Cardiovascular Drug Therapy in the Elderly

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Abstract: Pharmacokinetic considerations in the elderly include absorption, bioavailablility, drug distribution, half-life, drug metabolism, and drug excretion. There are numerous physiologic changes with aging that affect pharmacodynamics with alterations in end-organ responsiveness. This article discusses use of cardiovascular drugs in the elderly including digoxin, diuretics, β-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, nitrates, calcium channel blockers, α-adrenergic blockers, antiarrhythmic drugs, lipid-lowering drugs, and anticoagulants. This article also discusses the adverse effects of cardiovascular drugs in the elderly, medications best to avoid in the elderly, and the prudent use of medications in the elderly.

Key Words: cardiovascular drugs, pharmacokinetics, pharmacodynamics

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Cardiovascular disease is the greatest cause of morbidity and mortality in the elderly, and cardiovascular drugs are the most widely prescribed drugs in this population. Because many cardiovascular drugs have narrow therapeutic windows in the elderly, the incidence of adverse effects from using these drugs is also highest in the elderly. The appropriate use of cardiovascular drugs in the elderly requires knowledge of age-related physiologic changes, the effects of concomitant diseases that alter the pharmacokinetic and pharmacodynamic effects of cardiovascular drugs, and drug interactions.

PHARMACOKINETIC CONSIDERATIONS IN THE ELDERLY

Absorption

Age-related physiologic changes that may affect absorption include reduced gastric secretion of acid, decreased gastric emptying rate, reduced splanchnic blood flow, and decreased mucosal absorptive surface area (Table 1). Despite these physiologic changes, the oral absorption of cardiovascular drugs is not significantly affected by aging, probably because most drugs are absorbed passively.[1]

Bioavailability

There are almost no data available for age-related changes in drug bioavailability for routes of administration other than the oral route.[2] The bioavailability of cardiovascular drugs depends on the extent of drug absorption and on first-pass metabolism by the liver and/or the wall of the gastrointestinal (GI) tract. In the elderly, the absolute bioavailability of drugs such as propranolol, verapamil, and labetalol is increased because of reduced first-pass hepatic extraction.[3] However, the absolute bioavailability of prazosin in the elderly is reduced.[4]

Drug Distribution

With aging, there is a reduction in lean body mass[5] and in total body water,[6] causing a decrease in volume of distribution (Vd) of hydrophilic drugs. This leads to higher plasma concentrations of hydrophilic drugs such as digoxin and angiotensin converting enzyme (ACE) inhibitors with the first dose in the elderly.[7] The increased proportion of body fat, which occurs with aging, also causes an increased Vd for lipophilic drugs. This leads to lower initial plasma concentrations for lipophilic drugs such as most β-blockers, antihypertensive drugs, and central α-agonists.

The level of α_1-acid glycoprotein increases in the elderly.[8] Weak bases such as disopyramide, lidocaine, and propranolol bind to α_1-acid glycoprotein. This may cause a reduction in the free fraction of these drugs in the circulation, a decreased Vd, and a higher initial plasma concentration.[9] In the elderly, there is also a tendency for plasma albumin concentration to be reduced.[10] Weak acids, such as salicylates and warfarin, bind extensively to albumin. Decreased binding of drugs such as warfarin to plasma albumin may result in increased free-drug concentrations, resulting in more intense drug effects.[11]

Half-Life

The half-life of a drug (or of its major metabolite) is the length of time in hours that it takes for the serum concentration of that drug to decrease to half of its peak level. This can be described by the kinetic equation $t_{1/2} = 0.693 \times \text{Vd/Cl}$, where $t_{1/2}$ is directly related to drug distribution and inversely to clearance. Therefore, as previously mentioned, changes in Vd and/or Cl due to aging can affect the half-life of a drug. In elderly patients, an increased half-life of a drug means a longer time until steady-state conditions are achieved. With a prolonged half-life of a drug, there may be an initial delay in

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TABLE 1. Physiologic Changes With Aging Potentially Affecting Cardiovascular Drug

Process	Physiologic Change	Result	Drugs Affected
Absorption	Reduced gastric acid production	Reduced tablet dissolution and decreased solubility of basic drugs	
	Reduced gastric emptying rate	Decreased absorption for acidic drugs	
	Reduced GI mobility, GI blood flow, absorptive surface	Less opportunity for drug absorption	
Distribution	Decreased total body mass. Increased proportion of body fat	Increased Vd of highly lipid-soluble drugs	Decreased by β blockers, central α agonists
	Decreased proportion of body water	Decreased Vd of hydrophilic drugs	Decreased by digoxin and ACE inhibitors
	Decreased plasma albumin, disease-related increased α_1-acid glycoprotein, altered relative tissue perfusion	Changed % of free drug, Vd, and measured levels of bound drugs	Increased by disopyramide and warfarin, lidocaine, propranolol
Metabolism	Reduced liver mass, liver blood flow, and hepatic metabolic capacity	Accumulation of metabolized drugs	Increased by propranolol, nitrates, lidocaine, diltiazem, warfarin, labetalol, verapamil, mexiletine
Excretion	Reduced glomerular filtration, renal tubular function, and renal blood flow	Accumulation of renally cleared drugs	Digoxin, ACE inhibitors, antiarrhythmic drugs, atenolol, sotalol, nadolol

Adapted from Hui KK. Gerontologic considerations in cardiovascular pharmacology and therapeutics. In: Singh BN, Dzau VJ, Vanhoutte PM, et al, eds. *Cardiovascular Pharmacology and Therapeutics*. New York, NY: Churchill-Livingstone; 1994:1130.

maximum effects of the drug and prolonged adverse effects. Table 2 lists the pharmacokinetic changes, routes of elimination and dosage adjustment for common cardiovascular drugs used in the elderly.

Drug Metabolism

Decreased hepatic blood flow, liver mass, liver volume, and hepatic metabolic capacity occur in the elderly.[12] There is a reduction in the rate of many drug oxidation reactions (phase 1) and little change in drug conjugation reactions (phase 2). These changes in the elderly may result in higher serum concentrations of cardiovascular drugs that are metabolized in the liver, including propranolol, lidocaine, labetalol, verapamil, diltiazem, nitrates, warfarin, and mexiletine.

