Cardiovascular Disease in Older Adults

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LEARNING OBJECTIVES

1. Design a pharmacotherapy regimen for older adult patients with risk factors for cardiovascular disease such as hypertension, hyperlipidemia, and diabetes.
2. Evaluate the risk-benefit of antiplatelet therapy for primary and secondary prevention of cardiovascular events in older adults.
3. Assess for the severity of valvular heart disease and the risks of medication therapy in older adult patients.
4. Develop a pharmacotherapy regimen for older adult patients with atrial fibrillation.

ABBREVIATIONS IN THIS CHAPTER

ACS	Acute coronary syndrome
AF	Atrial fibrillation
AS	Aortic stenosis
ASCVD	Atherosclerotic cardiovascular disease
CAD	Coronary artery disease
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
DPP4	Dipeptidyl peptidase-4
DES	Drug-eluting stent
DHP CCB	Dihydropyridine calcium channel blocker
DOAC	Direct oral anticoagulant
GLP-1	Glucagon-like peptide-1
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
HTN	Hypertension
ICH	Intracranial hemorrhage
ISH	Isolated systolic hypertension
OAC	Oral anticoagulant
PCI	Percutaneous coronary intervention
SBP	Systolic blood pressure
SGLT2	Sodium-glucose cotransporter-2
TAVR	Transcatheter aortic valve replacement
TIA	Transient ischemic attack
VKA	Vitamin K antagonist

Table of other common abbreviations.

INTRODUCTION

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality in adults. Age is a strong risk factor related to the development of hypertension (HTN), hyperlipidemia, diabetes, and coronary artery disease (CAD) as well as mortality once patients develop established CVD. Although many well-conducted studies have evaluated the risk-benefit of pharmacotherapy in adults with CVD, these studies either excluded older patients altogether or enrolled few older adults. As the global population ages, evidence-based strategies to manage CVD must be developed in older adults. This review describes and evaluates the available pharmacotherapy options for primary and secondary prevention of CVD in older adults, with careful attention given to the risk-benefit of drug therapy in this ever-growing patient population.

Pharmacokinetic and Pharmacodynamic Changes in Older Adults

Several age-associated changes in pharmacokinetics and pharmacodynamics affect pharmacotherapy for older adults (Hubbard 2013). Age-related increases in the body fat/water ratio and decreases in plasma protein alter drug distribution: fat-soluble drugs have an increased volume of distribution (and potentially diminished effectiveness), whereas highly protein-bound drugs may have a greater free (active) concentration. Such changes in distribution may be exacerbated by conditions that increase body water such as chronic kidney disease (CKD), heart failure (HF), and ascites. Decreases in liver mass, blood flow, and the activity of certain drug-metabolizing enzymes decrease the clearance of many drugs; therefore, drug doses may need to be reduced. Smoking, alcohol, caffeine, and concomitant medications may also affect drug metabolism. The age-related reduction in glomerular filtration rate (GFR) in older adults slows the elimination of many drugs and may require

reduced drug doses, which is exacerbated in the presence of acute or chronic kidney disease (AGS 2019; Hubbard 2013). Reduced renal function is common in older adults, and drugs cleared renally should be dose adjusted according to the CrCl or estimated GFR (eGFR). Intrinsic changes associated with aging in cardiac pacemaker cells and conduction systems make older adults more susceptible to drug-induced cardiac conduction disorders, including prolonged QT intervals, bradycardia, tachyarrhythmias, and torsades de pointes. These changes may not alter drug effectiveness; however, medications that are prone to cause bradycardia or prolong the QTc interval should be monitored more closely.

Assessment of Frailty

Frailty is a common clinical syndrome in the older adult population. Frailty increases a person's risk of poor clinical health outcomes, including falls, hospitalizations, and mortality (Xue 2011). Assessing frailty in older adults helps when considering drug therapy for older adults. In patients with known CAD, myocardial infarction (MI) would be considered a stressor event; thus, patients who are frail may be at greater risk of adverse outcomes than fit older individuals. Given these data, identifying patients with frailty is essential in managing acute coronary syndrome (ACS) in these patients. Many models, tools, and questionnaires for frailty have been developed that can be used for assessing older adults; however, each has its respective strengths and limitations (Rockwood 2005; Fried 2001).

The phenotype and cumulative deficit models are the two best-established international frailty models (Rockwood

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BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:
- General knowledge of the physiologic and pharmacologic changes in older adults with CVD
- General drug knowledge of the risk-benefit of medication use in older adults
- General knowledge of the pathophysiology of CVD in older adults
- General drug knowledge of the medications pertinent within primary and secondary prevention of CVD

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:
- American Diabetes Association (ADA). Standards of medical care in diabetes 2019. Diabetes Care 2019;42(suppl 1):S1-S193.

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2005; Fried 2001). Although both models have been extensively validated, they are less practical for use in clinical practice. The phenotype model identifies frailty on the basis of five physical characteristics: unintentional weight loss of 4.5 kg (10 lb) within the past year, exhaustion, low energy expenditure, slow walking speed, and reduced grip strength. Individuals with no characteristics are identified as fit, those with one or two characteristics are identified as pre-frail, and those with three or more characteristics are identified as frail. The cumulative deficit model identifies frailty on the basis of a range of deficits, which can be clinical signs, symptoms, diseases, and disabilities. A frailty index score is calculated as a proportion of the number of deficits present to the total possible in the model. Although the cumulative deficit model is very flexible, at least 30 deficits are required for a model to be valid, limiting the usefulness of this model in clinical practice.

The FRAIL scale is a simple, validated questionnaire that combines the Fried and Rockwood concepts of frailty and can be given over the telephone or to patients in a waiting room. One point is given for each of the following, and individuals who have 3 or more points are considered frail: **f**atigue, **r**esistance (inability to climb 1 flight of stairs), **a**mbulation, (inability to walk 1 block), **i**llnesses (having more than 5), and **l**oss of more than 5% of body weight.

Frailty tools and questionnaires have also been developed and validated for use in clinical practice. Although these tools and questionnaires are readily available, their use may only be appropriate in certain health care settings. For example, performance-based tools such as walking speed or the Timed Up and Go test can determine the presence or absence of frailty. However, the guidelines caution against using these tools in acutely ill hospitalized patients because acute illness can temporarily affect performance.

Deprescribing

Older adults commonly take several medications and supplements, making them vulnerable for drug-drug and drug-food interactions (AGS 2019). Deprescribing of medications can simplify a patient's overall medication regimen while reducing the risk of harm from polypharmacy. Deprescribing is defined as a systematic process of identifying and discontinuing drugs when existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences (Scott 2015). The deprescribing protocol involves five simple steps: (1) ascertain a reason for all medications currently prescribed, (2) consider the overall risk of drug-induced harm associated with the required intensity of the deprescribing intervention, (3) assess each drug for its eligibility to be discontinued, (4) prioritize drugs for discontinuation, and (5) implement and monitor the drug discontinuation regimen (Figure 1). Older adults with CVD may benefit from the deprescribing of medications such
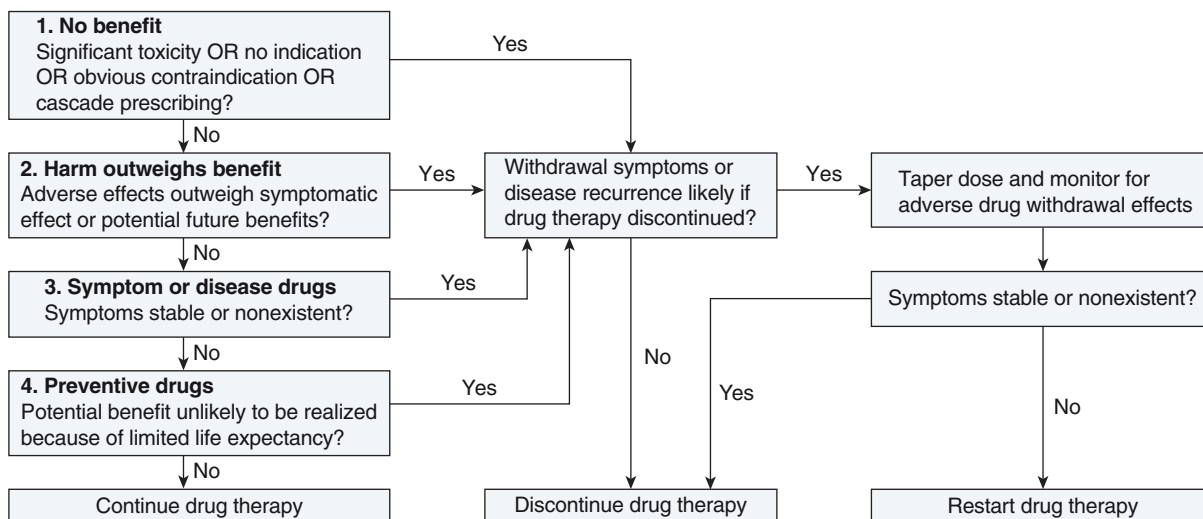
Figure 1. Algorithm for deciding order and mode in which drug use could be deprescribed.

Reprinted with permission from Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy. The process of deprescribing. JAMA Intern Med 2015;175:827-34.

as antiplatelet agents, NSAIDs, anticoagulants, and antihypertensive medications, given that these medications are commonly associated with adverse effects, and cardiovascular (CV) benefit versus adverse event risk must be evaluated.

Updated BEERS Criteria

Deprescribing may be assisted by applying the recently updated American Geriatrics Society (AGS) Beers Criteria for Potential Inappropriate Medication Use in Older Adults (AGS 2019). The AGS Beers Criteria document is a useful resource for clinicians to improve medication selection, educate clinicians and patients, and reduce adverse drug events; it also serves as a tool for evaluating quality of care, cost, and patterns of drug use in older adults. The goal continues to be improving the care of older adults by reducing their exposure to potentially inappropriate medications that have an unfavorable balance of benefits and harms compared with alternative treatment options. However, these criteria are not meant to be applied in a punitive manner because medication therapy decisions in older adults are not always clear-cut, and clinicians must consider several patient-specific factors when considering initiating or discontinuing medications no longer indicated. Table 1 highlights pertinent CV medications together with drug-specific recommendations included in the 2019 AGS Beers Criteria.

