treatment in this highly impaired population.

Finally, subjects with cognitive impairment might represent a subpopulation at high risk for brain hypoperfusion. Yet in this condition the data are not clear-cut. In fact, one study of 1385 subjects with mild cognitive impairment (mean age 73.6, baseline MMSE 28/30) has found a faster progression of cognitive decline over 2 years among subjects with repeated detection of high BP (≥140/90 mmHg) [81]. In keeping with these data, subjects with mild cognitive impairment (mean age 67.8, baseline MMSE 26/30) have been found to have an increased risk of conversion to Alzheimer's disease after 5 years, while antihypertensive treatment reduced the risk [82]. Conversely a subsequent study conducted with ambulatory BP monitoring in a sample of 172 older subjects with dementia or mild cognitive impairment (mean age 79, MMSE 22/30) has observed an increased risk of cognitive decline after 9 months among subjects with lower mean daytime SBP (<129 mmHg) actively treated with antihypertensive drugs [83]. Another study of 141 subjects with mild cognitive impairment (mean age 74) has observed an independent association between orthostatic hypotension and increased risk for conversion to dementia after 2 years [84]. Therefore, the presence of mild cognitive impairment might be a caveat for possible detrimental effects of excessive BP lowering, at least among oldest old and for subjects with orthostatic hypotension and overt dementia. ABPM seems to be more useful than clinical measure in predicting the cognitive detrimental effects of low BP.

On the whole, the presence of functional disability, motor impairment, and cognitive impairment might be useful markers of increased vulnerability to antihypertensive treatment. These factors together with old age can suggest a more prudent approach to vascular risk factor prevention, including antihypertensive treatment [85]. A treatment discontinuation randomized trial of 385 older subjects 75+ with mild cognitive decline (mean age 81, MMSE 26/30) was recently published. Subjects were included if they took at least one antihypertensive drug, and SBP was ≤160 mmHg. After 16 weeks SBP went from 148.8 mmHg to 154.2 mmHg, but no positive effect was evident on cognitive function, psychological status, or daily functioning [86]. Further studies of treatment de-intensification are warranted, with the aim of identifying the role of different BP measures (clinical vs. ambulatory) and different BP targets for specific subgroups of frail older subjects.

Conclusion

Oldest old subjects represent a fast-rising share of world population who lacks firm indications regarding prognostic meaning of BP values and preventive or harmful effects of antihypertensive treatment. The need to differentiate antihypertensive treatment targets according to age and health status introduced by European guidelines represents an opportunity to personalize medical approach to this diverse population group. Observational and intervention studies published during the last years suggest that a strict BP control might be beneficial in some older subjects (as shown by SPRINT trial) but might harm other ones, probably the frailest. Comprehensive geriatric assessment is useful in detecting vulnerability indicators, and simple cognitive and functional measures should be used to screen for older subjects who need a more cautious approach. Future epidemiological and intervention studies targeting specific profiles of frailty are warranted, to support personalized antihypertensive treatment strategies for oldest old subjects.

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New Challenges in Aortic Stenosis in the Elderly: From Epidemiology to TAVI

9

Andreas W. Schoenenberger and Manuel Martínez-Sellés

9.1 Pathology and Epidemiology

There are three principal causes of valvular aortic stenosis (AS): congenital, rheumatic, and degenerative. While congenital AS clinically manifests at younger ages and rheumatic AS dwindled in importance with the decline in rheumatic fever, age-related degenerative calcific AS is now the most common cause of valvular AS in adults [1]. Degenerative calcific AS is the result of a progressive calcification of the aortic valves based on a process of inflammation, lipid accumulation, and calcification. This dynamic process resembles the process of atherosclerosis in many regards. Some clinical risk factors of atherosclerosis have also been identified as risk factors of calcific AS, including hypertension, hyperlipidemia, smoking, and diabetes [2]. Degenerative calcific AS occurs in patients with congenitally normal tricuspid aortic valves, but a congenitally bicuspid aortic valve seems to be an important additional risk factor of degenerative calcific AS development [1, 3].

Prevalence of severe degenerative calcific AS increases with age (Fig. 9.1) [4]. Severe degenerative AS occurs only rarely before the age of 70 years. In persons aged 85 years and older, prevalence approximates 10 % and therefore is a frequent health problem in the oldest old. Current estimates consistently reveal that AS incidence will rise in developed countries in the forthcoming years due to the demographic and epidemiologic changes.

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_9

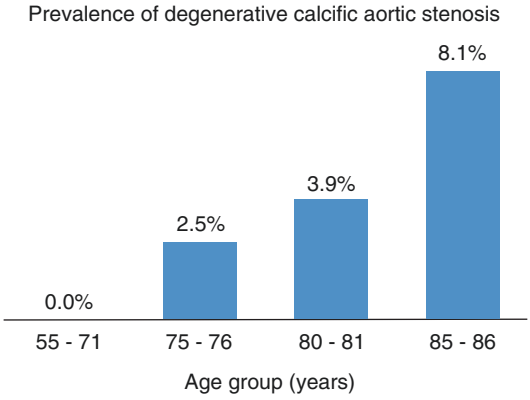

Fig. 9.1 Prevalence of degenerative calcific aortic stenosis [4]. Aortic stenosis was defined based on combined criteria of velocity ratio ≤0.35 and aortic valve area ≤1.2 cm^2

9.2 Clinical Manifestations and Impact of Aortic Stenosis

Degenerative AS usually evolves slowly over the years. There is a long latent period, during which the patient remains asymptomatic. Angina pectoris is a frequent first clinical manifestation of advanced AS. Angina usually results from the increased oxygen need of the hypertrophied myocardium and a reduced oxygen delivery due to secondary coronary vessel compression. Concurrent coronary artery disease is not mandatory but is often present in older patients with AS. Syncope due to cerebral hypoperfusion is another frequent clinical manifestation of AS. It typically occurs upon exertion when arterial pressure decreases secondary to systemic vasodilation. Elderly patients are more likely to suffer syncope in advanced AS than younger patients are, because they often have concurrent atherosclerotic changes in the cerebral vasculature facilitating cerebral hypoperfusion. Furthermore, the baroreceptor function, which counteracts the systemic hypotension, may be impaired at old age. Another important clinical manifestation of AS is exertional dyspnea and/or heart failure. While in younger patients these symptoms usually do not develop until very late in the progression of AS, dyspnea and signs of heart failure may develop earlier in elderly patients who have further comorbid conditions of the heart or lungs.

All these symptoms are of great relevance in old patients. Symptoms such as angina or dyspnea not only adversely affect life quality but may also lead to disability. Due to the high prevalence of other comorbid conditions, such as sarcopenia, arterial pressure decrease upon exertion may strongly affect gait and physical function. The risk of deleterious consequences after a syncope is also higher in old vs. young patients, because elderly patients more frequently (i.e., about 5 %) suffer fractures after a syncope due to concurrent osteoporosis.

Degenerative AS is a chronic progressive disease. When symptoms develop, the prognosis is poor in the absence of a specific treatment, with impaired quality of life and high short-term mortality. Data from the PARTNER trial show that without aortic valve replacement, the 2- and 3-year mortality rate were 68.0 % and 80.9 %, respectively, despite an up-to-date standard therapy with drugs and, if indicated, balloon aortic valvuloplasty [5, 6].

9.3 Transcatheter Aortic Valve Implantation (TAVI)

Open-heart surgical aortic valve replacement (sAVR) was the standard treatment for severe aortic stenosis up until a few years. The results of sAVR were satisfactory in old patients with degenerative AS, with improved survival and quality of life [7]. However, it has to be realized that evidence regarding sAVR was mainly based on retrospective studies and registries conducted in younger patients. In fact, the decision to perform sAVR in octogenarians remains a challenge, mainly due to increased operative morbidity and mortality. It is estimated that approximately one third of patients were denied sAVR, typically due to a high surgical risk [8]. Moreover, many elderly patients with severe AS either refuse or are not referred for sAVR evaluation, despite evidence that sAVR can be performed safely in selected octogenarians.

Transcatheter aortic valve implantation (TAVI) is a new therapeutic option that involves providing aortic valve replacement through a catheter. The tip of the catheter wears the replacing valve, which was squeezed down on an inflatable balloon or a self-expandable system. The catheter is usually inserted through the femoral artery or through a small incision in the chest over the heart. The replacing valve is subsequently positioned inside the faulty aortic valve and unfolded. This procedure is believed to be associated with less interventional risk than sAVR and, therefore, was first used in older patients with high surgical risk.

Successful TAVI results in substantial hemodynamic and clinical improvement in patients with severe AS and high surgical risk. The PARTNER trial found a markedly lower 2-year and 3-year mortality rates of 43.3 % and 54.1 %, respectively, with TAVI as compared to the standard therapy (mortality rates of 68.0 % and 80.9 %, respectively) [5, 6]. The PARTNER trial also showed that mortality rates of TAVI and sAVR were similar [9]. TAVI not only dramatically improved survival as compared to a standard therapy but also markedly improved dyspnea functional class as well as quality of life. At 1 year after TAVI, 74.8 % of the surviving patients who had undergone TAVI, as compared with only 42.0 % of the surviving patients who had received standard therapy, were asymptomatic or had mild symptoms (New York Heart Association class I or II) (Fig. 9.2) [10].

Current guidelines recommend TAVI in patients with severe symptomatic AS, who are not suitable for sAVR as assessed by a multidisciplinary heart team involving cardiologists, cardiac surgeons, and other specialists [11, 12]. Also, TAVI can be considered in high-risk patients who may still be suitable for sAVR, but in whom TAVI is favored by the heart team based on an individual benefit-to-risk assessment [11]. Elderly patients are often included in this high-risk group, mostly due to associated comorbidity. Comorbidity has great influence on the prognosis of these patients. In fact, the real benefit in terms of survival of TAVI in elderly patients with high comorbidity is controversial. Consequently, it is essential to enhance risk prediction of patients scheduled for TAVI and to identify those most likely to benefit from TAVI [13, 14]. Current guidelines recommend that TAVI should not be performed, if comorbid conditions reduce life expectancy to less than 1 year [11].

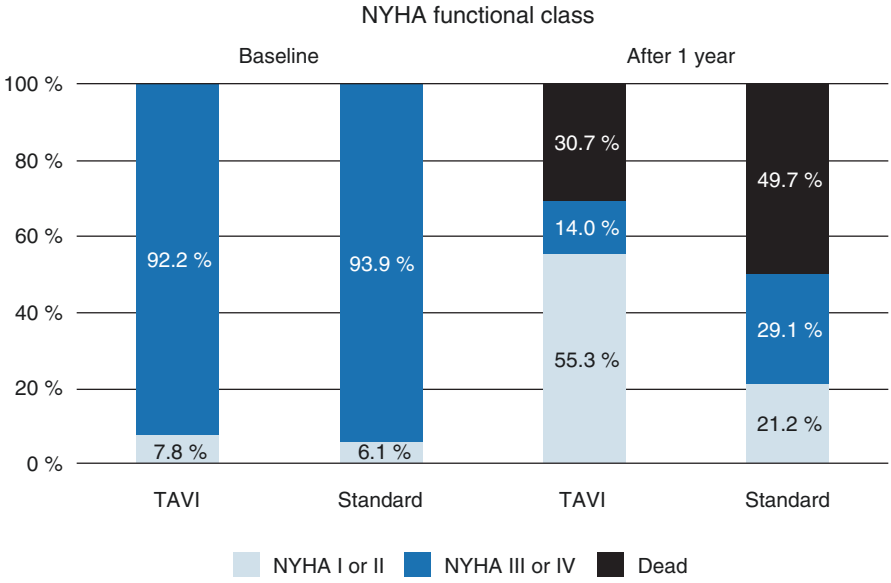

Fig. 9.2 Symptom status in patients with severe aortic stenosis over time with transcatheter aortic valve implantation (TAVI) and without TAVI (standard therapy) [10]. *Abbreviations*: *NYHA* New York Heart Association, *TAVI* transcatheter aortic valve implantation

9.4 Geriatric Aspects

According to the aforementioned selection criteria, TAVI is mainly performed in elderly patients. Therefore, concurrent geriatric problems are frequently found. A recent study found cognitive impairment in approximately one of three patients undergoing TAVI, and approximately two of five patients had mobility impairment and/or were malnourished (Table 9.1) [15]. Comprehensive geriatric assessment (CGA) is a process suitable to detect these problems. CGA differs from the standard medical evaluation in its concentration on older people with their complex problems and its emphasis on functional status [16]. It is important to perform CGA routinely and systematically in every patient, as it is well known that the geriatric problems often go undetected, if patients are not routinely screened for their presence [17].

Concurrent geriatric problems are of great relevance. First, geriatric problems are important for risk prediction. Studies provided evidence that frailty, calculated based on the presence of geriatric problems, may improve risk prediction (Table 9.2) [15, 18, 19]. One recent study in TAVI patients showed that frailty predicts mortality with high accuracy similar to established risk scores (i.e., EuroSCORE or Society of Thoracic Surgeons score) [18]. Frailty also predicted functional decline, whereas the established risk scores were not predictive of this important outcome after TAVI [15]. Second, detected geriatric problems are important to improve quality of care. For example, detection of cognitive impairment implies to undertake preventive steps for delirium prevention during and shortly after TAVI, because

Table 9.1 Prevalence of geriatric problems among patients receiving TAVI [15]

Geriatric problem	Definition	Frequency
Cognitive impairment	MMSE <27 points	32.8 %
Mobility impairment	TUG ≥20 s	38.7 %
Malnutrition	MNA <12 points	44.5 %
Disability for BADL	BADL with ≥1 activity with limitation	26.9 %
Disability for IADL	IADL with ≥1 activity with limitation	60.5 %

Abbreviations: *BADL* basic activities of daily living, *IADL* instrumental activities of daily living, *MMSE* mini-mental state exam, *MNA* mini nutritional assessment, *TUG* timed get up and go test

Table 9.2 Frailty is an important predictor of outcomes after transcatheter aortic valve implantation (TAVI) [15, 18]

Predictor	Outcome			
	Functional decline[a]		Mortality[b]	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
Logistic EuroSCORE[c]	0.79 (0.31–2.02)	0.62	4.02 (0.86–18.70)	0.09
STS score[c]	1.14 (0.44–2.95)	0.78	5.47 (1.48–20.22)	0.01
Frailty index[c]	3.31 (1.21–9.03)	0.02	3.68 (1.21–11.19)	0.02

Abbreviations: *CI* confidence interval, *OR* odds ratio, *STS* Society of Thoracic Surgeons
[a]Functional decline was defined as a decrease of ≥1 point in the ability to perform basic activities of daily living (BADL) between baseline and follow-up
[b]Mortality 1 year after transcatheter aortic valve implantation (TAVI)
[c]All predictors were used after dichotomization at standard cut points (EuroSCORE ≥20 % vs. <20 %, STS score ≥5 % vs. <5 %, frailty index ≥3 vs. <3 points)

patients with cognitive impairment are at highest risk of developing delirium periprocedurally. Furthermore, cognitive impairment should give rise to ensure drug adherence after the intervention, because these patients are at the highest risk of being nonadherent. Third, elderly patients with geriatric problems should be considered candidates for geriatric rehabilitation. Studies provided evidence that inpatient rehabilitation specifically designed for geriatric patients has the potential to improve outcomes related to function, admission to nursing homes, and mortality [20]. Considering these important consequences, CGA should be performed in all patients undergoing TAVI.

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Aging Kidney: Vascular Characteristics and Assessment

10

Andrea Ungar, Marcello Amato, and Alice Ceccofiglio

10.1 The Aging Kidney: Anatomical and Functional Modifications

Renal aging is a multifactorial process where gender, race, and genetic background and several key mediators such as chronic inflammation, oxidative stress, the renin–angiotensin–aldosterone system, impairment in kidney repair capacities, and background cardiovascular disease play a significant role [1]. Features of the aging kidney include macroscopic and microscopic changes and important functional adaptations, none of which is pathognomonic of aging. The principal anatomical modification is a gradual renal mass reduction that is more pronounced in the renal cortex than in the medulla [2, 3]. From a microscopic point of view, the aging kidney displays glomerular, tubular–interstitial, and vascular changes.

