Cardiovascular Disease

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21.1 Introduction

The number and proportion of adults over the age of 65 worldwide is increasing at a rapid rate due to improved sanitation, nutrition, access to health care, and medical advances in prevention, diagnosis, and treatment for both communicable and non-communicable diseases [1]. In the USA, 13 % of the current population is over the age of 65 and it is estimated that the proportion will increase to 19 % by the year 2030, including 19 million people aged 85 and older [2].

In parallel, the global burden of cardiovascular disease (CVD) has increased exponentially over the last 25 years despite remarkable advances in CVD prevention and treatment [1]. In the USA, approximately 40 million adults over the age of 65 report one or more cardiovascular (CV) disorders and CVD is the leading cause of major morbidity and mortality in that population [3]. Notably, although advancing age is the most potent predictor of CVD, it is a non-modifiable risk factor. Nonetheless, biological aging and the effects of aging on the CV system vary considerably from individual to individual, and there is evidence that behavioral factors, including diet, physical activity, and smoking, modulate the aging process and the incidence of age-related disease. It is therefore essential that cardiovascular providers understand the marked interactions between aging and CVD, the impact of co-existing disease processes, limitations of currently available evidence, and the inherent complexities involved in providing patient-centered care aligned with individual patient preferences. This chapter examines the principal effects of aging on the CV system, geriatric factors that modulate CVD in older adults, and differences in the management of CVD in older compared to younger individuals.

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21.2 Aging and the Heart

Biological aging has a fundamental effect on the development and progression of CVD through two different but synergistic mechanisms. Age-associated vascular changes do not independently cause vascular disease, but alterations in cellular and molecular mechanisms, especially those responsible for regeneration and response to stress, greatly increase the vulnerability of the heart and vasculature to the development of CVD [4, 5]. In addition, the longitudinal nature of aging allows for the accumulation of genetic risk factors, acquired risk factors (e.g., hypertension), lifestyle choices, and environmental factors, which taken together, greatly increase the likelihood of developing CVD with increasing age. Cardiovascular changes associated with aging are widespread and include alterations in both structure and function. Table 21.1 lists major changes in the heart, vasculature, hemodynamics, and response to exercise that impact the clinical presentation of CVD in older adults.

21.3 Traditional Cardiovascular Risk Factors

21.3.1 Hypertension

Age-associated increased central arterial stiffness, increased peripheral resistance, and impaired vascular reactivity contributed to hypertension being the most prevalent risk factor for CVD in older adults [6]. By age 75, approximately 80 % of women and 70 % of men in the USA are classified as hypertensive, yet they have the lowest rates of optimal control [7, 8]. With vascular aging, the systolic blood pressure

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Table 21.1 Cardiovascular changes associated with aging

Arterial structure and function
Increased lumen size
Increased wall thickness (intimal-media thickening)
Increased calcification
Increased tortuosity of large vessels
Increased collagen cross-linking
Degeneration and fragmentation of elastin
Decreased endothelial function
Increased stiffness of large and medium-sized arteries (decreased distensibility)
Cardiac anatomy
Increased atrial size (LA>RA)
Increased LV wall mass and thickness
Increased LV stiffness (decreased compliance)
LV fibrosis and collagen accumulation
Degeneration (calcific) of valve leaflets and annulus
Decreased LV cavity size and longitudinal shortening
Fibrosis, calcification, and degeneration of conducting system
Decline in number of sinoatrial node pacemaker cells
Hemodynamics
Increase in systolic blood pressure
Increase in pulse wave velocity
Earlier reflection of pulse wave and augmentation of blood pressure in late systole
Decrease in aortic peak flow velocity
Reduction in peak LV filling rate
Decreased ratio of early LV filling (E) to atrial filling (A)
Changes during exercise
Decrease in maximum heart rate (220-age)
Decline in heart rate variability
Increase in atrial and ventricular ectopy
Reduced cardiac output reserve
Reduction in end systolic volume reserve
Reduction in VO_2 Max
Impaired peripheral vasodilation

LA left atrium, *RA* right atrium, *LV left ventricular*/ventricle, *A-V* atrioventricular, *VO2 Max* maximal oxygen consumption

Table 21.2 Clinical trials of hypertension in older adults

		Risk reduction %				
Trials	*N*	Age	CVA	CAD	CHF	All CVD
Australian [152]	582	60–69	33 %	18 %	NR	31 %
EWPHE [153]	840	>60	36 %	20 %	22 %	29 %
Coope [154]	884	60–79	42 %	−3 %	32 %	24 %
STOP_HTN [155]	1627	70–84	47 %	13 %	51 %	40 %
MRC [156]	4396	65–74	25 %	19 %	NR	17 %
HDFP [157]	2374	60–69	44 %	15 %	NR	16 %
SHEP [158]	4736	≥60	33 %	27 %	55 %	32 %
SYST-Eur [159]	4695	≥60	42 %	26 %	36 %	31 %
STONE [160]	1632	60–79	57 %	6 %	68 %	60 %
Syst-China [161]	2394	≥60	38 %	33 %	38 %	37 %
HYVET [10]	3845	≥80	30 %	28 %	64 %	34 %
SPRINT [11]	9361	≥50	11 %	12 %	33 %	25 %

CAD coronary artery disease, *CHF* congestive heart failure, *CVA* cerebrovascular accident, *CVD* cardiovascular disease, *EWPHE* European Working Party on High Blood Pressure in the Elderly, *HDFP* Hypertension Detection and Followup Program, *MRC* Medical Research Council, *NR* not reported, *SHEP* Systolic Hypertension in the Elderly Program, *STONE* Shanghai Trial of Nifedipine in the Elderly, *STOP-HTN* Swedish Trial in Old Patients with Hypertension, *Syst-China* Systolic Hypertension in China, *Syst-Eur* Systolic Hypertension in Europe

increases progressively, whereas the diastolic blood pressure peaks at approximately age 50 and then plateaus before declining after 60 years of age in both men and women. As a result, isolated systolic hypertension (ISH, defined as systolic blood pressure over 140 mmHg and diastolic blood pressure below 90 mmHg) is the dominant form of hypertension in older adults. In turn, ISH is strongly associated with an increased risk for stroke, end-stage renal disease, myocardial infarction (MI), heart failure, and CV and all-cause mortality. While the treatment of hypertension at any age (including the very elderly), reduces CV and cerebrovascular events (Table 21.2), optimal treatment thresholds and target blood pressures have not been clearly defined [9, 10].

In the Hypertension in the Very Elderly Trial (HYVET), 3845 patients 80 years of age or older (mean 83.6 years, 60.5 % women) with systolic blood pressure ≥160 mmHg were randomized to the diuretic indapamide 1.5 mg or matching placebo [10]. Perindopril or placebo was added as needed to achieve a target blood pressure <150/80 mmHg. The primary outcome was fatal or nonfatal stroke. After a mean follow-up of 1.8 years, active treatment was associated with a 30 % reduction in the primary outcome, and reductions in secondary outcomes of incident heart failure and all-cause mortality. The results of HYVET led to a recommendation by several hypertension guideline committees to aim for a goal of <150 mmHg when treating systolic hypertension in patients ≥80 years of age.

More recently, the Systolic Blood Pressure Intervention Trial (SPRINT) randomized 9361 patients ≥50 years of age (28.2 % ≥75 years of age) at increased cardiovascular risk (as defined by subclinical or clinical CVD, chronic kidney disease, 10-year risk of CVD ≥15 % based on the Framingham Risk Score, and/or age ≥75 years) and with baseline systolic blood pressure 130–180 mmHg to intensive treatment (target blood pressure <120 mmHg) or standard treatment (target blood pressure <140 mmHg) [11]. Patients with diabetes mellitus, symptomatic heart failure in the preceding 6 months, recent acute coronary syndrome (ACS), prior stroke, orthostatic systolic blood pressure <110 mmHg, unintentional weight loss (a component of frailty), or residence in a nursing home or assisted living facility were excluded. Women and patients with multimorbidity were also under-represented. The primary outcome was a composite of myocardial infarction (MI), other ACS, stroke, heart failure, or cardiovascular death. The study was stopped prematurely at a median follow-up of 3.26 years due to a significant benefit of intensive treatment on the primary outcome (2.19 % per year with standard treatment vs. 1.65 % per year with intensive treatment, hazard ratio 0.75, 95 % CI 0.69–0.89, $p<0.001$). Outcomes were similar in patients ≥75 years of age compared to those <75 years but the absolute benefit was numerically greater in

the older subgroup. All-cause mortality, CV mortality, and incident heart failure were significantly reduced with intensive treatment, but there was no effect on MI, ACS, or stroke. The number needed to treat for 1 year to prevent one primary outcome event was 185. The mean number of blood pressure medications was 1.8 in the standard treatment group and 2.8 in the intensive treatment group. Serious adverse events, including acute kidney injury, electrolyte abnormalities, hypotension, and syncope (but not injurious falls) were all significantly more frequent in the intensive therapy group. Annual rates of serious adverse events attributed to antihypertensive treatment were 1.44 % in the intensive therapy group and 0.77 % in the standard therapy group (number needed to harm 149). The incidence of adverse events was similar among patients older or younger than age 75. The effects of intensive treatment on quality of life and cognitive function have not yet been reported.

The implications of SPRINT for treatment of older adults with hypertension are uncertain, as the modest absolute benefit with respect to major CV events and death must be balanced against the potential for adverse events, increased burden of medications, and unknown impact on quality of life, functional status, and cognition. In addition, a substantial proportion of older adults would not have met the SPRINT inclusion/exclusion criteria, and the applicability of the findings to these individuals is unknown. Based on the results of HYVET and current guidelines, it is reasonable to treat individuals ≥75 years of age who are suitable candidates for antihypertensive drug therapy to a target systolic blood pressure of <140 mmHg (age 75–79 years) or <150 mmHg (age ≥80 years). More aggressive treatment should be individualized based on the clinical profile and patient preferences.

