Demographics and cardiovascular disease burden
Coronary artery disease is the leading cause of death in people aged 65 years and above. In the elderly patients cardiovascular drugs are the most commonly prescribed drugs. While the elderly make up only 14% of the US population, people over the age of 65 years of age consume more than 30% of all prescription drugs.

In 2002, nearly 930,000 people experienced cardiovascular death in the US. Of these, 84% were over 65 years of age. Similar figures have been obtained in other countries. The prevalence of heart failure has dramatically increased over the last few decades, and congestive heart failure (CHF) currently affects 10 per 1,000 subjects over 65 years of age. Focus of this review were 1) age related changes in cardiovascular system 2) age related changes in pharmacokinetics and pharmacodynamics generally and cardiovascular drugs and 3) current treatment strategies in old age for specific drug classes.

Effects of aging on the cardiovascular system
Cardiac structure and function
There is a progressive reduction in the number of pacemaker cells in the sinus node, down to 10% by age 75 as compared to the number of cells seen at age 20.

Aging leads to arterial stiffening with a consequent increase in pulse wave velocity. This leads to an increase in central aortic pressure and left ventricular hypertrophy (LVH). LVH is largely secondary to increased ventricular myocyte size and modest increase in collagen levels. There is an age-related increase in left atrial dimension, left ventricular wall thickness and ventricular mass and minimal increase in left ventricular cavity size with an increase in the end-diastolic volume. There is decreased uptake of intracellular calcium by the sarcoplasmic reticulum, prolonging the contraction phase of the ventricle. Prolonged contraction of the hypertrophied left ventricle maintain a normal ejection time in the presence of late augmentation of aortic impedance thus preserving systolic cardiac function at rest. This results in a reduction in early left ventricular filling rate. With advancing age, there is also increasing fibrous tissue and amyloid deposition in the ventricular wall causing further stiffening of the ventricle. During exercise, cardiac output is maintained by an increase in left-ventricular end-diastolic volume and not by an increase in heart rate, thus relying on the Frank-Starling mechanism. Despite the decrease in the early diastolic filling phase, the preload is still maintained because of vigorous atrial contraction in late diastole. Since elderly people rely on atrial systole for ventricular filling, they are more prone to develop symptomatic CHF when in atrial fibrillation where the atrial contraction is lost.

Vascular regulatory response
In the vascular system, there is age-related dilation, medial thickening and thickening of the intima. In the elderly, the increase in systolic blood pressure is mostly due to increase in aortic impedance and not due to increase in peripheral vascular resistance. Arteriolar vasoconstrictor responses to activation of the sympathetic nervous system (SNS) decrease with aging. The aging process is associated with a progressive impairment in endothelium-dependent vasodilatation with a relative preservation of endothelium-independent vasodilatation. An impaired cardiovascular response to postural changes with reduced blood pressure homeostasis and increased risk of hypotension after attaining the upright posture is observed with aging. Although impaired baroreceptor sensitivity was thought to be the main factor involved, recent studies have demonstrated that vein capacitance is significantly altered in healthy elderly individuals in the presence of preserved baroreceptor reflex. Aging is associated with increased activity of SNS. Age-related cardiovascular responses to SNS stimulation have been reported to be reduced.

With aging, the cardiac myocytes decrease in number secondary to apoptosis but increase in their size.

Age-related changes in pharmacokinetics and pharmacodynamics
Pharmacokinetics deals with the processes that affect the concentration of the drug in the body whereas pharmacodynamics determines the biochemical and physiological effects of the drug on the body.

Bioavailability
Bioavailability is defined as the fraction of drug that reaches systemic circulation when administered by route other than intravenous as compared to the amount that reaches circulation with the intravenous administration. The bioavailability of drugs depends on the chemical properties of the drug, route of administration, absorption, first-pass metabolism in the liver and distribution. The rate of absorption of most oral drugs is delayed in the elderly as compared to younger patients. Early studies reported significant age-related effects including reduced
gastric acid secretion and gastric emptying, reduced splanchnic blood flow, and reduced absorptive capacity of the small intestine. Aging is associated with a reduction on first-pass metabolism. This is probably a result of a reduction in liver mass and blood flow.

**Drug distribution**

Changes in body composition associated with aging are characterized by a relative increase in body fat mass and a reduction in lean body mass. As a consequence, polar drugs that are mainly water-soluble tend to have smaller volumes of distribution (VD), resulting in higher serum levels in elderly subjects. Digoxin falls into this category. Loading doses of digoxin need to be reduced to accommodate these changes. By contrast, nonpolar compounds tend to be lipid-soluble and so their VD increases with age. The main effect of an increase in VD is a prolongation of half-life.

