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Cardiac drug therapy—considerations in the elderly

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Abstract

Elderly individuals constitute a majority of patients encountered in current cardiovascular clinical practice. Management of these patients is a clinical challenge owing to a multitude of factors. Although medications such as statins have been shown to reduce cardiovascular mortality in the general population, evidence supporting the use of these drugs in patients greater than 75 years of age is sparse. Furthermore, aging associated changes in organ function and associated comorbidities influence the pharmacokinetics of multiple medications and can potentiate drug toxicity. In this article, we review the evidence behind the use of common cardiovascular medications in elderly patients and discuss pertinent clinical challenges.

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1 Introduction

Never before in the history of mankind has our planet contained such a large percentage of elderly people. In the United States in 1900, elderly who were 65 years and above represented only 4% of the population. In 2000, nearly 13% of population was elderly, and by year 2050 this number is expected to double.[1] This demographic also represents the patient group with the highest burden of cardiovascular disease in addition to other comorbidities. It is estimated that more than half of elderly patients use more than two medications. This polypharmacy results in drug interactions and adverse effects that are often overlooked in clinical practice.[2] Furthermore, elderly people have been excluded from most cardiovascular drug trials. Thus, there is limited randomized trial data on the use of these medications in this age group. Here, we review the evidence and the rationale behind the use of common cardiovascular medications in elderly patients and discuss pertinent clinical challenges.

2 Changes in drug pharmacokinetics in the elderly

Aging leads to progressive impairment in the absorption and excretion of multiple drugs.

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2.1 Absorption

Elderly patients have been shown to have decreased gastric acid secretion and splanchnic blood flow which can lead to decreased absorption of various drugs. However, there is a concomitant decrease in gastrointestinal motility which can increase absorption due to longer transit times. This can be further complicated by the concurrent widespread use of antacids that interfere with drug absorption.[3] These factors make dose and effect prediction very tricky in the elderly. Aging also influences the pharmacokinetics of drug distribution. Elderly patients have been shown to have a lower total body water content. Lipophilic drugs have increased volume of distribution with a prolonged half-life and water-soluble drugs tend to have a smaller distribution volume in the elderly. This leads to increased concentrations of water soluble drugs that can lead to toxicity. In addition, lower serum protein levels in this population lead to increased free (non-protein bound) concentrations of drugs that accentuates drug toxicity for a given dose.[4]

2.2 Metabolism

Hepatic metabolism of drugs can be divided into Phase I metabolism driven primarily by Cytochrome P450 monoxygenase enzymes and Phase II metabolism that involves conjugative reactions. Alterations in these processes can lead to increased half-life that can precipitate drug toxicity. Aging is associated with a decrease in liver mass, hepatic blood flow and metabolic (cytochrome) activity. This leads to decreased hepatic delivery of the drug and reduced phase I metabolism.

As the hepatic first-pass effect could be reduced, the bioavailability of some drugs can be increased in the elderly.[4] Hepatic drug clearance of certain drugs can be reduced by up to 30%. Assessing the magnitude of age-related hepatic dysfunction is extremely challenging and requires careful dose titration and monitoring for adverse effects to minimize side effects.

2.3 Excretion

Most drugs used in clinical practice are excreted through the kidneys. Renal excretion is decreased (up to 50%) in about two thirds of elderly subjects, secondary to age-related decline in glomerular function and the effect of other comorbidities such as hypertension.[5] Aging leads to decreased renal blood flow and reduction in the total number of functioning nephrons. This can potentiate persistence of various drugs and metabolites in the circulation. Dosing based on estimated glomerular filtration rate is extremely critical in preventing adverse effects of drugs with the caveat that commonly used tools may not be accurate. Decrease in muscle mass with aging is associated with reduced serum creatinine levels which can falsely assure of preserved renal function. Clinicians have to be vigilant of this in practice while adjusting medication dosages.

3 Anticoagulant use in elderly

Antiplatelet and anticoagulant drugs are perhaps the most common cardiovascular drugs used in the elderly due to increased burden of atherosclerotic cardiovascular disease and atrial fibrillation (AF) with age. Despite evidence supporting efficacy of these medications, there are a number of important concerns regarding the use of these medications in elderly. Advanced age is associated with platelet dysfunction, decrease coagulation factors synthesis and increase fragility of blood vessels.[6] Furthermore, the presence of concomitant physical and medical issues increases the risk of mechanical and non-mechanical falls and ultimately the risk for major bleeding. Clinical decision making is the selection of elderly patients for anticoagulation is challenging as aging is also associated with a simultaneous increase in thrombosis and bleeding risks, as measured by routinely used risk predictor tools such as $CHADS_2VaSC$ and HAS-BLED. This makes the clinician taking care of elderly patients a vital tool in providing the best possible care. Here, we review some clinical decision points pertinent to the selection of direct acting oral anticoagulants (DOACs) in the elderly patient (Table 1).