Pharmacotherapy Considerations for Older Adults

Hypertension

Approaches to pharmacotherapy targeted for HTN in older adults have evolved over the past decade as they pertain to drug selection and preferred blood pressure targets. One key factor in evaluating HTN in older adults is determining whether individuals have isolated systolic hypertension (ISH), which is common in older adults and drives treatment decisions toward certain antihypertensive medication classes. Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) increase through the sixth decade of life, followed by a decrease in DBP and an increase in SBP. As a result, older adults often have a large pulse pressure secondary to the increase in SBP and decrease in DBP, which has been associated with a higher CV mortality risk in some analyses. The updated 2017 American College of Cardiology/American Heart Association (ACC/AHA) guidelines continue to advocate treatment decisions driven by compelling indications for specific classes of antihypertensive medications and comorbidities (Whelton 2018). Thiazide and thiazide-like diuretics are one of the two preferred antihypertensive medication choices in older adults, especially if ISH is present. In the SHEP trial, chlorthalidone, a thiazide-like diuretic, lowered the risk of the primary outcome of stroke by 36%, CAD by 25%, and overall CV events by 32% compared with placebo in older adults (60 and older) (SHEP 1991). In the HYVET trial, indapamide, a thiazide-like diuretic, lowered the risk of the primary outcome of stroke by 30%, CV mortality by 23%, and all-cause mortality by 21% compared with placebo in older adults (80 and older) (Beckett 2008). Dihydropyridine calcium channel blockers (DHP CCBs) are also first-line antihypertensive medication choices in ISH and are preferred to thiazide diuretics at times to minimize the risk of electrolyte abnormalities and urinary frequency issues with thiazide diuretics. Nitrendipine, a DHP CCB, showed efficacy in the Sys-Eur and Sys-China trials at lowering the risk of stroke by 42% and 30% (primary outcome), respectively, compared with

Table 1. Summary of the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Medications That Are Potentially Inappropriate in Most Older Adults

Medications/Medication Classes	Rationale	Recommendation	Quality of Evidence	Strength of Recommendation
Dipyridamole – Oral, short acting	May cause orthostatic hypotension; more effective alternatives available; IV form acceptable for use in cardiac stress testing	Avoid	Moderate	Strong
Peripheral α₁-adrenergic antagonists for treatment of HTN	High risk of orthostatic hypotension and associated harms, especially in older adults; not recommended as routine treatment for HTN; alternative agents have superior risk-benefit profile	Avoid use as an antihypertensive	Moderate	Strong
Central α-adrenergic-agonists Clonidine for first-line treatment of HTN Other CNS α-adrenergic agonists Guanabenz Guanfacine Methyldopa Reserpine (> 0.1 mg/day)	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for HTN	Avoid as first-line antihypertensive Avoid other CNS α-agonists as listed	Low Low	Strong Strong
Disopyramide	May induce HF in older adults because of potent negative inotropic action; strongly anticholinergic; other antiarrhythmic drugs preferred	Avoid	Low	Strong
Dronedarone	Worse outcomes have been reported in patients taking dronedarone who have permanent AF or severe or recently decompensated HF	Avoid in individuals with permanent AF or severe or recently decompensated HF	High	Strong
Digoxin for first-line treatment of AF or HF	Use in AF: Should not be used as a first-line agent HF: Evidence for benefits and harms of digoxin is conflicting. Higher dosages are not associated with additional benefit and may increase risk of toxicity Renal function: Decreased renal clearance of digoxin may lead to increased risk of toxic effect	Avoid this rate-control agent as first-line therapy for AF Avoid as first-line therapy for HF If used: Avoid dosages > 0.125 mg/day	AF: Low HF: Low Dosage: Moderate	AF: Strong HF: Strong Dosage: Strong
Immediate-release nifedipine	Potential for hypotension; risk of precipitating myocardial ischemia	Avoid	High	Strong
Amiodarone	Effective for maintaining sinus rhythm but has greater toxicities than other antiarrhythmics May be reasonable first-line therapy in patients with concomitant HF or substantial left ventricular hypertrophy if rhythm control is preferred to rate control	Avoid as first-line therapy for AF unless patient has HF or substantial left ventricular hypertrophy	High	Strong

Table 1. Summary of the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (*continued*)

Potentially Inappropriate Medications: Drugs to Be Used with Caution in Older Adults

Drug(s)	Recommendation	Rationale	Quality of Evidence	Strength of Evidence
Aspirin: Primary prevention of CVD	Use with caution in adults ≥ 70	Risk of major bleeding from aspirin increases markedly in older age. Several studies suggest lack of net benefit when used for primary prevention in older adults with CV risk factors, but evidence is not conclusive	Moderate	Strong
Dabigatran Rivaroxaban	Use with caution for treatment of VTE or AF in adults ≥ 75	Increased risk of GI bleeding compared with warfarin and reported rates with other DOACs when used for long-term treatment of VTE or AF in adults ≥ 75	Moderate	Strong
Prasugrel	Use with caution in adults ≥ 75	Increased risk of bleeding in older adults	Moderate	Weak

Potentially Inappropriate Medications in Older Adults Because of Drug-Disease or Drug-Syndrome Interactions That May Exacerbate the Disease or Syndrome

Drugs	Disease	Recommendation	Rationale	Quality of Evidence	Strength of Recommendation
Cilostazol	HF	Avoid in HF	Potential to increase mortality in older adults with HF	Low	Strong
Diltiazem/verapamil	HF	Avoid in HFrEF	Potential to promote fluid retention and/or exacerbate HF	Moderate	Strong
NSAIDs COX-2 inhibitors	HF, Stage 4 CKD or higher (CrCl < 30 mL/min)	Use with caution in patients with HF who are asymptomatic; avoid in patients with symptomatic HF / Avoid	Potential to promote fluid retention and/or exacerbate HF / May increase risk of acute kidney injury and further decline of renal function	NSAIDs: Moderate COX-2: Low NSAIDs and COX-2: Moderate	NSAIDs: Strong COX-2: Strong NSAIDs and COX-2: Strong
Pioglitazone Rosiglitazone	HF	Use with caution in patients with HF who are asymptomatic; avoid in patients with symptomatic HF	Potential to promote fluid retention and/or exacerbate HF	High	Strong
Dronedarone	HF	Avoid in HF	Potential to increase mortality in older adults with HF	High	Strong
Peripheral, nonselective α_1-adrenergic antagonists	Syncope, Urinary incontinence	Avoid in orthostatic hypotension; may result in syncope / Avoid	Cause orthostatic BP changes / Aggravation of incontinence	High / Moderate	Weak / Strong
Aspirin > 325 mg/day Non–COX-2 inhibitors	History of gastric or duodenal ulcers	Avoid unless other alternatives are not effective and patient can take gastroprotective agent (i.e., proton pump inhibitor)	May exacerbate existing ulcers or cause new/ additional ulcers	Moderate	Strong

(Continued)

Table 1. Summary of the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (*continued*)

Potentially Clinically Important Drug-Drug Interactions That Should Be Avoided in Older Adults

Object Drug	Interacting Drug	Risk Rationale	Recommendation	Quality of Evidence	Strength of Evidence
RAS inhibitor (ACEI/ARB) Amiloride Triamterene	Another RAS inhibitor	Increased risk of hyperkalemia	Avoid routine use	Moderate	Strong
ACEIs	Lithium	Increased risk of lithium toxicity	Avoid: Monitor lithium concentrations	Moderate	Strong
Loop diuretics	Lithium	Increased risk of lithium toxicity	Avoid: Monitor lithium concentrations	Moderate	Strong
Warfarin	Amiodarone	Increased risk of bleeding	Avoid, when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	Ciprofloxacin	Increased risk of bleeding	Avoid, when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	Macrolides (excluding azithromycin)	Increased risk of bleeding	Avoid, when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	Trimethoprim/ sulfamethoxazole	Increased risk of bleeding	Avoid, when possible; if used together, monitor INR closely	Moderate	Strong
Warfarin	NSAIDs	Increased risk of bleeding	Avoid, when possible; if used together, monitor closely for bleeding	High	Strong

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BP = blood pressure; CKD = chronic kidney disease; COX = cyclooxygenase; CV = cardiovascular; CVD = cardiovascular disease; DOAC = direct oral anticoagulant; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; IV = intravenous; RAS = renin-angiotensin system; VTE = venous thromboembolism.

Information from: 2019 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2019;67:674-94.

placebo in older adults (60 and older) (Liu 1998; Staessen 1997). Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have shown benefit as add-on therapy to either thiazide-like diuretics or CCBs in ISH clinical trials (Bavishi 2016). In addition, data support ACEI/ARB use in older adults if there is a compelling indication (e.g., MI). β-Blockers should only be used in older adult patients with HTN if a compelling indication exists (e.g., heart failure with reduced ejection fraction [HFrEF]) because β-blockers are less beneficial at lowering CV events in younger and older adult patients with essential HTN (Wiysonge 2017). This is based on a proven inferior CV risk reduction with atenolol compared with losartan in the LIFE-ISH trial (Kjeldsen 2002). Furthermore, the ACC/AHA guidelines highlight that atenolol is no better than placebo at reducing CV mortality and should no longer be used to treat essential HTN in patients at any age (Whelton 2018). In patients with resistant HTN, the strongest evidence supports the role for mineralocorticoid receptor antagonists as the fourth antihypertensive add-on therapy to first-line therapies (Whelton 2018).

The ACC/AHA HTN guidelines for preventing, detecting, evaluating, and managing HTN in adults have a class 1 recommendation for an SBP treatment goal of less than 130 mm Hg for noninstitutionalized ambulatory community-dwelling adults 65 and older with an average SBP of at least 130 mm Hg (Whelton 2018). Furthermore, these guidelines recommend that, in those 65 and older, comorbidities, life expectancy, clinical judgment, patient preference, and risk-benefit be considered when determining the intensity of blood pressure lowering and the choice of antihypertensive treatment (Whelton 2018). The SPRINT trial findings were a main driver for these lower blood pressure treatment targets advocated in the 2017 ACC/AHA HTN guidelines in all populations, including older adults (SPRINT Research Group 2015). The SPRINT trial showed the benefit of treating to an SBP target of less than 120 mm Hg (intensive treatment arm) compared with less than 140 mm Hg (standard treatment arm) in patients at least 50 years of age, with 28% of the study including patients 75 and older. In the analysis of those 75 and older (mean 80 years), the composite CV primary outcome occurred in 2.59% of the intensive treatment arm compared with 3.85% of the standard treatment arm, showing a statistically significant difference (HR 0.66; 95% CI, 0.51–0.85; p=0.001) (Williamson 2016). The findings from the overall SPRINT study and the subanalysis in those 75 and older lend support in treating patients to lower blood pressure targets, which national guidelines have previously advocated. One key note is that the mean SBP in the intensive treatment arm of 123.4 mm Hg led to the guideline recommendations to target less than 130 mm Hg compared with less than 120 mm Hg. In addition, blood pressure in SPRINT was measured by repeated automated blood pressure readings with ideal blood pressure steps (e.g., resting for 5 minutes, back supported, feet uncrossed), which produces a 5- to 10-mm Hg lower blood pressure than in typical clinical practice. Data are limited for evidence-based blood pressure targets in those 85 and older. In summary, the most current data and the U.S. guidelines support an SBP target of less than 130 mm Hg for most patients 65 and older.