10.1.1 Glomerular Changes

The number of functioning glomeruli decreases during lifetime, while the proportion of hyaline and sclerotic glomeruli increases from 1 % in the young adult to 20–30 % in the 80-year-old adult (Fig. 10.1) [4]. In response to the reduced number

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_10

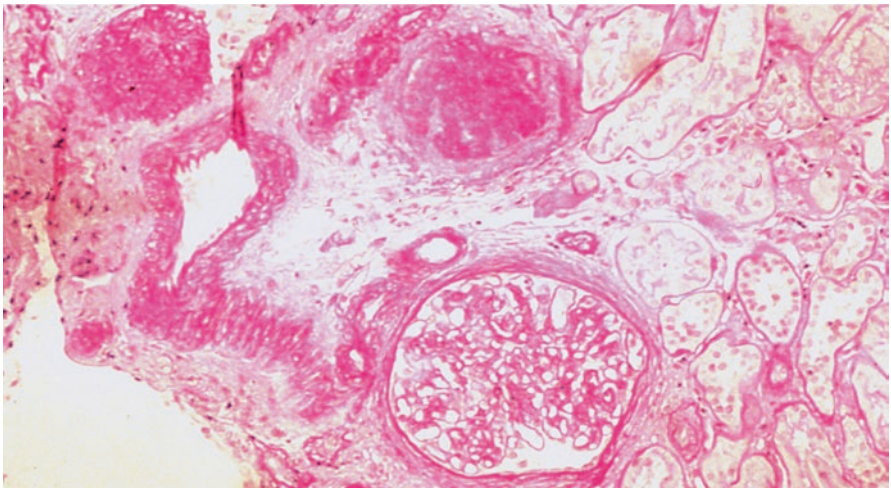

Fig. 10.1 Sclerotic glomeruli in the aging kidney

of functioning glomeruli, the aging kidney is characterized by a hyperfiltering condition with an increase in glomerular plasma flow and intracapillary pressure. However, this adaptation mechanism may accelerate glomerulosclerosis in the long term because it raises intraglomerular pressure [2, 5, 6]. Glomerular basement membrane thickening is another typical feature of the aging glomeruli [3] as it is a mesangial expansion [7]. Glomerulosclerosis prevails in the cortical zone and determines a complete atrophy of the glomerulus, while direct shunts between afferent and efferent arterioles bypass the glomerular tuft in juxtamedullary nephrons [8]. Probably, this is the explanation for the flow preservation in the medulla of the aging kidney.

10.1.2 Tubulointerstitial Changes

As described for glomeruli, the overall number of tubules decreases with age [9], the proximal tubular length is also markedly reduced, while the distal tubules and the collecting duct develop more diverticula that may give rise to form simple renal cysts [4, 10]. Tubular dilatation may be accompanied by accumulation of hyaline material and basement membrane thickening. When extended, this process may lead to a sort of "thyroidization" of the kidney, a common feature in end-stage kidney disease [9]. Expanded interstitial volume, infiltration of mononuclear cells, and diffuse areas of fibrosis are all hallmarks of the aging kidney [11]. Alterations in tubular function go along with anatomical involvement, particularly in renal aging, and decrease the capacity of diluting and concentrating urine [12, 13]. Enhanced proximal sodium reabsorption coupled to reduced distal fractional reabsorption allows maintenance of a normal sodium balance under steady-state conditions in the elderly [14]. However, this functional resetting limits the ability to conserve sodium

in response to low-salt intake and makes elderly people predisposed to volume depletion and acute kidney injury [15]. Inadequate activation of the renin–angiotensin system and reduced aldosterone secretion (hyporeninemic hypoaldosteronism) play a leading role into this phenomenon [16] as well as in nocturnal natriuresis, another frequent alteration in old people [17]. On the other hand, aged individuals display also a relative inability to excrete sodium excess in response to salt load, a multifactorial alteration predisposing to salt retention, hypertension, and cardiovascular congestion. Resistance to the natriuretic effect of atrial natriuretic peptide is a key step into this process [18]. Alterations in tubular handling of electrolytes extend to potassium. Due to tubular atrophy and tubular–interstitial scarring, Na–K ATPase activity is reduced in the elderly, resulting in a high risk for hyperkalemia. Reduction in GFR, hyporeninemic hypoaldosteronism, dehydration, and metabolic acidosis all enhance the tendency to hyperkalemia in the elderly, and the administration of potassium-sparing drugs may precipitate serious clinical events in individuals harboring these risk factors [19]. Even though the renal regulation of acid–base balance is globally conserved in the aging kidney [20], the capacity of generating ammonia is clearly impaired [21]. Elderly subjects are more prone than young individuals to develop acidosis in response to acid load (such as after a high-protein meal or in stress conditions which activate proteolysis) mainly because of the incapacity to increase ammonia and H+ synthesis [22–24]. Impaired proton pump activity in the cortical collecting duct is a critical element in the deranged response to acid load in the elderly [21, 25]. Renal-dependent metabolic acidosis has been implicated in a constellation of alterations in the elderly including hypercalciuria, decreased citrate excretion, enhanced protein catabolism, muscle wasting, bone dissolution, cardiomyopathy, and progression of CKD [26].

10.1.3 Vascular Changes

Structural changes in renal vasculature include intimal and medial hypertrophy, arteriolosclerosis, and overt atherosclerotic lesions [27]. Increased irregularity and tortuosity of pre-glomerular vessels, direct shunts between afferent and efferent vessels (see above), wall thickening and narrowing of the vascular lumen of afferent arterioles [28], and an alteration mainly depending on vascular smooth muscle cell proliferation are observed [29]. In addition, micro-infarctions triggered by cholesterol emboli are often observed along with atherosclerosis of the aorta and renal arteries in elderly patients with diabetes and hypertension. Interlobular arteries in the elderly show fibro-intimal hyperplasia [27], a feature typically observed in patients with chronic hypertension regardless of age.

10.1.4 Functional Changes

Renal blood flow (RBF) decreases with age, falling from 600 ml/min/1.73 m^2 in the young adult to 300 ml/min/1.73 m^2 by the age of 80 [30, 31]. This decrease is due

to both a reduction in renal mass and a progressive reduction in mean blood flow per unit of tissue mass. The decrease in blood perfusion seems to be mainly due to organic abnormalities of intrarenal vessels but also to an impairment of functional vasomotility [31, 32]. GFR decreases less than RBF, so that filtration fraction calculated as [GFR/RBF-FF]- increases [8]. This phenomenon may be due to two possible mechanisms: (1) hyperfiltration of functioning glomeruli due to an efferent arteriole vasoconstriction greater than the afferent one, with a consequent increase in intraglomerular pressure [37], and (2) RBF decrease limited to the cortex, so that medullary flow relatively rises [30–32, 34].

10.1.5 Renal Autoregulation in the Elderly

In healthy subjects, the kidney maintains a constant RBF and GFR regardless of renal perfusion pressure (RPP) over a defined range (80–180 mmHg). This is possible, thanks to intrarenal autoregulation, mediated by myogenic control of arteriolar tone and tubuloglomerular feedback (TGF). The first one consists of changes in the afferent arteriolar tone—vasoconstriction or vasodilation—[35], independently of the local nervous system [36]. This phenomenon is probably mediated by stretch receptors in response to modifications of perfusion pressure [36]. Tubuloglomerular feedback (TGF) is mediated by specialized cells in the macula densa, a region of the thick ascending limb of the loop of Henle adjacent to the glomerular vascular pole. These cells sense changes in the tubular flow, probably through chloride delivery, directly modified by GFR and RBF changes [37]. Via afferent arteriolar resistance, TGF modifies RBF and GFR and consequently normalizes tubular flow. The primary mediators of TGF feedback are not completely understood. Certain studies propose angiotensin II as the main mediator, but it has been demonstrated that it acts only as sensitivity modulator of the feedback response [38]. In fact, angiotensin II modulates TGF activity on the afferent arteriole and directly increases the efferent arteriole tone, with a consequent increase in both glomerular capillary pressure and in filtration fraction when GFR is reduced [39, 40]. Other vasoactive substances like prostaglandins, endothelin, and various endothelium-derived factors modulate autoregulation mechanisms. These autacoids induce variations on GFR and RBF by acting on afferent and efferent arteriole tone, but they also influence other renal functions such as tubular absorption and excretory activity.

10.1.6 Renal Adaptation Capacity During Stress Conditions in the Aging Kidney

The vulnerability of the aging kidney, which manifests itself in the presence of pathological conditions or administration of drugs normally tolerated by the young, is mainly due to an enhanced response to vasoconstrictive stimuli. This hemodynamic reaction can also occur in stressful situations of everyday life such as physical exercise [41]. This tendency may be secondary to the reduction of renal autacoid

modulatory capacity, particularly at the vasodilating prostaglandin level. In our research, we demonstrate that, in the healthy elderly, the renal response to adrenergic activation by mental stress is characterized by a prolonged and pronounced vasoconstriction, due to the lack of prostaglandin modulation of vasoconstrictor factors' activity (Figs. 10.2 and 10.3) [42]. This can explain the greater vulnerability of the aging kidney when NSAIDs are administered, particularly when vasoconstrictive factors, such as during hypotension, hemorrhage, or congestive heart failure, are activated [42].

10.2 Assessment of GFR

Assessment of glomerular filtration ratio (GFR) in elderly people is essential for risk stratification (global, preoperative, etc.), for the use of diagnostic imaging using contrast agents, and for establishing the correct dose of antibiotics and other kidney-excreted drugs.

The gold standard for the evaluation of GFR is inulin clearance, an invasive technique clearly unsuitable for clinical use. Levels of serum creatinine are a poor indicator of renal function in the elderly, since the combination of a reduced muscle mass and physical inactivity maintain levels of serum creatinine normal even for a GFR reduced by more than 50 %. Estimation of GFR is calculated by mathematical formulas which give a rapid, but often imprecise, estimate. Furthermore different formulas present varying degrees of accuracy according to the population considered. In this commentary, our aim is to illustrate the different formulas available, including the new BIS-1 and BIS-2, and offer clinicians a practical guide.

10.2.1 Cockcroft–Gault Equation

This equation generally overestimates renal function because it represents an estimation of creatinine clearance, i.e., the actual filtrate plus tubular secretion of creatinine [43]. Compared to the measurement of creatinine clearance, it presents the advantage of not requiring the measurement of urinary excretion of creatinine. The equation is based on serum creatinine, age, weight, and a corrective index for the female sex. The results are expressed in mL/min, so data on height is required to normalize the value to body surface area. In the original paper, 249 subjects were enrolled, of which 59 aged 70 years or more, with an average creatinine clearance inferior to 40 mL/min. The equation presents two flaws: the tendency to underestimate in advanced age (probably because the few old subjects enrolled in the original study had a reduced muscle mass and therefore produced less creatinine) and to overestimate in case of overweight/obesity or edema. This is due to the fact that in the equation, weight is used as a proxy of muscle mass and therefore of creatinine generation; adipose tissue however does not generate creatinine [44]. One possible solution is to use the ideal, rather than the real, weight [45], but today there are poor indications to use this equation.

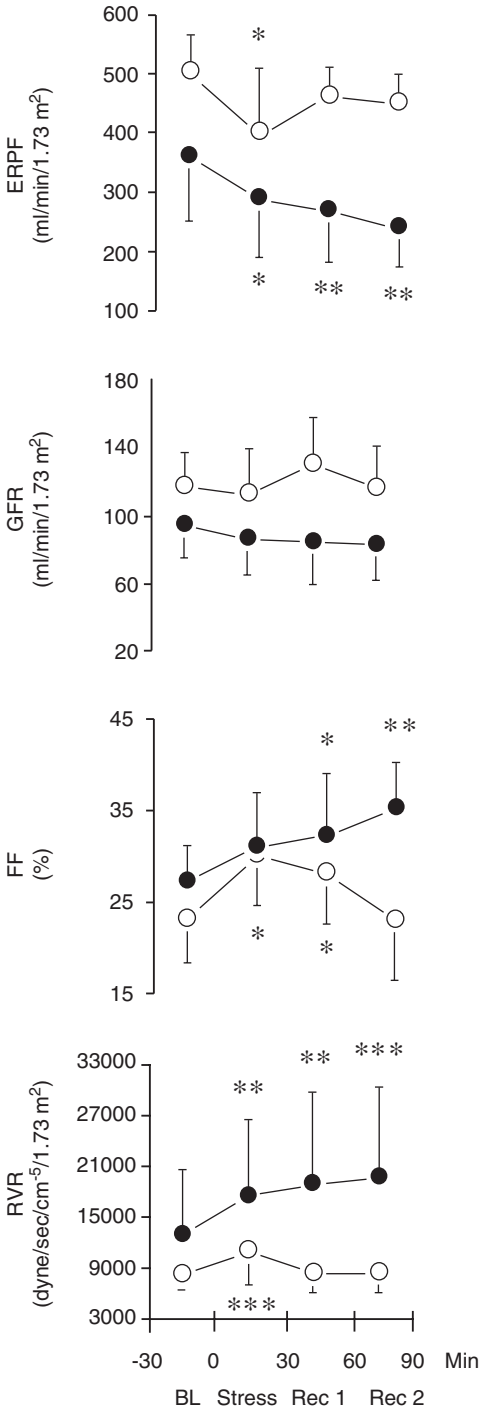

Fig. 10.2 Effects of mental stress on renal hemodynamics (mean – SD). ● Elderly ($n = 8$), ○ young ($n = 8$). *$P < .05$, **$P < .01$, and ***$P < .001$ vs. baseline (least significant difference test, ANOVA). *FF* filtration fraction, *RVR* renal vascular resistance. In the elderly, renal vasoconstriction during and after blood pressure increase determined by mental stress is more pronged and pronounced than in the young (From Castellani et al. [42])

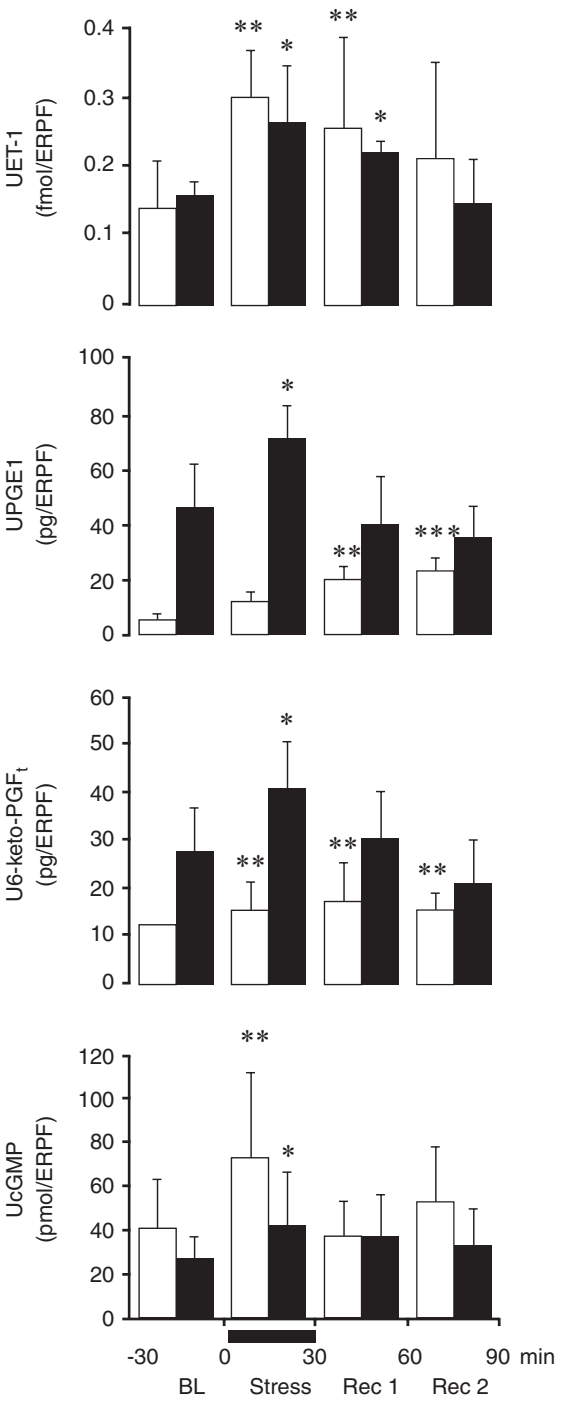

Fig. 10.3 Effects of mental stress on UET-1, UPGE2, 6-keto-PGFm, and UcGMP (mean + SD). ■ Elderly ($n = 8$), □ young ($n = 8$). *P <.05, **P <.01, and ***P <.001 vs. baseline (least significant difference test, ANOVA). In the elderly subjects, the vasodilating prostaglandins increased only during mental stress, while in the younger subjects, the two urinary vasodilating PGs had risen progressively from the start of mental stress application to the end of the experiment, probably for counterbalancing ET-1 increase (From Castellani et al. [42])

10.2.2 MDRD Equation

The four-variable MDRD equation (by the Modification of Diet in Renal Disease (MDRD) study group) is based on creatinine blood levels, age, sex, and ethnicity [46]. The original version included serum urea nitrogen and albumin concentration but was later simplified; in 2006 it was recalculated for use with standardized serum creatinine assay; [47] results are provided directly in mL/min × 1.73 m^2. It has been studied measuring the relationship between creatinine blood levels and GFR measured with radioisotopic techniques in adults with chronic renal failure. The original equation was validated in a population with an average age of 51 years; persons aged 65 years or more represented 22 % of the sample; even in successive validations in larger populations, elder individuals were poorly represented [48]. The main defect of the equation is the lack of validation for estimated normal-high filtrates. This is because the MDRD study did not include healthy individuals; therefore, there is a paucity of data for GFR >60 mL/min × 1.73 m^2 [49]. Other studies have highlighted possible errors in specific subgroups of patients, such as kidney transplant recipients [50], diabetics [51], or in regions outside North America, Europe, or Australia (specific adaptations have been developed in Chinese [52] and Japanese [53] population).