DOACs have been approved for the treatment of non-valvular AF and venous thromboembolic disease. DOACs have fewer drug and food interactions, quick onset, and ease of use that require no routine monitoring compared to vitamin K antagonists and have gained popularity among all age groups. Currently, four DOACs namely dabigatran, rivaroxaban, apixaban and edoxoban have been approved in the United States. The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial showed that dabigatran was as effective as warfarin in stroke prevention in non-valvular AF across all age groups. However, in a subgroup analysis of patients > 75 years, dabigatran was associated with a significantly increased risk of major bleeding compared to warfarin (dabigatran 150 mg *vs.* warfarin; HR 1.18; dabigatran 110 mg *vs.* warfarin; HR = 1.01).[7] In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition

Table 1. Anticoagulants in elderly.

Drugs	Effect of aging	Clinical use implications
Aspirin	Increased risk of bleeding	Lower doses are recommended (81 mg po daily)
$P2Y_{12}$ receptor blockers	Increased risk of bleeding.	Prasugrel should be avoided in patients ≥ 75 years and with history of TIA or Stroke, because of the increased risk of fatal and intracranial bleeding.
Unfractionated heparin	Patients > 60 years of age may have higher serum levels and clinical response (longer aPTTs) as compared to younger patients receiving similar dosages.	Lower dosages may be required for older patients.
Low molecular weight heparin	Increase risk of bleeding, injection-associated bleeding and serious adverse reactions in the elderly. Renal impairment increase risk of bleeding.	Dosage alteration and adjustment are required for elderly patients. Avoid use in severe renal impairment. In ≥ 75 years of age with STEMI avoid intravenous bolus
Warfarin	Increase risk of serious bleeding secondary to age related changes in metabolism and polypharmacy with possible drug to drug interaction.	Close monitoring is required.
DOAC	Renal impairment can increase risk of bleeding in elderly	More convenient to use. Close monitoring of renal function is required.

DOAC: direct acting oral anticoagulants; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischemic attack.

Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial comparing rivaroxaban to warfarin, there were fewer intracranial bleeds in elderly patients on rivaroxaban.[8] However, rate of gastrointestinal bleeding was higher in the patients > 75 years (4.9% *vs.* 4.4%) compared to those on warfarin. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial showed that apixaban was superior to warfarin in reduction of stroke and non-inferior in reduction of venous thromboembolism in elderly patients.[9] In addition, apixaban has been shown to be superior to warfarin in reduction of major and intracranial bleeds in the elderly. This makes apixaban an attractive choice for use in the elderly. However, in practice use of apixaban is limited by renal dysfunction with a contraindication in patients with creatinine clearance less than 30 mL/min. The Edoxaban versus warfarin in patients with atrial fibrillation (ENGAGE AF-TIMI 48) trial demonstrated that edoxaban 30 mg once a day was non-inferior to warfarin in prevention of stroke in non-valvular AF patient across all age groups.[10] Further, at a dose of 30 mg, edoxaban was superior to warfarin in reducing the risk of gastrointestinal bleeding and all-cause mortality across all age group, including the elderly. A meta-analysis of trials of all DOACs for stroke prevention showed a better efficacy and safety profile of DOACs over warfarin even in the subgroup of patients greater than 75 years.[11] In another meta-analysis of ten randomized trials evaluating approximately 25,000 elderly patients (> 75 years), there was no increase in clinically relevant bleeding with use of DOACs compared to warfarin with equal efficacy.[12]

Overall, the existing data indicates that there is reason to favor DOACs over warfarin in most elderly patients. Trial data show that apixaban is an optimal DOAC choice in the elderly if there are no contraindications. However, optimal balance of bleeding and thromboembolic risk is quintessential with the use of these medications in the elderly. This risk ratio appears to be dynamic and changes temporally. Thus, clinicians have to be vigilant of the relative risk of thrombosis and bleeding at various times of follow up to tailor therapy accordingly.