Safety of antihypertensive medications in older adults is an important consideration. The most recent evaluation of the safety of antihypertensive medication use in older adults is with the SPRINT subanalysis previously discussed. In the SPRINT subanalysis, there was no statistically significant difference in the absolute rate of serious adverse effects with a 2.4% rate in the intensive arm and a 1.4% rate in the standard arm (HR 1.71; 95% CI, 0.97–3.09). In addition, no statistically significant differences in the incidence of syncope, electrolyte abnormalities, and acute kidney injury or renal failure were noted in the study arms. Furthermore, no statistical difference in orthostatic hypotension occurred in the intensive versus standard blood pressure arms of the study, respectively (1.9% vs. 1.3%; HR 1.44; 95% CI, 0.77–2.73). The intensive study arm had a nonsignificant lower rate of falls than the standard treatment group (4.9% vs. 5.5%, respectively; HR 0.91; 95% CI, 0.65–1.29) (Williamson 2016). Even though the SPRINT trial showed more intensive blood pressure targets not resulting in more serious adverse effects, there is still a need to monitor blood pressure in older adults more closely. Older adults may have a greater potential to develop adverse effects if they have hepatic and/or renal dysfunction, given that they may metabolize antihypertensive drugs more slowly. Further assessment of patients' potential fall risk is necessary because this relates to their potential for orthostatic hypotension, especially when prescribing several antihypertensive medications and when they have ISH with a large pulse pressure.

Hyperlipidemia

Pharmacotherapy for hyperlipidemia management in older adults continues to evolve, and treatment has been substantiated in both primary and secondary prevention of CVD. Statins remain the primary mode of managing hyperlipidemia and are supported by the most evidence for CV event reduction in younger and older adults. A recent meta-analysis by the Cholesterol Treatment Trialists' Collaboration evaluated the efficacy and safety of statin therapy in older adults in 28 randomized controlled trials (CTT Collaboration 2019). The investigators found that statin therapy or more intensive statin therapy regimens in those 75 and older produced a 21% relative risk (RR) reduction (RR 0.79; 95% CI, 0.77–0.81) in major CV events per each 1-mmol/L reduction in LDL (CTT Collaboration 2019). These reductions in CV events persisted in individual coronary events or strokes, but not with CV morality. Of note, those 75 and older in major statin randomized controlled trials accounted for only 8% of patients in the trials. The 2018 ACC/AHA guidelines on managing blood cholesterol advocate statin therapy primarily

in patients age 40–75, given that most patients included in clinical trials were in this age range. Guidelines further advocate at least moderate-intensity statins in those older than 75 with known atherosclerotic cardiovascular disease (ASCVD), and high-intensity statins may be reasonable for these patients after evaluating ASCVD risk, adverse effects, drug-drug interactions, patient frailty, and patient preferences (Grundy 2019).

One common adverse event associated with statin treatment is statin-associated muscle symptoms (SAMS). A meta-analysis of individuals 65 and older compared with those younger than 65 has reported no difference in SAMS (i.e., myopathy, muscle adverse effects, rhabdomyolysis) (Iwere 2015). The previously discussed meta-analysis of patients 75 and older compared with patients younger than 75 is currently evaluating any differences in risk of diabetes, SAMS, and cognitive effects with statin exposure from randomized controlled trials (CTT Collaboration 2019). Dementia or cognitive decline has occurred in meta-analyses of statin trials, irrespective of patient age. The rate of cognitive symptoms increases with age, so this should be a key area to monitor in older adult patients, and statins should be avoided in patients with already established dementia or cognitive decline. Of note, one contributing factor to the presumed higher risk of adverse effects in older adults is the potential for these patients to be taking more medications, increasing the likelihood of drug-drug interactions that can result in adverse effects.

PCSK9 inhibitors are the most recent FDA-approved class of medications proving CV event lowering in patients with established CVD already receiving maximum statin therapy. Both the FOURIER and the ODYSSEY OUTCOMES trials have shown that evolocumab and alirocumab can further reduce the risk of future CV events in patients with established CVD already receiving statin therapy (Schwartz 2018; Sabatine 2017). The mean patient ages in FOURIER and ODYSSEY OUTCOMES were 62.5 plus or minus 9.1 and 59.5 plus or minus 9.3 years, respectively, showing that many of the patients enrolled in these trials were 65 and older. Neither study has evaluated the 65 and older population separately from the overall study population. According to limited data analyses, PCSK9 inhibitors should be used with caution in patients 65 and older until more data analyses are available to assess their efficacy and safety in this population. PCSK9 inhibitors have shown no difference in any adverse event compared with placebo in the landmark trials FOURIER and ODYSSEY OUTCOMES.

The REDUCE-IT trial is the first evaluation of omega-3 fatty acid to show a lower CV event rate when icosapent ethyl is added to the regimens of patients with hypertriglyceridemia and known clinical ASCVD or diabetes mellitus with CV risk factors receiving statin therapy compared with statin therapy alone (Bhatt 2019). Forty-six percent of patients in the REDUCE-IT trial were 65 and older. The primary end point showed a lower rate of composite CV events with icosapent ethyl (17.2%) than with placebo (22.0%) (p<0.001). No significant difference occurred in adverse effects or serious adverse effectss in the REDUCE-IT trial when icosapent ethyl was compared with placebo in a population with almost 50% of patients older than 65.

The IMPROVE-IT trial evaluated ezetimibe as add-on therapy to statin therapy in the post-ACS population. Enrollees (mean patient age 63.6 ± 9.8) were randomized to statin therapy or statin plus ezetimibe therapy after an ACS event. The primary outcome had a significant 2.0% absolute lower risk of a major event (32.7% simvastatin plus ezetimibe vs. 34.7% simvastatin, p=0.016) over the 7-year study (Cannon 2015). In the subgroup analysis of patients 75 and older in IMPROVE-IT, the absolute risk reduction with the addition of ezetimibe to simvastatin was not associated with a significant increase in safety issues among older patients (Bach 2019). Ezetimibe when added to statin therapy had no significant adverse effects compared with statin monotherapy in the IMPROVE-IT trial and had a similar 10% discontinuation rate in both study arms.

The cost-effectiveness of hyperlipidemia medications in older adults should be considered as it relates to primary versus secondary CV prevention. In addition, the presence of several comorbidities, life expectancy, drug-drug interactions, and overall medication tolerance must be factored in. The 2018 ACC/AHA guidelines for managing blood cholesterol support statin therapy as cost-effective in those with established ASCVD who are 40–75 years of age. The cost-effectiveness for those older than 75 for secondary prevention remains strongly supported as long as the patient's life expectancy is more than 5 years (Grundy 2019). No specific analyses evaluating the cost-effectiveness of hyperlipidemia treatment in older adults have been conducted by the Institute for Clinical and Economic Review. Furthermore, when considering the cost of using nonstatin therapy, ezetimibe is the next most cost-effective option for patients maximized on statin therapy in the secondary prevention population (Grundy 2019). Finally, given current costs, PCSK9 inhibitors should be reserved for older adult patients maximized on a statin plus ezetimibe needing further lipid-lowering therapy in the secondary prevention with more than a 5-year life expectancy.

Diabetes Mellitus

The American Diabetes Association (ADA) specifically develops recommendations for managing diabetes in older adults in its "Standards of Medical Care in Diabetes," which is now updated in real time throughout the year and contains specific recommendations for glycemic control in the older adult population (ADA 2019). One key factor in determining the best approach to managing diabetes and specifically glycemic control in older adults is determining their A1C target. This could be as strict as the traditional less than 7% target, or it

could be less than 7.5% for a patient with a few comorbidities or even less than 8.5% for patients with very complex/poor health (long-term care facility or end-stage chronic illnesses or moderate to severe cognitive impairment or two or more activities of daily living dependencies). The main therapies that will be discussed for use in older adults with diabetes include metformin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, and dipeptidyl peptidase-4 (DPP4) inhibitors. Metformin remains the mainstay first-line therapy for all patients with type 2 diabetes without contraindications. Major contraindications that can arise are drug allergy to metformin or stage 4 or greater CKD, where the risk of metformin outweighs the benefit. The ADA has specific recommendations not to start or discontinue metformin therapy in patients with an eGFR less than 30 mL/minute/1.73 m^2. If individuals have an eGFR of 30−45 mL/minute/1.73 m^2, they should not be initiated on metformin and, if already taking metformin, should not receive more than 1000 mg/day.

The SGLT2 inhibitors are the newest class of antihyperglycemic medications on the U.S. market. There are four FDA-approved medications in this class, with two now having shown benefit in further lowering CV risk in patients with diabetes and established CVD or with several CV risk factors. According to clinical trial data from the EMPA-REG (empagliflozin), CANVAS (canagliflozin), and DECLARE-TIMI 58 (dapagliflozin), SGLT2 inhibitors are recommended in both younger and older adult patients as the next treatment option after metformin in patients with established CVD and/or a history of HF or CKD (Wiviott 2019; Neal 2017; Zinman 2015). The mean patient ages were 63.1, 63.3, and 63.9 years for the EMPA-REG, CANVAS, and DECLARE-TIMI 58 trials, respectively, indicating benefit in older adults, given that almost 50% of patients were older than 65. None of these trials showed a statistical difference between those 65 and older and those younger than 65 in subgroup analyses. The DAPA-HF trial evaluated patients with HFrEF with and without diabetes and the mean age of patients in the trial was 66 years-old (McMurray 2019). Dapagliflozin demonstrated a significant 4.9% absolute reduction in the combined endpoint of worsening HF or CV death in patients with HFrEF. Therefore these agents may be utilized in the treatment of chronic conditions regardless of DM-status in the near future.

Glucagon-like peptide-1 agonists, like SGLT2 inhibitors, have had glycemic and CV event-lowering benefit in younger and older adult patients in the LEADER (liraglutide), SUSTAIN (semaglutide), and REWIND (dulaglutide) trials (Gerstein 2019; Marso 2016a, 2016b) and are preferred in patients with a history of ASCVD. The mean patient ages in these trials were 64.3 and 64.6 years for the LEADER and SUSTAIN trials, respectively. The DPP4 inhibitors have not had the same CV event lowering in the younger or older adult population as the SGLT2 inhibitors and GLP-1 agonists, but they have shown

CV safety. Overall, DPP4 inhibitors are well tolerated and safe as add-on therapy to metformin, but they generally do not reduce A1C more than 1%. As discussed earlier, the key factors when determining best approaches to initiating therapy beyond metformin in older adults with diabetes include determining the presence of ASCVD, renal function, how far from A1C goal, and complexity of the regimen.

The adverse effect profile for the core group of medication classes discussed, including metformin, SGLT2 inhibitors, GLP-1 agonists, and DPP4 inhibitors, is consistent across adult and older adult populations. As mentioned previously, the key factor in determining metformin safety in older adults is ensuring that patients have an eGFR of at least 30 mL/minute/1.73 m^2 for continued use and an eGFR of at least 45 mL/minute/1.73 m^2 for initiation to reduce the risk of lactic acidosis. The main adverse effects related to SGLT2 inhibitors in both younger and older adults included the potential for overdiuresis and dehydration, leading to a potential for hypotension and acute kidney injury. Additional adverse effects include weight loss, euglycemic diabetic ketoacidosis, amputation risk (canagliflozin), and risk of genital mycotic and UTIs. Some of these adverse effects could benefit patients needing better blood pressure control or weight loss. The ADA recommends SGLT2 inhibitors or GLP-1 agonists as second-line agents after metformin for patients with established ASCVD and prefers SGLT2 inhibitors in patients with CKD or HF. Individuals with prior genital infections or UTIs should be screened to determine whether SGLT2 inhibitors are the best option.