Drug Excretion

With aging there is a reduction in the total numbers of functioning nephrons and thereby a parallel decline in both glomerular filtration rate and renal plasma flow.[13,14] The age-related decline in renal function is likely the single most important physiologic change causing pharmacokinetic alterations in the elderly. The change in renal function with aging is insidious and poorly characterized by serum creatinine determinations, although serum creatinine measurements remain one of the most widely used tests for gauging renal function. To estimate renal function from a serum creatinine value requires its being indexed for muscle mass, which is difficult in even the most skilled hands. Creatinine is a byproduct of creatine metabolism in muscle, and its daily production correlates closely with muscle mass. Thus, the greater the muscle mass, the higher the "normal serum creatinine." For example, in a heavily muscled male, a serum creatinine value of 1.4 mg/dL might be considered normal, though such a value may be considered grossly abnormal in an individual with less muscle, such as an aged individual. A safer way to estimate renal function in the elderly is by use of a urine-free formula such as the Cockcroft-Gault formula[15]:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{body weight (kg)}}{72 \times S_{creat}\ (\text{mg/dL})}$$

For women, the results of this equation can be multiplied by 0.85 to account for the small muscle mass of most women. It should be appreciated that creatinine clearance is reciprocally related to serum creatinine concentrations, such that a doubling of serum creatinine represents an approximate halving of renal function. The axiom that glomerular filtration rate is reciprocally related to serum creatinine is most important with the first doubling of serum creatinine. For example, a serum creatinine value of 0.6 mg/dL in an elderly subject doubles to 1.2 mg/dL, and with this doubling, creatinine clearance falls from 80 mL/min to about 40 mL/min.

The National Kidney Foundation guidelines use the Modification of Diet in Renal Disease Study (MDRD) equation to estimate glomerular filtration rate.[16] The MDRD equation is: glomerular filtration rate (mL/min/1.73 m^2) = $186 \times S_{creat}^{-1.154} \times age^{-0.203} \times 0.742$ if female $\times$ 1.210 if black.[16]

The reduced clearance of many drugs primarily excreted by the kidneys causes their half-life to be increased in the elderly. Cardiovascular drugs known to be excreted by the kidney, via various degrees of filtration and tubular secretion, include digoxin, diuretics, ACE inhibitors, antiarrhythmic medications (bretylium, disopyramide, flecainide, procainamide, and tocainide), and the β-blockers (atenolol, bisoprolol, carteolol, nadolol, and sotalol). Typically, a renally-cleared compound begins to accumulate when creatinine clearance values drop below 60 mL/min. An example of this phenomenon can be seen with ACE inhibitors,[17] wherein accumulation begins early in the course of renal functional decline. Moreover, ACE inhibitor accumulation in the

TABLE 2. Pharmacokinetic Changes, Route of Elimination, and Dosage Adjustment of Selected Cardiovascular Drugs in the Elderly

Drug	$t_{1/2}$	Vd	Cl	Primary Route(s) of Elimination	Dosage Adjustment
α-adrenergic agonists centrally acting					
Clonidine	—	—	—	Hepatic/renal	Initiate at lowest dose; titrate to response
Guanabenz	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
Guanfacine	↑	—	↓	Hepatic/renal	Initiate at lowest dose; titrate to response
Methyldopa	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
α_1 selective adrenergic antagonists peripherally acting					
Doxazosin	↑	↑	↑*	Hepatic	Initiate at lowest dose; titrate to response
Prazosin	↑	—	—	Hepatic	Initiate at lowest dose; titrate to response
Terazosin	↑	—	—	Hepatic	Initiate at lowest dose; titrate to response
Angiotensin converting enzyme inhibitors					
Benazepril	↑	—	↓	Renal	No adjustment needed
Captopril	NS	—	↓	Renal	Initiate at lowest dose; titrate to response
Enalapril	—	—	—	Renal	Initiate at lowest dose; titrate to response
Fosinopril	—	—	—	Hepatic/renal	No adjustment needed
Lisinopril	↑	NS	↓	Renal	Initiate at lowest dose; titrate to response
Moexipril	—	—	—	Hepatic/renal	Initiate at lowest dose; titrate to response
Perindopril	—	—	↓	Renal	Initiate at lowest dose; titrate to response
Quinapril	—	—	—	Renal	Initiate at lowest dose; titrate to response
Ramipri	—	—	—	Renal	Initiate at lowest dose; titrate to response
Trandolapril	—	—	—	Hepatic/renal	Initiate at lowest dose; titrate to response
Angiotensin II receptor blockers					
Candesartan	—	—	—	Hepatic/renal	No adjustment needed
Eprosartan	—	—	↓	Hepatic/biliary/renal	No adjustment needed
Irbesartan	NS	—	—	Hepatic	No adjustment needed
Losartan	—	—	—	Hepatic	No adjustment needed
Olmesartan	—	—	—	Renal/biliary	No adjustment needed
Telmisartan	—	—	—	Hepatic/biliary	No adjustment needed
Valsartan	↑	—	—	Hepatic	No adjustment needed
Antiarrhythmic agents					
Class I					
Disopyramide	↑	—	↓	Renal	Initiate at lowest dose; titrate to response
Flecainide	↑	↑	↓	Hepatic/renal	Initiate at lowest dose; titrate to response
Lidocaine	↑	↑	NS	Hepatic	Initiate at lowest dose; titrate to response
Mexilitine	—	—	—	Hepatic	No adjustment needed
Moricizine	—	—	—	Hepatic	No adjustment needed
Procainamide	—	—	↓	Renal	Initiate at lowest dose; titrate to response
Propafenone	—	—	—	Hepatic	No adjustment needed
Quinidine	↑	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Tocainide	↑	—	↓	Hepatic/renal	No adjustment needed
Class II (see β blockers)					
Class III					
Amiodarone	—	—	—	Hepatic/biliary	No adjustment needed
Bretylium	—	—	—	Renal	Initiate at lowest dose; titrate to response
Dofetilide	—	—	—	Renal	Adjust dose based on renal function
Ibutilide	—	—	—	Hepatic	No adjustment needed
Sotalol	—	—	—	Renal	Adjust dose based on renal function
Class IV (see calcium channel blockers)					
Other antiarrhythmics					
Adenosine	—	—	—	Erythrocytes/vascular endothelial cells	No adjustment needed
Atropine	—	—	—	Hepatic/renal	Use usual dose with caution

(*Continued*)

TABLE 2. (*Continued*)