10.2.3 CKD-EPI Equations

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) aimed at developing more accurate equations for GFR estimated as higher than 60 mL/min/1.73 m^2. This new formula, known as CKD-EPI, pooled information from three large databases of 12,000 subjects, with and without renal disease, using as a reference test iothalamate clearance [54]. The average ages in the development and in the external validation study were, respectively, 47 and 50 years (subjects aged 65 years or more, 13 % and 15 %, respectively). The variables adopted by the CKD-EPI were the same as in the MDRD equation (creatinine expressed by standardized assay). The CKD-EPI equation has a lower bias for the estimation of GFR >60 mL/min/1.73 m^2, with important repercussions on public health and clinical practice: the prevalence of chronic kidney disease, especially among women and Caucasians, is reduced but remains high among the elderly [55]. The new equation however cannot overcome the principal limits of serum creatinine as an endogenous marker of glomerular filtration; indeed all creatinine-based equations should be used with caution in subjects with an altered generation and/or secretion of creatinine: subjects with a reduced muscle mass (limb amputations, cachexia, sarcopenia, muscular dystrophy), athletes with an increased muscle mass, drugs which modify creatinine secretion, etc.). For a few years now, there has been a growing interest in cystatin C (CysC), as a possible substitute for creatinine as a marker of GFR. CysC satisfies the ideal marker criteria: endogenous production at a constant rate, freely filtrated by the glomerulus,

tubular catabolism, and no extrarenal elimination. Furthermore CysC depends less on muscle mass compared to creatinine. However serum CysC levels could be altered, and therefore unreliable, in the presence of systemic infections [56] and thyroid dysfunction [57] and during steroidal therapies [58]. The effects of smoking, obesity, and age still need to be clarified [59]. Issues such as dosage method standardization, definition of a range of normal values, and high costs need to be solved. In 2012, the CKD-EPI group developed two new equations for GFR estimation: one equation uses CysC, age, sex, and ethnicity and the other combines CysC and creatinine with age, sex, and ethnicity [60]. The sample included over 5000 subjects, persons aged 65 years or more were 13 % and 21 % of the populations, respectively, in the development and validation group. The equation that combines creatinine and CysC resulted in a more accurate GFR estimation across the whole range of values, even in specific subgroups, such as persons with a BMI lower than 20 kg/m^2, in which creatinine-based formulas tend to underestimate GFR. Furthermore this equation allows a more correct classification of subjects with GFR values in the 45 and 60 mL/min/1.73 m^2 range, identifying those not affected by renal failure. Cohort studies and meta-analysis conducted on general population studies show that formulas based on CysC, alone or combined with creatinine, establish GFR as a predictor of mortality in various populations, starting from a GFR <85 mL/min/1.73 m^2 [61]. GFR values estimated with creatinine only have a J-shaped correlation with all cause of mortality. Non-GFR-related factors which influence serum creatinine levels, such as muscle mass, diet, and physical activity, alter the link between GFR and mortality [62]. Creatinine levels lower than those normally expected from the corresponding GFR values in subjects in precarious health conditions and at high risk of mortality seem to be the responsible mechanisms. Non-GFR-dependent factors which influence CysC levels seem to reinforce the association between GFR and mortality; [63] a possible explanation is that obesity, inflammation, and diabetes are all conditions that increase CysC serum levels [64]. In a recent cohort study of individuals aged 80 years or older, CKD-EPI$_{CysC}$ and CKD-EPI$_{creatinine/CysC}$ equations appear to predict with greater accuracy mortality, renal replacement therapy, and severe cardiovascular events compared with MDRD and CKD-EPI$_{creatinine}$ equations [65].

All the above-described equations have been validated and should be used in subjects aged 18–70 years old; nonetheless, CKD-EPI and MDRD should be preferred over Cockcroft–Gault formulas in elderly population [66]. MDRD and CKD-EPI equations compared to a reference GFR measurement, in older Caucasians, overestimated GFR (especially for GFR >60 mL/min/1.73 m^2), whereas CKD-EPI$_{cysC}$ was unbiased; all three CKD-EPI equations appear to be more accurate than MDRD [67]; CysC-based equations' superiority was proved not only in Caucasian elderly population [68].

At present, the latest KDIGO guidelines (2012) recommend use of CKD-EPI creatinine in clinical practice. It is suggested that CysC equations (CKD-EPI$_{CysC}$ – CKD-EPI$_{creatinine/CysC}$) be used:

- In the 59–45 mL/min/1.73 m^2 range, in the absence of markers of kidney damage for confirmation of chronic kidney disease
- In specific circumstances when GFR calculated with creatinine alone is less accurate [69]

10.2.4 BIS Equations

In 2012 the Berlin Initiative Study (BIS) research group proposed to develop new equations, accurate at estimating GFR in persons aged 70 years or more [70]. The population consisted of 610 subjects, a subset of a larger cohort study. Four variables were considered: age, sex, serum creatinine, and serum CysC. Ethnicity was not included because of the homogeneity of the population. The difference between BIS-1 and BIS-2 is the use, in the latter, of CysC. In the validation, iohexol was used as the reference test. The average age of the sample was 78.5 years old. Results were compared to the GFR estimations achieved through the known equations. Both the two new equations have shown more precision and accuracy in GFR measurement compared to the other formulas, especially in the group with values >30 mL/min/1.73 m^2. In the sample, all the other equations tended to overestimate GFR values, especially MDRD, and to a lesser extent Cockcroft–Gault. The addition of CysC values to the equation appears advantageous in the studied population, as it appears to reduce the effects of sex and age, supporting its potential use in the presence of a reduced muscle mass. Both equations confirm a high prevalence of GFR values <60 mL/min/1.73 m^2 in the over 70 population and the lowest rate of reclassification compared to the other formulas. The study sample consisted only of Caucasian individuals, with a slightly or moderately reduced renal function: therefore their predictive value for different ethnicities or in the case of severe renal failure is unknown. Nowadays few external validation studies exist with opposing results on the benefit of BIS compared to CKD-EPI equations in elderly [71–75]. Further validation studies of these equations in the elderly population are warranted also as a predictor of important outcomes.

Tables 10.1 and 10.2 illustrate the pros and cons of each formula, in different clinical settings [42].

In conclusion, estimation of GFR, considered easy and intuitive by most physicians, remains a complex process, especially in the elderly, and a greater awareness about the limits of the various GFR estimation formulas is auspicable.

Table 10.1 Pros and cons for each GFR-estimating formula

Equations for GFR estimation	Variables	Pros	Cons
Cockcroft–Gault – 1976	Cr Age Weight Sex	No 24-h urine collection required Easiness Widely studied	Body weight requested It correlates with ClCr, but not with GFR (GFR overestimated) Correction for body surface area is needed, in order to normalize to mL/min/1.73 m^2 Underestimation in advanced age Overestimation in the presence of overweight/obesity or edema
Four-variable MDRD – 2006	Cr Age Sex Ethnicity	Recommended by the 2002 KDOQI guidelines Widely studied Correlation to GFR Body weight not required Results already normalized for body surface area	Systematic underestimation for GFR >60 mL/min/1.73 m^2 Poorly validated in the elderly
CKD-EPI – 2009	Cr Age Sex Ethnicity	Recommended by the 2012 KDIGO guidelines Better correlation with GFR than MDRD, especially for GFR >60 mL/min/1.73 m^2	Bias due to the use of three databases Poorly validated in the elderly
CKD-EPI Cys/Cr-CysC – 2012	Cr CysC Age Sex Ethnicity	CysC less influenced by age, sex, ethnicity More accurate and precise, in particular for GFR >60 mL/min/1.73 m^2 and for BMI <20 kg/m^2 Suggested by the 2012 KDIGO guidelines in special conditions Probably more useful in case of reduced muscle mass	CysC influenced by systemic infections, thyroid dysfunction, steroidal therapies Problems for the dosage method standardization, lack of normal values range, cost Poorly validated in the elderly
BIS 1 – 2012	Cr Age Sex	More precision and better correlation with mGFR in the elderly, especially with GFR >30 mL/min/1.73 m^2	Validated for Caucasians only Validated for over 70 years old subjects only Limited external validation
BIS 2 – 2012	Cr CysC Age Sex	More precision and better correlation with mGFR in the elderly, especially with GFR >30 mL/min/1.73 m^2 CysC less influenced by age, sex, ethnicity Probably more useful in case of reduced muscle mass	

Table 10.2 GFR-estimating formulas in different clinical context

Subgroup	Suggested equation	To avoid/not suggested equation
Age included between 18 and 70 years old	MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$	BIS-1 and BIS-2
Age >70 years old	CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$; BIS-1 and BIS-2[a]	C-G
Normal weight	MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$; BIS-1, BIS-2 if old and GFR >30 mL/min/1.73 m^{2}[a]	
Overweight (BMI >25 kg/m^2) or edema	MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$	C-G
Underweight (BMI <20 kg/m^2), sarcopenia, amputations, cachexia	C-G (?); CKD-EPI$_{Cys\ c}$; CKD-EPI$_{Cr\text{-}Cys\ c}$; BIS-2 if old and GFR >30 mL/min/1.73 m^{2}[a]	
GFR >60 mL/min/1.73 m^2	CKD-EPI$_{Cr}$;CKD-EPI$_{CysC}$;CKD-EPI$_{Cr\text{-}CysC}$	MDRD, BIS-1
GFR <60 mL/min/1.73 m^2	MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$; BIS-1, BIS-2 if old and GFR>30 mL/min/1.73 m^{2}[a]	
Ethnicity other than Caucasian	MDRD; CKD-EPI$_{Cr}$; CKD-EPI$_{CysC}$; CKD-EPI$_{Cr\text{-}CysC}$	BIS-1 and BIS-2

[a]Validated in Caucasian only; *BIS* Berlin Initiative Study; *BIS-1* BIS formula with serum creatinine, sex, and age included; *BIS-2* BIS formula with cystatin C, serum creatinine, sex, and age included; *BMI* body mass index; *ClCr* creatinine clearance; *C-G* Cockcroft–Gault equation; *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration; *Cr* serum creatinine; *Cr-CysC* formulas based on the combined use of serum creatinine and cystatin C; *CysC* cystatin C; *GFR* glomerular filtration rate; *mGFR* measured glomerular filtration rate; *MDRD* Modification of Diet in Renal Disease

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Risk Assessment in Cardiac and Noncardiac Surgery in Older Patients

11

Alessandra Pratesi, Samuele Baldasseroni, and Iacopo Olivotto

11.1 Complexity of Risk Assessment in Older Patients Candidate to Surgery

Over the past 20 years, the number of older people undergoing surgery has increased exponentially, with projections suggesting that close to 50 % of the surgical activity in the USA will focus on the elderly population within the next few years [1]. This will unavoidably result in an increase prevalence of elderly patients evaluated preoperatively for different surgical indications [2], due to the increase in average length of life, improvement in surgical and anesthetic techniques, and significant reduction in intra- and perioperative mortality and morbidity [3, 4]. Despite these remarkable significant improvements, surgical risk, perioperative complications, mortality, and severe disability remain significantly higher in the elderly as compared to younger surgical candidates [5].

Estimated perioperative risk is critical in determining the final surgical indication. While many surgical procedures can enhance quality and duration of life, only a careful and individualized assessment is capable of decreasing both predictable and untoward risk of adverse events in elderly patients, who are increasingly vulnerable and frail. To this aim, the need is felt for clinical tools that are effective in predicting classic outcomes (such as length of stay and mortality) but also able to stratify risk of outcomes that are specifically geriatric, such as delirium, cognitive deterioration, disability, and risk of institutionalization.

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_11

A national survey in the United Kingdom has shown that the preoperative estimate of comorbidity, *frailty*, and overall risk was related to suboptimal intra- and postoperative medical care in a cohort of elderly who died within 30 days of surgery [6]. Increasing interest is focusing not only on the evaluation of outcome measures typically included in clinical studies (survival, major complications, mitigation of symptoms) but also on the use of patient-centered outcomes and disability-free survival, which often represents the true goal for elderly patients [7]. However, these and other fundamental outcomes such as risk of prolonged stay in the intensive care unit or prolonged ventilation are still largely neglected in the scientific literature. The Society of Thoracic Surgeons established a Quality Measurement Task Force to develop a method to evaluate adult surgery quality of care [8]. In its "postoperative risk-adjusted major morbidity," one of the main parameters of poor performance is the occurrence of prolonged ventilation/intubation, as defined in Society of Thoracic Surgeons (STS) website [9].

Various factors need consideration in assessing the risk of surgery. These are generally divided into patient-related and surgery-specific risks, the latter including, among others, level of urgency, type of surgery, duration of the operation, and risk of bleeding. For elective surgery, patient-related risk assessment often consists of an evaluation 1–4 weeks before intervention, including a standard past medical history, physical exam, laboratory tests, and radiological imaging. These items are usually collected by an anesthetist according to the recommendations of the American Society of Anesthesiologists (ASA) Physical Status Classification [10], which provide the possibility of requiring further investigations before surgery, alerting support services and admitting the patients directly on the day of surgery. Such assessment is considered sufficient for young or adult patients but may inadequate in the elderly. Indeed, aging is associated with a paraphysiological or pathological decline of the functional reserve in multiple organ systems, with reduced adaptation to stress, leading to an increasing prevalence of comorbidity and loss of functional autonomy often concomitant with a reduction in social resources. All these changes compromise the ability of older patients to tolerate surgical procedures and increase their risk of mortality and morbidity and of decline in functional status. The aging process per se entails a progressive reduction of physical performance and overall autonomy. This process [11], genetically determined in its temporal trajectory, is linked to progressive modifications of biological processes [11]. Nevertheless the individual phenotype is heavily influenced by lifestyle and environmental background, as well as prior history of disease [11]. For these reasons, the age group of octogenarians, for example, is far from homogeneous. Yet, extensive literature shows that chronological age preserves its value as an independent risk factor for surgery and anesthesia. For example, Naughton et al. [12] showed in over 1500 cardiovascular patients that an age >70 years increases risk of death at 6 months following elective noncardiac surgery by 3.57 times (OR, 95 % CI: 2.22–5.73). Chronological age is always the first item in surgical risk scores whether as a continuous or dichotomous variable [13], although it is not a factor ever leading per se to exclusion excluding from surgery.

Table 11.1 American Society of Anesthesiologists physical status grade

I. A normal healthy patient
II. A patient with mild systemic disease
III. A patient with severe systemic disease
IV. A patient with severe systemic disease that is a constant threat to life
V. A moribund patient who is not expected to survive without the operation
VI. A declared brain dead patient whose organs are being removed for donor purposes

11.2 Reliability and Validity of Risk Scores in the Elderly

Accurate risk perioperative evaluation of elderly cardiac patient must have different objectives: first, to identify those who can benefit from the intervention and have a sustainable operatory risk and second, to identify in advance those who will need intensive care in the postoperative period. The ideal tool for risk stratification in the elderly surgical candidates should be reliable, accurate both for elective surgery and in the emergency setting, developed and validated specifically in elderly populations, and comprehensive of predictive information regarding the functional and cognitive status and level of noncardiac comorbidities [13].

To date, risk scores generally adopt a purely specialty-oriented – anesthesiologic, surgical, or cardiological – perspective. One of the best-known risk scores is the "American Society of Anesthesiologists Physical Status score (ASA-PS)" [14] (Table 11.1) which categorizes patients into five categories of anesthesiological risk, with a recently added one dedicated to organ donors [15]. The score is fast and easy to use but has several limitations: it is not adjusted for sex, age, and anthropometric features, and its application to geriatric patients is limited by the lack of specific parameters for this age group. It has been recently demonstrated [16] that this instrument has low individual predictive power (predicting not more than 15–16 % of perioperative complications), with disappointing positive and negative predictive values close to 50 % and 80 %, respectively [16].

The most widely used surgical risk score is the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM), developed in 1991 by Copeland et al. [17]. In its final version, this score incorporates 18 variables (12 physiological variables recorded before surgery include symptoms, signs, and laboratory test and 6 surgical variables), and via two mathematical algorithms calculate a risk value for mortality and morbidity. The POSSUM is used for the assessment of procedural risk both in the elective and emergency setting for urology, vascular, hepatobiliary, and gastrointestinal surgery [18]. The POSSUM is reliable in predicting hospital mortality but has little power in capturing risk of perioperative complications [19].

In a cardiological perspective, an interesting risk score is the Revised Cardiac Risk Index (RCRI) (Table 11.2), based on a previous score by Goldman et al. [20] and Lee et al. [21], which has been developed and tested in different populations

Table 11.2 Revised Cardiac Risk Index (RCRI)

1. High-risk surgery: intraperitoneal; intrathoracic; suprainguinal vascular
2. History of ischemic heart disease: history of MI; history of positive exercise test; current chest pain considered due to myocardial ischemia; the use of nitrate therapy; ECG with pathological Q waves
3. History of congestive heart failure: pulmonary edema, bilateral rales or S3 gallop; paroxysmal nocturnal dyspnea; CXR showing pulmonary vascular redistribution
4. History of cerebrovascular disease: prior TIA or stroke
5. Preoperative treatment with insulin
6. Preoperative creatinine >2 mg/dL – 176.8 μmol/L

[22]. This score is effective in predicting cardiovascular complications during noncardiac surgery, although its ability to predict cardiovascular mortality is not as accurate [22]. Of note, the performance of RCRI seems considerably improved by the addition of NT-proBNP and CRP titration [23]. Seen from the geriatric perspective, however, this score has some fundamental limitations. For example, elderly heart patients often die of noncardiovascular causes in the perioperative period, and the use of creatinine levels to assess renal function is fallacious in this age group.

With regard to cardiac surgical risk scores, the most widely used and validated scores in clinical practice are the European System of Cardiac Operative Risk Evaluation (EuroSCORE) I [24] and II [25] and the score of the Society of Thoracic Surgeons (STS) [26].