4 Antiarrhythmic drug use in elderly

The prevalence of cardiac arrhythmias, including atrial fibrillation, ventricular arrhythmia, and sudden cardiac death increases with age. There are multiple age related changes responsible for this trend. These include degenerative changes and fibrous infiltration of cardiac tissue and conduction system. Furthermore, aging is associated with electrophysiological changes in cardiac ion channels that lead to cardiac arrhythmias. For a number of reasons, the elderly are at increased risk to the side effects of antiarrhythmic medications (Table 2). Aging associated changes in the rate of absorption, distribution, metabolism and elimination of antiarrhythmic drugs probably contribute to this risk.[13] In contrast to the younger patient, rhythm control choices in the elderly are very limited. Class Ic agents such as flecainide and propafenone cannot be used frequently in the elderly based on the results of the Cardiac Arrhythmia Suppression trial which demonstrated an increased risk of pro-arrhythmia with the use of class Ic agents in patients with structural heart disease.[14] The frequent occurrence of concomitant atherosclerotic vascular disease, left ventricular hypertrophy and myocardial dysfunction in the elderly make them poor candidates for therapy with these agents. Sotalol is primarily excreted by the kidneys and has restricted use in the elderly due to poor renal clearance. Amiodarone with its extensive side effect profile appears to the only available "safe" anti-arrhythmic choice in the elderly patient with AF.[15] However, use of amiodarone in the elderly imposes a huge clinical challenge. Amiodarone is a potent inhibitor to a number of drug metabolizing enzymes and drug transporters, including CYP3A4, CYP2C9, and P-glycoprotein. In addition, the expected hepatic, thyroid and pulmonary side effects of amiodarone are much more pronounced in the elderly population. Very close monitoring of renal and

Table 2. Anti-arrhythmic agents in the elderly.

Drug	Effect of Aging	Clinical use implication
Class I	Class I antiarrhythmic drugs can precipitate heart block or sinus bradycardia in the elderly. Pro-arrhythmic effect is more common in elderly due to increase prevalence of ischemic heart disease. Disopyramide has anticholinergic properties and is known to worsen symptoms of prostatism.	Use with caution
Class II	Symptomatic bradycardia is more common	Avoid concomitant use of other AV blockers.
Class III	Adverse effects are more common	A lower maintenance dose of 100 mg/d Amiodarone is commonly used for the elderly
Class IV	Bradycardia and severe constipation are more common in the elderly	Treat constipation aggressively. Avoid concomitant use of other AV blockers.

AV: atrioventricular nodal blockers.

liver function is crucial when prescribe these drugs to avoid serious adverse effects.

5 Statins used in the elderly

Although clinical trials of statin and other cholesterol lowering agents have shown benefits for both primary and secondary prevention in patient with hyperlipidemia and coronary artery disease, most of these trials have excluded elderly patients. So, the true effect of these medications in this age group is not well established. It has been shown that total cholesterol levels increase with age in men from puberty to the age of fifty followed by a plateau phase and then a reduction.[16] In females, the level of cholesterol is slightly higher than male before the age of 25, and they are equal to men at ages of 55–60 s and slightly exceed those in males after age of 65. HDL-cholesterol levels do not change much with age.

Despite overwhelming evidence supporting the use of statins for primary and secondary prevention of cardiovascular event, specific data on risk versus benefit of statins in the elderly population is sparse. The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)[17] was the first trial designed specifically to investigate the effects of pravastatin, 40 mg daily in the elderly aged 70−82 years; however, it was conducted in patients with pre-existing vascular disease or at a high risk of cardiovascular disease, including stroke. Although this was not a primary prevention trial, no benefit in terms of reduction in total mortality was observed in subjects without cardiovascular disease. The Study Assessing Goals in the Elderly (SAGE) trial compared the effect of intensive (atorvastatin 80 mg/d) compared with moderate (pravastatin 40 mg/d) statins in secondary prevention cohort of 893 men and women 65 to 85 years of age with coronary artery disease.[18] There was no difference in the primary outcome of ischemic duration on ambulatory holter monitoring between the two groups at one year follow up, although there was a significant reduction in all-cause mortality in the intensive treatment arm. A per-person meta-analysis of the Cholesterol Treatment Trialists that included 170,000 participants from 26 randomized trials showed that statin therapy significantly reduces major vascular events that parallel reductions in LDL-cholesterol even in the subgroup of patients greater than 75 years (annual event rate: 4.8% *vs.* 5.4%; HR (95% CI): 0.85 (0.73–0.79).[19] However, data on the use of statins for primary prevention in the very elderly (> 85 years) is lacking.[20]