Management of hypertension in older adults is often complicated by orthostatic or post-prandial hypotension [12], which may be associated with light-headedness and increased risk for falls and syncope. In addition, "white coat" hypertension is common in older adults (i.e., office blood pressure higher than home blood pressure), and older individuals with stiff arteries may exhibit pseudohypertension (blood pressure measured by sphygmomanometer higher than central aortic pressure) [13, 14]. For these reasons, it is important to measure blood pressure in the sitting and standing positions and, when feasible, to obtain blood pressure readings in the home environment [12]. In some cases, 24-hour ambulatory blood pressure monitoring may be helpful in determining the presence and severity of hypertension, as well as the variability in blood pressure readings [15]. In patients with significant orthostatic hypotension (decline in systolic blood pressure ≥20 mmHg on standing), titration of anti-hypertensive therapy should be very gradual and should include periodic assessments of orthostatic blood pressure changes and evaluation for symptoms attributable to orthostasis.

21.3.2 Hyperlipidemia

Dyslipidemia remains an important risk factor for CVD in older adults up to age 85; after age 85, the association of lipid levels with CVD is less clear [16–18]. In addition, the strength of association between cholesterol levels and CVD declines with age, such that total cholesterol and LDL cholesterol become less predictive of CV events at older age. Factors affecting the relationship between cholesterol and CVD risk at increased age include survival bias among individuals with low CVD risk despite increased cholesterol levels, and the impact of co-existing diseases (e.g., malignancy, chronic inflammatory disorders) and malnutrition (a common condition in older adults). Statins are highly efficacious for the treatment of dyslipidemia, and numerous trials have documented the benefits of statins on CVD outcomes [19–22]. However, few patients over age 80 have been enrolled in these trials, and patients with complex comorbidity have been excluded. In addition, statin side effects, such as myalgias, may be more common in older adults, and there is weak evidence that statins may be associated with cognitive impairment in some individuals. Recognizing the paucity of evidence on statins in older patients, current guidelines recommend that treatment decisions consider anticipated benefits and adverse effects (including their time horizon), life expectancy, comorbidities, and individual treatment priorities [23]. In addition, the guidelines advise caution in using high intensity statin therapy in individuals over 75 years of age.

21.3.3 Diabetes Mellitus

Diabetes mellitus (DM) is a powerful and independent predictor of the development and progression of CVD in older adults, imparting an increase in relative risk of CAD of 1.4 in men and 2.1 in women 65 and older with a significant sex interaction (i.e., stronger association in women) [24]. Although the relative risk in individuals over the age of 65 is lower than in younger individuals with DM, the high prevalence of DM in older adults results in greater excess risk [25].

Management of CV risk in patients with DM should focus on treating co-existing CVD risk factors, including hypertension and dyslipidemia, which are present in 71 and 65 % of older diabetics, respectively [21]. Additionally, utilization of an angiotensin-converting enzyme inhibitor (ACE-I) in older adults with diabetes is effective for reducing CV mortality [26]. Regular physical activity and maintaining a healthy body weight should be encouraged. Additional recommendations for managing DM in older adults are provided in Chap. 23.

21.3.4 Smoking

Smoking accounts for 30 % of the attributable risk of all strokes and 36 % of first acute coronary events [27]. In older adults the prevalence of smoking decreases but it still remains a significant risk factor. Although the relative risk for MI or death as a result of smoking in an individual over the age of 70 is twice that of an individual age 55–60, older patients are less likely to receive smoking cessation counselling or interventions [28].

Individuals who smoke should be advised of the risks associated with smoking and given guidance on cessation strategies. Elderly individuals may be resistant to changing life-long habits, but the negative effects of continued smoking irrespective of age demand continued efforts to promote smoking cessation.

21.4 Geriatric Syndromes and Cardiovascular Disease

21.4.1 Multimorbidity

Multimorbidity, defined as the presence of 2 or more chronic conditions, increases exponentially with age and is present in over 70 % of individuals 75 years or older [29]. By the age of 65, more than 60 % of individuals have 2 or more chronic conditions, >25 % have 4 or more chronic conditions, and nearly 10 % have 6 or more conditions; by age 85, >50 % of individuals have 4 or more chronic conditions and 25 % have 6 or more conditions. The accumulation of chronic conditions culminates in a vastly heterogeneous population of older adults for whom balancing the management of multiple medical problems becomes paramount.

Among Medicare beneficiaries with CVD, the burden of multimorbidity is substantial; for example, over 50 % of individuals with a diagnosis of heart failure or stroke have 5 or more co-existing chronic medical conditions [29]. In older adults with CVD, the most common concomitant non-CVD conditions are arthritis, anemia, and diabetes mellitus, with prevalence rates ranging from 40 to 50 %. Other common conditions include chronic kidney disease, cognitive impairment, chronic obstructive lung disease, and depression, each of which much be considered when developing individual treatment strategies for the management of CVD [30].

21.4.2 Polypharmacy and Drug Interactions

Older adults with multimorbidity are frequently seen by numerous general and specialist providers which can result in competing management strategies and numerous prescriptions for medications. Polypharmacy, often defined as concomitant use of five or more medications, is associated with markedly increased risk for drug–drug interactions, drug–disease interactions, and therapeutic competition (the recommended treatment for one condition may adversely affect and/or compete with another co-existing condition) [31]. Approximately 50 % of older adults are taking at least one medication with no active indication, and many of these drugs are initiated during hospitalization, such as stress ulcer prophylaxis and antipsychotics for delirium [32]. Careful medication reconciliation including prescribed medicines, over the counter pharmaceuticals, and herbal therapies should be performed at each provider interaction. Adverse consequences of polypharmacy including poor adherence, adverse drug events, hospitalization, and mortality are related not only to the number of medications but also to the regimen complexity, so attention should be given to limiting the number of medications as well as simplifying the dosing schedule [32–34].

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently taken by older adults to relieve burdensome pain or for treatment of arthritis. However, NSAIDs, including the cyclo-oxygenase 2 (COX-2) inhibitors, increase the risk of atherothrombotic vascular events and incident heart failure [35]. In addition, NSAIDs have adverse interactions with many CV medications, including diuretics, other anti-hypertensive agents, and antithrombotic drugs. NSAIDs have also been associated with worsening renal function and increased risk for gastrointestinal bleeding. For these reasons, the FDA and the American Heart Association suggest minimizing the use of NSAIDs when feasible, and using the lowest possible doses for the shortest period of time [36]. Polypharmacy and medication management are discussed in greater detail in Chap. 5.

21.4.3 Cognitive Impairment

Approximately 13 % of community dwelling adults over the age of 65 have a diagnosis of dementia. However, the total burden of disease is likely to be much higher due to under-recognition of dementia by patients, families, and health care providers, particularly in the early stages [37, 38]. In people over the age of 80, the prevalence of dementia increases to 40 %, and in advanced heart failure patients, 30–60 % have comorbid dementia [39, 40]. Older individuals with CVD also have a high prevalence of mild cognitive impairment (the prodromal phase of dementia) as compared to individuals without CVD, and patients with cognitive impairment and CVD have worse outcomes than those with CVD alone. Older adults with heart failure have a twofold increased risk of impaired cognition, including deficits in attention, executive function, and episodic memory, and these impairments tend to be more pronounced during episodes of

decompensation [41]. Executive dysfunction, in particular, can reduce the ability to adhere to recommended therapies and participate in disease management programs [42]. In part for these reasons, the presence of cognitive impairment increases cost, management complexity, and mortality rates in older adults with CVD. Diagnosis and management of dementia are discussed in Chap. 4.

21.4.4 Frailty

Frailty is a geriatric syndrome that represents an accelerated path of biological decline across multiple interrelated organ systems and a loss of homeostatic reserve in response to stressors [43]. Although different criteria for frailty have been proposed, the frailty phenotype originally described in the Cardiovascular Health Study comprises unintentional weight loss, exhaustion, weakness, slowness, and low physical activity (pre-frail: 1–2 criteria; frail: ≥3 criteria) [43]. More recently, cognitive impairment has emerged as an additional component of frailty [44]. The estimated prevalence of frailty in community cohorts is 7 % but increases to 20 % in individuals over age 80. In older patients hospitalized with CVD, especially heart failure, it is estimated that frailty rates approach 50 % [45]. Frailty is associated with an increased risk of adverse outcomes including falls, functional decline, disability, institutionalization, and death [43, 46, 47]. A bidirectional relationship exists between frailty and CVD such that frailty is an independent predictor of the development and progression of a wide range of CV disorders [48]. Conversely, the presence of CVD increases the risk of frailty, and older adults with concomitant frailty and CVD have significantly worse outcomes than those with CVD alone (hazard ratios ranges from 2 to 4 depending on the specific disease). Chapter 1 provides a comprehensive discussion of the recognition and management of frailty.

21.4.5 Comprehensive Geriatric Evaluation

Although disease-focused evaluation of symptoms may facilitate assessment of the primary CV diagnosis, it does not allow for a more comprehensive evaluation of the multitude of factors that may impact optimal management. Implementing a more patient-centered approach to prioritizing goals of care within the context of co-existing multimorbidity, geriatric syndromes, cognitive impairment, and social and psychological factors can result in a management strategy better aligned with patient preferences. Table 21.3 provides an overview of commonly used tools for assessment of geriatric patients. The reader is also referred to Chap. 8 for practical guidance on office based geriatric assessment.

Table 21.3 Screening tools for common geriatric conditions

Geriatric condition	Assessment tool
Frailty	Fried frailty scale: grip strength, gait speed, exhaustion, weight loss, and physical activity questionnaire [43] Short physical performance battery [162] Rockwood frailty index
Functional status	Katz activities of daily living [163] Lawton instrumental activities of daily living [164] Timed up and go [165] Functional reach [166]
Cognition	Montreal cognitive assessment (www.mocatest.org) Mini-Cog [167] Mini mental state examination (MMSE)
Weight loss/ Sarcopenia	Grip strength Body mass index or weight change, 3–5 % decline [43, 168, 169] annually
Depression	Geriatric depression scale [170] Patient health questionnaire-9 [171]

21.5 Cardiovascular Diseases Common in Older Adults

21.5.1 Coronary Artery Disease

While chest pain or discomfort is the most common presenting symptom in patients of all ages with coronary artery disease (CAD), dyspnea is frequently the presenting symptom in older adults and women, particularly in the presence of multimorbidity. Atypical or non-specific symptoms are also common in older adults with CAD and may include weakness, confusion, decline in functional status, reduced physical activity, nausea, and loss of appetite. For these reasons, a high clinical suspicion for CAD in older adults should be maintained (especially the very elderly). Older adults may also be less likely to recognize or report symptoms of CAD due to reduced physical activity or cognitive impairment. Further, older adults may minimize symptoms owing to fear of possible interventions, hospitalization, and loss of independence.