The EuroSCORE was developed in 1999 based on the risk factors and mortality of 19,030 patients undergoing elective coronary artery bypass in 1995 in 128 European cardiac surgery centers. The score predicts the risk of death at 30 days in the form of logistic EuroSCORE (i.e., as a percentage risk) or as an additive EuroSCORE (<3 low risk, 3–6 medium risk or >6 high risk). However, among the patients originally considered, only 3200 (17 %) were subjected to associated procedures such as aortic valve replacement. The score was therefore developed assuming the intervention of isolated coronary artery bypass graft (CABG) as the basic risk model. As a consequence, mitral and aortic valve replacement or mitral plasty, alone or in combination with CABG, all fall in the same risk profile [24]. In order to overcome these and improve risk assessment in a variety of interventions besides CABG, the EuroSCORE II was developed, which is more complex than the previous version, although the risk factors considered are substantially the same [25]. Although definitely a step forward, the EuroSCORE II still shows limitations in the evaluation of those patients who are more complex and therefore at greater surgical risk [27].

The STS score is a risk model developed by the Society of Thoracic Surgeons on the basis of demographic and clinical data in the adult population and is used for predicting risk of operative mortality and morbidity after cardiac surgery. The STS is based on data from more than 100,000 patients including valvular patients and, compared to EuroSCORE, does take into consideration morbidity outcomes such as risk of surgical revision, stroke, acute renal failure, prolonged ventilation and hospitalization, and surgical wound infection. It is periodically updated [26]. Despite

these methodological strengths, this model is validated exclusively for some procedures (single CABG; single aortic valve replacement, mitral valve replacement, or mitral plastic; CABG + valve one of the above procedures), effectively excluding more complex surgical interventions frequent in the elderly.

Another score, the Age, Creatinine, and Ejection Fraction (ACEF), recently developed based on a limited number of risk factors, has shown similar results in terms of accuracy as EuroSCORE [28], with better performance of patients undergoing elective cardiac surgery [29].

Comparing these scores (STS, EuroSCORE I and II, ACEF), different results may be observed depending on the surgical procedure. With regard to coronary artery bypass grafting, a recent meta-analysis including more than 19,000 patients showed that both logistic and additive EuroSCORE significantly overestimated mortality [30], while STS risk model shows an acceptable calibration capacity and a c-index for mortality of 0.81 [31]. In isolated aortic valve surgery, EuroSCORE II has lower discrimination power (ability to differentiate between low- and high-risk patients) if compared with the STS score but a better calibration capacity (comparison between predicted and observed end point) than logistic EuroSCORE, ACEF and STS [32]. The performance of EuroSCORE I and II and STS in predicting short- and midterm mortality in combined aortic valve replacement and coronary artery bypass procedures was reported similar, with an area under the ROC curves for additive EuroSCORE of 0.76, for logistic EuroSCORE of 0.75 and for STS score of 0.75 [33, 34]. All these scores show a relatively poor performance in the evaluation of patients at intermediate and high risk [35] and even poorer in long-term risk prediction [36]. When used in very old patients, these risk scores show their most important limits, as risk is not stratified by age group or by cardiac condition or type of intervention. Furthermore, important variables such as liver function, irradiation, frailty, and others are not considered by any of these scores. Such considerations suggest the need for novel risk scores specifically developed for the elderly population.

11.3 Role of Comorbidity, Functional Status, and *Frailty* in Surgery Risk Stratification

Comorbidity is defined as the simultaneous presence of two or more diseases in the same patient, an occurrence that becomes more common and changes phenotype with increasing age, because in the elderly, comorbidities are usually chronic, as opposed to acute in the young [37]. From the epidemiological point of view, significant comorbidity in the elderly is associated with increased risk of death [38], rehospitalization, disability, and poor quality of life [39]. Comorbidity influences the diagnostic and therapeutic process, as the coexistence of several diseases hinders the interpretation of clinical signs and symptoms. A classic example is represented by breathlessness in an elderly suffering from heart failure, chronic obstructive airways disease, and anemia.

The high prevalence of comorbidity in the elderly plays a central role in their exclusion from clinical trials [40]. In most geriatric cardiology studies, comorbidity is simply assessed in terms of disease count, rather than weighted on type of disease. However, this approach shows significant limitations, particularly when the outcome is not limited to mortality and morbidity, but includes the risk of becoming disabled. Marchionni et al. [41] clearly demonstrated that in elderly individuals with heart failure, the risk of becoming disabled is related to their disease index but increases differently in patients with COPD or cerebrovascular disease: in the first instance risk progresses arithmetically, in the second exponentially. This study demonstrated that the interplay between two chronic conditions is much more complex than the simple sum of risks, confirming the fallacy of a disease-count approach.

Finally, evaluation of comorbidity in the elderly must necessarily include an assessment of the severity of individual diseases. Among many studies, the Index of Coexisting Disease (ICED), Greenfield et al. [42], and the Geriatric Index of Comorbidity (GIC) [43] are worth mentioning. The ICED predicts risk of disability in patients suffering from chronic disease and consists of two subscales: the first subscale comprises a list of 14 chronic conditions with clinical severity increasing from 0 to 4, with the possibility to classify also diseases that are not on the list, and the second subscale includes 12 domains in which the functional disability is graded from 0 to 2. The ICED was validated in eight populations including patients with myocardial infarction or coronary artery bypass grafting [44]. The GIC consists of a list of 15 diseases with severity grading from 0 to 4, with the possibility to build four classes of comorbidity basing on the presence of one or more associated diseases [43]. While these scores are certainly able to characterize the level and severity of comorbidity, it is important to emphasize how – in many chronic conditions of the elderly – symptom severity may show a remarkably different association with risk of death as opposed to risk of disability. This geriatric paradox is best exemplified by severe osteoarthritis, in which the risk of becoming disabled is high when the symptoms are poorly controlled by drugs, but the risk of death appears low or even negligible.

The assessment of surgical risk in elderly patients cannot be considered comprehensive unless it includes evaluation of global functional status, defined as the capability of the physical and cognitive abilities to perform normal activities of daily living and to maintain sufficient social network. This concept is quantified in geriatric medicine by the basic activities of daily living (BADL) [45] and instrumental activities of daily living (IADL) [46] scales. The predictive value of these scales is supported by a wealth of solid literature. Fukuse and coll. [47] showed that in older patients undergoing thoracic surgery, a reduction of autonomy, measured by the number of lost BADL points, is able to predict major perioperative complications, independent of other risk factors.

Predicting the likelihood of remaining disabled following surgery is challenging, due to the complexity of capturing preoperative levels of physiological homeostatic reserves and vulnerability to stressful events, i.e., features that constitute the concept of *frailty* [47]. The conceptual definition of *frailty* is much

discussed in geriatric medicine [48]. Campbell defines *frailty* as "a condition or syndrome which results from a multi-system reduction in reserve capacity to the extent that a number of physiological systems are close to, or past, the threshold of symptomatic clinical failure" [49]. Given this definition, there are two models of *frailty* suitable for the stratification of surgical risk of the elderly. They are summarized in the model called "frailty phenotype" arising from the Cardiovascular Health Study [50] and in the "deficit accumulation model of frailty" created by the Canadian Study of Health and Aging [51]. The first substantially recognizes a set of five domains: unintentional weight loss, muscle strength measured by handgrip, the feeling of self-reported exhaustion, walking speed, and the amount of physical activity habitual self-reported [50]. The Canadian model builds a *frailty* index from a list of over 70 both functional and clinical items, exploring the physical, cognitive, and disability in daily life, scoring from 0 to 7 for increasing fragility [51]. Both models have been tested in the stratification of surgical risk of elderly patients, proving adequate in predicting long-term adverse outcomes [48] but showing limitations related to the complexity of their implementation in clinical routine.

In this perspective, the assessment of surgical risk of elderly (including risk of disability) should be based on two key principles: the first is that clinical tools need to be simple and reproducible, because of the complexity of the surgical setting, and the second is that risk scores must have the ability to stratify perioperative risk as well as identify modifiable factors that may improve outcome [48]. Thus, in the preoperative setting, it appears very reasonable to rely on surrogate, but reliable, measures of *frailty* such as physical performance tests. The strength of the upper limbs measured with the dynamometer (handgrip test) or the gait speed performed in a short corridor is tools that have proved their worth in the field of surgical stratification of elderly patients [52, 53]. The attention toward measures of physical performance in the field of geriatric cardiology and cardiac surgery has significantly increased in recent years. Di Bari et al. have shown [54] that the Short Physical Performance Battery [55] is an independent predictor of prognosis in elderly patients with heart failure as powerful as the New York Heart Association (NYHA) class. Furthermore, at Duke University, Afilalo et al. [56] have demonstrated in 131 elderly undergoing cardiac surgery that reduced gait speed identifies a subpopulation at higher independent risk of mortality and morbidity. Of note, risk is 2–3 times higher for each level of the STS score [57] used for surgical preoperative screening by cardiac surgeons.

11.4 Role of Comprehensive Geriatric Assessment (CGA) in Preoperative Cardiac Surgery

The rapid increase in the number of elderly people, due to extended life expectancy, is accompanied by an increased demand for cardiac surgery, to an extent that one of the most important topics in cardiology and geriatrics today is represented by the

difficult choice of when and who to refer for cardiac surgery in this age group. As discussed, current risk prediction models have poor performance and are overall inaccurate in elderly patients, generally overestimating operative risk [58]. Nevertheless, the perception that older patients have lower functional reserves and more extensive comorbidity leads cardiologists and cardiac surgeons to hesitate in proposing cardiac surgery to the elderly. Nevertheless, despite a number of adverse features including increased incidence of diabetes, dyslipidemia, hypertension, and left main disease, rates of surgical mortality reported in the literature in octogenarians have fallen significantly, due to a reduction in the incidence of postoperative complications such as stroke and acute pump failure [59]. Contemporary cardiac surgical procedures can thus be performed safely and with therapeutic benefit in adequately selected nonagenarians [60, 61]. A recent study [62] analyzing the variations in the surgical population and type of intervention between 2001 and 2010 has shown a reduction in isolated CABG procedures with a concomitant increase in interventions on the valves (largely comprised aortic valve replacements) and thoracic aorta. With regard to age, there has been a significant reduction in patients <70 years and an increase in those >80 years of age, with no change in the 70–79 year group. As a result, the average age at intervention has increased of about 10 years, with an increase in the proportion of frail patients in all age groups. However, particularly among patients >80 years, although only the oldest and most frail patients showed a significant increase in total hospital stay and intensive care unit stay. Based on the evidence available, it thus appears unjustified to deny access to cardiac surgery to any patient solely based on age, as the elderly receive comparable benefits compared to younger in terms of symptoms, functional recovery, and quality of life [63, 64].

In order to maximize the benefit of surgery for the elderly, however, it is critical to improve selection of optimal candidates. The Comprehensive Geriatric Assessment (CGA), developed in 1991, is a "multidimensional interdisciplinary diagnostic process focused on determining a frail elderly person's medical, psychological and functional capability in order to develop a coordinated and integrated plan for treatment and long term follow up" [65] (Fig. 11.1). This tool includes assessments of medical, psychiatric, functional, and socioeconomical domains followed by a tailored management plan including rehabilitation; the team includes a minimum experienced medical, nursing, and therapy staff. The evaluation consists in the administration of standardized assessment tools to gather information in a semi-structured way. For example, this might include basic and instrumental activities of daily living for functional evaluation [45], Geriatric Depression Scale for psychological screening [66], or the Mini Mental State Examination (MMSE) for cognition [67]. Only few studies incorporated disabilities in activities of daily living as a predictor of outcomes after cardiac surgery [68, 69].

An effective test for the identification of frail elderly patients is the Short Physical Performance Battery (SPPB). The SPPB consists of three timed physical performance tests (walking speed, rising from a chair, and balance), each with a score from 0 to 4: a total score of 5 out of 12 identifies frailty. The SPPB is a powerful

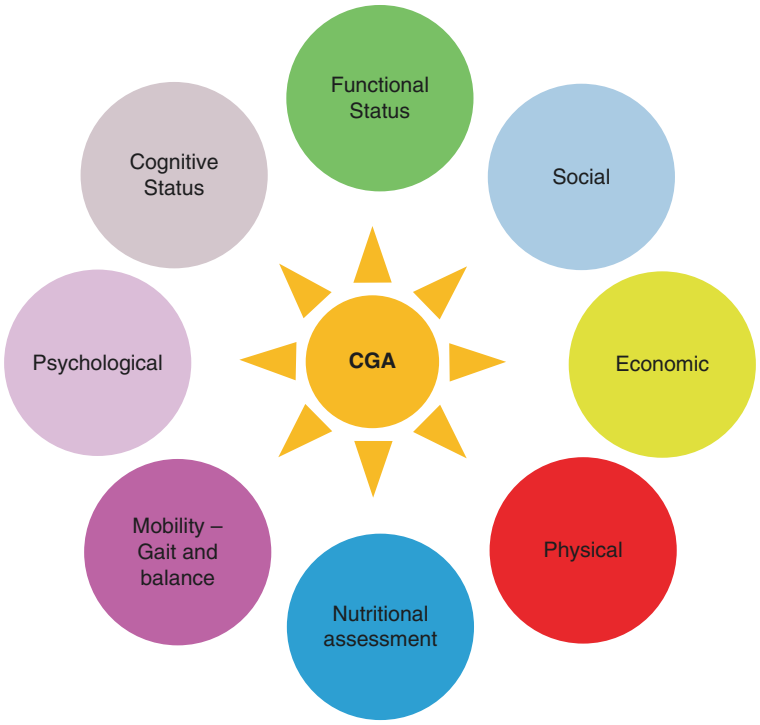

Fig. 11.1 Comprehensive Geriatric Assessment

predictor of mortality in the elderly population, even after adjusting for age, sex, levels of multimorbidity, and cognitive status [55, 70].

In contrast to scales as the SPPB, which are composed of multiple items, gait speed and the measurement of the upper limb strength by a dynamometer are measurable indicators of frailty which can be employed as single items [71–73]. Gait speed has shown excellent intra- and inter-investigator reproducibility. The most important predictor in the test is not the total distance walked, which can vary in the different tests from 3 to 10 m, as the time needed to cover each meter [74]. At present, 5 m is the most commonly used distance, as it takes into account the possible occurrence of cardiopulmonary symptoms for longer distances. Of note, a pooled analysis of nine cohort studies showed a reduction of approximately 12 % in risk of death at 5 and 10 years follow-up for each 0.1 m/s increment of gait speed [75]. A patient with a walking speed lower than 0.8 m/s is at greater risk of loss of autonomy, declining health status, institutionalization, and death [76, 77].

Until recently, there were no studies specifically focusing on the use of gait speed as a predictor of postoperative mortality and morbidity in elderly cardiac surgery patients. A pioneering study in this field was conducted by Afilalo et al. [56], in 131 patients undergoing cardiac surgery at 70 years of age or more (mean age of

75.8 ± 4.4 years). Overall, 46 % were defined as slow walkers (time to walk 5 m ≥6 s) before cardiac surgery. The primary end point (a composite of in-hospital postoperative mortality or major morbidity) occurred in 23 %. Slow gait speed independently predicted the composite end point after adjusting for the STS risk score (odds ratio: 3.05; 95 % CI: 1.23–7.54). A subsequent study by the same group confirmed these results: slow walking and the presence of high-level disability (at least three impairments in Nagi's scale) were associated with a significant increase in adjusted risk. Among the risk scores evaluated, the Parsonnet score and STS-PROMM demonstrated the best discriminative ability for mortality or major morbidity in elderly patients [78].

Another important study [69] defined *frailty* as any impairment in activities of daily living, ambulation, or a documented history of dementia. Of 3826 elderly patients, 157 (4.1 %) were frail. Frail patients were older, were more likely to be female, and had risk factors for adverse surgical outcomes. By logistic regression, *frailty* was an independent predictor of in-hospital mortality (odds ratio 1.8; 95 % CI: 1.1–3.0), as well as institutional discharge (odds ratio 6.3; 95 % CI: 4.2–9.4) and of reduced midterm survival (hazard ratio 1.5; 95 % CI: 1.1–2.2). Sundermann and coll. [79] tested a more complex evaluation tool, called Comprehensive Assessment of Frailty (CAF), including unintentional weight loss, weakness (handgrip at dynamometer), self-reported exhaustion (through a specific questionnaire), slowness of gait speed (time to walk 4 m), low activity (IADL), evaluation of standing balance, a test to assess body control, laboratory tests (serum albumin, creatinine, and brain natriuretic peptide), and measure of forced expiratory volume in 1 s (FEV1). This protocol was applied to 400 patients ≥74 years. Median *frailty* score was 11; median of logistic EuroSCORE was 8.5 % and of STS score was 3.3 %. There was a significant correlation between *frailty* score and observed 30-day mortality ($P < 0.05$). The evident limit of this study was the complexity of the evaluation, which makes its application in the real world unrealistic. Fortunately, the same study group simplified the assessment and created the "Frailty predicts death One yeaR after Elective Cardiac Surgery Test (FORECAST)" [80], limited to the more predictive variables. These were chair rise (the patient gets up and down from a chair three times, and time is measured); weakness (in the last 2 weeks); stair (patient climbs as many stairs as he is able to); Clinical Frailty Scale; and creatinine. At a 1-year follow-up, mortality rate was 12.2 %. Patients who died within 1 year had a median *frailty* score of 16 compared to 11 in survivors ($P = 0.001$).