Drug	$t_{1/2}$	Vd	Cl	Primary Route(s) of Elimination	Dosage Adjustment
Antithrombotics					
Anticoagulants					
Argatroban	—	—	—	Hepatic/biliary	Use usual dose with caution
Bivalirudin	—	—	—	Renal/proteolytic cleavage	Adjust dose based on renal function
Dalteparin	—	—	—	Renal	Use usual dose with caution
Desirudin	—	—	—	Renal	Adjust dose based on renal function
Enoxaparin		—	—	Renal	Adjust dose based on renal function
Fondaparinux	↑	—	↓	Renal	Use usual dose with caution
Heparin	—	—	—	Hepatic/reticuloendothelial system	Use usual dose with caution
Lepirudin	↑	—	↓	Renal	Adjust dose based on renal function
Tinzaparin	—	—	—	Renal	Use usual dose with caution
Warfarin	NS	NS	NS	Hepatic	Initiate at lowest dose; titrate to response
Antiplatelets					
Abciximab	—	—	—	Unknown	Use usual dose with caution
Aspirin	—	—	↓	Hepatic/renal	Use usual dose with caution
Clopidogrel	NS	—	—	Hepatic	Use usual dose with caution
Dipyridamole	—	—	—	Hepatic/biliary	Use usual dose with caution
Eptifibatide	—	—	—	Renal/plasma	Use usual dose with caution
Ticlopidine	—	—	↓	Hepatic	Use usual dose with caution
Tirofiban	↑	—	↓	Renal	Use usual dose with caution
Thrombolytics					
Alteplase	—	—	—	Hepatic	Use usual dose with caution
Reteplase	—	—	—	Hepatic	Use usual dose with caution
Streptokinase	—	—	—	Circulating antibodies/reticuloendothelial system	Use usual dose with caution
Tenecteplase	—	—	—	Hepatic	Use usual dose with caution
Urokinase	—	—	—	Hepatic	Use usual dose with caution
β-adrenergic blockers					
Nonselective without ISA					
Nadolol	NS	—	—	Renal	Initiate at lowest dose; titrate to response
Propranolol	↑	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Timolol	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
β_1 selective without ISA					
Atenolol	↑	NS	↓	Renal	Initiate at lowest dose; titrate to response
Betaxolol	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
Bisoprolol	—	—	—	Hepatic/renal	Initiate at lowest dose; titrate to response
Esmolol	—	—	—	Erythrocytes	Use usual dose with caution
Metoprolol	NS	NS	NS	Hepatic	Initiate at lowest dose; titrate to response
β_1 selective with ISA					
Acebutolol	↑	↓	—	Hepatic/biliary	Initiate at lowest dose; titrate to response
Nonselective with ISA					
Carteolol	—	—	—	Renal	Initiate at lowest dose; titrate to response
Penbutolol	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
Pindolol	—	—	—	Hepatic/renal	Initiate at lowest dose; titrate to response
Dual acting					
Carvedilol	—	—	—	Hepatic/biliary	Initiate at lowest dose; titrate to response
Labetalol	—	—	NS	Hepatic	Initiate at lowest dose; titrate to response
Calcium channel blockers					
Amlodipine	↑	—	↓	Hepatic	Initiate at lowest dose; titrate to response
Bepridil	—	—	—	Hepatic	Use usual dose with caution
Diltiazem	↑	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Felodipine	—	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Isradipine	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
Nicardipine	NS	—	—	Hepatic	No initial adjustment needed

(*Continued*)

TABLE 2. (*Continued*)

Drug	$t_{1/2}$	Vd	Cl	Primary Route(s) of Elimination	Dosage Adjustment
Nifedipine	↑	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Nimodipine	—	—	—	Hepatic	Use usual dose with caution
Nisoldipine	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
Verapamil	↑	NS	↓	Hepatic	Initiate at lowest dose; titrate to response
Diuretics					
Loop					
Bumetanide	—	NS	—	Renal/hepatic	No initial adjustment needed
Ethacrynic acid	—	—	—	Hepatic	No initial adjustment needed
Furosemide	↑	NS	↓	Renal	No initial adjustment needed
Torsemide	—	—	—	Hepatic	No initial adjustment needed
Thiazides					
Bendroflumethiazid	e—	—	—	Renal	No initial adjustment needed
Benzthiazide	—	—	—	Unknown	No initial adjustment needed
Chlorothiazide	—	—	—	Renal	No initial adjustment needed
Chlorthalidone	—	—	—	Renal	No initial adjustment needed
Hydrochlorothiazid	e—	—	↓	Renal	No initial adjustment needed
Hydroflumethiazide	—	—	—	Unknown	No initial adjustment needed
Indapamide	—	—	—	Hepatic	No initial adjustment needed
Methyclothiazide	—	—	—	Renal	No initial adjustment needed
Metolazone	—	—	—	Renal	No initial adjustment needed
Polythiazide	—	—	—	Unknown	No initial adjustment needed
Quinethazone	—	—	—	Unknown	No initial adjustment needed
Trichlormethiazide	—	—	—	Unknown	No initial adjustment needed
Potassium-sparing					
Amiloride	—	—	↓	Renal	No initial adjustment needed
Spironolactone	—	—	—	Hepatic/biliary/renal	No initial adjustment needed
Triamterene	↑	—	—	Hepatic/renal	Initiate at lowest dose; titrate to response
Aldosterone receptor antagonist					
Eplerenone	—	—	—	Hepatic	No initial adjustment needed
Aquaretic					
Conivaptan	—	—	—	No adjustment needed	
Endothelin receptor antagonist					
Bosentan	—	—	—	Hepatic/biliary	Use usual dose with caution
Human B-type natriuretic peptide					
Nesiritide	—	—	—	Cellular internalization and lysosomal proteolysis/proteolytic cleavage/renal filtration	Use usual dose with caution
Inotropic and vasopressor agents					
Inamrinone	—	—	—	Hepatic/renal	Initiate at lowest dose; titrate to response
Digoxin	↑	↓	↓	Renal	Initiate at lowest dose; titrate to response
Dobutamine	—	—	—	Hepatic/tissue	Initiate at lowest dose; titrate to response
Dopamine	—	—	—	Renal/hepatic/plasma	Initiate at lowest dose; titrate to response
Epinephrine	—	—	—	Sympathetic nerve endings/plasma	Initiate at lowest dose; titrate to response
Isoproterenol	—	—	—	Renal	Initiate at lowest dose; titrate to response
Metaraminol	—	—	—	Hepatic/biliary/renal	Initiate at lowest dose; titrate to response
Methoxamine	—	—	—	Unknown	Initiate at lowest dose; titrate to response
Midodrine	—	—	—	Tissue/hepatic/renal	No initial adjustment needed
Milrinone	—	—	—	Renal	Adjust based on renal function
Norepinephrine	—	—	—	Sympathetic nerve endings/hepatic	Initiate at lowest dose; titrate to response
Phenylephrine	—	—	—	Hepatic/intestinal	Initiate at lowest dose; titrate to response
Vasopressin	—	—	—	Hepatic	Adjust dose based on hepatic function and response
Lipid-lowering Agents					
BAS					
Cholestyramine	—	—	—	Not absorbed in GI tract	No adjustment needed
Colestipol	—	—	—	Not absorbed in GI tract	No adjustment needed
Colesevelam	—	—	—	Not absorbed in GI tract	No adjustment needed

(*Continued*)

TABLE 2. (*Continued*)