The common adverse effects of GLP-1 agonists include the risk of hypoglycemia (primarily with concurrent sulfonylurea, meglitinides, and/or insulin use), weight loss, and GI symptoms (e.g., diarrhea, nausea, vomiting). One consideration with GLP-1 agonists in older adults is determining the patient's ability to inject himself or herself with the medication. Finally, DPP4 inhibitors are well tolerated in both adult and older adult patients and have minimal major adverse effects in all ages. Overall, data are limited to support higher rates of adverse effects with these core medication classes in older adults.

The cost-effectiveness of diabetes medication use in older adults should be considered because it relates to glycemic control, safety, and long-term outcomes. Better glycemic control lowers the risk of microvascular complications, which is established in both the adult and the older adult populations (ADA 2019). More recent data analyses support SGLT2 inhibitors and GLP-1 agonists to further lower the risk of macrovascular (e.g., CV) complications, especially in those with established ASCVD. The future risk of both micro- and macrovascular complications needs to be factored in the cost-effectiveness analyses. No specific analyses of the cost-effectiveness of antihyperglycemic treatment in older adults have been performed by the Institute for Clinical and Economic Review.

ANTIPLATELET THERAPY IN OLDER ADULT PATIENTS

Aspirin for Primary Prevention

In 2016, the U.S. Preventive Services Task Force advocated initiating aspirin on the basis of age and a 10-year CVD risk of at least 10%, as defined by available risk estimators. However, recently published studies have questioned aspirin's role in the primary prevention of CV events in a variety of patient populations, including older adults (Table 2).

The Japanese Primary Prevention Program was a multicenter, randomized, open-label, parallel-group clinical trial conducted at outpatient centers throughout Japan (Ikeda 2014). The primary end point was a composite of death from CV causes, nonfatal stroke, and nonfatal MI. Serious extracranial hemorrhage requiring transfusions or hospitalization was a key secondary safety end point, with a key interest in GI events. A preplanned review at the first annual examination showed that the incidence of primary outcome events was much lower than originally estimated, and subsequent interim analyses led to terminating the trial early for futility, given the lack of a primary end point benefit. Patients in the

aspirin group had more safety events such as serious extracranial hemorrhage requiring hospitalization or transfusion (0.86% vs. 0.51%), GI hemorrhage (1.41% vs. 0.42%), GI ulcer (2.61% vs. 1.24%), or erosive gastritis (1.22% vs. 0.55%).

The ASCEND trial enrolled participants with diabetes but without known ASCVD. Much like the Japanese Primary Prevention Program, the primary end point required modification because of a lower-than-expected event rate. The primary end point, defined as a composite of nonfatal MI, nonfatal stroke or transient ischemic attack (TIA), or death from any vascular cause, was significantly reduced by 12%. The primary safety outcome of first occurrence of any major bleeding event was increased by 29% (4.1% in the aspirin group vs. 3.2% in the placebo group; rate ratio 1.29; 95% CI, 1.09–1.52, p=0.003). No differences in all-cause mortality were observed (ASCEND Study Collaborative Group 2018).

The ARRIVE trial enrolled patients with as estimated moderate risk of a first CV event, defined as a 20%–30% risk of CVD within 10 years (Gaziano 2018). The primary end point was a composite outcome of time to first occurrence of CV death, MI, stroke, unstable angina, or TIA. In the intention-to-treat analysis, there was no significant difference in the primary

Table 2. Key Studies of Aspirin for Primary Prevention of CVD

Study	Comparisons	Patients	Mean Age (SD)	Diabetes n (%)	Median Follow-Up (yr)	Primary End Point Efficacy	Primary Safety End Point
Japanese Primary Prevention Program	Aspirin 100 mg daily vs. placebo Follow-up: 6.5 yr	14,464	70.6 (6.2)	4903 (34)	6.5	Aspirin: 2.77% vs. placebo 2.96% HR 0.94; 95% CI, 0.77–1.15, p=0.54	Extracranial hemorrhage requiring transfusion or hospitalization Aspirin 0.86% vs. placebo 0.51%; HR 1.85; 95% CI, 1.22–2.81; p=0.004
ASCEND	Aspirin 100 mg daily vs. placebo	15,480	63 (9.2)	15,480 (100)	7.4	Aspirin 8.5% vs. placebo 9.6%, rate ratio: 0.88, 95% CI, 0.79–0.97, p=0.01	Major bleeding: Aspirin 4.1% vs. placebo 3.2%, rate ratio 1.29; 95% CI, 1.09–1.52; p=0.003
ARRIVE	Aspirin 100 mg daily vs. placebo	12,546	64 (7.1)	0 (0)	5	Aspirin 4.29% vs. placebo 4.48% HR 0.96, 95% CI, 0.81–1.13, p=0.60	GI bleeding: Aspirin 0.97% vs. placebo 0.46%; HR 2.11; 95% CI, 1.36–3.28; p=0.007
ASPREE	Aspirin 100 mg daily vs. placebo	19,114	74 (not reported)	2057 (11)	5	Aspirin 21.5 events per 1000 person-yr vs. placebo 21.2 events per 1000 person-yr HR 1.01; 95% CI, 0.92–1.11, p=0.79	Major hemorrhage Aspirin 3.8% vs. placebo 2.8% HR 1.38; 95% CI, 1.18–1.62; p<0.001

end point, but when each component of the primary composite end point was evaluated separately, MI was slightly reduced in the aspirin group (0.98% vs. 1.84%) in the per protocol analysis (HR 0.53; 0.36–0.79; p=0.0014). There was no effect on mortality, but in the safety analysis, GI bleeding events were about 2 times higher in the aspirin group.

The ASPREE trial enrolled participants 70 and older who were free of CVD, dementia, and disability at trial entry (McNeil 2018a, 2018b, 2018c). Aspirin conferred no benefit with respect to the prespecified composite primary end point of death, dementia, or persistent physical disability, an issue of considerable importance in older adults (McNeil 2018a). The aspirin group had no CV benefit, whereas major bleeding was higher with aspirin use. The rate of the secondary end point of death from any cause was higher with aspirin (HR 1.14; 95% CI, 1.01–1.29) (McNeil 2018b,c). This finding is at odds with the results of previous primary prevention trials of aspirin, including the ASCEND and ARRIVE trials.

Given these data, it is not surprising that the recently released ACC/AHA primary prevention of CVD guidelines recommend against routine aspirin use for primary prevention of ASCVD in adults older than 70, with a strongly worded class of recommendation (class III: harm), together with level of evidence category B. Low-dose aspirin (defined as 75–100 mg daily) may be considered in patients age 45–70 who are at a high risk of ASCVD without a high bleeding risk (Arnett 2019).

Although these data certainly call into question aspirin's benefit for primary prevention of CVD, important questions remain before a definitive verdict can be given. Optimal dosing of aspirin has recently become a subject of debate (Rothwell 2018; Capodanno 2011). Of note, a pharmacodynamic study of patients with diabetes and CAD questioned the efficacy of fixed low doses of aspirin for primary prevention in patients of different body weight categories. With minimum and maximum body weights of 43 kg and 177 kg in patients in the ARRIVE trial, whether the same neutral results would be replicated by tailoring the aspirin dose on the basis of body weight is currently not known. Of importance, adherence in all of these trials declined throughout, to the point that around 30% of patients originally assigned to receive aspirin discontinued treatment, whereas in the placebo groups, almost 10% of patients in the placebo groups received aspirin therapy. This crossover of treatment groups may also have contributed to the lack of benefit. The Japanese Primary Prevention Program and the ARRIVE trials may have been underpowered to detect differences in the primary efficacy end points. Enteric-coated aspirin was used in many of these trials, which could have reduced aspirin's overall effectiveness, given the varying absorption and antiplatelet effect of enteric-coated aspirin versus nonmodified formulations of aspirin. Finally, these trials did not assess the safety of discontinuing aspirin in patients who have received aspirin for many years; thus, concerns of rebound thrombotic events after aspirin discontinuation cannot be ruled out.

Secondary Prevention: ACS

Dual Antiplatelet Therapy Post-ACS

Adults 75 and older are a heterogeneous group because of their comorbidities and differences in cognition and functional status. A rapidly increasing subgroup of patients with ACS, adults 75 and older are estimated to represent one-third of all ACS episodes, with non–ST-segment-elevation ACS as the most common presentation (Jaguszewski 2015). However, neither the European Society of Cardiology nor the AHA/ACC ACS guidelines provide specific pharmacotherapy recommendations for older adults (Roffi 2015; Amsterdam 2014).

Choice of Antiplatelet Therapy in Older Adults

The current ACC/AHA and European Society of Cardiology guidelines recommend the more potent $P2Y_{12}$ inhibitors prasugrel and ticagrelor over clopidogrel in patients presenting with ACS; however, the risk-benefit ratio in older adults is less clear, given that many of the patients enrolled in randomized trials were younger than 75 (Levine 2016). Recently published substudies provide important context on using prasugrel and ticagrelor in older adults.

A prespecified analysis of the PLATO trial investigated the effect and treatment-related complications of ticagrelor versus clopidogrel in older adults (75 and older) with ACS compared with those younger than 75 (Husted 2012). Of the original 18,622 patients enrolled, 2878 (15.5%) were 75 and older. The primary composite outcome of CV death, MI, or stroke occurred in 17.2% of older adults receiving ticagrelor and 18.3% of patients receiving clopidogrel (HR 0.89; 95% CI, 0.74–1.08). The clinical benefit of ticagrelor over clopidogrel did not differ between patients 75 and older and those younger than 75 (interaction p=0.56). Secondary end points of MI (interaction p=0.33), CV death (interaction p=0.47), stroke (interaction p=0.17), definite stent thrombosis (interaction p=0.81), and all-cause mortality (interaction p=0.76) were also no different. Ticagrelor was more effective than clopidogrel in reducing all-cause mortality over the full age range of the study (interaction p=0.99). An analysis of 12-month composite event rates showed that ticagrelor was more effective than clopidogrel regardless of age (interaction p=0.82).

The PLATO-defined overall major bleeding was similar between patients receiving ticagrelor and patients receiving clopidogrel and was not significantly different between age subgroups (14.2% for ticagrelor-treated patients vs. 13.5% for clopidogrel-treated patients; HR 1.02; 95% CI, 0.82–1.27; interaction p=0.89). Dyspnea rates were higher in older adults than in younger patients in both treatment groups, and the risk of dyspnea was higher with ticagrelor than with clopidogrel, with no evidence of an age-treatment interaction (18.% in ticagrelor-treated patients vs. 12.2% in clopidogrel-treated patients; HR 1.63; 95% CI, 1.33–1.90; interaction p=0.21). Therefore, age alone should not inhibit ticagrelor use in older adults.