A further clinical implication of multidimensional geriatric evaluation is the ability to identify patients at high risk of developing delirium during hospitalization. Rudolph et al. [81] recently validated a scoring system to predict delirium after cardiac surgery, as defined by the Confusion Assessment Method [82]. They enrolled 122 elderly cardiac surgery patients that underwent a delirium assessment pre- and postoperatively beginning on postoperative day 2. Delirium occurred in 52 % of the patients, and multivariate analysis identified four independent variables associated with delirium: previous stroke, MMSE scores, abnormal serum albumin, and the Geriatric Depression Scale Scores.

11.5 Role of Comprehensive Geriatric Assessment (CGA) in Preoperative Noncardiac Surgery

Solid evidence from randomized controlled trials demonstrates that a geriatric intervention guided by CGA has positive effects on health, functional status, and mortality in hospitalized elderly patients [83]. In the last years, an increasing number of studies have assessed whether the CGA was able to increase our accuracy in predicting the prognosis of elderly subjects candidate to intervention. In many fields of surgery and medicine, trials have been performed to estimate whether malnutrition, cognitive impairment, disability, or poor social resources impact on postoperative mortality, length of stay, and institutionalization. A Japanese study [47], involving 120 patients with mean age of 70.3 undergoing thoracic surgery, showed that patients with a MMSE ≤24 developed postoperative complications, including delirium, four times more often than patients >24, also. Functional dependency estimated by the Barthel Index also correlated strongly with postoperative complications. Furthermore, patients with malnutrition (defined as low levels of albumin, transferrin, and peripheral lymphocyte) were more likely to suffer postoperative complications. The authors concluded that intensive care of elderly patients after thoracic surgery might be improved by CGA.

Of particular interest is a study by a French group focusing on lung oncology, showing that a preoperative multidimensional geriatric assessment, targeted to measure global functional status and performed by a team of geriatricians in collaboration with anesthesiologists and surgeons, was able to reduce perioperative mortality as well as risk of institutionalization at discharge [84]. Likewise, in elderly patients undergoing elective surgery for colorectal cancer [85], a standardized CGA was able to independently predict severe complications (potentially life-threatening without or with lasting disability or fatal). Based on the preoperative CGA assessment, patients were categorized into three groups: "fit," "intermediate," and "frail"; frail were those patients who were dependent in personal activities of daily living or had a pathological score at some test (MNA < 17; CIRS >4; GDS > 13; MMSE < 24) or took more than seven medications a day. Extermann and Hurria reviewed studies of CGA in older adults and concluded that CGA predicted survival, chemotherapy toxicity, postoperative morbidity, and mortality in cancer patients [86].

An attractive study extended the concept of CGA applied to oncological patients, creating the Preoperative Assessment of Cancer in the Elderly (PACE) [87]. This includes, besides CGA, the evaluation of fatigue with Brief Fatigue Inventory (BFI), physical performance with Eastern Cooperative Oncology Group Performance Status (ECOG-PS), and a measure of the degree of sickness or physical state prior to anesthesia and surgery according to ASA grade. This international multicenter prospective study, based on a cohort of 460 patients with a mean age of 76.8 years candidate to breast, genitourinary, or gastro-intestinal elective surgery, demonstrated that moderate/severe fatigue, dependence in IADLs, and impaired PS were the most important independent predictors of postoperative complications [88].

Furthermore, dependence in ADLs and IADLs and impaired PS was associated with increased length of stay [88].

A study by Richter et al. [89] is partly in disagreement with these results. In a cohort of 62 patients >60 years of age, scheduled to undergo pelvic floor surgery, 32 received additional preoperative assessment of function (BADL/IADL); time up and go; clock-drawing test, MNA, and GDS; and social support scale, compared with 30 patients receiving usual care. There were no differences in primary outcome (scores of the Physical Component Summary and Mental Component Summary of the Medical Outcomes Study Short Form 36 Health Survey), but almost all the patients were "fit": 87.5 % had no deficiencies in BADL/IADL and 87.5 % performed the Get Up and Go test in less than 20 s; almost had no malnutrition, completed the Clock Test correctly and scored perfectly on the social support scale. Thus, the cohort enrolled in the study appears scarcely representative of the real world.

As a result of these investigations, in 2012 the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society collaborated to draft Guidelines [90] in which CGA emerged as a critical tool for preoperative evaluation. It was concluded that all geriatric patients should be assessed to investigate functional status, mobility, fall risk, cognitive impairment, depression, *frailty*, and nutritional status, with the same priority given to the examination of cardiac, renal, or pulmonary function. Intuitively, a comprehensive preoperative assessment represents only the first step of elderly patient management; in the perioperative period, an expert team coordinated by a geriatrician should intervene to prevent and treat complications and develop a plan for rehabilitation or long-term care.

In the literature, there are few studies comparing traditional management with a CGA-guided one. An exploratory trial [91] demonstrated clear benefits from *proactive care of older people undergoing surgery* (POPS' model) with better pain control, earlier mobilization, reduction in length of stay, and medical complication after elective orthopedic surgery. The team preoperatively assessed the patient, using CGA methodology¸ in order to get the patient as "fit as possible" for surgery, involving healthcare professionals and caregivers. The patient was then followed through hospitalization until discharge, with timely organization of rehabilitation or long-term care. Another interesting study included patients aged over 65 years scheduled for orthopedic, urological, or gastrointestinal surgery [92] with one or more difficulties in mobility, cognition, functional autonomy, polypharmacy, comorbidity, or social support. The pre-pilot group consisted of 141 patients assessed in the clinic or by a senior nurse focusing on cognition (MMSE), falls, nutrition, functional ability (BI), continence, and carer roles. The intervention consisted of a pre-assessment collected by a senior nurse followed by referral pathways created to deal with issues identified during screening. After the operation, the same multidisciplinary team

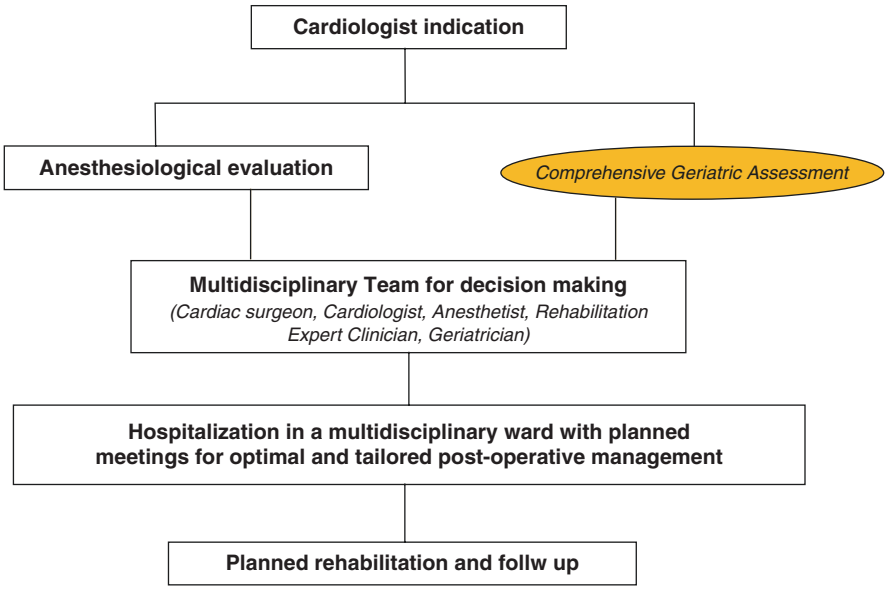

Fig. 11.2 Example of management of old patient candidate to heart surgery

discussed the pre-assessed rehabilitation needs and discharge planning. In the 172 study patients, these interventions resulted in significant fewer surgical cancellation and postoperative complications, as well as a short length of stay. These studies share certain limitations, which include a considerable heterogeneity of the surgical patient population, the fact that CGA interventions usually delivered by a non-geriatrician internist, and the variability in outcome measures used [93]. To this regard, the 2014 guidelines on perioperative management of the elderly by the Association of Anesthetists of Great Britain and Ireland [94] concluded that "pre-operative assessment of the higher-risk elderly patient, involving a structured multifactorial approach, therefore, should be undertaken by both a senior geriatrician and a senior anesthetist with specific subspecialty training in geriatrics" and recommended the minimum components of preoperative geriatric assessment. To date, despite clear evidence supporting its benefits, CGA has not yet translated into routine clinical practice.

In conclusion, many efforts are still needed to improve the capacity of selection and management of elderly surgical patients, in both pre- and postoperative. Greater collaboration among health professionals is desirable by drafting shared paths and protocols (i.e., Fig. 11.2), which needs to include specific tools such as CGA in its core domains (Fig. 11.3).

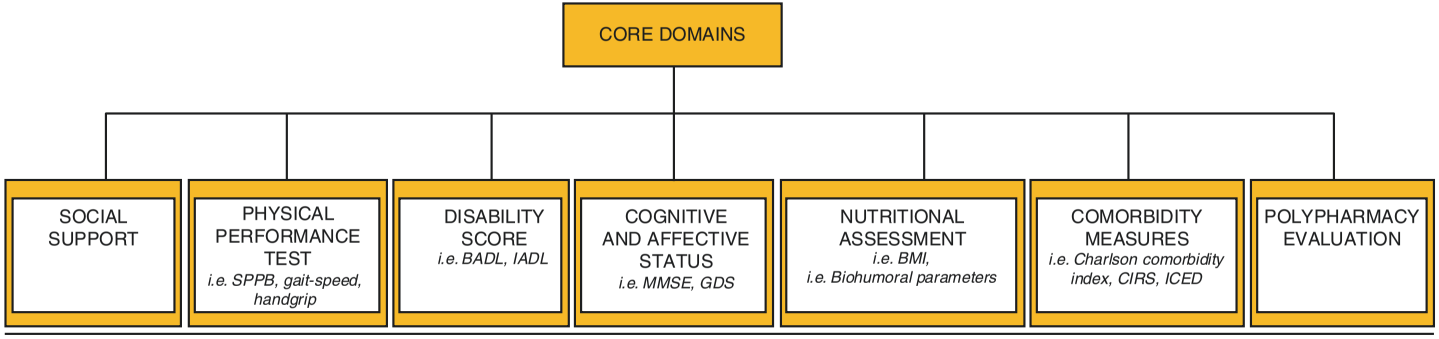

Fig. 11.3 Core domains of Comprehensive Geriatric Assessment in elderly candidate to surgery. *SPPB* Short Physical Performance Battery [55], *BADL* basic activities of daily living [45], *IADL* instrumental activities of daily living [46], *MMSE* Mini Mental State Examination [67], *GDS* Geriatric Depression Scale [66], *BMI* Body Mass Index, Charlson Comorbidity Index [95], *CIRS* Cumulative Illness Rating Scale [96], *ICED* Index of Coexistent Disease [42]

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Atrial Fibrillation in the Elderly

12

Stefano Fumagalli, Debbie Gabbai, Luigi Padeletti, Harry J. Crijns, and Gregory Y.H. Lip

12.1 Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia in the elderly [1, 2] (Fig. 12.1). The Framingham Heart Study, the Cardiovascular Health Study, and the Olmsted County Study all show that the incidence of AF exponentially grows in general population from 60 years of age, reaching 60 cases per 1000 person-years in those age over 80 [4]. The prevalence of arrhythmia follows the same trend. Over 75 and 85 years of age, AF is present in 17 and 23 % of people, respectively [4]. Given the aging population, current projections estimate that by 2060 17.9 million persons will be diagnosed with AF, of these 13.4 million (77.1 %) will be over 75 years of age (Fig. 12.2) [2]. Therefore, AF plays an important role in the elderly due to the associated complications and the resulting disability. In the elderly, the arrhythmia is often silent (up to 27.5 % of cases over 85 years), and optimal prevention strategies may be particularly challenging [5].

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_12

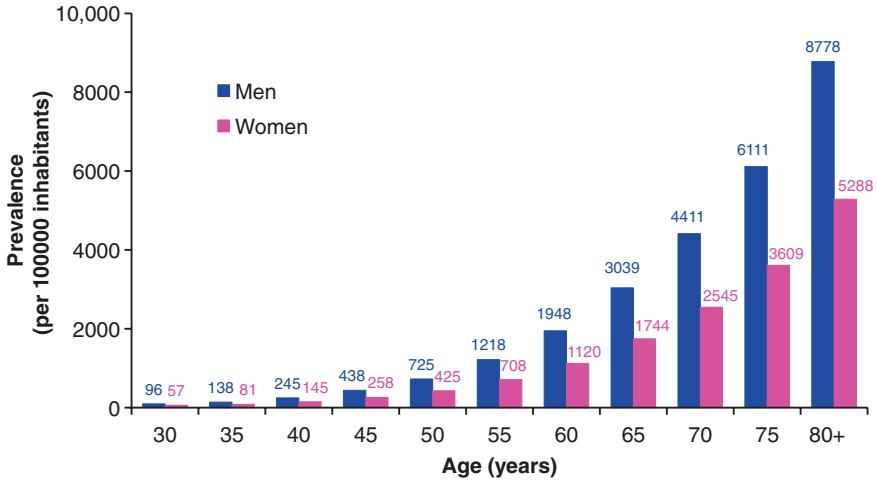

Fig. 12.1 Estimated 2010 prevalence of atrial fibrillation in the developed countries participating to the "Global Burden of Disease Study" (Figure drawn by the data reported in Ref. [3])

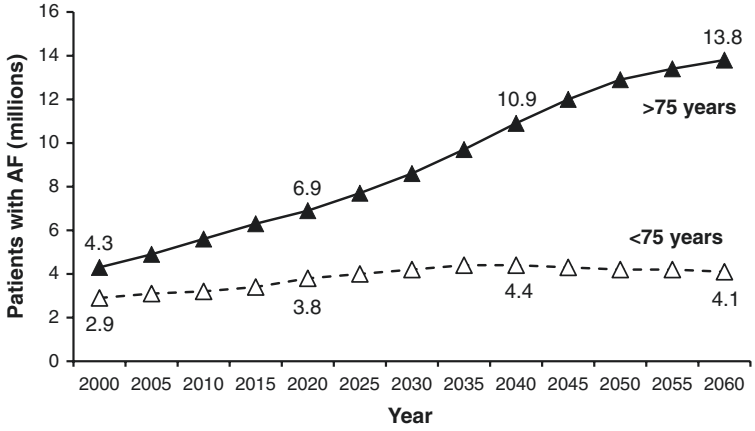

Fig. 12.2 Estimated numbers of adults with atrial fibrillation in the European Union between 2000 and 2060 (Figure drawn by the data reported in Ref. [2])

12.2 Aging and Changes of Atrial Structure

Aging modifies some characteristics of atrial structure, facilitating the development of AF and increasing the risk of cardio-embolic events. Multi-slice CT imaging studies have shown that the end-systolic diameter of the left atrium progressively increases from 30 mm for ages ≤40 years to 48 mm in those over 80 years (Fig. 12.3) [6]. The thickness of the anterior left atrium also increases from 2 to 3.7 mm. The Framingham Heart Study has recently confirmed, in a longitudinal analysis, that the size of the left atrium increases progressively with age, in both sexes, by

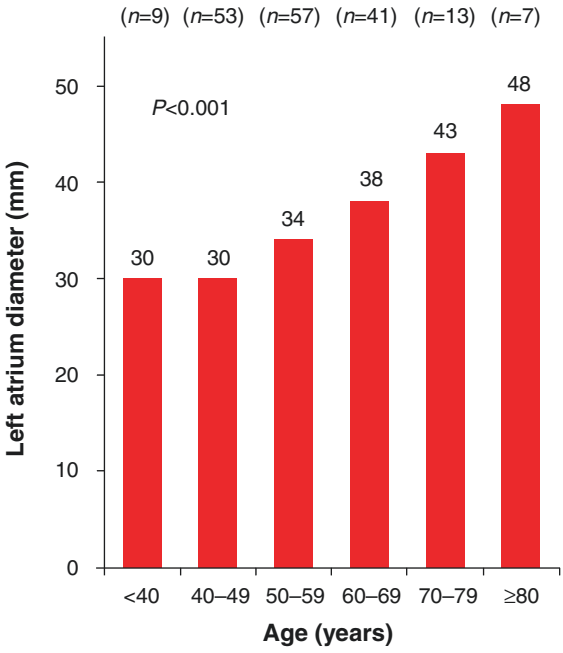

Fig. 12.3 Left atrium dimensions gradually increase with age. The number of subjects in whom the measure was obtained is reported in brackets (Figure drawn by the data reported in Ref. [6])

approximately 0.6 mm per decade [7]. These modifications can partially be attenuated through the control of some cardiovascular risk factors such as obesity and hypertension [7]. In uncontrolled hypertension, the atrial diameter increases with age by 50 %, at a rate of 0.9 mm per decade [7]. Aging changes both the geometry and structure of the atrial myocardium. In addition, biopsy samples obtained during cardiac surgery have shown an age-related increase of the connective-fibrous tissue, from 10 % of atrial mass in subjects <50 years to 17 % in subjects >70 years [8]. Tissue acetylcholinesterase, a marker of the autonomic nervous system activity, also decreases with age, in association with a decrease in number and extension of nerve fibers [9]. The ostium of the left atrium auricula and the diameter of the pulmonary veins become progressively larger, growing from 12 to 28 mm and from 10 to 24, respectively, between age 30 and 90 years [6].