Drug	$t_{1/2}$	Vd	Cl	Primary Route(s) of Elimination	Dosage Adjustment
SCAI					
Ezetimibe	—	—	—	Small intestine/hepatic/biliary	No adjustment needed
FADS					
Fenofibrate	—	—	—	Renal	Initiate at lowest dose; titrate to response
Gemfibrozil	—	—	—	Hepatic/renal	No adjustment necessary
Nicotinic acid	—	—	—	Hepatic/renal	No initial adjustment needed
HMG CoA reductase inhibitors					
Atorvastatin	↑	—	—	Hepatic/biliary	No initial adjustment needed
Fluvastatin	—	—	—	Hepatic	No initial adjustment needed
Lovastatin	—	—	—	Hepatic/fecal	No initial adjustment needed
Pravastatin	—	—	—	Hepatic	No initial adjustment needed
Rosuvastatin	—	—	—	Hepatic/fecal	No initial adjustment needed
Simvastatin	—	—	—	Hepatic/fecal	Initiate at lowest dose; titrate to response
Neuronal and ganglionic blockers					
Guanadrel	—	—	—	Hepatic/renal	Initiate at lowest dose; titrate to response
Guanethidine	—	—	—	Hepatic/renal	Initiate at lowest dose; titrate to response
Mecamylamine	—	—	—	Renal	Initiate at lowest dose; titrate to response
Reserpine	—	—	—	Hepatic/fecal	Initiate at lowest dose; titrate to response
Vasodilators					
Alprostadil	—	—	—	Pulmonary/renal	Initiate at lowest dose; titrate to response
Cilostazol	—	—	—	Hepatic/renal	No adjustment necessary
Diazoxide	—	—	—	Hepatic/renal	Initiate at lowest dose; titrate to response
Epoprostenol	—	—	—	Hepatic/renal	Initiate at usual dose with caution
Fenoldopam	—	—	—	Hepatic	No adjustment necessary
Hydralazine	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
ISDN	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
ISMN	NS	—	NS	Hepatic	No adjustment necessary
Isoxsuprine	—	—	—	Renal	Initiate at lowest dose; titrate to response
Minoxidil	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
Nitroglycerin	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
Nitroprusside	—	—	—	Hepatic/renal/erythrocytes	Use usual dose with caution
Papaverine	—	—	—	Hepatic	Initiate at lowest dose; titrate to response
Pentoxifylline	—	—	↓	Hepatic/renal	Use usual dose with caution; dose reduction may be needed
Sildenafil	—	—	—	Hepatic/fecal	Initiate at lowest dose; titrate to response

*Increase in Cl is small compared to increase in Vd.

$t_{1/2}$ indicates half-life; Vd, volume of distribution; Cl, clearance; ↑, increase; ↓, decrease; —, no information or not relevant; NS, no significant change; LMWH, low molecular weight heparin; ISA, intrinsic sympathomimetic activity; BAS, bile acid sequestrants; SCAI, selective cholesterol absorption inhibitors; FADS, fibric acid derivatives; ISDN, isosorbide dinitrate; ISMN, isosorbide mononitrate.

Adapted from *Cardiovascular Pharmacotherapeutics.* 2nd ed. New York, NY: McGraw Hill; 2003:1033–1036.

elderly is poorly studied in the case of many of the ACE inhibitors particularly as relates to the "true level of renal function" when an otherwise healthy elderly subject undergoes formal pharmacokinetic testing. Thus, it has not been uncommon for elderly subjects with serum creatinine values as high as 2.0 mg/dL to be allowed entry into a study whose primary purpose is to determine the difference in drug handling of a renally cleared compound in young versus elderly subjects.

PHARMACODYNAMICS

There are numerous physiologic changes with aging that affect pharmacodynamics with alterations in end-organ responsiveness (Table 3). Increased peripheral vascular resistance is the cause of systolic and diastolic hypertension in the elderly.[18] Inappropriate sodium intake and retention may contribute to increased arteriolar resistance and/or plasma volume. Cardiac output, heart rate, renal blood flow, glomerular filtration rate, and renin levels decline with aging. Increased arterial stiffness, resulting from changes in the arterial media and an increase in arterial tonus and arterial impedance, increases systolic blood pressure, and contributes to a widened pulse pressure. Maintenance of α-adrenergic vasoconstriction with impaired β-adrenergic-mediated vasodilation may be an additional contributory factor to increased peripheral vascular resistance. The cardiovascular response to catecholamines and carotid arterial baroreflex sensitivity are both decreased in the elderly. Left ventricular (LV) mass and left atrial dimension are

TABLE 3. Characteristics of the Elderly Relative to Drug Response

Physiologic Changes	Changes in Response
Decreased cardiac reserve	Potential for heart failure
Decreased LV compliance due to thickened ventricular wall, increased blood viscosity, decreased aortic compliance, increased total and peripheral resistance	Decrease of cardiac output
Decreased baroreceptor sensitivity	Tendency to orthostatic hypotension
Diminished cardiac and vascular responsiveness to β agonists and antagonists	Decreased sensitivity to β agonists and antagonists
Suppressed renin-angiotensin-aldosterone system	Theoretically decreased response to ACE inhibitors, but not observed
Increased sensitivity to anticoagulant agents	Increased effects of warfarin
Concurrent illnesses	Increased drug-disease interactions
Multiple drugs	Increased drug-drug interactions
Sinus and AV node dysfunction	Potential for heart block

AV indicates atrioventricular.

Adapted from Hui KK. Gerontologic considerations in cardiovascular pharmacology and therapeutics. In: Singh BN, Dzau VJ, Vanhoutte PM, Woosley RL, eds. *Cardiovascular Pharmacology and Therapeutics.* New York, NY: Churchill-Livingstone; 1994:1130.

increased, and there is a reduction in both the LV early diastolic filling rate and volume.[18]

The pharmacodynamic, chronotropic, and inotropic effects of β-agonists and β-blockers on β_1-adrenergic receptors are diminished in the elderly.[19–21] The density of β-receptors in the heart is unchanged in the elderly, but there is a decrease in the ability of β-receptor agonists to stimulate cyclic adenosine monophosphate production.[22] There are also age-related changes in the cardiac conduction system, and an increase in arrhythmias in the elderly. In the Framingham study, the prevalence of atrial fibrillation was 1.8% in persons 60–69 years old, 4.8% in those 70–79 years old, and 8.8% in those 80–89 years old.[23] In a study of 3624 elderly patients (mean age 81 years), the prevalence of atrial fibrillation was 16% (1160) in elderly men and 13% (2464) in elderly women.[24]

In elderly patients with unexplained syncope, a 24-hour ambulatory electrocardiogram (ECG) should be obtained to rule out the presence of second degree or third degree atrioventricular block or sinus node dysfunction with pauses >3 seconds not seen on the resting ECG. These phenomena were observed in 21 of 148 patients (14%) with unexplained syncope.[25] These 21 patients included 8 with sinus arrest, 7 with advanced second degree atrioventricular block, and 6 with atrial fibrillation with a slow ventricular rate not drug-induced. Unrecognized sinus node or atrioventricular node dysfunction may become evident in elderly persons after drugs such as amiodarone, β-blockers, digoxin, diltiazem, procainamide, quinidine, or verapamil are administered. Therefore, clinical use of these drugs in the elderly must be carefully monitored.