21.5.2 Acute Myocardial Infarction

Ischemic heart disease is the leading cause of mortality in both men and women in the USA, with nearly 85 % of deaths occurring in individuals 65 years and older and over 50 % in those 75 and older [49, 50]. The high prevalence of ischemic heart disease in older adults contributes to the increased number of deaths, but greater in-hospital and 6-month mortality rates are also a significant factor.

A critical step in optimum management of older adults with acute myocardial infarction (AMI) is prompt diagnosis and re-vascularization, if appropriate, but such treatment is contingent upon recognition of symptoms and the presence of diagnostic electrocardiographic (ECG) changes. In the Global Registry of Acute Coronary Events (GRACE), almost 50 % of participants >85 years with an ACS presented with dyspnea rather than chest pain [51]. In the Framingham cohort, silent or unrecognized infarcts accounted for almost 60 % of all MIs in individuals over age 85 [52]. Current practice guidelines recommend that an ECG should be obtained and reviewed within 10 min of presentation in individuals with symptoms consistent with ACS. In older adults, particularly women, the time to first ECG is considerably longer than in younger patients and it is more likely to be non-diagnostic [52]. The higher prevalence of non-specific symptoms, pre-existing ECG abnormalities, and non-ST segment elevation MI (NSTEMI) in elderly patients can further delay treatment initiation.

Reperfusion therapy in the form of fibrinolysis or more commonly primary percutaneous coronary intervention (PCI) in ST-elevation MI (STEMI) is associated with reduced in-hospital mortality, subsequent heart failure, and long-term morbidity and mortality [53, 54]. Despite a greater incremental benefit obtained by elderly patients, they are less likely to receive reperfusion therapy [55]. In the Myocardial Infarction National Audit Project (MINAP), only 55 % of patients ≥85 presenting with STEMI received reperfusion therapy as compared to 84 % of patients age 65 or younger. Primary PCI is the treatment of choice if performed within 90 min of arrival to the hospital and within 12 h of onset of symptoms. [56] Increased actual and perceived risks in older adults undergoing PCI likely contribute to lower utilization rates.

21.5.2.1 Antiplatelet Therapy

In the second International Study of Infarct Survival-2 (ISIS-2) [57], early aspirin therapy in patients with STEMI reduced 35-day mortality by 23 % overall with corresponding effects in individuals over the age of 70. Chronic aspirin therapy following MI also decreases recurrent MI, stroke, and all-cause mortality irrespective of age. Clopidogrel in addition to aspirin reduces recurrent MI and death in the 12 months following hospital admission for ACS, whether or not PCI is performed [58, 59]. Table 21.4 summarizes clinical trials of antiplatelet agents in the treatment of ACS, including outcomes and caveats for older adults. Older adults are at increased risk for bleeding complications associated with all antiplatelet agents, including aspirin, and the use of dual antiplatelet therapy (e.g., aspirin with clopidogrel) and especially triple therapy (2 antiplatelet agents and an anticoagulant) further increases risk. Compared to clopidogrel, prasugrel is associated with increased risk of intracranial hemorrhage in patients ≥75 years of age and is not recommended for use in that age group except in patients at high risk for stent thrombosis [60]. Similarly, vorapaxar is associated with significantly higher risk of bleeding in patients over age 75 [61].

21.5.2.2 Antithrombotic Therapy

Activation of thrombin plays an important role in the pathway of ACS and blockade of thrombin by heparin is a recommended therapy. Unfractionated heparin is associated with higher rates of bleeding in older adults as a result of low protein binding and impaired renal function [62]. If appropriate, low molecular weight heparin (LMWH) provides a more reliable therapeutic effect and has been shown to reduce recurrent angina, MI, and death [63]. However, LMWH should be used with caution in patients with stage IV-V chronic kidney disease (est. creatinine clearance <30 cc/min).

Following a large anterior MI, the risk of apical LV thrombosis warrants treatment with warfarin for at least 3 months to reduce thromboembolic events [64]. As noted above, the risk of bleeding on triple antithrombotic therapy is increased in older adults, and this factor should be carefully considered in therapeutic decision-making [65]. As a general principle, intensive antithrombotic therapy should be continued for as short a duration as clinically warranted, especially in patients at high risk for bleeding complications.

21.5.2.3 Secondary Prevention

In addition to aspirin, oral beta-blockers reduce recurrent events and mortality irrespective of age in both the acute phase and during long-term follow-up after ACS [66–68]. Risk factors for drug–disease interactions with beta-blockers (i.e., bradycardia, hypotension, exacerbation of acute heart failure) are more common in older adults but should not preclude administration of these medications; close observation and careful titration are recommended [69].

Angiotensin-converting enzyme inhibitors (ACE-I) are beneficial in older adults following AMI, particularly in the setting of LV dysfunction and heart failure. ACE-I therapy initiated in the hospital and continuing after discharge reduces mortality, hospitalizations, and the progression of LV dysfunction [70, 71]. Angiotensin receptor blockers (ARBs), including losartan and valsartan, have comparable effects to ACE-I and are appropriate second line agents when ACE-I are not tolerated due to cough [72, 73]. Combination treatment with an ACE-I and ARB does not reduce mortality but increases risk of adverse drug events.

21.5.3 Stable Coronary Artery Disease

The management of chronic CAD with or without antecedent MI focuses on optimum risk factor modification and symptom control. As a result of vascular aging and

Table 21.4 Antiplatelet therapy for use in acute coronary syndromes or coronary artery disease

	Trial[a] (sample size)	Intervention vs control	Outcomes	Age (years)	Bleeding risk	Precautions/Geriatric considerations (per Lexicomp®)
Irreversible cyclo-oxygenase inhibitors						
Aspirin	ISIS-2 [57] *N*=17,187	Aspirin (162.5 mg) Versus Placebo	35 day CV mortality: • 9.4% in aspirin group versus 11.8% in Placebo group • 23% reduction in odds of primary outcome in the aspirin group compared with placebo • Outcome % by age: <60 years: 4.5% in aspirin group versus 5.5% in Placebo group 60–69 years: 10.9% in aspirin group versus 14.0% in Placebo group ≥70 years: 17.6% in aspirin group versus 22.3% in Placebo group	<60=45% 60–69=35% ≥70=20% (Aspirin group)	Major bleeding: • 0.4% in Both groups	• Risk for peptic ulcers and/or hemorrhage • CNS adverse effects in elderly even with low doses • >325 mg Potentially inappropriate according to BEERS criteria
	M-HEART II [172] *N*=752	Aspirin 325 daily Versus Sulotroban 800 mg four times daily Versus Placebo 6 h before planned percutaneous transluminal coronary angioplasty	Death, myocardial infarction, or clinically important restenosis at 6 months: • 30% in Aspirin group versus 41% in Placebo group • OR 0.63 (p=0.05) compared to placebo	Mean in Aspirin group=58 (±10)		
Adenosine diphosphate (ADP P2Y12) receptor inhibitors						
Clopidogrel	CURE [59] *N*=12,562	Clopidogrel 300 mg loading dose+75 mg daily Versus Placebo (In addition to Aspirin in both groups)	Composite of death from CV causes, nonfatal MI or stroke: • 9.3% in Clopidogrel group versus 11.4% in Placebo group • RR 0.8 (p<0.001) • Outcome % by age: ≤65 years: 5.4% in Clopidogrel group versus 7.6% in Placebo group +>65 years: 13.3% in Clopidogrel group versus 15.3% in Placebo group	Mean in Clopidogrel group=64.2 (±11.3)	Major bleeding: • 3.7% in Clopidogrel group versus 2.7% in Placebo group • RR 1.38 (p=0.001)	• Plasma concentrations of the main metabolite were significantly higher in the elderly (≥75 years) • Use with caution in hepatic or renal impairment
	PCI CURE [58] *N*=2658	Clopidogrel 300 mg loading dose Versus Placebo (In both groups Aspirin 75–325 mg and PCI after randomization)	Composite of CV death, MI, or urgent target-vessel revascularization within 30 days of PCI: • 8.8% in clopidogrel group versus 12.6% in Placebo group • RR 0.69 (95%CI 0.54–0.87) • Outcome % and RR by age: ≥65 years: 13.4% in Aspirin group versus 16.9% in Placebo group And RR 0.79 (95% CI 0.57–1.08) <65 years: 5.9% in Aspirin group versus 9.8% in Placebo group And RR 0.59 (95% CI 0.41–0.84)	Mean in Clopidogrel group=61.6 (±11.2)	Major bleeding: PCI to 30days- • 1.6% in Clopidogrel group versus 1.4% in Placebo group • RR 1.13 (p=0.69) PCItofollowup(8months)- • 2.7% in Clopidogrel group versus 2.5% in Placebo group • RR 1.12 (p=0.64)	
	CHARISMA [173] *N*=9478	Clopidogrel 75 mg+Aspirin (75–162 mg) daily Versus Placebo+Aspirin (75–162 mg) daily	CV death (including hemorrhagic death), MI, or stroke (from any cause): • 7.3% in Clopidogrel group versus 8.8% in Placebo group • HR 0.83 (p=0.010)	Median=64 IQR=56–71	Severe bleeding: • 1.7% in Clopidogrel group versus 1.5% in Placebo group • HR 1.1 (p=0.51)	

(continued)

Table 21.4 (continued)