In conclusion, the atria seem to encounter a real aging process ("wrinkles in the atrium") that could justify the increased incident risk of AF in the elderly [10]. Whether age, increase in atrial size, degree of fibrosis, and presence of arrhythmia are causes, effect or epiphenomenon of extra-cardiac alterations still needs to be clarified [10].

12.3 Aging and Risk of Stroke and Systemic Cardio-embolism

Epidemiological studies have shown that, with AF, the incidence of cardio-embolic stroke increases exponentially with age [1, 11]. In a registry study conducted in Dijon, for example, the incidence of cardio-embolic stroke was 28 per

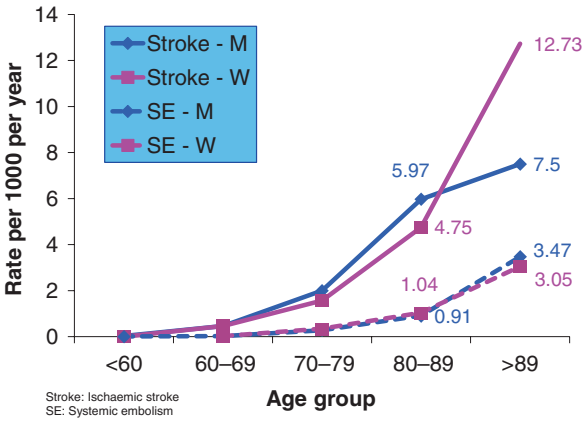

Fig. 12.4 Age-specific rates of a first AF-related incident ischemic stroke and systemic embolism (*SE*) in the Oxford Vascular Study. The results derive from the experience of about 100 family doctors (nine general UK practices) participating between 2002 and 2012 (*M* men, *W* women) (Figure drawn by the data reported in Ref. [12])

100,000 person-years in men aged 50–60 years and 216 per 100,000 person-years in men >80 years [11]. At advanced ages, the incidence of disease is higher in women [11]. A recent UK community survey showed that the incidence of cardio-embolic stroke was as high as 12.7 per 1000 per year in AF women ≥90 years [12] (Fig. 12.4). About 20 % of all ischemic strokes are AF related [11].

Furthermore, the incidence of cryptogenic stroke progressively increases with age, representing, in >75 years patients, the second cause of disease [13]. The use of loop recorders, allowing long EKG monitoring, demonstrated that 25.5 % of all cryptogenic strokes could be attributed to AF [14]. Asymptomatic forms of arrhythmia play an important role in the genesis of silent cerebrovascular disease in type 2 diabetic patients [15].

The European Community Stroke Project Study, which enrolled 4462 subjects, with a first ischemic stroke, demonstrated that patients with cardio-embolism had a more severe form of disease [16] with a greater incidence of delirium, coma, motor impairment, aphasia, dysphagia, and urinary incontinence [16] and higher in-hospital and short- (3 months, 32.8 vs. 19.9 %, p <0.001) and long-term (2 years, 57 vs. 31 %, p <0.001) mortality [11, 16].

Thus, survivors of AF-related strokes are at increased risk of disability and more frequently need assistance in basic activities of daily living and institutionalization in nursing homes [16]. AF-related disability-adjusted life years progressively increase with age [3]. The higher severity of cardio-embolic stroke can be explained by the more frequent involvement of the anterior portion of the circle of Willis [16]. All these reasons support the fact that age is one of the most important variables linked to AF-related stroke [17].

The incidence of systemic cardio-embolism (SE) was 0.24 per 100 patient-years (11.5 % of all cardio-embolic events), involving lower limbs and renal and mesenteric circulation. SE mortality was 25 %, while 20 % of survivors had some kind of residual disability [18].

12.4 AF and Chronic Kidney Disease

The prevalence of chronic kidney disease increases with age, ranging from 20 % in subjects aged 60–69 years to over 45 % in subjects >70 years. In the Atherosclerosis Risk Communities Study (ARIC), a cohort of 10.328 subjects, after a 10-year follow-up, the risk of developing AF was independently associated with renal function [19]. When compared to those with a normal glomerular filtration rate (GFR), the relative risk of developing new arrhythmic events was 1.57 and 2.84 higher in those with a GFR of 30–59 and 15–29 ml, respectively [19].

The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study showed that in 11,527 AF patients, followed up from 1996 to 2003, the incidence of cardio-embolism was directly related to the degree of chronic renal impairment, increasing from 1.63 to 4.22 events per 100 person-years for GFR values ranging from ≥60 to <45 ml/min/1.73 m^2 [20]. Recently, a large Danish cohort study has further clarified the relationship between AF, chronic kidney disease, and clinical outcomes in 132,732 patients, hospitalized between 1997 and 2008 with a diagnosis of AF [21]. The prevalence of non-end-stage and end-stage kidney failure was 2.7 % and 0.9 %, respectively. During follow-up, the incidence of ischemic stroke and cardio-embolic events was higher with impaired kidney function, with a relative risk of 1.49 and 1.83 in patients with non-end-stage disease and in those requiring dialysis. A similar trend was observed for risk of myocardial infarction and major bleeding [21]. Total mortality was higher in AF patients with impaired kidney function [21].

These evidences led the investigators of ROCKET AF trial to elaborate and validate the R_2CHADS_2 score, in which two additional points are assigned in subjects with chronic renal failure, defined by a GFR < 60 ml/min [22]. Even if this score presents some limitations (it was derived in a selected trial cohort that excluded patients with severe renal impairment or presenting some risk of stroke) [23], it reflects the awareness that AF patients with chronic renal failure have a higher risk of thromboembolism and major bleeding [23].

12.5 AF and Peripheral Artery Disease

The prevalence of peripheral artery disease is high among AF patients [24], and, in a review of ten observational studies, it was found to be associated with a 1.3–2.5 times greater stroke risk [25].

Less is known about the mechanisms linking the condition to arrhythmia development. In the Framingham Heart Study, the incidence of AF on a median follow-up of 12 years was 13.1 % (N = 698/5331), and it was lower in those with a pulse pressure ≤40 mmHg than in those with a pulse pressure >61 mmHg (5.6 vs. 23.3 %). After multivariate adjustment, pulse pressure, but not mean arterial pressure, was associated with an increased risk of arrhythmia development [26]. The observational "Atrial Fibrillation Registry for Ankle-Brachial Index Prevalence

Assessment-Collaborative Italian Study" (ARAPACIS), conducted on 2027 patients, analyzed the relation between peripheral arterial disease and non-valvular AF. The study showed that abnormal ankle-brachial index (ABI) values (≤0.90) are found in 21 % of AF patients and have a direct association with the arrhythmic burden [27]. A higher prevalence of a previous ischemic stroke was observed in patients with a pathologic ABI when compared to those with a normal one (17 vs. 10 %, $p < 0.001$) [27]. Later, the same study found that an ABI ≤ 0.90 was an independent predictor of vascular events, vascular death, and MI [28]. More recently, arterial stiffness was found to be an independent predictor of left atrium dimensions even after adjustment for interventricular septum thickness [29]. Hence, aortic mechanical characteristics, possibly through inflammation cascade, could play a role in promoting and maintaining AF [29, 30].

12.6 AF and Dementia

The incident risk of dementia is about twice higher in patients with AF. In a cohort of 6584 subjects, the Rotterdam Study investigators reported that AF prevalence increased with the severity of cognitive impairment, from 2.1 % in normal cognitive status to 6 and 13 % in mild cognitive impairment and dementia [31]. The Olmsted County Study confirmed this association [32].

More recently, the Cardiovascular Health Study evaluated in a longitudinal analysis the changes in cognitive profile of the 5150 participants enrolled between 1989 and 1993. During a mean follow-up of 7 years, cognitive performance test (assessed by a modified version of the Mini-Mental State Examination) decreased progressively with age. The presence of AF was associated with a higher score reduction in those older than 75 years [33] (Fig. 12.5). These data confirm the observations of "The Adult Changes in Thought Study," where the incidence of dementia had a 38 % risk increase in arrhythmic patients, growing from 25 to 47.9 events per 1000 person-years [34].

A meta-analysis of observational studies showed an association between AF and dementia in the subgroup of patients with a previous stroke (OR = 2.4) [35]. In an extensive review of literature, eight out of 11 studies published between 1990 and 2012 (three cross-sectional, two case-control, and three prospective cohorts) were found to report a significant correlation between cognitive decline and the arrhythmia. Among cross-sectional studies, patients with AF had a 1.7 to a 3.3 greater risk of cognitive impairment, and a 2.3-fold increased risk of dementia, compared to those in sinus rhythm [36].

All these findings would suggest that the arrhythmia could produce cognitive changes not only through cardio-embolic events but also through the increased production of beta-amyloid [35]. Evidence shows a possible pathway linking vascular disease to reduced beta-amyloid clearance, which would determine a further worsening of vascular disease. This mechanism, sustained by protein tau hyperphosphorylation, would result in white and gray matter reduction [37]. Furthermore, variation in the concentration of inflammatory mediators could help to explain the

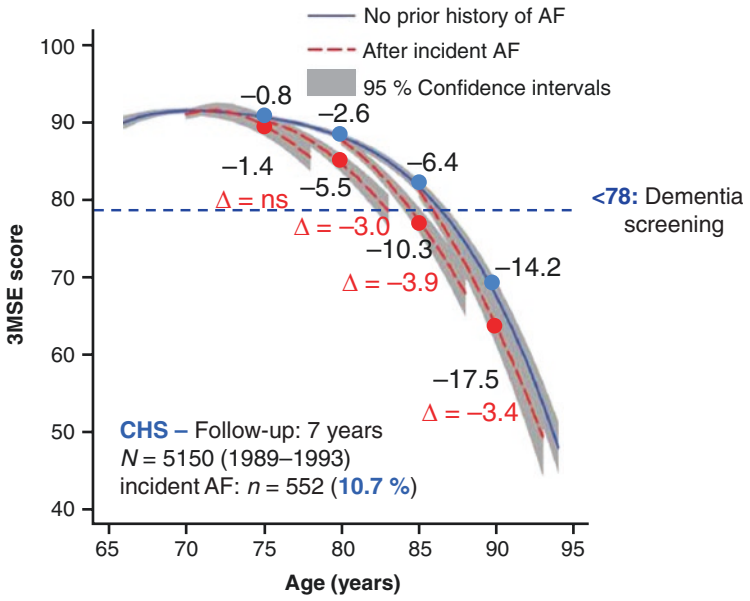

Fig. 12.5 Predicted trajectories of the "modified Mini-Mental State Examination" (3MSE) in the Cardiovascular Health Study (CHS) participants. An incident atrial fibrillation determines a steeper decline of cognitive function. The 3MSE score ranges between 0 (worst) and 100 (best performance) (Adapted from Ref. [33]. (License by Wolters Kluwer Health, Inc.))

association between the arrhythmia and the risk of dementia. Beside a higher CPR level, AF patients show higher concentrations of pro- (e.g., interferon, interleukin-1, interleukin-6, tumor necrosis factor-α) and anti-inflammatory (e.g., transforming growth factor-β) cytokines. Similar changes can be also observed in dementia [38].

12.7 Anticoagulant Therapy in Elderly AF Patients

Oral anticoagulant therapy (OAT) with vitamin K antagonists proved to be extremely effective in reducing the incidence of cardio-embolism in patients with non-valvular AF. A meta-analysis of the original historical trials demonstrated that OAT, compared to placebo, reduces the risk of stroke by 62 % and all-cause mortality by 26 % [39, 40]. The benefit of OAT is also significantly higher compared to that of aspirin, with a 36 % additional risk reduction [39, 40].

The "Birmingham Atrial Fibrillation Treatment of the Aged Study" (BAFTA) first explored the effects of OAT, compared with aspirin, in the elderly (inclusion criteria, age ≥75 years). After a mean follow-up of 2.7 years, in the 973 patients enrolled (mean age 81.5 years), OAT significantly reduced the combined risk of stroke, cardio-embolism, and intracranial hemorrhage compared to aspirin (1.8 vs. 3.8 % per year, RR = 0.48; $p = 0.003$) [41].

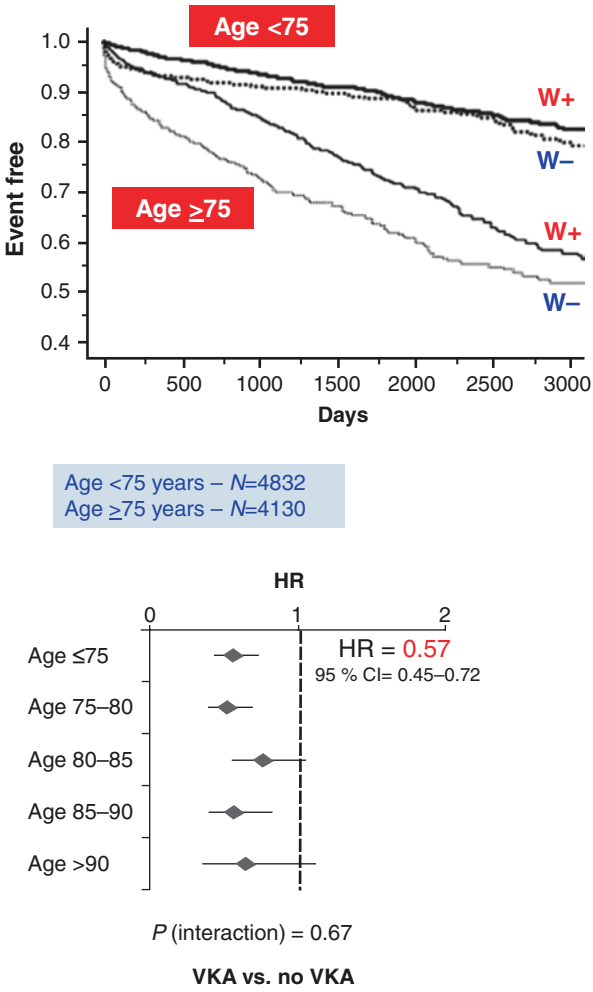

Fig. 12.6 The influence of warfarin (W) on all-cause mortality in "The Loire Valley Atrial Fibrillation Project" by age-group (<75 vs. ≥75 years) (*upper panel*). The benefit of therapy (vitamin K antagonist, *VKA*) is maintained independently of age even in subjects aged >90 years (*lower panel*). (*HR* hazard ratio) (Adapted from Ref. [43]. (License by Wolters Kluwer Health, Inc.))

Subsequently, a sub-analysis of ATRIA study analyzed in 13,559 patients the net clinical benefit (avoided ischemic stroke – provoked hemorrhagic strokes) of OAT by age group. Interestingly, the benefit of anticoagulation increased with age, reaching the statistical significance for those aged 75–84 and ≥85 years [42]. In the "Loire Valley Atrial Fibrillation Project," which enrolled 4832 patients <75 years and 4130 patients ≥75 years, the benefit of warfarin vs. placebo to prevent stroke, thromboembolism, and mortality was maintained through all age strata, even in subjects older than 85 and 90 years [43] (Fig. 12.6).

As shown in a Swedish registry enrolling 182,678 subjects, the risk of cardio-embolism was progressively higher for increasing scores not only of CHA_2DS_2-VASc but also of the HAS-BLED, the instrument used to assess the bleeding risk [44].

In addition, the results of an Italian prospective multicenter registry enrolling 4093 elderly patients (mean age, 84 years) receiving anticoagulants for AF or deep vein thrombosis showed that bleeding could be minimized (1.87 events per 100 patient.years) by the adoption of tight monitoring protocols [45]. In multivariate analysis, the incidence of hemorrhagic events was associated with the presence of deep vein thrombosis, prior bleeding, an active cancer, and a history of falls [45].

Despite all these findings recommending the adoption of the OAT in elderly AF patients, anticoagulation is still largely underused at older ages. Data from the Euro Heart Survey on Atrial Fibrillation study showed that among 5329 enrolled patients, the use of vitamin K antagonists significantly decreased with age, going from 64 % in the < 65 years group to 56 % in the > 80 years group [46]. These findings were later confirmed by the results of the EURObservational Research Programme-Atrial Fibrillation General Pilot Registry [47]. Moreover, time in the therapeutic range (TTR) was found to be associated with cognitive performance, measured by the Mini-Mental State Examination [48]. Conversely, during follow-up of AF patient with normal cognitive status at baseline, incidence of dementia progressively increases with lower values of TTR [49].

12.8 Non-VKA Oral Anticoagulants

Compared to warfarin, non-VKA oral anticoagulants (NOACs) are characterized by a more foreseeable biological effect, due to their pharmacokinetic and pharmacodynamic characteristics, a reduced interaction with drugs and food, as well as a better safety profile. All randomized controlled trials demonstrated a reduced incidence of intracranial hemorrhage [50–55]. The elderly (age > 75 years) subgroup in the RE-LY study (Randomized Evaluation of Long-Term Anticoagulation Therapy), in the ROCKET AF study (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), in the ARISTOTLE study (Apixaban for Reduction in Stroke and Other Events in Atrial ThromboembolLic Fibrillation) and in the ENGAGE AF-TIMI 48 trial (The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 trial) were, respectively, 40, 38, 31, and 40 % of all enrolled patients. The subgroup analysis showed no significant age-related differences in the primary efficacy outcome (new cases of stroke and cardio-embolism) compared to warfarin [50–55]. The incidence of major bleeding, with both rivaroxaban and apixaban, did not show any age-related differences [52–54]. Apixaban consistently reduced major bleeding across all age groups [56]. In older patients treated with dabigatran, the incidence of major hemorrhage was not different between dabigatran 110 and 150 mg twice a day, while intracranial hemorrhage was lower in dabigatran 110 mg twice a day, which represent the current recommended dose in the elderly [51, 54].