The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk recommended the following for secondary prevention elderly patients: "*In individuals with clinical ASCVD > 75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it*". Similar recommendations are given regarding statin use for primary prevention in elderly diabetic patients.[21] Both recommendations are Class IIa with level of evidence E (expert opinion). Regarding primary prevention statin use in patients without diabetes, the pooled cohort equation is recommended to estimate 10-year risk of atherosclerotic cardiovascular disease. However, one has to realize that the risk calculator has only been validated in patients 40–79 years old and is not applicable to elderly patients > 80 years.[22] The ongoing study of STAtins for Reducing Events in the Elderly (STAREE) trial (NCT02099123) evaluating the role of atorvastatin 40 mg to prolong overall survival or disability free survival amongst healthy elderly people (≥ 70 years) may help provide a definitive evidence-based approach to the use of statins in this population.

In addition to controversies regarding benefits, statin use in elderly is not without complications. Side effects such as myalgia are sometimes difficult to differentiate from other causes and may result in premature termination of the medication and decrease in overall quality of life and exercise capacity. Statins can also affect platelet function, and this may increase the risk of bleeding in elderly, especially if they are already on antiplatelet or anticoagulation drugs.[23] Thus, the decision to treat dyslipidemia in elderly should be individualized. Healthy elderly patients should not be denied statin therapy simply because of their age. However, clinical judgment should be exercised regarding the use of statins in the elderly patient with multiple comorbidities and limited life expectancy.

6 Antihypertensive drugs in elderly

Hypertension is very common problem in elderly in the United States, reaching a prevalence as high as 60% to 80% in the age group > 70 years. Old people tend to have sluggish baroreceptor and sympathetic neural responses, as well as impaired cerebral autoregulation.[24] Thus, when lowering blood pressure in elderly these changes should be kept in mind to avoid adverse effects, particularly postural hypotension, which can increase the risk of falls and major fractures.[25] It is noteworthy that in elderly patients, cardiovascular disease risk relates directly with the systolic and pulse pressures and inversely with the diastolic pressure. Although there is data guiding treatment of systolic pressure,

Table 3. Anti-hypertensive agents in elderly.

Antihypertensive	Effect of aging	Clinical use implication
Dihydropyridine CCB (amlodipine, felodipine, lercanidipine, nifedipine	Risk of postural hypotension and falls increase with age	Close follow up. Patients need to be educated about postural hypotension
Non-dihydropyridine CCB (diltiazem, verapamil)	Bradycardia and severe constipation are more common in the elderly	Treat constipation aggressively Avoid concomitant use of other AV blockers
Diuretics	Increase risk of postural hypotension, dehydration, renal injury and electrolyte disturbance.	Close monitoring of renal function and electrolytes. Patients need to be educated about postural hypotension. A lower initial dose should be considered and titrate to response
ACE inhibitors/ARBs	Increase risk of postural hypotension, dehydration, renal injury and electrolyte disturbance	Close monitoring of renal function and electrolytes. Patients need to be educated about postural hypotension. A lower initial dose should be considered and titrate to response
Beta blockers	Lipid soluble beta-blockers (e.g.,metoprolol) can cross blood brain barrier and cause CNS side effects which are more common in elderly.	Close monitoring for adverse effects in older patients. A lower initial dose should be considered and titrate to response If CNS side effect become an issue, water soluble beta blocker may be used

ACE: angiotensin converting enzyme; ARBs: angiotensin receptor blockers; AV: atrioventricular nodal blockers; CCB: calcium channel blocking agents; CNS: central nervous system.

there are no clear data that provide guidance related to the threshold diastolic blood pressure that can be tolerated in elderly.[26] Effect of aging on commonly used anti-hypertensive drugs is summarized in Table 3. There are several potential limitations for achieving goal blood pressure in elderly. Lowering blood pressure has been shown to lead to impaired mental function, confusion, sleepiness, dizziness and syncope with postural hypotension.[27] This can result in significant impairment in the quality of life. In addition, most of the trials that showed benefit from the treatment of hypertension in elderly were conducted in relatively healthy patients. Therefore, caution should be exercised when applying these data to frail elderly patients.

7 Summary

In conclusion, managing cardiovascular disease in the elderly is challenging secondary to a multitude of factors. Age related physiological changes in the elderly combined with the effects of polypharmacy complicate use of various drugs. More importantly, lack of standardized evidence on efficacy and safety of multiple therapeutic regimens imposes clinical decision making challenges. Careful assessment of risk-benefit ratio and attention to overall wellbeing should be of paramount importance while treating these patients.

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