	Trial[a] (sample size)	Intervention vs control	Outcomes	Age (years)	Bleeding risk	Precautions/Geriatric considerations (per Lexicomp®)
Prasugrel	TRITON-TIMI-38 [60] *N*=13,608	Prasugrel 60 mg loading dose Versus Clopidogrel 300 mg loading dose	Composite rate of CV mortality, nonfatal MI, or nonfatal stroke: • 9.9% in Prasugrel group versus 12.1% in Clopidogrel group • 0.81 HR $p<0.001$	Median=61 IQR=53–69	Major bleeding: • 2.4% in Prasugrel group versus 1.8% in Clopidogrel group • HR 1.32 ($p=0.03$)	• Not recommended for use in elderly ≥75 years unless high cardiac risk due to risk of fatal intracranial bleeding and lack of certain benefit in this age group • AUC of the active metabolite was 19% higher in ≥75 years of age
Tricagrelor (Brilinta)	PLATO [61] *N*=18,624	Tricagrelor 180 mg loading dose, 90 mg twice daily Versus Clopidogrel 300 mg loading dose with 75 mg daily	Composite of CV mortality, MI, or stroke at 12 months: • 9.8% in Ticagrelor group versus 11.7% in Clopidogrel group • 0.84 HR p <0.001	Median=62 43% of the participants were ≥65 years and 15% were ≥75 years of age	Bleeding: • 11.6% in Ticagrelor group versus 11.2% in Clopidogrel group ($p=0.43$)	• Avoid use in severe hepatic impairment • Caution in renal impairment, hyperuricemia, or gouty arthritis
Protease-activated receptor-1 (PAR-1) antagonists						
Vorapaxar	TRACER [174] *N*=12,944	Vorapaxar 40 mg loading dose 2.5 mg daily Versus Placebo with stratification (intention to use a glycoprotein IIb/IIIa inhibitor (vs. none) and parenteral direct thrombin inhibitor (vs. other antithrombinagents)	Composite of CV mortality, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization at 2 years: • 18.5% in Voraxapar group versus 19.9% in Placebo group • HR 0.92 ($p=0.07$)	Median =64 IQR=58–72 ≥75=16.9%	Moderate and severe BLEEDING (GUSTO) 2 years: • 7.2% in Voraxapar group versus 5.2% in Placebo group • HR 1.35 ($p<0.001$)	• Moderate/severe bleeding was much higher for vorapaxar in the ≥74 year quintile at 13% vs 8.4% with placebo
Glycoprotein IIB/IIIA inhibitors (IV use only)						
Abciximab	GUSTO IV-ACS [175] *N*=7800	Abciximab 24 h or 48 h (0.25 mg/kg bolus followed by a 0.125 μg/kg per min maxi of 10 μg/min Versus Placebo (all receive aspirin)	30-day death from any cause or MI 24 h: • 8.2% in Abciximab group with OR 1 (95% CI 0·83–1·24) 48 h: • 9.1% in Abciximab group with OR 1.1 (95% CI 0·94–1·39) Versus 8% in Placebo group	Mean=65 (±11)	Major bleeding requiring blood transfusion: 24 h: Abciximab—2% 48 h: Abciximab—3% ($p<0.05$) Versus 2% in placebo	• Use with caution in patients >65 years and <75 kg=due to increased risk of bleeding
Eptifibatide	PURSUIT [176] *N*=10,948	Eptifibatide Bolus dose of 180 μg/kg+infusion of 1.3 μg/kg/min, or bolus dose of 180 μg/kg+infusion of 2 μg/kg/min Versus Placebo	30-day death from any cause or MI: • 14.2% in Eptifibatide versus 15.7% in Placebo • 1.5% absolute reduction ($p=0.04$) • Odds ratio closer to null for more than 65 year olds	Median=64 IQR=55–71	Major (TIMI): • 10.6% in Eptifibatide versus 9.1% in Placebo ($p=0.02$)	• Dose reduction for renal impairment (CrCl <50 ml/min) Increased bleeding risk in older patients and <70 kg
Tirofiban	RESTORE [177] *N*=2139	Tirofiban Bolus 10 μg/kg Versus Placebo over a 3-minute period	Composite end point (mortality, MI, CABG recurrent surgical or interventional revascularization of target vessel or ischemia) at 30 days: • 10.3% in Tirofiban group versus 12.2% in Placebo group • 16% relative reduction ($p=0.160$)	Mean=59.2	Major bleeding: • 5.3% in Tirofiban group versus 3.7% in Placebo group ($p=0.096$)	• Elderly patients receiving tirofiban with heparin or heparin alone had a higher incidence of bleeding

CV cardiovascular, *MI* myocardial infarction, *HR* hazard ratio, *OR* odds ratio, *RR* relative risk, *IQR* interquartile range

[a]Trial acronyms: *ISIS-2* The Second International Study of Infarct Survival, *M-HEART II* Multi Hospital Eastern Atlantic Restenosis Trial; *CURE* Clopidogrel in Unstable angina to prevent Recurrent Events; *PCI CURE* Percutaneous Coronary Intervention Clopidogrel in Unstable angina to prevent Recurrent Events, *CHARISMA* Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; *TRITON-TIMI* Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction, *PLATO* The Study of Platelet Inhibition and Patient Outcomes, *TACER* Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome, *GUSTO-IV ACS* glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes, *PURSUIT* Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; *RESTORE* Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis

accumulation of risk factors, CAD in older adults tends to affect multiple arteries and to be more diffuse and more severe than in younger adults. Diagnostic stress testing is indicated in older adults to investigate suspected CAD but baseline ECG abnormalities warrant concomitant imaging (echo, magnetic resonance imaging, or nuclear perfusion) to improve accuracy. Physical limitations may restrict the use of exercise stress testing but pharmacological stress testing (e.g., adenosine, regadenoson or dobutamine) provides a suitable alternative. Coronary computed tomographic angiography (CTA) is an alternative to stress imaging in selected cases; a limitation of this technique is the need for intravenous contrast administration and potential risk for acute kidney injury. Coronary angiography is appropriate in selected older patients with markedly abnormal stress test findings and/or limiting symptoms that do not respond adequately to medical therapy.

Management of stable CAD is designed to alleviate symptoms, improve quality of life, and reduce the risk of adverse ischemic events. First line anti-anginal therapy should include a beta-blocker if tolerated. Alternative medications include calcium channel blockers, nitrates and ranolazine. Side effects from beta-blockers and calcium channel blockers are more common in older adults and may include fatigue, weakness, and loss of energy, constipation, dizziness, low blood pressure, lower extremity swelling, and depressive symptoms.

Elective PCI for the management of stable angina symptoms is an alternative treatment strategy and may be beneficial in individuals intolerant of optimal medical therapy or in those who remain symptomatic despite medications. Although PCI is effective in reducing symptoms, data from the COURAGE trial indicate that routine PCI in patients with chronic stable CAD does not reduce mortality or risk of MI compared to optimal medical therapy alone (including aggressive CV risk reduction) [74]. The findings of COURAGE were similar in patients younger or older than 65 years.

In appropriately selected patients, coronary artery-bypass grafting (CABG) reduces symptoms and improves quality of life. In high risk individuals, CABG also confers a mortality benefit [75]. Older patients undergoing CABG are more likely than younger patients to have multimorbidity, cognitive impairment, reduced functional status, and more advanced and diffuse CAD [76]. As a result, perioperative morbidity and mortality are higher, with higher rates of respiratory failure, bleeding, acute kidney injury, atrial fibrillation, heart failure, and delirium. In addition, postoperative cognitive impairment is more common in elderly individuals. For additional information on cardiothoracic surgery, see Chap. 10.

21.5.4 Heart Failure

Heart failure is primarily a disorder of older adults in part because CV aging, especially increased vascular and myocardial stiffness, increases vulnerability for developing heart failure [77]. In addition, heart failure is the "final common pathway" for nearly all CV disorders afflicting older adults. Heart failure affects 5.7 million Americans with approximately 870,000 new cases annually in individuals ≥55 years. It is the most common cause of hospital admission in individuals >65 years of age and is responsible for an estimated 1 million hospital discharges as primary diagnosis each year at a cost of approximately $30 billion in 2012 [78]. Heart failure contributes to more than 250,000 deaths annually in the USA, of which >85 % are in individuals over the age of 65. Mortality rates in advanced heart failure approach those of metastatic lung cancer; however, these poor outcomes are infrequently communicated to and comprehended by patients and families. Not only does heart failure account for significant adverse health outcomes, it has a major impact on quality of life, disability, and independence in elderly patients. See Chap. 6 for further discussion of palliative and end-of-life care in advanced heart failure.

Dyspnea on exertion, reduced exercise tolerance, orthopnea, lower extremity and abdominal swelling, and general fatigue are characteristic symptoms in both young and older adults with heart failure. Reduced baseline physical activity in older adults due to disability or sedentary life style can mask exertional symptoms. In contrast, non-specific symptoms including confusion, reductions in physical activity and functional status, nausea and loss of appetite are more common expressions of heart failure in elderly patients.

The goals of heart failure management in older adults should focus on reduction of symptom severity, improving quality of life, maintenance of functional status and independence, avoidance of hospitalization and institutionalization, and extending life in alignment with patient-centered goals. An interprofessional team approach to care is critical and should incorporate cardiovascular, non-cardiovascular, and social factors. Studies have shown that team care reduces readmissions and improves quality of life in older patients with heart failure. However, recent data indicate that up to two-thirds of readmissions are due to causes other than heart failure, which underscores the need to individualize care and to address prevalent comorbidities [79].

21.5.4.1 Medical Therapy

The mainstay of treatment for heart failure with reduced ejection fraction (HFrEF) includes beta-blockers, ACE-I or ARBs, diuretics, and mineralocorticoid antagonists. In addition, digoxin and vasodilators can be beneficial in selected

cases. During long-term use beta-blockers improve LV systolic function and reduce hospital admissions and mortality [80, 81]. These effects are evident for all stages of heart failure and across all age groups, including beneficial effects in the elderly. Beta-blockers shown to be effective in clinical trials and approved for use in the USA for treatment of heart failure include metoprolol succinate and carvedilol. Bisoprolol and nebivolol have also demonstrated improved outcomes in heart failure patients but are not FDA approved for that indication [82, 83]. As with use in coronary artery disease, side effects and adverse events are more common in older adults; hence, it is appropriate to start with low doses, titrate gradually, and monitor closely.

ACE-I have favorable effects on left ventricular remodeling and are beneficial in patients with HFrEF irrespective of symptoms [84–86]. However, since most landmark ACE-I trials included low numbers of elderly patients, the benefits of these agents in patients over 75–80 years of age are less well established. Nonetheless, ACE-I for HFrEF carry a class I indication regardless of age [42]. ARBs are a suitable alternative in the setting of ACE-I intolerance and benefits of ARBs have been shown in both young and older adults [87, 88]. ACE-I and ARBs are generally well tolerated but should be started at lower doses in older adults and titrated slowly while monitoring closely for hypotension, renal dysfunction, and electrolyte abnormalities (especially hyperkalemia).