In a meta-analysis of RE-LY, ROCKET AF, and ARISTOTLE studies, NOACs compared to warfarin were associated with a lower incidence of intracranial hemorrhage (relative risk reduction, RRR −51 %), with similar incidence of systemic

major bleeding [57]. Moreover the combined effect of the three molecules, on prevention of all cardio-embolic events, showed RRR of 22 %, compared to warfarin [57]. A meta-analysis of the ten major randomized controlled clinical trials on NOACs, including only over 75 years patients, found that the risk of major or clinically relevant bleeding did not differ between NOACs and conventional therapy (6.4 vs. 6.3 %, OR = 1.02, 95 % CI = 0.73–1.43). Importantly, the incidence of stroke and other thromboembolic events was significantly reduced (3.3 vs. 4.7 %, OR = 0.65, 95 % CI = 0.48–0.87), with a number needed to treat of 71 [58].

The use of NOACs in patients with kidney impairment is a matter of particular importance in elderly patients, considering the high prevalence of the condition [59], and the significantly increased risk associated with both cardio-embolism [20, 21] and hemorrhage [60]. The European Heart Rhythm Association (EHRA) recommendations suggest that NOACs are reasonable choice in patients with mild-to-moderate chronic kidney impairment [61]. Present EHRA guidelines do not recommend dabigatran, which is mainly excreted by kidneys, for GFR lower < 30 ml/min [61]. In ROCKET AF, 20.7 % of patients had a GFR between 30 and 49 ml/min; their mean age was higher (79 vs. 71 years). There was no interaction between degree of kidney impairment, efficacy, and safety of the drug. Fatal bleeding had a lower incidence in rivaroxaban-treated patients (0.28 vs. 0.74 per 100 patient.years; $p = 0.047$) [52, 62]. A sub-analysis of ARISTOTLE study confirmed that GFR ≤50 ml/min (17 % of the enrolled subjects, mean age 77.6 years) did not affect the efficacy of apixaban. The benefit in terms of major bleeding events was even found to be higher in the presence of kidney impaired function, with an RRR higher than 50 % when compared to the warfarin [53, 63]. Based on these evidences, EHRA therefore recommends the use of rivaroxaban and apixaban, at reduced doses, up to GFR of 15 ml/min [61].

In a real-world scenario, in 134,414 Medicare patients, dabigatran, when compared to warfarin, was associated with a reduction of stroke incidence (HR = 0.80, 95 % CI = 0.67–0.96), intracranial hemorrhages (HR = 0.34, 95 % CI = 0.26–0.46), and hence mortality (HR = 0.86, 95 % CI = 0.77–0.96). Only gastrointestinal bleeding had a higher incidence in women ≥75 years and in men >84 years [64]. Recent data seem to demonstrate that older patients treated with NOACs have greater psychological satisfaction, lower therapy-related burden, higher awareness of benefits, and lower psychological stress [65].

12.9 Rhythm and Rate Control of AF in Elderly Patients

Real-world data from the EURObservational Research Programme-Atrial Fibrillation General Pilot Registry show that the use of rate-control strategy was more frequently adopted in the elderly, with lower proportions of electrical cardioversion, transcatheter ablation, and prescription of antiarrhythmic drugs. Among rate-control agents, while beta- blockers were prescribed regardless of age, digoxin and nondihydropyridine calcium channel blockers were more often used in older patients [47]. These findings are partially motivated by the results of a sub-analysis

of the "Atrial Fibrillation Follow-Up Investigation of Rhythm Management Study" (AFFIRM) which, in patients between 70 and 80 years of age, showed that rate control, compared to rhythm control of AF, was associated with lower mortality and hospitalization rates [66]. However, the evidence is conflicting. In a sub-analysis, the AFFIRM investigators found that, in the follow-up, the presence of sinus rhythm was associated with a lower risk of death, as was warfarin use. Conversely, the use of antiarrhythmic drugs was linked to increased mortality [67].

The incidence of adverse events related to antiarrhythmic drug therapy constitutes an important clinical issue. Patients treated with amiodarone, the most effective agent to prevent AF recurrences, present more complications compared to those receiving propafenone or sotalol (18 vs. 11 %, $p = 0.06$) [68]. Recent findings from the ARISTOTLE study showed that, in warfarin treated subjects, amiodarone lowers TTR [69]. A meta-analysis demonstrated that the number needed to harm ranges between 9 for quinidine and 27 for amiodarone, propafenone, and sotalol [70].

Nevertheless, also drugs used for the rate-control strategy were found to be not surely effective. A wide AF cohort showed that the risk of mortality was lower for patients receiving β-blockers or calcium channel blockers, with β-blockers determining the largest risk reduction, whereas digoxin use was associated with greater mortality [71]. However, in a meta-analysis of ten studies evaluating the influence of beta-blockers in heart failure patients, there were no benefits in terms of survival and hospitalization in the presence of AF [72]. In a population study, the use of digoxin in elderly patients with AF increased mortality independently from heart failure [73]. Findings from a sub-analysis of the "Dutch Rate Control Efficacy in Permanent AF: A Comparison Between Lenient Versus Strict Rate Control II trial" showed that digoxin therapy did not increase morbidity, hospitalization rates, and mortality [74].

Regarding invasive procedures, some observations seem to demonstrate that AF ablation could be also suitable over 75 years in appropriately selected patients. After a mean follow-up of 3 years, compared to those receiving medical therapy, ablated subjects were more often in sinus rhythm (83 vs. 22 %, $p < 0.001$) and had lower incidence of stroke and bleeding and higher life expectancy at 1 and 5 years [75]. Furthermore, AF ablation was associated with improved functional status and health-related quality of life [76].

Conclusions

In elderly patients, AF represents an important clinical issue. The coexistence of anatomic changes and comorbidities greatly increases the prevalence of the arrhythmia, which, especially in older individuals, more often determines stroke and dementia. AF frequently worsens the course of common conditions in the elderly, such as chronic heart failure, pneumonia, non-ST-elevation myocardial infarction, and urinary infections [77, 78]. Thus, in aged patients a comprehensive management of the arrhythmia should aim not at the simple control of rhythm or rate but at reducing morbidity and at improving health-related quality of life and survival.

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Treatment of Acute Coronary Syndromes in Elderly Patients

13

Leonardo Bolognese and Stefano Savonitto

Elderly patients represent a large proportion of patients admitted to the hospital with an acute coronary syndrome (ACS) and will be even more represented in the forthcoming decades. According to Italian coronary care unit (CCU) registries, 40 % of the patients admitted with NSTEMI are ≥75 years [1], as compared to 28 % of those with STEMI (Fig. 13.1). As a matter of fact, it has been known for years that the most frequent presentation of ACS among elderly patients is the NSTE form [3], which is typically associated with more extensive coronary artery disease, less identifiable culprit lesion, less obvious revascularisation options and more comorbidities [4].

There is no uniformly accepted definition of "elderly" in terms of age cutoff. The only two specific and prospective studies addressing treatment strategies in elderly patients with ACS used the cutoff of ≥75 years [5, 6]. This cutoff is the most commonly used in recent years, whereas older papers used lower cutoffs, such as 60–65 years. This issue is important when interpreting the literature, since the relation between age and outcome (particularly mortality but also bleeding) shows a dramatic worsening around the age of 75 [7]. Moreover, increasing age does not imply just more years but also a change in the overall characteristics of the ACS population. The proportion of women increases from <30 % when a study population has a mean age of 60–63 years (as in most RCTs) to 50 % in study populations with a mean age of 80 years (Fig. 13.2). Elderly populations will also have >70 % hypertensive patients, 35 % diabetics, 20 % with an estimated glomerular filtration rate (eGFR) <60 ml/min as well as more patients with prior myocardial infarction (MI), stroke, atrial fibrillation and peripheral arterial disease [5–11]. All these conditions imply specific problems when deciding treatment strategies. Finally, most RCTs

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A. Ungar, N. Marchionni (eds.), *Cardiac Management in the Frail Elderly Patient and the Oldest Old*, DOI 10.1007/978-3-319-43468-1_13

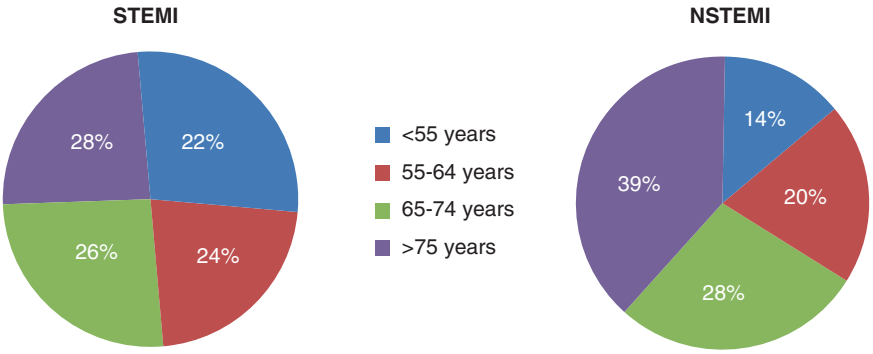

Fig. 13.1 Percent distributions of age classes in patients with ST elevation (*STEMI*) and non-ST elevation (*NSTEMI*) myocardial infarction admitted to the Italian coronary care unit (CCU) network. Data are from the CCU surveys of the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) conducted between 2000 and 2014 (Data from Ref. [1], [2]])

and guidelines on ACS do not consider frailty, which has been shown to profoundly affect outcome in the elderly [12], among the variables to be collected and analysed to guide treatment strategies.

In 2007, two scientific statements of the American Heart Association Council on Clinical Cardiology reviewed the existing literature on the treatment of non-ST-segment elevation ACS (NSTEACS) [13] and ST-segment myocardial infarction (STEMI) [14] in the elderly: these documents highlighted the fact that the elderly is largely underrepresented in the study populations of RCTs that form the basis of clinical practice guidelines.

13.1 Risk Stratification in Elderly ACS Patients

Risk stratification in elderly ACS patient is difficult because supporting evidence is scarce. One critical point, especially in the very old, is the prediction of the cause of death in the short-medium term, since this information may help in decision-making for invasive procedures. Among the general elderly population, the Italian administrative data drawn from the National Institute of Statistics have shown that cardiovascular disease is reported as the cause of death (CoD) in 41 % of men and 49 % of women [15], much greater than the 30 % reported in the United States by the Centers for Disease Control and Prevention [16], but similar to the 40 % cardiovascular CoD reported among male Medicare beneficiaries >67 years hospitalised and followed up for 2 years in the United States [17]. Among elderly patients hospitalised for noncardiovascular illness, cardiovascular deaths contributed to total mortality in about 40–50 % of the cases [18, 19]. Even among patients with cardiovascular diseases other than an ACS, such as those with nonvalvular atrial fibrillation [20] or aortic stenosis [21], CV death accounts for 40 % of overall mortality at follow-up. However, when an elderly patient becomes hospitalised for an ACS, cardiovascular events will represent more than 70 % of the causes of death at follow-up. This has

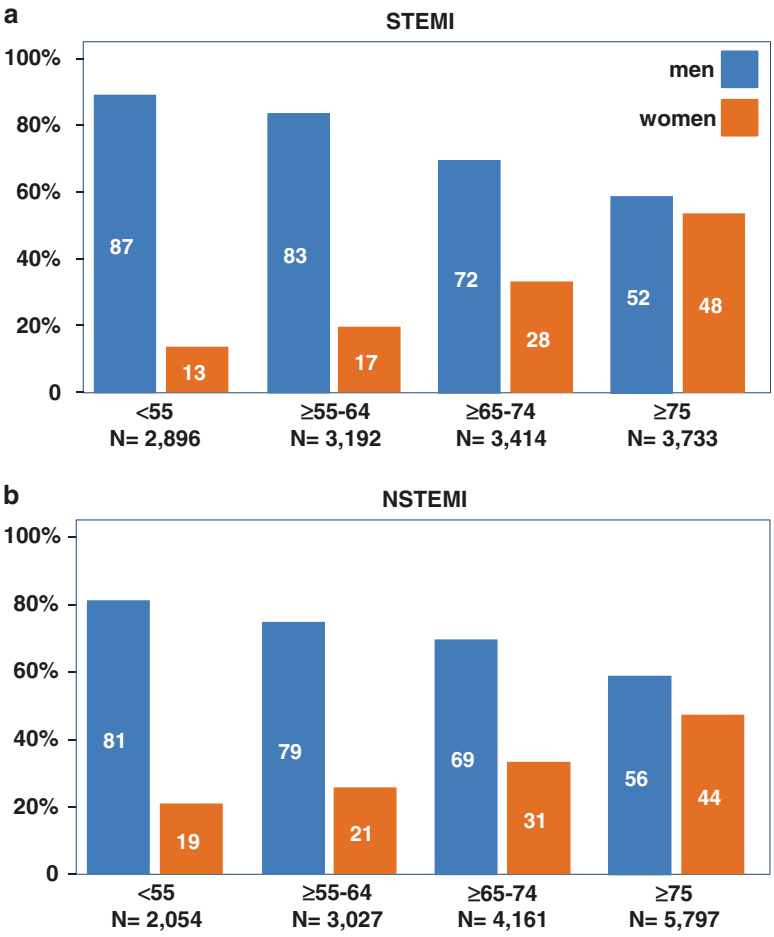

Fig. 13.2 Proportions of men and women in patients with ST elevation (STEMI, panel **a**) and non-ST elevation (NSTEMI, panel **b**) myocardial infarction admitted to the Italian coronary care unit (CCU) network. Data are from the CCU surveys of the Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) conducted between 2000 and 2014 (Data from Ref. [[1], [2]])

been recently shown in the Italian Elderly ACS study, where the contribution of cardiovascular deaths to overall mortality in the following year was as great as 80 %, and most of these deaths were of ischaemic origin [22]. This finding was surprisingly similar to those reported in a population of US veterans hospitalised for an ACS [23]. Also very similar data came from the subanalysis of the elderly population enrolled in the PLATelet inhibition and patient Outcomes (PLATO) [24] and TRILOGY [7] trials. For these reasons, risk stratification with regard to overall mortality, but also for CV death, may be extremely important in order to select treatment strategies and, specifically, for the high-risk and high-cost procedures, also for an estimate of "futility".

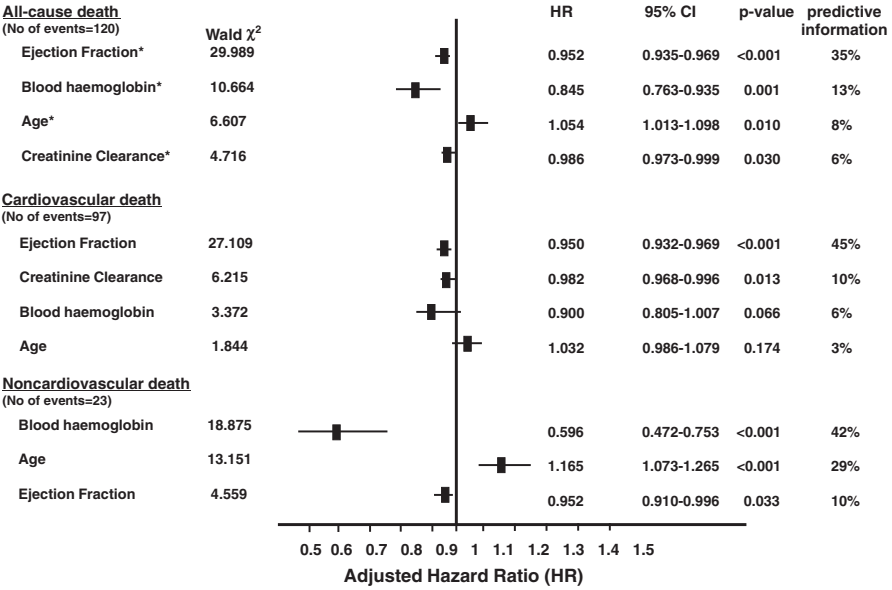

Fig. 13.3 Independent predictors of overall and cardiovascular mortality at 1 year in patients with NSTEACS aged ≥75 years (Modified from Ref. [22])

The independent predictors of total and cardiovascular death among elderly patients with NSTEACS have been investigated in the Italian Elderly ACS study, using the full database of the randomised clinical trial and registry [22]. As shown in Fig. 13.3, lower values of ejection fraction, estimated glomerular filtration rate (eGFR) and blood haemoglobin and older age were independent predictors of CV death, although three of these four predictors were also predictors of non-CV death. Starting from the same database, a simple risk prediction score for 1-year mortality was developed from the randomised trial (313 patients) by using logistic regression analysis and validated in the registry cohort of the study patients (332 patients) [25]. The risk score included five statistically significant covariates: previous vascular event, haemoglobin level, estimated glomerular filtration rate, ischaemic electrocardiographic changes and elevated troponin level. The model allowed a maximum score of 6. The score demonstrated a good discriminating power (c statistic 0.739) and calibration, even among subgroups defined by gender and age. When validated in the registry cohort, the scoring system confirmed a strong association with the risk for all-cause death. Moreover, a score ≥3 (the highest baseline risk group) identified a subset of patients with NSTEACS most likely to benefit from an invasive approach.