USE OF CARDIOVASCULAR DRUGS IN THE ELDERLY

Digoxin

Digoxin has a narrow toxic-therapeutic ratio, especially in the elderly.[26] Decreased renal function and lean body mass may increase serum digoxin levels in this population. Serum creatinine levels may be normal in elderly persons despite a marked reduction in creatinine clearance, thereby decreasing digoxin clearance and increasing serum digoxin levels. Older persons are also more likely to take drugs that interact with digoxin by interfering with bioavailability and/or elimination. Quinidine, cyclosporin, itraconazole, calcium preparations, verapamil, amiodarone, diltiazem, triamterene, spironolactone, tetracycline, erythromycin, propafenone, and propantheline can increase serum digoxin levels. Hypokalemia, hypomagnesemia, hypercalcemia, hypoxia, acidosis, acute and chronic lung disease, hypothyroidism, and myocardial ischemia may also cause digitalis toxicity despite normal serum digoxin levels. Digoxin may also cause visual disturbances,[27] depression, and confusional states in older persons, even with therapeutic blood levels.

Indications for using digoxin are slowing a rapid ventricular rate in patients with supraventricular tachyarrhythmias such as atrial fibrillation, and treating patients with congestive heart failure (CHF) in sinus rhythm associated with abnormal LV ejection fraction that does not respond to diuretics, ACE inhibitors, and β-blockers with a class IIa indication.[28] Digoxin should not be used to treat patients with CHF in sinus rhythm associated with normal LV ejection fraction. By increasing contractility through increasing intracellular calcium ion concentration, digoxin may increase LV stiffness and increase LV filling pressures, adversely affecting LV diastolic dysfunction. Because almost half the elderly patients with CHF have normal LV ejection fractions,[29,30] LV ejection fraction should be measured in all older patients with CHF, so that appropriate therapy may be given.[31] Many older patients with compensated CHF who are in sinus rhythm and are on digoxin may have digoxin withdrawn without decompensation in cardiac function.[32,33]

A post hoc subgroup analysis of data from women with a LV ejection fraction <45% in the Digitalis Investigator Group (DIG) study showed by multivariate analysis that digoxin significantly increased the risk of death among women by 23% (absolute increase of 4.2%).[34] A post hoc subgroup analysis of data from men with a LV ejection fraction <45% in the DIG study showed that digoxin significantly reduced mortality by 6% if the serum digoxin level was 0.5–0.8 ng/mL, insignificantly increased mortality by 3% if the serum digoxin level was 0.8–1.1 ng/mL, and significantly increased mortality by 12% if the serum digoxin level was ≥1.2 ng/mL.[35]

Another post hoc subgroup analysis of data from all 1926 women with systolic or diastolic heart failure in the DIG study showed that digoxin significantly increased mortality by 20% in women.[36] However, digoxin did not increase

mortality in women with a LV ejection fraction <35% and a serum digoxin level of 0.5–1.1 ng/mL.[37] In women with a LV ejection fraction <35% and a serum digoxin level ≥1.2 ng/mL, digoxin significantly increased mortality 1.83 times.[37]

Therapeutic levels of digoxin do not reduce the frequency or duration of episodes of paroxysmal atrial fibrillation detected by 24-hour ambulatory ECGs.[38] In addition, therapeutic concentrations of digoxin do not prevent the occurrence of a rapid ventricular rate in patients with paroxysmal atrial fibrillation.[38,39] Many elderly patients are able to tolerate atrial fibrillation without the need for digoxin therapy because the ventricular rate is slow as a result of concomitant atrioventricular nodal disease.

Some studies have suggested that digoxin may decrease survival after acute myocardial infarction (MI) in patients with LV dysfunction.[40,41] Leor et al[42] showed that digoxin may exert a dose-dependent deleterious effect on survival in patients after acute MI, although other studies have not confirmed this finding.[43,44] Eberhardt et al[45] demonstrated in the Bronx Longitudinal Aging study that digoxin use in the elderly without evidence of CHF was an independent predictor of mortality. The results of the DIG study trial demonstrated that digoxin could be used in older subjects with CHF, but in lower doses than that previously employed in clinical practice.[46]

Diuretics

The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure recommended as initial drug treatment of hypertension thiazide-like diuretics or β-blockers because these drugs had been demonstrated to reduce cardiovascular morbidity and mortality in controlled clinical trials.[47] Moreover, the results of the Systolic Hypertension in the Elderly (SHEP) trial specifically show the safety and efficacy of a diuretic and β-blocker in the treatment of isolated systolic hypertension in the elderly.[48] In the elderly, a blanket recommendation for the starting medication in the treatment of hypertension is ill-advised, in part, because of the presence of comorbid conditions. For example, in elderly hypertensive patients with CHF and a reduced LV ejection fraction[49–53] or in those elderly patients with CHF with a normal LV ejection fraction,[53–55] therapy should include a diuretic, an ACE inhibitor, and a β-blocker.

Loop diuretics remain first-line drug therapy in the treatment of patients with decompensated CHF. Diuretics are multifaceted in their effect in CHF. First, they effect a reduction in plasma volume by triggering a time-dependent natriuretic response. This drop in plasma volume reduces venous return and thereby decreases ventricular filling pressures. These volume changes facilitate relief of congestive symptomatology, such as peripheral and/or pulmonary edema. Intravenous loop-diuretic therapy has also been shown to increase central venous capacitance, which may further contribute to improvement in congestive symptomatology. Both loop and thiazide-like diuretics undergo a mixed pattern of renal/hepatic elimination with the component of renal clearance being responsible for diuresis.[56] Age-related decreases in renal function may reduce the efficacy of conventional doses of diuretics in elderly patients. This "renal function-related resistance" can be easily overcome, if recognized, by careful upward titration of the diuretic dose. Resistance to diuretic effect in CHF may also derive from a pattern of variable and unpredictable absorption, particularly with the loop diuretic furosemide. This issue is resolvable with the use of a predictably absorbed loop diuretic, such as torsemide.[57]

A thiazide-like diuretic, such as hydrochlorothiazide, may be used in the occasional older patient with mild CHF. However, thiazide-like diuretics have diminished effectiveness at conventional doses when the glomerular filtration rate falls below 30 mL/min; accordingly, older patients with moderate-to-severe CHF should be treated with a loop diuretic, such as furosemide. Older patients with severe CHF or concomitant significant renal insufficiency may need combination diuretic therapy employing a loop diuretic together with the thiazide-like diuretic metolazone.[56] The slowly and erratically absorbed form of metolazone (Zaroxylyn) is the preferred form when combination therapy is being considered. Nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease both the antihypertensive and natriuretic effect of loop diuretics.[56] This is a particular problem when loop diuretics are being employed to manage CHF-related congestive symptomatology.[58] A final consideration is the sometimes insidious manner by which NSAIDs can interact with diuretics as several commonly used NSAIDs are now available over-the-counter.