**Protein binding**

Albumin is commonly reduced in elderly with malnutrition or acute medical illness whereas alpha1-acid glycoprotein is increased during acute medical illness. This change affects the distribution of drugs like amiodarone, warfarin and digoxin. The importance of such changes remains to be elucidated as the main factor determining drug effect is the free concentration of the drug.

**Drug clearance**

Drug clearance occur either by elimination of the drugs mainly by the kidneys or biotransformation into inactive compounds that takes part mostly in the liver. Structural changes of the kidney in the elderly include decreasing renal mass and number of glomeruli. There is an increase fraction of sclerotic glomeruli and tubulointerstitial fibrosis. Functional changes are characterized mainly by a progressive reduction in glomerular filtration rate. The rate of this reduction is approximately 1 ml/min/1.73 m² per year in individuals more than 40 years of age but tends to accelerate after 65 years of age. Reduction in renal function in elderly subjects particularly glomerular filtration rate, affects the clearance of many drugs including diuretics, digoxin, and beta-blockers. The serum creatinine, the product of muscle breakdown, gives a false estimate of the glomerular function in the elderly due to decrease in the muscle mass. Hence the creatinine clearance should be estimated either by 24-hour creatinine clearance, or at bedside by using the Cockcroft and Gault formula.

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\text{creatinine clearance} = \frac{(140\text{-age}) \times (\text{lean body weight in kg})}{72 \times \text{serum creatinine}} \times 0.85 \text{ for women}
\]

The lean body weight (LBW) is calculated by using the formula derived by Lott and Hayton which is:

- LBW (men) = 50 kg + 2.3 kg/inch above 5 feet
- LBW (women) = 45.5 kg + 2.3 kg/inch above 5 feet

The clinical importance of such reductions in renal excretion depends on the likely toxicity of the drug. Drugs with narrow therapeutic index, such as digoxin, are likely to cause serious adverse effects if they accumulate only marginally more than intended.

Drug clearance by the liver depends on the capacity of the liver to extract the drug from the blood passing through the organ, the amount of hepatic blood flow, and microsomal enzyme activity. The reduction in liver blood flow with aging will mainly affect the clearance of drugs with a high excretion ratio such as glyceryl nitrate, lidocaine, and propranolol. Oxidative metabolism in the liver is carried out by the cytochrome P450 (CYP) system. These enzymes are seen in 3 isoforms, CYP1, CYP2, and CYP3. CYP3 accounts for more than 25% of the liver protein and is responsible for the clearance of important cardiovascular drugs like CCB, beta-blockers, warfarin, quinidine, and HMG CoA reductase inhibitors.

**Age-related pharmacokinetic and pharmacodynamic changes for specific cardiovascular drug classes**

**Diuretics**

Diuretics are widely used in the elderly in the management of hypertension and CHF. Patients who have a potassium level of less than 3 mmol/l have a significant risk of developing ventricular arrhythmias. It is extremely difficult to draw any conclusions about loop diuretics as there is very little information on the pharmacokinetics of these drugs in healthy elderly subjects. No significant age-related pharmacokinetic changes have been demonstrated with the potassium-sparing agent's spironolactone and triamterene, whereas marked increases in area under curve (AUC) have been demonstrated for amiloride. No significant age-related changes in blood pressure response have been demonstrated with thiazide diuretics. Thiazide diuretics maintain a leading role as first-line agents in the management of hypertension because of their proven efficacy and low cost. Thiazide diuretics are generally well tolerated in elderly patients. Use of loop diuretics in the elderly population should be confined to the management of conditions characterized by fluid overload. Increasing rates of adverse events such as hyperkalemia during spironolactone treatment have been reported in patients over 65 years of age.