A frailty parameter (which, unfortunately, was not collected in the study) would have probably resulted as an independent predictor on non-CV and overall mortality [26–28].

13.2 Treatment of ST-Segment Elevation Myocardial Infarction

Primary angioplasty (pPCI) has emerged as the most effective and safe reperfusion strategy in elderly patients with STEMI. The TRatamiento del Infarto Agudo de miocardio eN Ancianos (TRIANA) trial was started in 2005 to compare the efficacy and safety of pPCI and fibrinolysis in very old STEMI patients [5]. This study, planned to enrol 570 patients, was interrupted after the enrolment of 266 patients over 33 months and showed a trend towards a reduction in the primary endpoint of 30-day death, re-MI or disabling stroke with pPCI (18.9 % vs. 25.4 %; odds ratio [OR], 0.69; 95 % confidence interval [95 % CI] 0.38–1.23). The incidence of each of the components of the primary endpoint was directionally lower with pPCI. A pooled analysis of this and two previous RCTs comparing pPCI with lytic therapy, published in the same paper, showed a trend towards mortality reduction and a significant reduction in death, re-MI and stroke at 30 days. The relevance of this RCT data for clinical practice finds confirmation from the analysis of the prospective, multicentre registry of the Reseau de Cardiologie de Franche Comte, comparing two periods of time in 2001 and 2006 [29]. From 2001 to 2006, pPCI became the preferential modality of reperfusion therapy over fibrinolysis [adjusted OR 6.9, 95 % CI 3.1–15], and this change in strategy was associated with a significantly lower 30-day mortality in 2006 (9.2 % vs. 23.3 %, $p < 0.001$).

A recent meta-analysis including 6,298 patients who underwent pPCI and stent implantation included in the drug-eluting stent in primary angioplasty (DESERT) cooperation database [11] confirmed that, despite the expected higher rate of death at long-term follow-up in elderly as compared to younger patients (HR 2.17 95 % CI 1.97–2.39, $p < 0.0001$), no impact of age was observed on the risk of re-MI, stent thrombosis and target vessel revascularisation.

A favourable outcome was described with regard to 199 patients aged ≥80 years treated within the Minneapolis regional STEMI system [30]: the median length of hospital stay was 4 days, in-hospital mortality was 11.6 % and 1-year mortality was 25.6 %. Of the 166 patients with age ≥80 who lived independently or in assisted living before hospital admission and survived, 150 (90 %) were discharged to a similar living situation or projected to such a living situation after temporary nursing home care.

13.3 Treatment of Non-ST-Segment Elevation Acute Coronary Syndrome

In recent Italian ACS registries, patients aged ≥75 years represent approximately 40 % of those with NSTEACS [1]. Over the last few years, inferential analyses from registries [31] and subgroup analyses of RCTs [8, 10] have suggested that an early invasive approach is associated with better outcome in elderly patients as compared to conservative treatment.

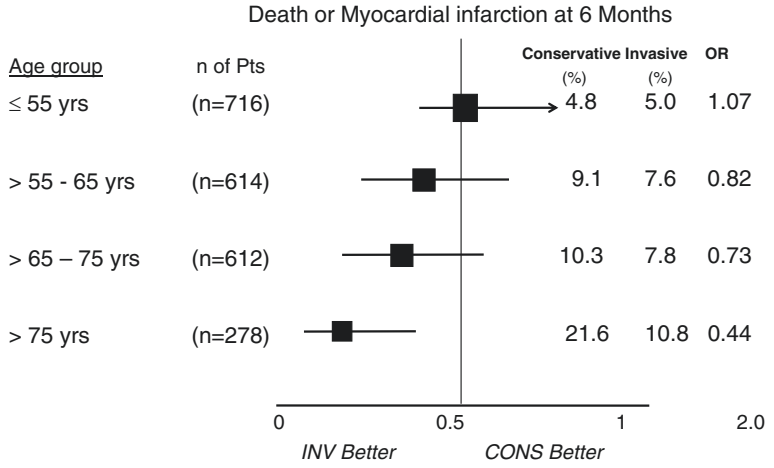

Fig. 13.4 Rates of all-cause mortality and myocardial infarction at 6 months after index admission in patients with NSTEACS patients enrolled in the TACTICS trial, according to age class (Data are from Ref. [8])

Among patients aged ≥75 years enrolled in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction (TACTICS–TIMI) 18 trial [8], the early invasive strategy conferred an absolute reduction of 10.8 percentage points (10.8 % vs. 21.6 %; $p = 0.016$) and a relative reduction of 56 % in death or MI at 6 months, a much higher benefit as compared to that observed in younger age groups (Fig. 13.4). In this study, thrombolysis in myocardial infarction (TIMI) major bleeding rates were almost prohibitive with the early aggressive strategy in patients ≥75 years of age (16.6 % vs. 6.5 %; $p = 0.009$), most likely due to the systematic upstream therapy with tirofiban and unfractionated heparin and the universal use of the femoral approach to catheterisation.

A collaborative analysis of individual data from the FRISC II–ICTUS–RITA-3 (FIR) trials [10], all comparing routine-versus-selective invasive strategy in NSTEACS, assessed outcomes up to 5 years after index admission. The composite of cardiovascular death or MI was significantly lower with the routine invasive strategy in patients aged 65–74 years (HR 0.72, 95 % CI 0.58–0.90) and in those aged ≥75 years (HR 0.71, 95 % CI 0.55–0.91), but not in those aged <65 years (HR 1.11, 95 % CI 0.90–1.38; $p < 0.001$ for interaction between treatment strategy and age). The interaction was driven by an excess of early MI in patients <65 years of age, whereas there was no heterogeneity between age groups concerning cardiovascular death. The benefits were smaller for women than for men ($p < 0.009$ for interaction).

The Italian Elderly ACS study [6] was the first RCT to enrol exclusively patients with NSTEACS and an age ≥75 years: patients were randomised to an early invasive (coronary angiography and, when indicated, revascularisation within 72 h) or an initially conservative (angiography and revascularisation only for recurrent ischaemia). The study was initially planned to enrol 504 patients with a primary endpoint set at 6-month follow-up but was subsequently modified to a 12-month

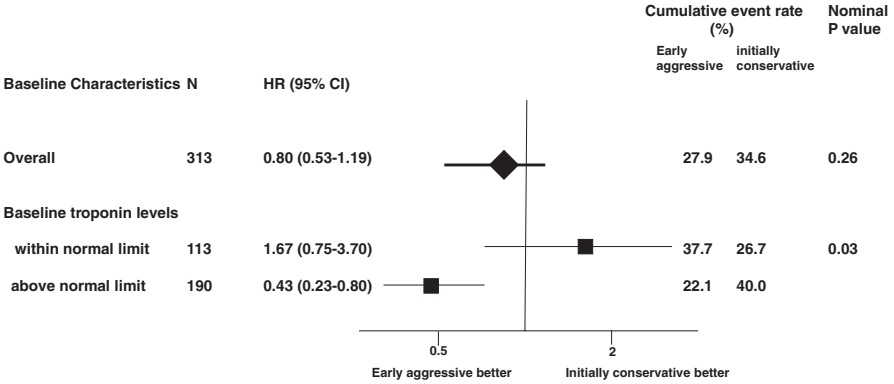

Fig. 13.5 Rates of the primary study endpoint [the composite of death, myocardial infarction, stroke and rehospitalisation for cardiovascular causes or bleeding] in the Italian Elderly ACS trial. Data are shown for the overall study population and in the subgroups with normal and elevated troponin levels on admission (Data are from Ref. [6])

primary endpoint with the sample size set at 313 patients; further 332 patients excluded from the trial for any reason were enrolled in a parallel registry. The mean age of the study population was 82 years, and 50 % were women. The primary endpoint (a net clinical benefit of all-cause mortality, MI, disabling stroke and repeat hospital stay for cardiovascular causes or severe bleeding) was significantly reduced by an early invasive approach in patients with elevated troponin levels on admission (61 % of the cases) (Fig. 13.5), though the benefit was not significant in the whole study population (27.9 % vs. 34.6 %; HR: 0.80; 95 % CI: 0.53–1.19), with a significant treatment per troponin status interaction ($p = 0.03$). All of the components of the primary endpoint trended towards benefit with the early invasive strategy. In this contemporary study only, one adjudicated case (0.6 %) of major bleeding was recorded during index admission, and three subsequent hospital admissions were due to severe bleeding (1.9 %). This remarkable safety may be due to a high rate (75 %) of radial approach to percutaneous coronary intervention (PCI) and a limited (20 % in patients undergoing PCI) use of GPIIb/GPIIIa inhibitors.

Finally in a recent metaregression analysis including all of the RCTs comparing treatment strategies in NSTEACS, a routine early invasive strategy has been confirmed to reduce the composite endpoint of death and MI (p for interaction = 0.044), as well as repeat hospitalisation (p for interaction <0.0001), to a greater extent in elderly than in younger individuals, without significant differences between men and women [32].

13.4 Cardiogenic Shock and Out-of-Hospital Cardiac Arrest

Elderly patients with cardiogenic shock and those resuscitated from an out-of-hospital cardiac arrest have traditionally been considered off-limits as candidates to PCI in the ACS scenario. A subgroup analysis of the SHOCK trial had shown a non-significant trend towards increased 30-day mortality (75 % vs. 53 %) when a total of 56 elderly patients with acute MI and cardiogenic shock had received

emergency revascularisation compared with initial medical stabilisation [33]. A recent meta-analysis of nonrandomised studies [34] has considered a total of 1935 patients with MI and cardiogenic shock aged ≥75 years, of which 468 had been treated by emergency revascularisation and 1467 with initial medical stabilisation. Despite a lower rate of successful revascularisation in elderly patients compared with their younger counterparts ($n=7$ studies; 88 % vs. 95 %, $p<0.0001$), patients who received emergency revascularisation experienced lower short-term (55 % vs. 72 %; OR = 0.48, 95 % CI = 0.33–0.69) and intermediate-term (60 % vs. 80 %; OR = 0.47, 95 % CI = 0.27–0.83) mortality. However, this kind of analysis does not allow to conclude whether the better outcome is attributable to patient selection or to the positive effect of emergency revascularisation.

Advanced age was not among the predictors of in-hospital mortality among patients undergoing emergency pPCI after an out-of-hospital cardiac arrest in the registry of pPCI of the Lombardy region in Italy [35]: in that study, significant independent predictors where the time delays between cardiac arrest and call of the emergency medical system, cardiogenic shock on admission, asystole as initial rhythm and Glasgow Coma Scale 3. A recent analysis of 6,972 patients aged ≥65 years (mean age 75.8 ± 7.0) survived after an out-of-hospital cardiac arrest and discharged alive from the hospital [36], a quarter of whom had an acute MI, showed that long-term survival was strongly dependent upon the neurological deficit at discharge and, overall, was not different from mortality after an episode of heart failure. Putting all this information together, it seems reasonable to proceed to emergency angiography in view of possible PCI in elderly patients resuscitated from out-of-hospital cardiac arrest unless the patient had been reanimated from asystole and does not present cardiogenic shock or Glasgow Coma Scale 3 on admission. A recent analysis of 15-year trends in the epidemiology, management and outcome of patients with cardiogenic shock complicating ACS in the Italian CCU network showed a 50 % adjusted reduction with regard to in-hospital mortality [2] associated with the systematic use of early revascularisation across the ACS spectrum and applied also to patients aged ≥75 years (Fig. 13.6).

13.5 Antithrombotic Treatment

Antithrombotic therapy is the mainstay of ACS management, both in patients managed invasively and in those treated conservatively. The use of anticoagulant and antiplatelet agents in elderly patients requires careful tailoring of dosing and prudent evaluation of the bleeding risk. A number of pathophysiological and pharmacological variables affect drug metabolism and disposition in a different way in the elderly as compared to younger patients [37, 38], and a detailed discussion of these specificities goes beyond the scope of the present paper. However, at least the following notes should be retained:

- The risk of gastroenteric bleeding with even low-dose aspirin increases with age and previous history of peptic ulcer [39]; therefore, the administration of a proton pump inhibitor is recommended in these patients [40].

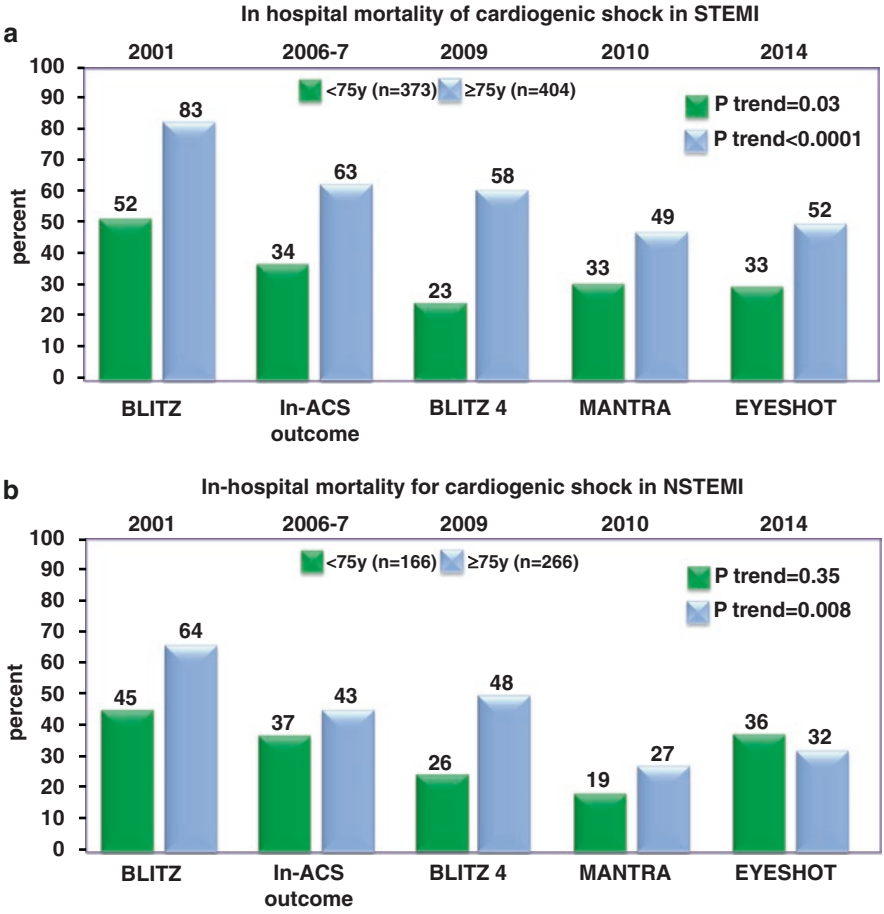

Fig. 13.6 In-hospital mortality among patients with STEMI (panel **a**) and NSTEMI (panel **b**) complicated by cardiogenic shock aged < and ≥ 75 years (Data are from Ref. [2])

- In elderly patients who are candidates to fibrinolytic therapy, the use of half-dose weight-adjusted tenecteplase is recommended [41], combined with enoxaparin at the dosage of 0.75 mg/kg without the initial intravenous bolus [42] and followed by clopidogrel 75 mg with no loading dose.
- In patients undergoing pPCI, it is reasonable to use bivalirudin rather than unfractionated heparin and a GPIIb/GPIIIa inhibitors, due to the much lower risk of bleeding [43].
- In the acute phase of NSTEACS, fondaparinux (2.5 mg o.d.) should be the anticoagulant of choice in patients treated conservatively [44], whereas enoxaparin should be dosed very carefully based on the eGFR. The intraprocedural use of bivalirudin has been associated with reduced bleeding in the elderly and also with lower 1-year mortality [45].
- Clopidogrel remains the ADP-receptor blocker of choice in most elderly patients. As compared to clopidogrel, the two more powerful inhibitors, prasugrel and

ticagrelor, had remarkably similar results, with a slight reduction in the ischaemic endpoint at the expense of an increased risk of major bleeding [24, 46]. Therefore, when an ADP-receptor blocker is indicated in adjunct to aspirin, the use of these newer agents should be restricted to patients with allergy to clopidogrel or after careful individual evaluation of the benefit-versus-risk ratio. The Elderly ACS-2 trial (NCT01777503) is specifically comparing reduced-dose prasugrel (5 mg o.d.) with clopidogrel in 2000 ACS patients aged ≥75 years undergoing early PCI.

13.6 Conclusion and Recommendations

Until 15 years ago, elderly patients with ACS had been poorly studied, and no specific trials had been performed in order to provide evidence with regard to risk-versus-benefit balance of an aggressive pharmaco-invasive treatment. As described in the present chapter, a few more recent and specific studies have provided evidence in favour of early revascularisation (whenever possible) in elderly ACS patients. The systematic use of the radial vascular approach, and a prudent antithrombotic treatment, has rendered early intervention safer in the elderly. A number of issues related to comorbid conditions, typical of the elderly population, such as diabetes, chronic kidney dysfunction and anaemia, have been described in the recent literature [4]. A summary of author recommendations is provided in Table 13.1.

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