Serum electrolytes need to be closely monitored in older patients treated with diuretics. Hypokalemia and/or hypomagnesemia, both of which may precipitate ventricular arrhythmias and/or digitalis toxicity, can occur with diuretic therapy.[59] Hyponatremia is not uncommon in the elderly treated with diuretics, particularly when thiazide-like diuretics are being employed.[60] Older patients with CHF are especially sensitive to volume depletion with dehydration, hypotension, and prerenal azotemia occurring in the face of excessive diuretic effect. Older patients with CHF and normal LV ejection fraction should receive diuretics more cautiously.

β-Adrenergic Blockers

β-Blockers are used in various cardiovascular disorders, with resultant beneficial and adverse effects.[61] β-Blockers are very effective antianginal agents in older and younger patients. Combined therapy with β-blockers and nitrates may be more beneficial in the treatment of angina pectoris than either drug alone.[61]

Diuretics or β-blockers have been recommended as initial drug therapy for hypertension in older persons, because these drugs have been shown to decrease cardiovascular morbidity and mortality in controlled clinical trials.[47,62] β-Blockers are especially useful in the treatment of hypertension in older patients who have had a prior MI, angina pectoris, silent myocardial ischemia, complex ventricular arrhythmias, supraventricular tachyarrhythmias, or hypertrophic cardiomyopathy.

Teo et al[63] analyzed 55 randomized controlled trials that investigated the use of β-blockers in patients after MI. Mortality was significantly decreased (19%) in patients receiving β-blockers, when compared with control patients. In the Beta Blocker Heart Attack Trial (BHAT), propranolol

TABLE 4. Effect of β Blockers on Mortality in Elderly Patients With Complex Ventricular Arrhythmias and Heart Disease

Study	Age (yr)	Mean Follow-up (mo)	Results
BHAT[64]	60–69 (33%)	25	Compared with placebo, propranolol reduced sudden cardiac death by 28% in patients with complex VA and 16% in patients without VA
Hallstrom[75]	62 (mean)	108	Reduced incidence of death or recurrent cardiac arrest in patients treated with β blockers vs. no antiarrhythmic drug (adjusted relative risk 0.62)
Aronow et al[71]	62–96 (mean 81)	29	Compared with no antiarrhythmic drug, propranolol caused a 47% significant decrease in sudden cardiac death, a 37% significant reduction in total cardiac death, and a 20% insignificant decrease in total death
Aronow et al[72]	62–96 (mean 81)	29	Among patients taking propranolol, suppression of complex VA caused a 33% reduction in sudden cardiac death, a 27% decrease in total cardiac death, and a 30% reduction in total death; abolition of silent ischemia caused a 70% decrease in sudden cardiac death, a 72% reduction in total cardiac death, and a 69% decrease in total death
Aronow et al[76]	62–96 (mean 81)	29	Incidence of sudden cardiac death or fatal MI was significantly increased between 6 AM and 12 AM, with peak hour at 8 AM and secondary peak at 7 PM in patients with no antiarrhythmic drug; propranolol abolished the circadian distributionof sudden cardiac death or fatal MI
CAST[77]	66–79 (40%)	12	Patients on β blockers (30% of study group) had a significant reduction in all-cause mortality of 43% at 30 d, 46% at 1 yr, and 33% at 2 yr: in patients on β blockers, arrhythmic death or cardiac arrest was significantly reduced by 66% at 30 d, 53% at 1 yr, and 36% at 2 yr; multivariate analysis showed β blockers to be an independent factor for reduced arrhythmic death or cardiac arrest by 40% and for all-cause mortality by 33%

VA indicates ventricular arrhythmias.

Reproduced from Aronow WS. Cardiovascular drug therapy in the elderly. In: Frishman WH, Sonnenblick EH, eds. *Cardiovascular Pharmacotherapeutics.* New York, NY: McGraw Hill; 1997:1273.

significantly decreased total mortality by 34% in patients 60–69 years old, and insignificantly reduced total mortality by 19% in patients 30–59 years old.[64] In the Norwegian Timolol Study, timolol significantly decreased total mortality by 43% in postinfarction patients 65–75 years old, and significantly reduced total mortality by 34% in postinfarction patients <65 years old.[65] Despite the utility of β-blockers in postmyocardial infarction patients, they are still being underutilized in older patients.[66–68]

β-Blockers decrease complex ventricular arrhythmias including ventricular tachycardia.[69–72] β-Blockers also increase the ventricular fibrillation threshold in animal models, and have been shown to reduce the incidence of ventricular fibrillation in patients with acute MI.[73] A randomized, double-blind, placebo-controlled study of propranolol in high-risk survivors of acute MI at 12 Norwegian hospitals demonstrated that patients treated with propranolol for 1 year had a statistically significant 52% decrease in sudden cardiac death.[70]

In addition, β-blockers decrease myocardial ischemia,[71,72,74] which may reduce the likelihood of ventricular fibrillation. Stone et al[74] demonstrated by 48-hour ambulatory ECGs in 50 patients with stable angina pectoris that propranolol, not diltiazem or nifedipine, caused a significant decrease in the mean number of episodes of myocardial ischemia and in the mean duration of myocardial ischemia, when compared with placebo. Furthermore, β-blockers reduce sympathetic tone.

Studies have demonstrated that β-blockers reduce mortality in older and younger patients with complex ventricular arrhythmias and heart disease (Table 4).[64,71,72,75–77] In the BHAT of 3290 patients comparing propranolol with placebo, propranolol reduced sudden cardiac death by 28% in patients with complex ventricular arrhythmias and by 16% in patients without ventricular arrhythmias.[64]

Hallstrom et al[75] performed a retrospective analysis of the effect of antiarrhythmic drug use in 941 patients resuscitated from prehospital cardiac arrest due to ventricular fibrillation between 1970 and 1985. β-blockers were administered to 28% of the patients, and no antiarrhythmic drug to 39%. There was a reduced incidence of death or recurrent cardiac arrest in patients treated with β-blockers versus no antiarrhythmic drug (relative risk 0.47; adjusted relative risk 0.62).