Mineralocorticoid receptor antagonists (aldosterone receptor antagonists), including spironolactone and eplerenone, reduce mortality in patients with New York Heart Association (NYHA) class II-IV HFrEF and are recommended in these patients unless contraindicated [89, 90]. Patients with NYHA class II heart failure should have a history of prior CV hospitalization or elevated plasma natriuretic peptide levels to be considered for mineralocorticoid receptor antagonists [42]. Mineralocorticoid receptor antagonists are not recommended if the estimated glomerular filtration rate (eGFR) is <30 mL/min/M^2 or if the serum potassium level is >5 meq/L. Adverse effects include hyperkalemia, especially in the setting of chronic kidney disease, but with close observation severe hyperkalemia is uncommon.

Diuretics, in combination with sodium restriction, are essential for treating acute decompensation and for maintaining euvolemia in the outpatient setting. In elderly patients, management of fluid and sodium balance must be considered in the context of social support, as well as functional and physical limitations. Titrating diuretic therapy according to daily weights and close monitoring of daily sodium and fluid intake may not be feasible in older adults with limited social support or significant functional, physical, or cognitive impairments.

Digoxin reduces heart failure symptoms and heart failure admissions in patients with HFrEF [91]. However, digoxin has no effect on mortality and it has a low therapeutic index with relatively high potential for serious adverse events, especially in older patients with reduced renal function. In older adults with preserved renal function (est. GFR ≥60 cc/min) digoxin may be useful as an adjunctive agent in patients who remain symptomatic despite standard therapy [92]. In such cases, low doses (e.g., 0.125 mg daily or every other day) should be utilized and levels should be monitored periodically, targeting a therapeutic range of 0.5–0.9 ng/ml [93].

The vasodilators hydralazine and isosorbide dinitrate are indicated in African American patients with moderate to severe heart failure symptoms, and they may also be useful in patients who are unable to take ACE-I or ARBs due to renal insufficiency or side effects [94, 95]. Limitations of these medications in older adults include the relatively high side effect profile and thrice daily dosing, which impacts the complexity of the regimen and may reduce medication adherence.

21.5.4.2 Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Therapy

Despite optimal medical therapy, patients with HFrEF are at an increased risk for sudden cardiac death due to ventricular arrhythmias. Implantable cardioverter-defibrillators (ICDs) reduce CV and all-cause mortality in selected patients and are recommended for individuals with irreversible heart failure (ischemic or non-ischemic), an LV ejection fraction ≤35 %, NYHA class II-III heart failure symptoms, and a life expectancy of at least 1 year [96, 97]. In the USA, >40 % of ICDs are implanted in patients over age 70 and 10–12 % are implanted in individuals over the age of 80. However, the majority of trials for primary and secondary prevention of sudden cardiac death with ICDs did not enroll patients over the age of 80 [98], and data from clinical trials and observational studies indicate that the mortality benefit of ICDs declines with age, primarily due to competing risks of death. For these reasons, the decision to implant an ICD in an older adult must be considered carefully and should include an estimation of the individual's likely benefit in the context of other medical problems. In addition, shared decision-making to ensure alignment with the patients' preferences and goals is essential. For example, frail individuals with recurrent hospital admissions are unlikely to benefit from an ICD. On the other hand, older adults who are otherwise suitable candidates should not be denied an ICD based solely on age. However, prior to implanting a device there should be a discussion about the potential for recurrent shock therapies and associated post-traumatic stress and anxiety, as well as options and preferences for disabling the device in the setting of terminal illness.

Cardiac resynchronization therapy (CRT) aims to improve hemodynamic parameters associated with impaired left ventricular function resulting from dyssynchronous LV contraction. In patients with HFrEF, a prolonged QRS dura-

tion (≥120 ms), and class II-IV symptoms, CRT has demonstrated improvements in symptoms, quality of life, and survival [99, 100]. Patients with left bundle branch block and QRS duration ≥150 ms are most likely to benefit, and there is evidence that women derive greater benefit than men. Although patients over the age of 80 were excluded from most of the randomized CRT trials, observational studies suggest that appropriately selected older adults often experience improved symptoms and quality of life. Therefore, CRT should be offered as an option in the management of advanced heart failure in older adults who are suitable candidates for the device.

21.5.4.3 Heart Transplant and Advanced Heart Failure Devices

Although there is no widely accepted upper age limit for heart transplantation, most transplant centers use a cut-off of either 70 or 75 years. Among patients 65–74 undergoing orthotopic heart transplantation, outcomes are comparable to those in younger individuals [101]. However, due to low availability of donor hearts, few individuals are selected for transplantation and they generally have low rates of co-existing diseases. To address this disparity, some centers are performing the procedure using hearts from older donors for an increasing number of older adults who previously would have been declined for transplantation.

Left ventricular assist devices (LVADs) for destination therapy (DT) are increasingly used in patients with advanced heart failure with reduced left ventricular ejection fraction who are ineligible for heart transplantation [102, 103]. As a result, many DT-LVAD candidates are older and have greater comorbidity than younger device candidates. LVAD implantation is associated with substantial morbidity and mortality despite improvements in device technology and operative skills. Currently, 2-year survival rates following LVAD implantation are less than 60 %, the overall stroke rates is 11 % [102], and 5-year costs are >$350,000 [104]. For these reasons optimal patient selection for DT-LVAD implantation is critical.

The prevalence of frailty in patients with advanced heart failure approaches 50 % as a result of reduced cardiac output, deconditioning, cognitive impairment, and muscle cachexia [105]. Additionally, hallmark symptoms of advanced heart failure, including exhaustion, reduction in physical activity, and weakness are also fundamental components of frailty. The presence of frailty and/or cognitive impairment negatively impacts short- and long-term outcomes. Whether elements of frailty can be reversed with restoration of adequate cardiac output has not been determined. The concept of "LVAD responsive" and "LVAD un-responsive" frailty has been proposed in an effort to optimize patient selection for DT-LVAD implantation, but additional studies are needed.

21.5.4.4 Heart Failure with Preserved Ejection Fraction

Up to 50 % of patients with heart failure have normal or near normal LV ejection fractions [i.e., heart failure with preserved ejection fraction (HFpEF)]. The majority of patients with HFpEF have antecedent hypertension (60–80 %), and HFpEF prevalence is substantially higher in women than in men. Multimorbidity is common and often includes other CV disorders, such as CAD, atrial fibrillation, and valvular heart disease. Although prognosis is somewhat better for HFpEF than for HFrEF, symptoms, quality of life, and hospitalization rates are similar between the two forms of heart failure. However, unlike HFrEF, for which numerous therapies have been shown to improve symptoms and clinical outcomes, to date no pharmacological or device-based interventions have demonstrated efficacy in HFpEF (Table 21.5). For this reason, current management of HFpEF focuses on optimizing blood pressure control (see above Sect. 23.3.1), treating ischemia in patients with concomitant CAD, controlling heart rate in patients with atrial fibrillation, and avoiding excess dietary salt and fluid intake. Diuretics are indicated to maintain euvolemia and minimize symptoms of shortness of breath and edema, but must be used judiciously to avoid over-diuresis, which may lead to reduced organ perfusion and pre-renal azotemia.

Cardiac amyloidosis is an increasingly recognized cause of HFpEF in older adults. Myocardial amyloid deposition may be due to a chronic systemic illness (e.g., multiple myeloma), systemic amyloidosis, or as a primary cardiac condition [106]. Senile systemic amyloidosis is a disease preferentially affecting older adults, especially men, and is present in approximately 25 % of individuals over the age of 80 [107]. This form of amyloidosis is derived from an inherited wild-type transthyretin (TTR), an amino acid transporter protein of thyroxine and retinol produced by the liver, and can involve the atria, conduction system and on occasion the entire heart [108]. A subset of TTR amyloidosis associated with specific mutations of the TTR gene has recently been identified. A common mutation (Val12Ile) is predominantly found in African Americans with an estimated carrier prevalence of 3–4 % [109].

The clinical presentation of cardiac amyloid is highly variable, ranging from asymptomatic disease that runs a relatively benign course to severe restrictive cardiomyopathy associated with heart failure, atrial fibrillation, conduction abnormalities, and poor prognosis. Echocardiography, magnetic resonance imaging, and nuclear scintigraphy are useful for evaluating suspected cardiac amyloid, but tissue biopsy is needed to confirm the diagnosis. Until recently, treatment was primarily supportive, but several novel agents currently under investigation show promise for slowing the rate of disease progression.

Table 21.5 Clinical trials in heart failure with preserved ejection fraction

Trial[a]	Patients	Treatment	LVEF	Age	Outcomes compared to placebo[b]
PEP-CHF [178]	850	Periondopril	65 (56–66)	75 (72–79)	Death/hospitalization by 1 year—HR 0.69 (0.47–1.01, $p=0.055$). HF hospitalization by 1 year—HR 0.63 (0.41–0.97, $p=0.033$)
CHARM-Preserved [179]	3023	Candesartan	54±9	67±11	CV death/HF admission—HR 0.89 (0.77–1.03, $p=0.118$). HF admission—HR 0.85 (0.72–1.01, $p=0.072$)
I-PRESERVE [180]	4128	Irbesartan	60±9	72±7	Death/hospitalization—HR 0.95 (0.86–1.05, $p=0.35$)
SENIORS (EF>35 % subgroup) [181]	643	Nebivolol	49±10	76±5	All cause death/CV hospitalization—HR 0.81 (0.63–1.04)
TOPCAT [182]	3445	Spironolactone	56 (51–62)	69 (61–76)	CV death/HF hospitalization/aborted SCD—HR 0.89 (0.77–1.04, $p=0.14$) HF hospitalization—HR 0.83 (0.69–0.99, $p=0.04$)
Aldo-DHF [183]	422	Spironolactone	67±8	67±8	Reduced E/e' avg 1.5 ($p<0.001$)
RELAX [184]	216	Sildenafil	60 (56–65)	69 (62–77)	No difference Δ VO2 peak at 24 weeks
ESS-DHF [185]	192	Sitaxsentan	61±12	65±10	Median 43 s relative increase in Naughton treadmill time ($p=0.03$)
DIG Ancillary [186]	988	Digoxin	55±8	67±10	HF hospitalization—HR 0.79 (0.59–1.04, $p=0.09$). Hospitalization for unstable angina—HR 1.37 (0.99–1.91, $p=0.06$)