The TRITON TIMI 38 trial compared prasugrel 10 mg daily with clopidogrel in patients with ACS with planned percutaneous coronary intervention (PCI) (Wiviott 2007). There was no net clinical benefit with prasugrel 10 mg daily over clopidogrel in older adults because of the higher risk of non–coronary artery bypass grafting–related bleeding with prasugrel, which led the current guidelines and the 2019 AGS Beers Criteria to recommend caution with using prasugrel 10 mg daily in older adults (75 and older) with ACS.

A population pharmacokinetic substudy from TRITON TIMI 38 found that older adults were exposed to higher levels of prasugrel active metabolite at the 10-mg dose, likely leading to higher bleeding risk. This study suggested that a reduced prasugrel dose lowers the risk of bleeding while maintaining efficacy. The pharmacodynamic and pharmacokinetic response of prasugrel 5 mg was formally evaluated in the GENERATIONS trial, which showed that prasugrel 5 mg in patients 75 and older was noninferior to prasugrel 10 mg in patients age 45–65 for the outcome of platelet inhibition (Erlinge 2013).

The Elderly ACS-2 trial studied whether prasugrel 5 mg daily was superior to standard-dose clopidogrel in older adults (75 and older) with ACS undergoing PCI (Savonitto 2018). However, following a median follow-up of 12 months, the trial was terminated because of futility for efficacy after 1443 patients (of the planned 2000 patients) were enrolled. The trial showed no difference in the primary end point of mortality, MI, disabling stroke, and rehospitalization for CV causes or bleeding (HR 1.01; 95% CI, 0.78–1.30; p=0.955); however, bleeding events were higher with prasugrel than with clopidogrel (4.1% vs. 2.7%; OR 1.52; 95% CI, 0.85–3.16; p=0.18). Therefore, according to current data, prasugrel should not be used in older adults (75 or older).

Duration of Dual Antiplatelet Therapy in Older Adults

The optimal duration of dual antiplatelet therapy (DAPT) remains unknown. In patients with ACS who undergo PCI with implantation of a drug-eluting stent (DES), the current guidelines recommend at least 1 year of DAPT, with the subsequent decision to either continue or discontinue DAPT made on the basis of individual patient risks of recurrent thrombotic events and major bleeding. In addition to patient-specific risk factors, procedural complications such as edge dissections, stent malapposition, poor stent expansion, delayed or absent endothelialization, stent strut fractures, DES polymer hypersensitivity, and new atherosclerosis within the stent should be considered. Older adults with any of these procedural complications are at increased risk of stent thrombosis and would benefit from extended DAPT similar to younger patients, given that procedural complications create risks of stent thrombosis regardless of age (Kirtane 2011).

Recently, two risk scores were developed to identify the risk-benefit of DAPT duration for individual patients: the DAPT score and the PRECISE-DAPT score. The PRECISEDAPT score was developed to predict the risk of bleeding in individual patients with CAD and coronary stenting treated with subsequent DAPT (i.e., aspirin plus a P2Y12 receptor inhibitor). The score requires input of patient characteristics such as Hgb, WBC, age, CrCl, and history of bleeding. A web-based calculator uses these variables to calculate a total score. Patients with scores of over 25 total points are recommended to have shorter DAPT durations (3–6 months compared with 12 months) (Costa 2017). The DAPT score (Table 3) was derived from the DAPT study, which evaluated a DAPT duration of 12 compared with 30 months, and was subsequently validated in the PROTECT trial (Yeh 2016; Mauri 2014). The DAPT score is unique because it is bidirectional, identifying patients at higher risk of recurrent thrombotic events than bleeding events (defined as a DAPT score of 2 or greater), whereas patients with a DAPT score of less than 2 are at higher risk of bleeding events than any potential thrombotic benefit. Both risk calculators include age and therefore may be used to determine the length of DAPT in older adults with ACS undergoing PCI with DES implantation, though the DAPT score is easier to calculate manually and does not require a web-based calculator.

Table 3. DAPT Score

Variable	Points
Patient Characteristics	
Age:	
≥ 75	−2
65–74	−1
≤ 64	0
Diabetes	1
Current cigarette smoker	1
Prior PCI or prior MI	1
CHF or LVEF < 30%	2
Index Procedure Characteristic	
MI at presentation	1
Vein graft PCI	2
Stent diameter < 3 mm	1
TOTAL SCORE	**−2 to 9 points**

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Information from: Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016; 315:1735-49.

Patient Care Scenario

L.S. is a 73-year-old woman (weight 56 kg) who presents to the ED with worsening back pain and chest tightness. Her medical history is notable for CAD with previous MI 5 years ago, hyperlipidemia, type 2 diabetes, smoking, and chronic low back pain. Her current blood pressure is 108/65 mm Hg and heart rate is 72 beats/minute. Initial ECG reveals ST-segment depressions in leads V_2–V_4, and initial cardiac enzymes reveal a troponin T of 0.19 ng/mL.

The following morning, L.S. is taken for cardiac catheterization, where she is noted to have 90% stenosis in her proximal left anterior descending (LAD) artery, together with 40% stenosis in her mid-left circumflex artery. Drug-eluting stents are placed in her LAD and left circumflex arteries. How long would you recommend dual antiplatelet therapy?

ANSWER

For this patient, factors affecting thrombosis and bleeding must be evaluated. Factors associated with increased bleeding risk include age and reduced body weight, whereas thrombotic risk factors include previous MI, smoking, type 2 diabetes, placement of two DESs in important coronary territories, and MI on presentation. The patient's DAPT score is 2; therefore prolonged DAPT beyond 12 months would be appropriate for her.

1. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735-49.

Secondary Prevention of Stroke in Older Adults

Antiplatelet Therapy

Antiplatelet therapy remains an option for preventing primary stroke in patients with significant risk factors in the absence of risk of major bleeding. In secondary prevention, the optimal agent or medication regimen is unclear. One recent study, the POINT trial, attempted to provide clarity (Johnston 2018).

The POINT trial enrolled 4881 patients (mean age 65) within 12 hours of an acute ischemic stroke with an NIH Stroke Scale score of less than 3, or high-risk TIA defined as an ABCD score of 4 or greater. Patients received either DAPT with clopidogrel 600 mg as a loading dose on day 1 followed by 75 mg daily in combination with aspirin (dosed 50−325 mg daily at the discretion of the individual investigators) or aspirin alone. The trial was terminated after 84% of the anticipated number of patients had been enrolled because prespecified safety and efficacy stopping boundaries had been crossed.

The composite primary efficacy outcome of ischemic stroke, MI, or death from vascular causes occurred in 5.0% of patients receiving DAPT compared with 6.5% of patients receiving aspirin alone (HR 0.75; 95% CI, 0.59−0.95; p=0.02), with a significant reduction in ischemic stroke driving the entire end point (4.6% vs. 6.3%; HR 0.72; 95% CI, 0.56−0.92; p=0.01). The primary safety end point of major hemorrhage occurred in 0.9% in the DAPT group compared with 0.4% in the aspirin-alone group (HR 2.32; 95% CI, 1.10−4.87; p=0.02). Minor hemorrhage was also higher in the DAPT group, but no differences occurred in hemorrhagic strokes (five patients in the combination group vs. three patients).

In a secondary analysis of the treatment effect according to time, the benefit of DAPT was greater in the first 7 and 30 days compared with the full 90 days of therapy (p=0.04 for days 0−7 and p=0.02 for days 0−30). The risk of hemorrhage with DAPT was greater from day 8 to day 90 than during the first 7 days (p=0.04 for days 8−90 and p=0.34 for days 0−7), suggesting that DAPT duration can be shortened to 30 days to reduce bleeding risk while maximizing the early benefits of DAPT.

VALVULAR HEART DISEASE IN OLDER ADULTS

Aortic Stenosis

The most common form of valvular heart disease in older adult patients is aortic stenosis (AS) (Eveborn 2013). One major reason for addressing AS is that it is a common cause of sudden cardiac death. Overall, the prevalence of AS is low in the non−older adult population but has been reported to be as high as 12.4% in those 75 or older (Eveborn 2013; Osnabrugge 2013). Most patients are asymptomatic for many years until AS develops to a moderate or severe form. Specific focus on the older adult population is warranted because many patients have decreased levels of activity, delaying the presentation of symptoms until the disease has progressed and is severe. Age is a major risk factor for AS, but congenital heart disease, history of heart infections, CKD, history of radiation to chest area, and traditional CV risk factors (e.g., diabetes, hyperlipidemia, HTN) all contribute to the development of AS.

Common symptoms of AS include chest pain, lightheadedness or dizziness, shortness of breath, fatigue associated with activity, and heart palpitations. These symptoms help predict survival in those without a surgical intervention. Average survival of patients is 5−6 years if they develop angina, 3 years if they develop syncope, and about 2 years if they develop HF symptoms from the time of presentation without surgery (Lester 1998). Often, in older adults, these symptoms may be absent until the patient has developed

moderate to severe AS. Once patients have developed symptoms and have severe AS, their survival rate is as low as 50% at 2 years and 20% at 5 years without aortic valve replacement (Ramaraj 2008). Because of the low survival rate of AS when untreated, surgical aortic valve replacement is the gold standard therapy for symptomatic severe AS.

Because HTN is one of the risk factors for developing AS, it is important to evaluate the best approaches for managing HTN in older adult patients who develop AS. In the past, antihypertensive treatment was thought to be a relative contraindication in severe AS, but newer studies have shown that treating blood pressure in patients with severe AS can reduce the progression of left ventricular pressure overload. There are no current guidelines for recommending antihypertensive treatment in AS. In general, however, β-blockers are avoided because of concerns for inducing left ventricular dysfunction. The theory behind potential benefits with renin-angiotensin system (RAS) blockade is related to the up-regulation of RAS in patients with AS, resulting in valve calcification (Marquis-Gravel 2016). Six studies evaluating the role of ACEIs in treating patients with AS and HTN have been conducted (Kang 2018). Despite their small size, these studies have shown the benefit of treating patients with AS who have concurrent HTN with ACEIs, making ACEIs the preferred agents. Nitrates in patients with moderate or severe AS are considered contraindicated, especially during acute presentation of symptoms, because these patients are at a higher risk of developing hypotension (Claveau 2015). Hydralazine can help improve cardiac output in mild or moderate AS but is generally avoided in severe AS.

Many patients with AS have concurrent HF, and management of both disease states needs to be reviewed. Heart failure is present in up to 25% of patients with AS (Kamperidis 2016). Similar to patients with HFrEF without AS, diuretics should be used as needed to reduce volume overload or to maintain euvolemia. Loop diuretic dosing is the same in patients with AS as in those without AS and should be driven by patient response to therapy. Both ACEIs and β-blockers are first line for patients with AS and HFrEF. Caution should be taken with β-blockers, especially in patients with acute decompensated HF. Treatment of HF should continue presurgery to repair the AS as well as postsurgery, depending on the symptoms and left ventricular function postsurgical repair.

Transcatheter Aortic Valve Replacement
In patients who may be at high risk of surgery, transcatheter aortic valve replacement (TAVR) has become a standard and established procedure. After the findings from the SURTAVI trial, the TAVR procedure is now recommended in the 2017 ACC/AHA guidelines for patients with valvular heart disease (Nishimura 2017). These new recommendations are made because TAVR can cause a 50% lower mortality rate than in medically treated patients and has results similar to surgical aortic valve replacement in both high- and intermediate-risk patients with severe AS.