Aronow et al[76] performed a prospective study in 245 elderly patients (mean age 81 years) with heart disease (64% with prior MI and 36% with hypertensive heart disease), complex ventricular arrhythmias diagnosed by 24-hour ambulatory ECGs, and LV ejection fraction ≥40%. Nonsustained ventricular tachycardia occurred in 32% of patients. Myocardial ischemia occurred in 33% of patients. Mean follow-up was 30 months in patients randomized to propranolol and 28 months in patients randomized to no antiarrhythmic drug. Propranolol was discontinued because of adverse effects in 11% of patients. Follow-up 24-hour ambulatory ECGs showed that propranolol was significantly more effective than no antiarrhythmic drug in reducing ventricular tachycardia (>90%), in decreasing the average number of ventricular premature complexes per hour (>70%), and in abolishing silent ischemia.

Multivariate Cox regression analysis showed that propranolol caused a significant 47% decrease in sudden cardiac death, a significant 37% reduction in total cardiac death, and an insignificant 20% decrease in total death.[71] Univariate Cox regression analysis showed that the reduction in mortality and

complex ventricular arrhythmias in elderly patients with heart disease taking propranolol was due more to an anti-ischemic effect than to an antiarrhythmic effect.[72] Table 4 also shows that there was a circadian distribution of sudden cardiac death or fatal MI, with the peak incidence occurring from 6 AM to 12 AM (peak hour 8 AM and secondary peak around 7 PM) in patients treated with no antiarrhythmic drug.[76] Propranolol abolished this circadian distribution of sudden cardiac death or fatal MI.[76]

In a retrospective analysis of data from the Cardiac Arrhythmia Suppression Trial (CAST), Kennedy et al[77] found that 30% of patients with an LV ejection fraction ≤40% were receiving β-blockers. Forty percent of these 1735 patients were between 66 and 79 years old. Patients on β-blockers had a significant reduction in all-cause mortality of 43% within 30 days, 46% at 1 year, and 33% at 2 years. Patients receiving β-blockers also had a significant decrease in arrhythmic death or cardiac arrest of 66% at 30 days, 53% at 1 year, and 36% at 2 years. Multivariate analysis showed that β-blockers were an independent factor for reducing arrhythmic death or cardiac arrest by 40%, for decreasing all-cause mortality by 33%, and for reducing the occurrence of new or worsening CHF by 32%. On the basis of these data,[64,71,72,75–77] β-blockers can be used in the treatment of older and younger patients with ventricular tachycardia or complex ventricular arrhythmias associated with ischemic or nonischemic heart disease, and with normal or abnormal LV ejection fraction, if there are no absolute contraindications to the drugs.

β-Blockers are also useful in the treatment of supraventricular tachyarrhythmias in older and younger patients.[78,79] If a rapid ventricular rate associated with atrial fibrillation persists at rest or during exercise despite digoxin therapy, then verapamil,[80] diltiazem,[81] or a β-blocker[82] should be added to the therapeutic regimen. These drugs act synergistically with digoxin to depress conduction through the atrioventricular junction. The initial oral dose of propranolol is 10 mg every 6 hours, which can be increased to a maximum of 80 mg every 6 hours if necessary.

β-Blockers have been demonstrated to reduce mortality in older persons with New York Heart Association Class II–IV CHF and abnormal LV ejection fraction treated with diuretics and ACE inhibitors with or without digoxin.[52,53,83–87] β-Blockers have also been shown to reduce mortality in older persons with New York Heart Association Class II–III CHF and normal LV ejection fraction treated with diuretics plus ACE inhibitors.[53,55,86,87]

Numerous drug interactions have been reported with β-blockers in the elderly.[61] Recently, quinidine, a known inhibitor of CYP2D6, was shown to decrease the hepatic metabolism of topically-applied ophthalmic timolol, with resultant exaggeration of the β-blocking effect of timolol.[88]

ACE Inhibitors

ACE inhibitors are effective antihypertensive agents. A meta-analysis of 109 treatment studies showed that ACE inhibitors are more effective than other antihypertensive drugs in decreasing LV mass.[89] Older hypertensive patients with CHF associated with abnormal[49–51] or normal[54] LV ejection fraction, LV hypertrophy, or diabetes mellitus should initially be treated with an ACE inhibitor.

ACE inhibitors reduce mortality in patients with CHF associated with abnormal LV ejection fraction.[49–51] The Survival and Ventricular Enlargement (SAVE) trial[90] and the combined Studies of Left Ventricular Dysfunction (SOLVD) treatment and prevention trials[91] also demonstrated that ACE inhibitors such as captopril or enalapril should be standard therapy for most patients with significant LV systolic dysfunction with or without CHF. In addition, ACE inhibitor therapy has been shown to be beneficial in the treatment of elderly patients (mean age 80 years) with CHF caused by prior MI associated with normal LV ejection fraction.[54] High-dose ACE inhibitor therapy remains the standard-of-care in the management of CHF. Low-dose ACE inhibitor therapy has been studied in CHF, but with less favorable results. For example, a recent trial compared low-dose lisinopril (2.5–5.0 mg/d) with high-dose lisinopril (32.5–35.0 mg/d), with the latter being associated with a more significant reduction in mortality and all-cause hospitalization rate.[92]

An observational prospective study was performed in 477 patients (mean age 79 years) with prior MI and an asymptomatic LVEF <40% (mean LVEF 31%).[93] At 34-month follow-up, patients treated with ACE inhibitors without β-blockers had a 17% significant reduction in new coronary events and a 32% significant reduction in CHF.[93] At 34-month follow-up, patients treated with β-blockers without ACE inhibitors had a 25% significant reduction in new coronary events and a 41% significant reduction in CHF.[93] At 41-month follow-up, patients treated with both β-blockers and ACE inhibitors had a significant 37% reduction in new coronary events and a significant 60% reduction in CHF.[93]

Treatment with ACE inhibitors should be initiated in elderly patients in low doses after correction of hyponatremia or volume depletion. It is important to avoid overdiuresis before beginning therapy with ACE inhibitors because volume depletion may cause hypotension or renal insufficiency when ACE inhibitors are begun or when the dose of these drugs is increased to full therapeutic levels. After the maintenance dose of ACE inhibitor is reached, it may be necessary to increase the dose of diuretics. The initial dose of enalapril is 2.5 mg daily and of captopril is 6.25 mg TID (thrice daily). The maintenance doses are 5–20 mg daily and 25–50 mg TID, and the maximum doses are 20 mg twice daily and 150 mg TID, respectively.