Age (in years) and LVEF (%) presented as mean±SD or median (IQR)
CV cardiovascular. *E/e' avg* echocardiographic mitral inflow velocity/tissue Doppler velocity ratio. *HR* hazard ratio with (95 % confidence interval). *LVEF* left ventricular ejection fraction, *SCD* sudden cardiac death
[a]Trial acronyms: *PEP-CHF* Perindopril in Elderly People with Chronic Heart Failure, *CHARM-Preserved* Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity—Preserved LVEF, *I-PRESERVE* Irbesartan in Heart Failure with Preserved Ejection Fraction Study, *SENIORS* Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure, *TOPCAT* Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist, *Aldo-DHF* Aldosterone Receptor Blockade in Diastolic Heart Failure, *RELAX* Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction, *ESS-DHF* Effectiveness of Sitaxsentan Sodium in Patients With Diastolic Heart Failure, *DIG* Ancillary Digitalis Investigation Group Ancillary Trial
[b]All-cause mortality was not significantly reduced in *any* trial

21.6 Valvular Heart Disease

21.6.1 Aortic Valve

Aortic stenosis (AS) is the most common valvular heart disease requiring intervention in older adults [110], with an estimated prevalence of severe AS of approximately 8 % by 85 years of age [111, 112]. Risk factors for developing AS include age, male sex, smoking, hypertension, and increased LDL cholesterol levels. Classical symptoms of AS include angina, syncope (and pre-syncope), and shortness of breath, which occur as a result of severe obstruction to left ventricular ejection. This culminates in increased LV systolic and diastolic pressures and prolonged emptying time of the LV. Pathological responses include increased myocardial mass and ischemia due to increased myocardial oxygen consumption in the face of decreased oxygen supply.

Surgical aortic valve replacement (SAVR) is the gold standard and definitive treatment for severe symptomatic AS. However, the decision to perform SAVR in elderly patients is challenging due to increasing comorbidities and the associated increase in operative mortality. Despite improved survival with SAVR compared to conservative medical therapy, 30–40 % of patients are denied or refuse surgery due to real or perceived increased perioperative risk [113].

Since 2002, transcatheter aortic valve replacement (TAVR) has emerged as a successful alternative therapy for patients at prohibitive or high operative risk [114, 115]. Initial studies demonstrated TAVR to be non-inferior to SAVR in patients with severe AS at high operative risk [116]. Additionally, in patients unable to undergo surgery due to prohibitively high risk, TAVR conferred a 20 % absolute reduction in all-cause mortality compared to medical therapy [117]. However, 1-year mortality following TAVR was 30 % and an additional 20 % had no significant improvement in quality of life or functional status. Similar results were also observed with a self-expanding bioprosthesis; i.e., non-inferiority to SAVR in high risk patients but with 26 % 1-year mortality. Even though procedural complications have decreased with increased operator experience, 1-year mortality rates have remained in excess of 20 %. While there is growing interest in TAVR, there is paucity of data on optimal patient selection for successful procedural and long-term outcomes. The ability to distinguish which patients will achieve significant improvements in quality and quantity of life from those for whom the procedure may be futile

is critical for aligning patient-centered goals with available therapeutic options [118]. Importantly, incorporating frailty indicators into risk assessment models shows promise for identifying patients likely to have a favorable or unfavorable outcome following TAVR [119]. See also Chap. 10 for further discussion of TAVR.

Aortic regurgitation in older adults occurs as a result of valve leaflet degeneration (e.g., rheumatic or calcific aortic valve disease, endocarditis) or dilatation of the ascending aorta and aortic root (e.g., long standing central aortic hypertension, atherosclerosis, and other disorders affecting the aortic root). Chronic moderate or severe aortic regurgitation leads to chronic LV volume overload and increased stroke volume. Over time increased LV dilatation and an imbalance between myocardial oxygen consumption and supply results in myocardial ischemia and LV dysfunction, ultimately leading to LV failure. Symptoms related to aortic regurgitation can manifest late in the disease process and may include shortness of breath, exercise intolerance, and angina. Treatment of aortic regurgitation in older adults is similar to that in younger individuals. Medical therapies aimed at reducing LV afterload, such as ACE-I or nifedipine, can provide symptomatic benefit [120, 121]. In patients with severe aortic regurgitation, valve replacement should be performed prior to the development of irreversible LV dysfunction (if feasible) [122].

21.6.2 Mitral Valve

The prevalence of mitral valve regurgitation increases with age as a consequence of ischemic heart disease, degenerative valve disease, or mitral valve annulus enlargement from LV dilatation in the setting of HFrEF. Chronic moderate or severe mitral regurgitation leads to LV volume overload with increasing left atrial and left ventricular pressures, pulmonary venous hypertension, and pulmonary arterial hypertension. As with aortic regurgitation, mitral regurgitation may not cause symptoms until LV dysfunction is evident. For those with mild to moderate disease, medical management with afterload reduction is appropriate [122]. In patients with severe mitral regurgitation, surgical mitral valve repair is the treatment of choice when feasible and is preferred to mitral valve replacement due to more salutary outcomes [123, 124]. Older adults with severe mitral regurgitation may be high risk surgical candidates or ineligible for surgery due to co-existing conditions such as chronic kidney disease, neurological disease, and pulmonary disease, and outcomes are less favorable in individuals with impaired LV systolic function. In addition, decision-making should consider patient preferences with respect to quality of life versus length of life, as well as functional, cognitive, and geriatric factors central to surgical outcomes regardless of type of procedure (also see Chap. 10).

For older adults at high or prohibitive surgical risk percutaneous transcatheter techniques to repair the mitral valve have emerged [125]. The EVEREST II trail randomized individuals with degenerative mitral valve regurgitation to mitral valve surgery or percutaneous repair using the MitraClip device [126]. Mortality at 4 years was similar between groups, although a small number of individuals who received the MitraClip required subsequent surgical intervention. In addition, the MitraClip was less efficacious in reducing the severity of mitral regurgitation. Although EVEREST II enrolled primarily low-risk surgical candidates, registry data have demonstrated that transcatheter mitral valve repair is safe and associated with advantageous clinical outcomes in older individuals with significant or prohibitive surgical risk. Nonetheless, additional studies are needed to better define the role of this technology in the management of older patients with moderate or severe mitral regurgitation.

The leading cause of mitral stenosis globally is rheumatic heart disease. In developed countries, however, the prevalence of mitral stenosis has declined, and in older adults mitral valve obstruction due to mitral annular calcification has become the most common cause of mitral stenosis [127]. Additional risk factors include systemic hypertension, genetic connective tissue disorders, and DM. Clinical features of rheumatic mitral stenosis tend to develop over several decades; as a result, the condition occasionally presents in older adults. Predominant symptoms include shortness of breath, fatigue, and weakness. Medical therapy includes sodium restriction, diuretics, and anticoagulation with warfarin in the presence of atrial fibrillation (AF). Rates of thromboembolic events in individuals with AF and mitral stenosis are high, ranging from 7 to 15 % annually [128]. Newer oral anticoagulants have not been studied in this setting and are not approved for AF attributable to valvular heart disease. Isolated rheumatic mitral stenosis (without significant mitral regurgitation) with favorable valve characteristics may be suitable for percutaneous mitral valvuloplasty, which often results in prompt improvement in symptoms and hemodynamics. In addition, 60–70 % of patients with successful valvuloplasty are free of recurrent stenosis at 10-year follow-up [129, 130]. Older adults often have unfavorable characteristics of the mitral valve and annulus, such as calcification, leaflet immobility, disease involving the subvalvular apparatus, and significant mitral regurgitation, which, taken together, may make them poor candidates for valvuloplasty. In addition, the presence of left atrial thrombus prior to the procedure is a contraindication. Surgical mitral valve replacement is an alternative for very symptomatic older adults who are not candidates for valvulopasty, but perioperative mortality rates are 5–15 % and recovery can be slow, especially in patients with diminished pre-operative functional status [131].

21.7 Arrhythmias

Age-related changes in the cardiac conduction system, including degeneration, fibrosis, and calcification (Table 21.1), lead to increasing prevalence of cardiac arrhythmias with age [132]. Aging is associated with a decrease in the number of cardiac myocytes and an increase in collagen content throughout the heart and conduction system. In addition, there is an increase in fat deposition adjacent to the sinoatrial node and progressive fibrosis of the node itself resulting in a gradual loss of sinoatrial pacemaker cells such that by age 75 only 10 % of these cells remain functional. The diversity of symptoms related to cardiac arrhythmias tends to be greater in older as compared to younger adults, and may include falls, weakness, fatigue, confusion, and exacerbations of other co-existing diseases. As a result, cardiac arrhythmias should be considered in the differential diagnosis of a broad spectrum of presenting symptoms.

21.7.1 Bradyarrhythmias

Individuals over the age of 65 account for more than 80 % of pacemakers placed in the USA, and approximately half of these pacemakers are for treatment of sick sinus syndrome [133]. Although bradyarrhythmias are the hallmark of sinus sick syndromes, the condition is frequently accompanied by tachyarrhythmias and atrial-ventricular conduction abnormalities. In particular, treatment of a supraventricular tachycardia can precipitate or exacerbate symptomatic bradyarrhythmias. Bradyarrhythmias commonly associated with sick sinus syndrome include chronic and inappropriate sinus bradycardia (i.e., too slow to maintain resting cardiac output and an inadequate response to stress), sinus pauses, and sinus arrest. Symptomatic bradycardia not attributable to a reversible cause (e.g., beta-blocker, donepezil, hypothyroidism) is a class I indication for pacemaker placement, and in the setting of sinus rhythm, a dual chamber device is appropriate. For individuals with symptomatic bradycardia due to medication, indications for that therapy should be reviewed, and only if compelling (e.g., beta-blocker for heart failure) should a pacemaker be considered; otherwise, an alternative medication should be used.