Pharmacotherapy considerations for valve thrombosis with antiplatelet monotherapy (aspirin), DAPT, and oral anticoagulant (OAC) therapy should be reviewed, given the increased use of TAVR. Initial TAVR studies used DAPT with aspirin plus clopidogrel for 6 months post-procedure (Popma 2014; Leon 2010). Since these initial studies, aspirin monotherapy has been evaluated in three small studies, where it showed no difference in ischemic events compared with DAPT (Rodés-Cabau 2017; Stabile 2014; Ussia 2011). After these studies, a meta-analysis comparing aspirin monotherapy and DAPT showed a higher rate of 30-day major or life-threatening bleeding with DAPT than with aspirin monotherapy (OR 2.24; 95% CI, 1.12–4.46), with no difference in 30-day mortality or ischemic events (Maes 2018). Data analyses are limited for using OAC therapy without a concurrent anticoagulation indication. The 2017 ACC/AHA guidelines give a level IIb recommendation for using vitamin K antagonists (VKAs) within the first 3 months post-TAVR in patients without a high risk of bleeding (Nishimura 2017). Furthermore, these guidelines give a level IIb that recommendation for clopidogrel 75 mg daily for the first 6 months after TAVR in addition to lifelong aspirin 75–100 mg daily. Many ongoing studies are evaluating the role of aspirin monotherapy, DAPT, and OAC in combination post-TAVR, which will further explain the best approach from an efficacy and safety standpoint.

ATRIAL FIBRILLATION IN OLDER ADULTS

Assessment of Stroke and Bleeding Risk
In general, most older adults with atrial fibrillation (AF) qualify for OAC therapy, given their age and respective comorbidities such as HTN, coronary heart disease, diabetes mellitus, and HF. In addition to these comorbidities, older adults with AF often have reduced renal function secondary to the loss of renal muscle mass and reduced glomerular and tubular function (Wang 2014; Piccini 2012). Therefore, optimizing OAC therapy is challenging in older adults, especially when trying to balance efficacy and bleeding risk, because the same patients at high risk of stroke also tend to be at high risk of bleeding (Oldgren 2011). Risk factors for developing stroke in AF together with bleeding risks are well described and summarized in Table 4.

Fall Risk Concerns in Older Adults Receiving Anticoagulation
In patients older than 80, physicians cite risk of falling as the primary factor discouraging warfarin use (Hylek 2006). Retrospective analysis of records from older adult patients with AF or atrial flutter who fell (42,913 receiving OAC therapy vs. 334,960 controls) indicated a significantly higher mortality risk in those receiving anticoagulation (6% vs.

Table 4. Risk Factors for Predicting Stroke and Bleeding in AF

Stroke Risk		Bleeding Risk		
CHADS$_2$	CHA$_2$DS$_2$-VASc	HEMORR$_2$HAGES	HAS-BLED	ATRIA
CHF (1 point)	CHF (1 point)	Hepatic or renal disease (1 point)	HTN (1 point)	Age ≥ 75 (2 points)
HTN (1 point)	HTN (1 point)	Ethanol abuse (1 point)	Abnormal hepatic or renal function (1 point)	HTN (1 point)
Age ≥ 75 (1 point)	Age ≥ 75 (2 points)	Malignancy (1 point)	Stroke (1 point)	Renal disease (eGFR < 30 mL/min/1.73 m^2 for dialysis-dependent (3 points)
Diabetes mellitus (1 point)	Diabetes mellitus (1 point)	Older (age > 75) 1 point	Bleeding history or predisposition for bleeding (anemia) (1 point)	Any prior hemorrhagic diagnosis (GI bleeding, ICH) (1 point)
Stroke or TIA (2 points)	Stroke or TIA (2 points)	Reduced Plt/function (1 point)	Labile INR (1 point)	Anemia (1 point) Hgb < 13% for men, Hgb < 12% for women
	Vascular disease: Prior MI, PAD, or aortic plaque (1 point)	Re-bleeding risk (1 point)	Age ≥ 65 (1 point)	
	Age 65–74 (1 point)	HTN (1 point)	Drugs: Aspirin, NSAIDs, antiplatelets (P2Y$_{12}$ inhibitors), alcohol excess (> 8 drinks/week) (1 point)	
	Female sex (1 point)	Anemia (1 point) Hgb < 13% for men, Hgb < 12% for women		
		Genetic: CYP2C9 SNPs (1 point)		
		Excessive falls (1 point)		
		Stroke (1 point)		

ICH = intracranial hemorrhage; PAD = peripheral arterial disease; SNP = single nucleotide polymorphism; TIA = transient ischemic attack.

3.1%; p=0.001). Indeed, preinjury warfarin use increased the odds of intracranial hemorrhage (ICH) by 40% and doubled 30-day mortality among Medicare beneficiaries with head trauma (Collins 2014). However, fall risk has not consistently increased bleeding risk. A prospective study was conducted in 515 patients (mean age 71.2 years) determined to be at high fall risk on the basis of two validated screening questions: (1) did you fall during the past year? If not, (2) did you notice any problem with gait, balance or mobility? Patients were followed for 12 months, and the primary end point was time to first major bleeding episode. A total of 35 patients (6.8%) had major bleeding at 12 months, but bleeding did not differ in patients deemed at high fall risk compared with patients deemed at low fall risk (8.0 vs. 6.8 per 100 patient-years,

p=0.64) (Donze 2012). In addition, evidence from a modeling study suggested that a patient with AF taking OACs would have to fall about 295 times a year before the risk of fall-related subdural hemorrhage would outweigh the benefit of stroke prevention (Man-Son-Hing 1999). Conversations between clinicians and patients and shared decision-making are important in light of these data, which provide another factor to include in the difficult balance of the risk-benefit of OACs in reducing stroke risk in older adults with AF.

Stroke Prevention in Older Adults with AF
Surveys administered to physicians show fear of bleeding as the most common reason for not prescribing OAC therapy in older adults. Despite these concerns, several trials show the

benefits of VKA treatment over placebo in patients with non-valvular atrial fibrillation (NVAF) (Aguilar 2007), and evidence suggests a generally positive balance of stroke to bleeding risk for warfarin in older adults. In 13,559 patients with NVAF (median age 73), patients 85 and older benefited from VKA therapy in an analysis that accounted for both the rate of VKA-associated ICH and the rate of ischemic strokes and systemic emboli. Compared with patients not receiving VKA therapy, patients receiving a VKA had a lower adjusted annual rate of thromboembolism (by 2.86 events per 100 patients), whereas the adjusted annual rate of ICH was 0.35 events per 100 patients higher. Rates for the entire cohort showed a 1.04% decrease in thromboembolism and a 0.24% increase in ICH, suggesting that patients older than 85 had a slightly higher benefit in stroke reduction with a similar rate of ICH (Singer 2009).

More recently, the consensus guidelines have recommended direct oral anticoagulants (DOACs) over warfarin for stroke prevention in AF (January 2019; Lip 2018). Age-based subgroup analyses of each DOAC show that age alone should not exclude patients from receiving DOACs. Rather, subgroup analyses of each major DOAC trial of AF showed that age did not significantly influence the overall results within each trial (Table 5). Apixaban and edoxaban caused less major bleeding in older adults than warfarin, whereas rivaroxaban and dabigatran caused no difference in major bleeding. All DOACs maintained their efficacy in the rate of stroke/systemic embolism.

Given these data, older adults who are candidates for DOACs should receive them preferentially to warfarin. Careful attention to baseline renal function, concomitant medications, and body weight is required for appropriate DOAC dosing in older adults.

Pharmacotherapy for Ventricular Rate Control in Older Adults

Atrial fibrillation is the most common form of cardiac arrhythmia and is associated with a high risk of morbidity and mortality. Therefore, patients should receive rate-controlling medications to prevent the negative consequences of uncontrolled AF (e.g., development of HF). The AFFIRM study showed a nonstatistically significant higher rate of mortality in patients maintained in sinus rhythm, which thus advocates ventricular rate control in patients with AF (AFFIRM 2002). The 2014 ACC/AHA/Heart Rhythm Society guidelines recommend achieving a resting heart rate of 110 beats/minute or less as the initial approach in patients as long as the patient has stable ventricular function and acceptable symptoms (January 2014). If the patient is still symptomatic at this heart rate, a more aggressive heart rate of less than 80 beats/minute can be targeted. The rate-controlling approaches with β-blockers, non-DHP CCBs, and digoxin are similar between the adult and older adult patient populations. A rate-control strategy is the initial approach over a rhythm-control strategy in older adults because of potential for concerns for polypharmacy, multiple comorbidities, and antiarrhythmic therapy drug interactions.

Drug selection between β-blockers, non-DHP CCBs, and digoxin in older adults should be based on comorbidities, concurrent drug therapy and potential drug interactions, renal function, and activity levels. Key areas to highlight are

Table 5. DOAC Safety and Efficacy in Patients Aged 75 Years or Older

Characteristic	RE-LY Dabigatran 150 mg	ROCKET-AF Rivaroxaban 20 mg	ENGAGE-AF TIMI 48 Edoxaban 60 mg	ARISTOTLE Apixaban 5 mg	AVERROES Apixaban 5 mg
n (age > 75)	7258	6229	8474	5678	1898
Comparator	Warfarin Target INR 2–3	Warfarin Target INR 2–3	Warfarin Target INR 2–3	Warfarin Target INR 2–3	Aspirin 81–324 mg once daily
Efficacy: Stroke or SE	Dabigatran 1.43% vs. warfarin 2.14% RR 0.67 (0.49–0.90)	Rivaroxaban 2.29% vs. warfarin 2.85% HR 0.80 (0.63–1.02)	Edoxaban 1.91% vs. warfarin 2.31% HR 0.83 (0.66–1.04)	Apixaban 1.56% vs. warfarin 2.19% HR 0.71 (0.53–0.95)	Apixaban 2.0% vs. aspirin 6.1% HR 0.33 (0.20–0.54)
Safety: Major bleeding	Dabigatran 5.10% vs. warfarin 4.37% RR 1.18 (0.98–1.42)	Rivaroxaban 4.86% vs. warfarin 4.40% HR 1.11 (0.92–1.34)	Edoxaban 4.01% vs. warfarin 4.83% HR not reported	Apixaban 3.33% vs. warfarin 5.19% HR 0.64 (0.52–0.79)	Apixaban 2.6% vs. aspirin 2.2% HR 1.21 (0.69–2.12)
ICH	Dabigatran 0.41% vs. warfarin 1.0% RR 0.42 (0.25–0.70)	Rivaroxaban 0.66% vs. warfarin 0.73% HR 0.80 (0.50–1.28)	Not reported	Apixaban 0.43% vs. warfarin 1.29% HR 0.34 (0.20–0.57)	Apixaban 0.6% vs. aspirin 0.7% HR 0.84 (0.28–2.41)

SE = systemic embolism.

that patients with comorbid HFrEF should avoid non-DHP CCBs because of the negative inotropic effect of non-DHP CCBs. In addition, the drug interactions with non-DHP CCBs and DOACs should be evaluated for patients receiving anticoagulation for AF. Renal function is a major factor when determining whether digoxin can safely be administered or whether it should be dose reduced or avoided altogether. Routine assessment for digoxin appropriateness should include digoxin concentrations (target range 0.5–2 ng/mL) as well as renal function to ensure the correct dose is being administered. The most common rate-controlling agents used are β-blockers in older adults with AF, which is consistent with the general adult population with AF.