**Beta-blockers**

Beta-blockers have been shown to reduce mortality in younger and older patients after myocardial infarction. Addition of beta-blockers to standard therapy of CHF can decrease mortality and morbidity in patients with CHF. Decreased responses to beta-blockers are seen with aging. Younger subjects who received beta-blockers had a marked decline in the heart rate as compared to the elderly who had a blunt decline in the heart rate. The lipophilic beta-blockers such as propranolol and metoprolol cross the blood brain barrier and affect the sleep pattern and may worsen depression. Beta-blockers also show significant interaction with drugs like amiodarone, digoxin and verapamil. Pharmacodynamic studies have generally shown a more pronounced hypotensive and bradycardic response to beta-blockers in elderly subjects with the exception of propranolol. Selective beta-blockers represent a first-line option for the management of hypertension and ischemic heart disease in elderly patients. It seems prudent to start with low doses (eg atenolol 25 mg per day) and slowly increases with close monitoring of heart rate response and postural blood pressure changes. Carvedilol is well tolerated in patients over 65 years of age.

**Calcium channel blockers (CCB)**

CCB are the most frequently used anti-hypertensive agents in the elderly. The decreased hepatic blood flow is presumed to be the reason for decreased clearance of these drugs. This results in the increased plasma concentration in the elderly as compared to the younger patients receiving the same dose of the drugs. Pharmacokinetic studies of dihydropyridine CCBs have shown a prolongation of half-life and an increase AUC in elderly patients. These age-related changes seem particularly marked for felodipine. Studies with diltiazem did not
show any significant age-related effect in half-life and AUC. However, for verapamil, most studies showed a longer half-life and greater AUC in elderly subjects. Pharmacokinetic studies of felodipine and nifedipine showed that plasma concentration of the drugs is significantly greater in the elderly compared with younger patients.14

**Angiotensin Converting Enzyme (ACE) inhibitors**

ACE inhibitors are widely used in elderly population in the treatment of hypertension, CHF, post myocardial infarction, and as renal function protective agents in diabetes. ACE inhibitors could result in renal failure in patients with bilateral renal artery stenosis by decreasing the action of angiotensin II in the efferent arterioles of the glomeruli. Hence renal function should be closely monitored. Other side effects are angioneurotic edema, cough, skin rash, hyperkalemia and hypotension.

An increased blood pressure lowering effect was demonstrated in elderly subjects receiving enalapril and perindopril whereas lisinopril and ramipril induced similar blood pressure responses in young and elderly subjects. Evidence supporting the use of ACE inhibitors in elderly patients is rapidly growing. A Meta-analysis of 32 randomized clinical trials has documented their effectiveness in reducing the mortality and morbidity of CHF.15 The benefits were similar in older and younger patients. In HOPE (Heart Outcomes Prevention Evaluation) study, 9,297 patients over 55 years of age with vascular disease or diabetes plus one other cardiovascular risk factor but no CHF were randomized to ramipril or placebo and follow-up for 5 years. 16 Ramipril reduced composite endpoint of myocardial infarction and cardiovascular death by 17.8% (p<0.001). Subgroup analysis in patients over 65 years of age yielded similar results. ACE inhibitors with a relatively long half-life such as perindopril seem to be particularly suitable for elderly subjects as the risk of first-dose hypotension is low compared with other agents. It seems prudent to withhold diuretic treatment for at least 2 days prior to the initiation of treatment with ACE inhibitors.

**Angiotensin receptor antagonist (ARA)**

Age-related effects seem less marked with irbesartan and valsartan. Of note, there is no pharmacodynamic study of the effects of ARA in young versus elderly subjects. The beneficial effects of valsartan in patients over 65 years of age with CHF were similar to those observed in younger patients.17 The same finding was also true for candesartan. The beneficial effects of ARA in patients post myocardial infarction were similar in patients over 65 years of age.

ARA have demonstrated efficacy when used alone or in combination with other agents in managing hypertension in the elderly.18 An ARA is an appropriate substitute for an ACE inhibitor in older patients who experience cough, or who may be at high risk for hypotension because of the ACE inhibitor effects on bradykinin.

**Antiarrhythmics**

Significant age-related increase in half-life has been reported for digoxin, disopyramide, lidocaine and quinidine. Therefore, these medications needed to be used with caution in elderly subjects. Five clinical trials comparing rate control versus rhythm control in patients with atrial fibrillation have been completed. These studies suggested that there are no definite advantages of rhythm control in patients over 65 years of age.19

Amiodarone is an iodine-rich antiarrhythmic drug for the treatment of atrial and ventricular arrhythmia. Amiodarone needs a loading dose due to its large volume of distribution. Dose adjustments are not required in patients with hepatic, renal or cardiac dysfunction. To minimize potential adverse effects, low maintenance doses (100 to 200 mg per day) are preferred. Close monitoring of chest X-ray, eyes, thyroid, and liver functions will avoid serious side effects with amiodarone use.