21.7.2 Supraventricular Tachycardias

Atrial fibrillation (AF) affects between 2.7 and 6 million individuals in the US and is the most common sustained cardiac arrhythmia with an estimated prevalence of 9 % in adults 65 and older [134]. AF is predominantly a disorder of older adults, with approximately 50 % of cases occurring in individuals 75 years of age or older. In addition, with the aging of the population it is projected that the median age for patients with AF will approach 80 years by mid-century. Although AF is more common in men than women, increasing prevalence of heart disease in women with aging and their longer life expectancy results in more women with AF at older age. In older adults, AF is nearly always associated with underlying CVD with hypertensive heart disease, ischemic heart disease, and valvular heart disease making up the overwhelming majority. AF can present with varied symptoms; a large proportion of older adults with AF experience mild or no symptoms, whereas others report fatigue, weakness, lightheadedness, decreased activity tolerance, chest discomfort, or shortness of breath. Palpitations, fluttering, and racing heartbeat are also commonly reported. In addition to symptoms caused by AF, the risk of stroke attributable to AF is substantial. In the Framingham Study, AF was associated with a two to threefold increased risk of stroke, and 23.5 % of strokes were attributed to AF in those over age 80 [135].

The management of AF should include (1) identification of underlying cause and potential reversibility, (2) control of symptoms through a rhythm or rate-control strategy, and (3) stroke prevention [136]. Reversible causes include hyperthyroidism, obstructive sleep apnea, alcohol, excess caffeine, drugs (prescribed, illicit, and herbal/OTC medications), and electrolyte imbalance. Additionally, optimum treatment of underlying CVD, such as controlling blood pressure, can reduce the burden of AF and help maintain sinus rhythm.

The balance between rhythm control (aiming to maintain sinus rhythm) and rate control (aiming to reduce ventricular response rate) strategies is complicated and controversial. The AFFIRM trial randomized older adults with AF to rate control or rhythm control and demonstrated a non-significant increase in mortality in individuals in the rhythm control group, as well as a significant increase in hospitalizations [137]. A key observation was that most strokes occurred in patients either not taking warfarin or with sub-therapeutic international normalized ratios (INR). This has contributed to the strong recommendation to maintain older adults with AF on anticoagulation whether or not they are in sinus rhythm. Medications commonly used as first line agents for rate control include beta-blockers and non-dihydropyridine calcium channel blockers (diltiazem, verapamil). Digoxin is relatively ineffective as a single agent but may be a useful adjunct in patients with inadequate rate control despite maximally tolerated doses of beta-blockers and/or calcium channel blockers.

A strategy of maintaining sinus rhythm is appropriate in patients with moderate or severe symptoms related to AF that do not respond to rate control interventions. In addition, rhythm control may be associated with improved quality of life and exercise tolerance, and there is preliminary evidence that cognitive outcomes may be better in patients with AF who are maintained in sinus rhythm [138]. Rhythm control usually includes a trial of antiarrhythmic drug therapy; how-

ever, available agents have relatively low efficacy rates and side effects are common. Catheter ablation of AF foci in the left atrium is an alternative to antiarrhythmic drugs for maintaining sinus rhythm. Success rates range from about 65–85 % but tend to be lower in older adults, who are also less often suitable candidates for the procedure due to an enlarged left atrium or other factors. The surgical Maze procedure is effective in maintaining sinus rhythm in up to 90 % of patients with AF, but is usually reserved for severely symptomatic patients or those undergoing cardiac surgery for another reason (e.g., CABG) [136].

Anticoagulation markedly reduces the risk of stroke in older patients with either paroxysmal or chronic AF, and since increasing age is associated with increasing stroke risk, the oldest patients derive the greatest absolute benefit from anticoagulation. Conversely, the oldest patients are also at increased risk for bleeding complications. As a result of this tension, decisions regarding anticoagulation in older adults with AF are often challenging. In general, if there are no significant contraindications or high risk co-existing conditions, older adults with AF should receive systemic anticoagulation. In other cases, risk assessment tools such as $CHADS_2$, CHA_2DS_2-VASc, ATRIA, and HAS-BLED can be useful for assessing benefits and risks of anticoagulation (see Table 21.6) [139–142]. In the past few years, new options for anticoagulation have become available; Table 21.7

Table 21.6 Risk prediction tools for anticoagulation use in atrial fibrillation

Prediction tool	Variables included (points)	Reported risk	
$CHADS_2$ [139]	C congestive heart failure (1) H hypertension (1) A age >75 years (1) D diabetes mellitus (1) S_2 prior stroke, TIA or thromboembolism (2)	$CHADS_2$ score	Annual stroke risk %
		0	1.9
		1	2.8
		2	4.0
		3	5.9
		4	8.5
		5	12.5
		6	18.2
CHA_2DS_2-VASc [140]	C congestive heart failure (1) H hypertension (1) A_2 age >75 years (2) D diabetes mellitus (1) S_2 prior Stroke, TIA or thromboembolism (2) V vascular disease (1)* A age 65–74 YEARS (1) Sc female sex (1)	CHA_2DS_2VASc Score	Annual stroke risk %
		0	0
		1	1.3
		2	2.2
		3	3.2
		4	4.0
		5	6.7
		6	9.8
		7	9.6
		8	6.7
		9	15.2
HAS-BLED [141]	H hypertension (1) A abnormal renal/liver function (1)** S prior stroke (1) B bleeding (1) L Labile INRs (1)*** E elderly >65 years (1) D drugs or alcohol (1)****	Score of ≥3 indicates increased 1 year bleeding risk on anticoagulation Risk is for bleeding requiring hospitalization or hemoglobin decrease >2 g/L or transfusion required	
ATRIA [142]	Anemia (3) Severe renal disease (3) Age ≥75 years (2) Prior bleeding (1) Hypertension (1)	ATRIA score	Major hemorrhage (% per year)
		0	0.4
		1	0.6
		2	1.0
		3	1.0
		4	2.6
		5	5.7
		6	5.0
		7	5.2
		8	9.6
		9	12.4
		10	17.3

ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation

Table 21.7 Anticoagulants—for use in patients with non-valvular atrial fibrillation (NVAF)

	Trial[a] (sample size)	Intervention vs control	Outcomes	Age	Bleeding risk	Precautions/geriatric considerations (per Lexicomp®)
Warfarin/ Vitamin K inhibitors	SPAF [187] *N* = 627	Group 1 (Anticoagulation) Warfarin Versus Placebo	Ischemic stroke and primary embolism: • 2.3 %/year in Warfarin group versus 7.4 %/year in Placebo group • Risk reduction in warfarin group was 67 % ($p = 0.01$)	Mean = 65 in Warfarin group Only 4 % above 75	Major bleeding: • 1.5 %/year in Warfarin group versus 1.6 %/year in Placebo group	Risk for bleeding complications secondary to falls, drug interactions, living situation, and cognitive status
	BAFTA [188]	Warfarin (target international normalized ratio 2–3) Versus Aspirin 75 mg daily	Fatal or disabling stroke, intracranial hemorrhage, or clinically significant arterial embolism: • 1.8 %/year in Warfarin group vs 3.8 %. year in Aspirin group • RR 0.48, 95 % CI 0.28–0.80, $p = 0.003$ • Outcomes by Age: 75–79 years: 2 %/year in Warfarin group vs 2.8 %.year in Aspirin group And 0.71 (95 % CI 0.29–1.65) $p = 0.57$ 80–84 years: 1.1 %/year in Warfarin group vs 3.8 %.year in Aspirin group And RR 0.30 (95 % CI 0.10–0.77) $p = 0.45$ ≥85 years: 2.8 %/year in Warfarin group vs 5.6 %.year in Aspirin group And RR 0.50 (95 % CI 0.17–1.31) p = n/a	Inclusion criteria was >75 year olds Mean = 81.5 (±4.2)		
Direct thrombin inhibitors						
Dabigatran	RE-LY [189] *N* = 18, 113	Dabigatran 110 mg or 150 mg twice daily Versus Warfarin	Stroke or systemic embolism: 1.53 %/year in 110 mg Dabigatran RR 0.91 (p <0.001) *and* 1.11 %/year in 150 mg Dabigatran RR 0.66 ($p < 0.001$) Versus 1.69 % in Warfarin group	≥75 years or 65–74 years with DM, HTN, CAD 110 mg: Mean = 71.4(±8.6) years 150 mg: Mean = 71.5(±8.8) years	Major bleeding: 2.71 %/year in 110 mg Dabigatran RR 0.8 ($p = 0.003$) *and* 3.11 %/year in 150 mg Dabigatran RR 0.93 ($p = 031$) Versus 3.36 % in Warfarin group	80 % excreted renally; dose adjustment for patients with kidney disease: 75 mg BID for eGFR 15–30 cc/min; not recommended for eGFR <15 cc/min Increase in bleeding risk with age
Xa inhibitors						

Rivaroxaban	ROCKET AF [190] *N* = 14, 264	Rivaroxaban 20 mg or 15 mg daily (CrCl 30–49 ml/min) Versus Warfarin	Stroke or systemic embolism: • 1.7 %/year in Rivaroxaban group versus 2.4 %/year in Warfarin group • HR 0.79 (p <0.001)	Median = 74 IQR = 65–78	Major and Minor bleeding : • 14.9 %/year in Rivaroxaban group versus 14.5 %/year in Warfarin group • HR 1.03 (p = 0.44) • *Subgroup analysis by age* (p = 0.118) <65 years = 14.6 %/year in Rivaroxaban group versus 15.3 %/year and HR 0.93 (95 % CI 0.78–1.11) 65–75 years = 19.48 %/year in Rivaroxaban group versus 19.99 % in Warfarin group and HR 0.98 (95 % CI 0.87–1.1) >75 years = 25.78 %/year in Rivaroxaban group versus 23.48 % in Warfarin group and HR 1.12 (95 % CI 1–1.25)	The mean AUC was 41 % greater in persons >75 years of age. Rivaroxaban's half-life in older adults was 11–13 h Dose reduction to 15 mg daily in patients with NVAF and creatinine clearance 15–50 cc/min; avoid in patients with creatinine clearance <15 cc/min Avoid in: – Moderate to severe hepatic impairment (Child-Pugh classes B and C) – Patients with any hepatic disease associated with coagulopathy
Apixaban	ARISTOTLE [191] *N* = 18, 201	Apixaban 5 mg twice daily Versus Warfarin 2.5 mg twice daily in patients with ≥ 2 risk factors: age ≥ 80 years, weight ≤ 60 kg, creatinine ≥ 1.5 mg/dL	Stroke or systemic embolism: • 1.27 %/year in Apixaban group versus 1.6 %/year in Warfarin group • HR 0.79 (p <0.001) • *Outcomes by age* (p = *0.12*) <65 years = 1 %/year in Apixaban group versus 0.9 %/year in Warfarin group 65–74 years = 1.3 %/year in Apixaban group versus 1.7 %/year in Warfarin group ≥75 years = 1.6 %/year in Apixaban group versus 2.2 %/year in Warfarin group	Median = 70 IQR = 63–76	Major or clinically relevant non-major bleeding: • 4.07/year in Apixaban group versus 6.01 % in Warfarin group • HR 0.68 (p <0.001)	Not recommended in: – Severe hepatic impairment (Child-Pugh class C) – Significant renal impairment (CrCl <30 mL/min) (not included in trials) – Systemic exposure increases with worsening renal function. Bleeding risk may be increased in severe renal impairment (CrCl <30 mL/min) – Patients with ESRD with or without hemodialysis have not been studied – Dosage reduction for patients with ≥2 risk factors: serum creatinine ≥1.5 mg/dL, ≥80 years of age, ≤60 kg
Edoxaban	ENGAGE AF-TIMI [192] *N* = 21,105	Edoxaban 30 or 60 mg daily Versus Warfarin	Stroke or systemic embolism: • 1.61 %/year in 30 mg Edoxaban group HR 1.07 p = 0.005 *and* 1.18 %/year in 60 mg Edoxaban group HR 0.79 p <0.001 Versus 1.5 %/year in Warfarin group	Median = 72 IQR = 64–78	Major bleeding: • 2.75 %/year in 30 mg Edoxaban group and HR 0.8 (p <0.001) *and* 1.61 %/year in 60 mg Edoxaban group HR 0.47 (p <0.001) Versus 3.43 %/year in Warfarin Group	Do not administer to patients with CrCl >95 mL/min Reduce dose to 30 mg/day in patients with CrCl of 15 to 50 mL/min or venous thromboembolism (DVT and/or PE) and body weight ≤60 kg Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B and C) or patients with CrCl <15 mL/min