Maintenance of Sinus Rhythm

The approach to AF to maintain sinus rhythm is commonly called a rhythm-control strategy. This strategy includes a combination of approaches, including cardioversion, antiarrhythmic drugs, and radiofrequency catheter ablation in the setting of appropriate anticoagulation and rate control. Randomized controlled trials comparing rate-control and rhythm-control strategies have not shown rhythm control to be superior to rate control in the general adult or older adult population.

Rate control is often preferred first to rhythm control, especially in older adults (e.g., adverse drug events, drug-drug interactions, drug-disease interactions with comorbidities, extensive monitoring with initiation [dofetilide and sotalol], and continued use [amiodarone]). If patients continue to have persistent symptoms, this is often the initial indicator that a change to rhythm control could improve these symptoms over rate control. Potential options for pharmacologic cardioversion in older adults include flecainide, dofetilide, propafenone, ibutilide, and amiodarone, depending on comorbidities and concurrent drug therapy to ensure avoidance of drug interactions. Dofetilide should not be used if the CrCl is less than 20 mL/minute and dronedarone should be avoided in patients with New York Heart Association class III/IV HF.

The Beers Criteria have identified antiarrhythmic medications to avoid in older adults. These criteria recommend avoiding dronedarone in older adults with permanent AF or recent decompensated HF. Digoxin is not recommended as an alternative agent for rate control in older adults with AF with or without HF, and doses should generally be no greater than 125 mcg/day. Amiodarone should be avoided unless the patient has HF or left ventricular hypertrophy.

CONCLUSION

Older adults represent a significant proportion of the overall population with CVD. Unlike younger patients, older adults are often underrepresented in clinical trials, leaving clinicians without optimal evidence for treating these patients. Pharmacists with a strong appreciation for the unique

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Practice Points

- Older adults with CVD are a heterogeneous patient population.
- Age by itself should not preclude the use of evidence-based pharmacotherapy in older adults, especially in those who are not frail or in those who have high functional status.
- Deprescribing medications in older adults may reduce the risk of adverse drug events.
- Older adults should receive traditional first-line guideline-directed therapy for primary and secondary prevention of CVD, though providers should be aware of changes in renal function, hepatic function, drug-drug interactions, and comorbid conditions.
- Older adults who develop AS should be initiated on and optimized with guideline-directed therapy for comorbid CV risk factors and conditions (e.g., HTN).
- Older adults should continue to be treated with rate-control and OAC therapies for AF before considering rhythm control.

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biologic and disease-oriented processes on the risk-benefit ratio of pharmacotherapy in older adults with CVD knowledge are well positioned to optimize medication therapy in these patients. Understanding the personal and familial preferences and goals of each patient regarding quality of life and longevity is essential, and considering functional status should be part of every therapeutic plan.

REFERENCES

Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database Syst Rev 2007;3:CD006186.

American Diabetes Association (ADA). Standards of Medical Care in Diabetes 2019. Diabetes Care 2019;42:S139-S147.

American Geriatrics Society (AGS) Beers Criteria Update Expert Panel. American Geriatrics Society 2019 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2019;67:674-94.

Amsterdam EA, Wenger NK, Brindis RG, et al. AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:344-426.

Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline for primary prevention of cardiovascular disease. A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation 2019;104:e596-e646.

ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529-39

Bach RG, Cannon CP, Giugliano RP, et al. Effect of simvastatin-ezetimibe compared with simvastatin monotherapy after acute coronary syndrome among patients 75 years or older. JAMA Cardiol 2019 Jul 17. [Epub ahead of print]

Bavishi C, Goel S, Messerli FH. Isolated systolic hypertension: an update after SPRINT. Am J Med. 2016;129:1251-1258.

Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008;358:1887-98.

Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380:11-22.

Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97.

Capodanno D, Patel A, Dharmashankar K, et al. Pharmacodynamic effects of different aspirin dosing regimens in type 2 diabetes mellitus patients with coronary artery disease. Circ Cardiovasc Interv 2011;4:180-7.

Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomized controlled trials. Lancet 2019;393:407-15.

Claveau D, Piha-Gossack A, Friedland SN, et al. Complications associated with nitrate use in patients presenting with acute pulmonary edema and concomitant moderate or severe aortic stenosis. Ann Emerg Med 2015;66:355-62.

Collins CE, Witkowski ER, Flahive JM, et al. Effect of pre-injury warfarin use on outcomes after head trauma in Medicare beneficiaries. Am J Surg 2014;208:544-9.

Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual datasets from clinical trials. Lancet 2017;389:1025-34.

Donze J, Clair C, Hug B, et al. Risk of falls and major bleeds in patients on oral anticoagulation therapy. Am J Med 2012;127:773-8.

Erlinge D, Gurbel PA, James S, et al. Prasugrel 5 mg in the very elderly attenuates platelet inhibition but maintains noninferiority to prasugrel 10 mg in nonelderly patients: the GENERATIONS trial, a pharmacodynamic and pharmacokinetic study in stable coronary artery disease patients. J Am Coll Cardiol 2013;62:577-83.

Eveborn GW, Schimmer H, Heggelund G, et al. The evolving epidemiology of valvular aortic stenosis: the Tronso study. Heart 2013;99:396-400.

Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-M57.

Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce the risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomized, double-blind, placebo-controlled trial. Lancet 2018;392:1036-46.

Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-bind, randomised, placebo-controlled trial. Lancet 2019;394:121-30.

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. Circulation 2019;139:e1082-e1143.

Hubbard RE, O'Mahoney MS, Woodhouse KW. Medication prescribing in frail older people. Eur J Clin Pharmacol 2013;69:319-26.

Husted S, James S, Becker RC, et al. Ticagrelor versus clopidogrel in elderly patients with acute coronary syndromes. A substudy from the prospective randomized platelet inhibition and patient outcomes (PLATO) trial. Circ Cardiovasc Qual Outcomes 2012;5:680-8.

Hylek EM, D'Antonio J, Evans-Molina C, et al. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. Stroke 2006;37:1075-80.

Ikeda Y, Shimada K, Teramoto T, et al. Low-dose aspirin for primary prevention of cardiovascular disease in Japanese patients 60 years or older with atherosclerotic risk factors. JAMA 2014;312:2510-20.

Iwere RB, Hewitt J. Myopathy in older people receiving statin therapy: a systematic review and meta-analysis. Br J Clin Pharmacol 2015;80:363-71.

Jaguszewski M, Ghadri JR, Diekmann J, et al. Acute coronary syndromes in octogenarians referred for invasive evaluation: treatment profile and outcomes. Clin Res Cardiol 2015;104:51-8.

January CT, Wann S, Calkins H, et al. 2019 ACC/AHA/HRS focused update of the 2014 ACC/AHA/HRS guideline for the management of patients with atrial fibrillation. Circulation 2019;140:e125-e151.

Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med 2018;379:215-25.

Kamperidis V, Delgado V, van Mieghem N, et al. Diagnosis and management of aortic valve stenosis in patients with heart failure. Eur J Heart Fail 2016;18:469-81.

Kang TS, Park S. Antihypertensive treatment in severe aortic stenosis. J Cardiovasc Imaging 2018;26:45-53.

Kirtane AJ, Stone GW. How to minimize stent thrombosis. Circulation 2011;124:1283-7.

Kjeldsen SE, Dahlof B, Devereux RB, et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. JAMA 2002;288:1491-8.

Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.

Lester S, Heilbron B, Dodek A, et al. The natural history and rate of progression of aortic stenosis. Chest 1998;113:1109.

Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 ACC/AHA guideline for the management of patients with non–ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. J Am Coll Cardiol 2016;68:1082-115.

Lip GYH, Banerjee A, Boriana G, et al. Antithrombotic therapy for atrial fibrillation. Chest guideline and expert panel report. Chest 2018;154:1121-201.

Liu L, Wang JG, Gong L, et al. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. J Hypertens 1998;16:1823-9.

Maes F, Stabile E, Ussia GP, et al. Meta-analysis comparing single versus dual antiplatelet therapy following transcatheter aortic valve implantation. Am J Cardiol 2018;122:310-5.

Man-Son-Hing M, Nichol G, Lau A, et al. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med 1999;159:677-85.

Marquis-Gravel G, Redfors B, Leon MB, et al. Medical treatment of aortic stenosis. Circulation 2016;134:1766-84.

Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016a;375:1834-44.

Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016b;375:311-22.

Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155-66.

McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019 Sep 19. doi: 10.1056/NEJMoa1911303. [Epub ahead of print]

McNeil JJ, Nelson MR, Woods RL, et al. Effect of aspirin on all-cause mortality in the healthy elderly. N Engl J Med 2018a;379:1519-28.

McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018b;379:1509-18.

McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. N Engl J Med 2018c;379:1499-508.

Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.

Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Circulation 2017;135:e1159-e1195.

Oldgren J, Alings M, Darius H, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. Ann Intern Med 2011;155:660-7.

Osnabrugge RL, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly. Disease prevalence and number candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol 2013;62:1002-12.

Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993–2007. Circ Cardiovasc Qual Outcomes 2012;5:85-93.

Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972-81.

Ramaraj R, Sorrell V. Degenerative aortic stenosis. BMJ 2008;336:550-5.

Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-95.

Rodés-Cabau J, Masson JB, Welsh RC, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve: the arte (aspirin versus aspirin + clopidogrel following transcatheter aortic valve implantation) randomized clinical trial. JACC Cardiovasc Interv 2017;10:1357-65.

Roffi M, Patrono C, Collet JP, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2015;37:267-315.

Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to body-weight and dose: analysis of individual patient data from randomized trials. Lancet 2018;392:387-99.

Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.

Savonitto S, Ferri LA, Piatti L, et al.; on behalf of the Elderly ACS-2 Investigators. Comparison of reduced-dose prasugrel and standard-dose clopidogrel in elderly patients with acute coronary syndromes undergoing early percutaneous revascularization. Circulation 2018;137:2435-45.

Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097-107.

Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy. The process of deprescribing. JAMA Intern Med 2015;175:827-34.

SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA 1991;265:3255-64.

Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med 2009;151:297-305.

SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-16.

Stabile E, Pucciarelli A, Cota L, et al. SAT-TAVI (single antiplatelet therapy for TAVI) study: a pilot randomized study comparing double to single antiplatelet therapy for transcatheter aortic valve implantation. Int J Cardiol 2014;174:624-7.

Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Lancet 1997;350:757-64.

Ussia GP, Scarabelli M, Mulè M, et al. Dual antiplatelet therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. Am J Cardiol 2011;108:1772-6.