**Digoxin**

Digoxin is widely used in heart failure from systolic dysfunction and for rate control in atrial fibrillation. In the body digoxin is mostly bound to the skeletal muscle and excreted unchanged by the kidneys. Elderly patients, due to their low muscle mass and compromised renal function are at increased risk of digoxin toxicity. Thus dosing should be estimated based on the lean body mass and the renal function. Digoxin has a narrow therapeutic index and the plasma level of digoxin does not reliably reflect the level of drug activity.20 Digoxin should be used in small dose with frequent monitoring in the elderly due to significant risk of toxicity. Various other medications interact significantly with digoxin resulting either in increase or decrease in plasma digoxin level.

In post hoc analysis of Digitalis Investigation Group trial, serum digoxin concentration over 1 ng/ml were associated with increased mortality particularly in male suggesting that the effectiveness of digoxin therapy in CHF may be optimized in the range of 0.5-0.8 ng/ml.21

**Statins**

The available evidence suggests that the pharmacokinetics of rosuvastatin is not significantly altered in elderly subjects. By contrast, age related increased in drug concentration and AUC have been observed with atorvastatin and simvastatin. The 4S study investigated the effects of simvastatin versus placebo in 4,444 patients 35-70 years of age with ischemic heart disease. 23 A significant reduction in all-cause mortality was observed with simvastatin. The risk reduction was similar in patient over 60 years of age. Significant elevations in liver enzymes occurred in 1% of patients in both groups. Similar findings were observed with pravastatin.

These drugs undergo extensive first-pass metabolism in the liver predominantly by the CYP-450 system except pravastatin. They are highly protein bound. After metabolism in the liver, the inactive compounds are excreted in the urine. The important adverse effects are elevation of liver enzymes and myopathy. The incidence of myopathy is increased in patients taking nicotinic acid, fibrates, erythromycin, and itraconazole.

**Antiplatelets and anticoagulants**

Pharmacokinetic studies of aspirin have demonstrated a significant reduction in clearance and a prolonged half-life in elderly subjects.24 An increased AUC in elderly subjects has been described with clopidogrel and ticlopidine. Although aspirin is widely used for primary and secondary cardiovascular prevention, clinical and epidemiological data indicate that the incidence of aspirin-related peptic ulcer disease increases with advance age.25 In the absence of solid evidence related to possible age-related pharmacokinetic or pharmacodynamic effects, the increased rate of gastrointestinal complications with aspirin is probably related to the reduction in gastrodupodenal defensive mechanisms with aging.

Warfarin is well absorbed after oral administration and is highly protein bound. Hence older patients with low albumin level need a lower dose. It has an average half-life of 36 hours and is metabolized by the CYP-450 system in the liver to inactive compounds and excreted in urine and stool. The medications that affect CYP-450
System significantly affect warfarin metabolism resulting in increase or decrease in its therapeutic effect. Some of the commonly used drugs that increase the international normalized ratio (INR) are alcohol, amiodarone, aspirin, propafenone, propranolol, cephalexin, trimethoprim-sulfamethoxazole, statins, omeprazole, cimetidine, metronidazole, macrolides, NSAIDs, asazol anti-fungals. Nafcitilin, rifampin, carbamazepine, griseofulvin, clolestyramine, barbiturates, chloridiazepoxide, sulcralfate, and high vitamin K content food deacrease the effect of warfarin. Concerns about a possible increase in bleeding rates in elderly subjects have also been expressed with warfarin. This has led to a significant underuse of this agent in elderly patients with atrial fibrillation despite the well known benefits of this agent in terms of stroke reduction.

Low-molecular-weight-heparin (LMWH) is cleared predominantly by the renal system. No significant differences were noted in the safety and effectiveness between the younger and older patients. No dose adjustment is needed in geriatric patients; however in patients with renal dysfunction elimination might be delayed. 26

**CONCLUSION**

In elderly cardiovascular patients, too many drugs are still used on the basis of data obtained from studies in younger subjects and personal experience. This approach is no longer justifiable in the era of evidence-based medicine. With significant age-related changes and comorbid conditions in the elderly, the use of medications requires close attention to the renal and hepatic function, volume status and skeletal muscle mass. Polypharmacy should be avoided. Medications should be started after weighing the potential benefits and side effects. The medications should be started at low doses and titrated gradually as necessary at low incremental doses. By elimination of unnecessary medications, anticipating potential side effects and drug interactions, medications can be used safely in the elderly.

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