HR hazard ratio, *OR* odds ratio, *RR* relative risk, *IQR* interquartile range, *CrCl* creatinine clearance, *DM* diabetes mellitus, *CAD* coronary artery disease, *HTN* hypertension; *CNS* central nervous system

[a]Trial acronyms: *SPAF* Stroke Prevention in Atrial Fibrillation, *BAFTA* Birmingham Atrial Fibrillation Treatment of the Aged Study, *RE-LY* Randomized Evaluation of Long-Term Anticoagulation Therapy, *ROCKETAF* Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, ENGAGE-TIMI = Effective Anticoagulation with Factor Xa Next Generation

summarizes some of the major AF trials and provides caveats for treating older adults. In general, the new oral anticoagulants (NOACs) are at least as effective as warfarin for stroke prevention in patients with non-valvular AF, including those ≥75 years of age. NOACs are also associated with lower risk for intracranial hemorrhage than warfarin, while the incidence of other major bleeding complications varies across agents. Among patients age 75 or older, gastrointestinal bleeding is more common with dabigatran and rivaroxaban than with warfarin, and this observation should be considered when selecting an anticoagulant in older patients [143]. In addition, as noted previously, bleeding risks are increased for individuals on triple antithrombotic therapy. While optimal management of patients with indications for both antiplatelet therapy and anticoagulation remains an area of active investigation, recent data suggest that clopidogrel in combination with warfarin is as effective as triple therapy (i.e., including aspirin) and associated with lower bleeding risk, and that it may be safe to shorten the duration of triple therapy in selected patients following PCI (Table 21.8) [65, 144].

In patients at high risk for stroke who are also poor candidates for anticoagulation, device therapy, such as the WATCHMAN device or LARIAT procedure, may be considered, although experience with these interventions in older adults is very limited [145]. The WATCHMAN left atrial appendage occlusion device is inserted via percutaneous catheterization, while the LARIAT procedure involves percutaneous closure of the left atrial appendage using a specialized suture delivery system; both have been approved by the FDA as alternative therapies for stroke prevention in selected patients with non-valvular atrial fibrillation.

21.7.3 Ventricular Arrhythmias

Ventricular arrhythmias, including isolated ventricular premature depolarizations, couplets, and runs of non-sustained ventricular tachycardia, increase in prevalence with age. Management of ventricular arrhythmias focuses on symptom severity and the risk of sudden cardiac death. In the absence of disturbing symptoms or very high frequency, ventricular premature depolarizations do not require treatment in the majority of patients. Non-sustained and sustained ventricular tachycardia (VT) in older adults are usually associated with structural heart disease, and treatment is predicated on the severity of symptoms and the underlying heart condition. In most cases, short runs of non-sustained VT do not require specific therapy. Patients with symptomatic sustained VT should be referred to an electrophysiologist for further evaluation and management. Patients with reduced LV ejection fraction (≤35 %) are at risk for sudden cardiac death, whether or not ventricular arrhythmias are manifest, and should be considered for an ICD (see above).

Table 21.8 Triple therapy for use in individuals on chronic oral anticoagulants (OAC)

Trial[a] z(sample size)	Intervention vs control	Outcomes	Age	Bleeding risk	Precautions/ geriatric considerations (per Lexicomp®)
WOEST [65] *N*=573	OAC+Clopidogrel (75 mg for 5 days, 300 mg 24 h or Loading dose of 600 mg before PCI +75 mg daily)+Aspirin (80–100 mg daily) (Triple) Versus OAC+Clopidogrel (Double)	Bleeding episode: • 44.4 % in Triple group versus 19.4 % in Double group ($p<0.001$) Composite secondary endpoint of death, myocardial infarction, stroke, target-vessel revascularization, and stent thrombosis: • 17.6 % in Triple group versus 11.1 % in Double group ($p<0.025$)	Mean=70.3 (±7)	See outcomes	Bleeding risk is very high compared to double therapy
ISAR-TRIPLE [144] *N*=614	OAC+Aspirin+Clopidogrel 75 mg for 6 weeks Versus OAC+Aspirin+Clopidogrel 75 mg for 6 months	Composite of death, myocardial infarction (MI), definite stent thrombosis, stroke, or TIMI major bleeding at 9 months: • 9.8 % in 6-week group versus 8.8 % in 6-month group • HR 1.14 ($p=0.63$) • Consistent across age	Mean=73.9 (±7.7) In 6-week group	TIMI Major Bleeding at 9 months: • 5.3 % in 6-week group versus 5 % in 6-month group • HR 1.35 ($p=0.44$)	6-week therapy not superior to 6-month therapy

OAC oral anticoagulant, *HR* hazard ratio
ISAR-TRIPLE Triple therapy in patients on oral anticoagulation after drug eluting stent implantation
[a]Trial acronyms: *WOEST* What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing

21.8 Cardiac Rehabilitation and Exercise

Regular physical activity, including structured cardiac rehabilitation, provides substantial benefits for older adults through multiple mechanisms [146, 147]. Physical activity improves physical strength and function, cardiovascular indices, social and psychological factors, and cognitive function. Despite these benefits, older adults are less likely to be active and tend towards a sedentary life due to reduced motivation, social barriers, and physical limitations. Older adults are also less likely to initiate and maintain participation in cardiac rehabilitation, even when recommended by their physicians [148]. Reasons for this are multifactorial and relate to both patients and providers. Compared to younger adults, referral rates to cardiac rehabilitation are lower following a qualifying event. There is also poor communication to and understanding by patients and their families of the benefits of cardiac rehabilitation. In addition, there may be significant social, financial, and psychological barriers to participation, including transportation issues, costs, and fears about ability to exercise.

Physical activity beneficial to cardiovascular health can also be achieved outside of the structure of a cardiac rehabilitation program, and indeed for many diagnoses (e.g., HFpEF, AF), formal cardiac rehabilitation is not covered by Medicare [149]. Individuals who remain physically active have a lower incidence of CVD as well as lower rates of frailty, disability, and cognitive decline. Currently, there are numerous activity programs, some of which may be covered by Medicare Advantage plans that specifically focus on older adults. Importantly, exercise programs for older adults must be able to accommodate and adapt to multimorbidity and physical limitations; nonetheless, the value of exercise even in the very elderly is substantial. Good communication between providers, physical therapists, patients, families, and trainers increases the feasibility and safety of exercise for older adults at any age and regardless of functional status (see also Chap. 17).

21.9 Advanced Care Planning and End-of Life

CVD is the leading cause of major morbidity and mortality in older adults and in the advanced stages often results in disabling symptoms that greatly diminish quality of life. Whereas evidence-based care often focuses on the primary goal of increasing longevity, symptom severity, complexity of care, and multimorbidity can undermine the perceived value of prolonging life. In addition, aggressive therapies expose patients to increasing risk of harm. For some elderly patients, living as long as possible may be the primary health care goal, but for others, achieving an acceptable quality of life, maintaining independence, avoiding hospitalization, or dying at home may be more important. Since these preferences are highly personal, conversations regarding goals of care and healthcare choices need to occur prior to life-threatening events [150].

The prognosis for an older adult with advanced heart failure is similar to that of advanced lung cancer; however, this information is infrequently communicated to patients and families. Even when eligible for advanced treatment options (DT-LVAD or rarely heart transplantation), the associated morbidity and mortality rates are high. This obliges providers to discuss patient preferences, short- and long-term goals, and views on life-prolonging therapies.

Palliative care and hospice services improve symptoms, patient and family quality of life, and in some cases may even prolong life [151]. In one non-randomized study of individuals with end-stage heart failure, those that received hospice care survived 81 days longer on average than those not in hospice programs. Patients enrolled in home hospice programs are far more likely to die in their own homes in alignment with their expressed wishes. In addition, there are fewer hospital admissions and doctor visits, as well as reduced overall expenditures. For some older adults, palliative care and hospice provide an acceptable patient-centered alternative to standard disease-focused care. For further information on palliative and end-of-life care, see Chap. 6.

21.10 Summary

Aging is associated with substantial changes in cardiovascular structure and function, as well as alterations in other organ systems that significantly impact the incidence, clinical features, response to therapy, and prognosis of virtually all cardiovascular disorders. In addition, the increasing prevalence of geriatric-specific conditions, including multimorbidity, polypharmacy, frailty, and physical and cognitive impairments, greatly increases the complexity of managing older adults with CVD. Although additional research is needed, optimal care of older adults with CVD requires an individualized multidisciplinary approach that is patient-centered rather than disease-centered, and which incorporates patient preferences and goals of care into the decision-making process.

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