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Hypertension 2018;71:e13-e115.

Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs. standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized clinical trial. JAMA 2016;315:2673-82.

Wiviott SD, Braunwald E, McCabe CH, et al. TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.

Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.

Wiysonge CS, Bradley H, Mayosi BM, et al. Beta-blockers for hypertension. Cochrane Database Syst Rev 2017;1:CD002003.

Wang X, Bonventre JV, Parrish AR. The aging kidney: increased susceptibility to nephrotoxicity. Int J Mol Sci 2014;15:15358-76.

Xue QL. The frailty syndrome: definition and natural history. Clin Geriatr Med 2011;27:1-15.

Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735-49.

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

Self-Assessment Questions

1. A 70-year-old man with a medical history of depression and gastroesophageal reflux disease (GERD) is given a diagnosis of hypertension (HTN). Today, his blood pressure is 146/76 mm Hg (142/70 mm Hg when repeated), which is similar to the values measured 3 months ago and his home blood pressure measurements (average is 140/70 mm Hg). He has a BMI of 28.0 kg/m², smokes ½ pack/day of cigarettes, and drinks 2 or 3 alcoholic beverages weekly. He eats a very healthy diet that is low in saturated fat and sodium and rich in fruits and vegetables. He exercises walking on the treadmill two times a week, 30 minutes per session. Which one of the following is best to recommend for this patient's blood pressure control?

   A. Amlodipine
   B. Metoprolol
   C. Losartan
   D. Spironolactone

2. A 76-year-old African American man with a medical history of HTN and diabetes is given a diagnosis of dyslipidemia. Today, his fasting lipid panel is TC 240 mg/dL, HDL 40 mg/dL, LDL 140 mg/dL, and TG 300 mg/dL. His 10-year atherosclerotic cardiovascular disease (ASCVD) risk is 22%. His blood pressure is at goal on olmesartan/hydrochlorothiazide 40/25 mg orally daily. He has seen a dietitian and has successfully implemented healthy lifestyle modifications that have lowered his blood pressure for the past few years. Which one of the following is best to recommend to lower this patient's dyslipidemia risk?

   A. Atorvastatin 20 mg by mouth daily
   B. Lovastatin 20 mg by mouth daily
   C. Ezetimibe 10 mg by mouth daily
   D. Evolocumab 140 mg subcutaneously every 2 weeks

3. A 72-year-old Hispanic man (height 69 inches, weight 80 kg) with a medical history of HTN, dyslipidemia, MI, chronic kidney disease (CKD), and type 2 diabetes presents for a follow-up. Today, his fasting glucose is 135 mg/dL, A1C is 8.0%, and SCr is 1.4 mg/dL. He takes metformin 1000 mg twice daily and insulin glargine 50 units subcutaneously every evening. He has seen a dietitian in the past and has successfully implemented healthy lifestyle modifications to improve his glycemic control. Which one of the following is best to recommend to improve this patient's glycemic control?

   A. Increase insulin glargine to 55 units subcutaneously every evening.
   B. Add regular insulin 5 units subcutaneously once daily before dinner and titrate the dose on the basis of 2-hour postprandial blood glucose values.
   C. Add canagliflozin 100 mg orally once daily.
   D. Add liraglutide 0.6 mg subcutaneously daily.

4. A 70-year-old white woman with a medical history of HTN, severe aortic stenosis (AS), and heart failure with reduced ejection fraction (HFrEF) (ejection fraction [EF] 35%) presents to the clinic for a follow-up on her blood pressure. Today, her blood pressure is 152/80 mm Hg with heart rate 70 beats/minute. Her blood pressure medications include lisinopril 20 mg orally daily and furosemide 40 mg orally daily. Which one of the following is best to recommend to manage this patient's blood pressure?

   A. Carvedilol 3.125 mg by mouth twice daily
   B. Atenolol 25 mg by mouth daily
   C. Amlodipine 5 mg by mouth daily
   D. Spironolactone 25 mg by mouth daily

5. A 78-year-old white man with a medical history of HTN, dyslipidemia, severe AS, and GERD presents for comprehensive medication management. He is now 2 days post-transcatheter aortic valve replacement (TAVR), and the team is determining the best plan to prevent valve thrombosis. According to the most current evidence balancing bleeding risk and future risk of ischemic events, which one of the following is best to recommend for this patient?

   A. Aspirin 81 mg by mouth daily indefinitely
   B. Clopidogrel 75 mg by mouth daily for 12 months and aspirin 81 mg by mouth daily indefinitely
   C. Apixaban 5 mg by mouth twice daily indefinitely
   D. Warfarin 5 mg by mouth daily adjusted to an INR goal of 2–3 indefinitely

6. A 75-year-old African American man with a medical history of HTN, dyslipidemia, HFrEF (EF 35%–40%), and atrial fibrillation (AF) presents for comprehensive medication management because he continues to have lightheadedness and palpitations. He has been treated with a β-blocker for HFrEF and AF for the past few years, but he continues to have bothersome symptoms of AF. His current medications include lisinopril 40 mg daily, metoprolol succinate 200 mg daily, furosemide 20 mg daily, atorvastatin 40 mg daily, and rivaroxaban 20 mg daily. His blood pressure is 130/80 mm Hg with heart rate 70 beats/minute today. According to the Beers Criteria, which one of the following is best to recommend for this patient to maintain sinus rhythm?

   A. Amiodarone
   B. Dronedarone
   C. Propafenone
   D. Sotalol

7. An 80-year-old Hispanic man with a medical history of HTN, dyslipidemia, and gout presents for comprehensive medication management. He was recently given a diagnosis of AF, and his primary care provider wants to initiate metoprolol succinate 25 mg daily. Which one of the following target heart rates is best to recommend as a rate-control strategy for this patient?

   A. Less than 110 beats/minute
   B. Less than 150 beats/minute
   C. Less than 60 beats/minute
   D. Less than 80 beats/minute

8. A 74-year-old woman with a medical history of HTN, type 2 diabetes, and an NSTEMI (non–ST-segment elevation myocardial infarction) (3 years ago) presents for comprehensive medication management. Today, her blood pressure is 140/74 mm Hg (138/70 mm Hg when repeated), which is similar to the value measured 3 months ago. Which one of the following is best SBP goal to recommend for this patient?

   A. Less than 130 mm Hg
   B. Less than 140 mm Hg
   C. Less than 145 mm Hg
   D. Less than 150 mm Hg

9. A 79-year-old white man presents to your clinic for medication management. His medical history is notable for chronic obstructive pulmonary disease (COPD), gout, glaucoma, osteoarthritis, hyperlipidemia, and HTN. The patient used to smoke but quit when his father died suddenly of a heart attack at age 50. His in-office blood pressure is 132/70 mm Hg, and his LDL obtained 6 months ago is 74 mg/dL. Which one of the following is best to recommend regarding aspirin use in this patient?

   A. Aspirin should be recommended because he is at high risk of ASCVD.
   B. The benefits of aspirin outweigh the risk for this patient.
   C. Aspirin should not be recommended according to the ARRIVE trial.
   D. Aspirin should not be recommended according to the ASCEND trial.

10. A 70-year-old African American man presents to the cardiology clinic for the first time. He recently had an episode of chest pain, was taken to the ED, and was discharged after his cardiac enzymes were negative. The patient's medical history is notable for HTN, hyperlipidemia, and type 2 diabetes. He currently smokes 2 packs of cigarettes per day but denies alcohol or illicit drug use. He had a colonoscopy 3 months ago, which was normal. His current cardiac medications include aspirin 81 mg daily, metformin 500 mg twice daily, sitagliptin 100 mg daily, atorvastatin 40 mg daily, amlodipine 10 mg daily, chlorthalidone 12.5 mg daily, and losartan 100 mg daily. In the office today, his blood pressure is 148/92 mm Hg and heart rate is 72 beats/minute. Which one of the following is best to recommend regarding this patient's aspirin use?

   A. Aspirin should be kept because the patient is at high risk of ASCVD and has a low bleeding risk.
   B. Aspirin should be kept because, according to the ARRIVE trial, the patient would likely benefit from daily aspirin.
   C. Aspirin should be discontinued because the patient has a low ASCVD risk.
   D. Aspirin should be discontinued and replaced with clopidogrel.

11. A 76-year-old woman (weight 56 kg) presents to the ED with worsening back pain and chest tightness. Her medical history is notable for coronary artery disease (CAD), hyperlipidemia, type 2 diabetes, and chronic low back pain. Her current blood pressure is 108/65 mm Hg and heart rate is 72 beats/minute. Initial ECG reveals ST-segment depressions in leads V_3–V_5, and initial cardiac enzymes show a troponin T of 0.14 ng/mL. The following morning, the patient is taken for cardiac catheterization, where she is noted to have a 90% stenosis in her proximal left anterior descending (LAD) artery, together with 40% stenosis in her mid-left circumflex artery. Drug-eluting stents (DESs) are placed in her LAD and left circumflex arteries. In addition to aspirin, which one of the following is best to recommend regarding this patient's antiplatelet therapy?

   A. Clopidogrel
   B. Ticagrelor
   C. Prasugrel
   D. Clopidogrel plus vorapaxar

Questions 12 and 13 pertain to the following case.

N.W. is a 70-year-old white woman admitted to the neurology floor after a witnessed TIA lasting 25–30 minutes. She is resting comfortably, but her physical examination is notable for weakness in her left arm. N.W.'s medical history is significant only for HTN. Her blood pressure is 144/82 mm Hg.

12. During rounds, N.W.'s medical team discusses antiplatelet monotherapy therapy versus dual therapy for her. According to current clinical data analyses, which one of the following is best to recommend for N.W.?

   A. Aspirin
   B. Clopidogrel
   C. Aspirin plus ticagrelor
   D. Aspirin plus clopidogrel

13. Regardless of your answer earlier, the medical team places N.W. on DAPT. Which one of the following is best to recommend as N.W.'s therapy duration?

    A. 1 week
    B. 1 month
    C. 3 months
    D. 12 months

14. An 82-year-old woman (weight 51 kg) presents to the ED with tachycardia and shortness of breath and receives a diagnosis of AF. Her medical history is notable for HTN, type 2 diabetes, GERD, CAD, hyperlipidemia, and COPD. Her SCr is 0.6 mg/dL. Which one of the following is best to recommend for this patient's stroke prevention?

    A. Edoxaban
    B. Rivaroxaban
    C. Dabigatran
    D. Warfarin

15. An 83-year-old woman with AF is brought to her cardiologist's office by her daughter, who is concerned about anticoagulation after her mother had a fall last week. The patient's medical history is significant for heart failure (HF) (EF 25%), a TIA 3 years ago, and CAD. Her examination is unremarkable, other than a mild bruise on her left thigh from her recent fall. Her cardiovascular (CV) medications include apixaban, lisinopril, carvedilol, spironolactone, torsemide, and digoxin. Which one of the following is best to recommend regarding apixaban use in this patient?

    A. Discontinue apixaban.
    B. Change to warfarin.
    C. Continue apixaban.
    D. Change to aspirin.