Older patients at risk for excessive hypotension should have their blood pressure monitored closely for the first 2 weeks of ACE inhibitor or angiotensin II receptor blocking therapy, and thereafter whenever the dose of ACE inhibitor or diuretic is increased. Renal function should be monitored in patients on ACE inhibitors to detect increases in blood urea nitrogen and serum creatinine, especially in older patients with renal artery stenosis. A rise in serum creatinine in an ACE inhibitor-treated congestive heart failure patient is not uncommonly the result of ACE inhibitor-induced alterations in renal hemodynamics. There is no specific rise in serum creatinine where corrective actions need be taken though logic would suggest the greater the increment in serum creatinine the more important the intervention. Typically, reducing or temporarily discontinuing diuretics and/or liber-

alizing sodium intake are sufficient measures to return renal function to baseline. Not uncommonly though, the administered ACE inhibitor is either stopped or the dose reduced. In most instances, ACE inhibitor therapy can be safely resumed as long as careful attention is paid to patient volume status.[94] Potassium-sparing diuretics or potassium supplements should be carefully administered to patients receiving ACE inhibitor therapy because of the attendant risk of hyperkalemia. In this regard, the Randomized Aldactone Evaluation Study (RALES) showed that, in persons with severe CHF treated with diuretics, ACE inhibitors, and digoxin compared with placebo, spironolactone 25 mg/d did not carry an excessive risk of hyperkalemia while resulting in a significant reduction in mortality and hospitalization for CHF.[95]

Angiotensin II Receptor Blockers

Angiotensin-II receptor blockers (ARBs) are the newest class of antihypertensive drugs to be approved. They have been studied fairly extensively in hypertension,[96–98] diabetic nephropathy,[99] and CHF,[100] with results comparable to those seen when these disease states are treated with ACE inhibitors. Although published reports on the experience with these drugs in the elderly are limited, the drugs seem to be safe if used with similar precautions as those recommended for ACE inhibitors, as described above.[96,98] These drugs are noteworthy in that they have a more favorable side-effect profile and, in particular, are not associated with cough, a fairly common side effect with ACE inhibitor therapy.[97] Likewise, in the Losartan Heart Failure Survival Study (ELITE II), losartan was associated with fewer adverse effects than was captopril.[101] Outcomes studies are supportive of ARBs, such as losartan and irbesartan, being superior to conventional non-ACE-inhibitor-based therapy in decreasing end-stage renal failure event rates in patients with Type II diabetic nephropathy.[102,103] In CHF the hope that ARBs are more effective therapy than ACE inhibitors has not been realized, as of yet, though additional studies are underway to establish the positioning of ARB in current heart failure regimens.

Nitrates

Nitrates are effective therapies for older individuals; however, caution should always be used because of the associated dangers of orthostatic hypotension, syncope, and falls, especially if the treatment is combined with diuretics and other vasodilators. Recently it was shown that nitrate headaches are less frequent in older patients and in individuals with renal dysfunction.[104]

Calcium Channel Blockers

Calcium channel blockers are effective antihypertensive and antianginal drugs in older patients. Verapamil[80] and diltiazem[81] are especially valuable in treating hypertensive patients who also have supraventricular tachyarrhythmias. However, recent reports have suggested an increased mortality risk with calcium channel blockers, especially with the use of short-acting dihydropyridines in older subjects.[105–107] With the use of longer-acting calcium blockers, such as the dihydropyridine nitrendipine, a strong mortality benefit was seen in patients with isolated systolic hypertension,[108] although many were receiving concurrent β-blocker therapy. In contrast, nisoldipine was shown to be less effective in protecting against cardiovascular mortality in diabetic patients with hypertension when compared with an enalapril-treated group.[109]

Verapamil improved exercise capacity, peak LV filling rate, and a clinicoradiographic heart failure score in patients with CHF, normal LV ejection fraction, and impaired LV diastolic filling.[110] However, calcium channel blockers such as verapamil, diltiazem and nifedipine may exacerbate CHF in patients with associated abnormal LV ejection fraction.[111] In addition, some calcium channel blockers have been shown to increase mortality in patients with CHF and abnormal LV ejection fraction after MI.[112] Therefore, calcium channel blockers such as verapamil, diltiazem, and nifedipine may be used to treat older patients with CHF associated with normal LV ejection fraction, but are contraindicated in treating older patients with CHF associated with abnormal LV ejection fraction.

Amlodipine and felodipine are 2 vasculospecific dihydropyridine agents that seem to be safer in patients having CHF, although neither of these drugs should be used to treat CHF.[28]

The age-associated decrease in hepatic blood flow and hepatic metabolic capacity may result in higher serum concentrations of verapamil, diltiazem, and nifedipine.[113] Therefore, these drugs should be given to older persons in lower starting doses and titrated carefully.

α-Adrenergic Blockers

α-adrenergic blockers are effective treatments for patients with hypertension and have become first-line treatments for men with symptomatic prostatism. Caution should be exercised when using these agents because of a significant incidence of postural hypotension, especially in patients receiving diuretics or other vasodilator drugs.[114,115] A more selective α_1-blocker, tamsulosin, has become available, which improves prostatism symptoms without having vasodilator effects.[116] However, the National Heart, Lung and Blood Institute withdrew doxazosin from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) after an interim analysis showed in patients on doxazosin there was a 25% greater rate of a secondary end point and combined cardiovascular disease than in patients on chlorthalidone, largely driven by the increased risk of CHF.[117] These findings have cast a shroud over the use of doxazosin in the elderly particularly if it is being contemplated as monotherapy in an elderly hypertensive.

Lidocaine

Intravenous lidocaine may be used to treat complex ventricular arrhythmias during acute MI.[78] Lidocaine toxicity is more common in the elderly, so older patients should be monitored for dose-related confusion, tinnitus, paresthesias, slurred speech, tremors, seizures, delirium, respiratory depression, and hypotension. Older patients with CHF or impaired liver function are at increased risk for developing central nervous system adverse effects from lidocaine.[118] In these patients, the loading dose should be decreased by

TABLE 5. Cardiovascular Drugs Regularly Detected as the Culprit in Some Common Disorders of the Elderly

Disorder	Drugs
Confusion states	β blockers, digoxin, methyldopa and related drugs, quinidine
Tinnitus, vertigo	Aspirin, furosemide, ethacrynic acid
Depression	β blockers, methyldopa, reserpine
Falls	All drugs liable to produce postural hypotension, glycerol trinitrates
Postural hypotension	All antihypertensives, antianginal drugs, β blockers, diuretics
Constipation	Anticholinergics, clonidine, diltiazem, diuretics, verapamil
Urinary retention	Disopyramide, midodrine
Urinary incontinence	β blockers, diuretics, labetalol, prazosin

Adapted from Hui KK. Gerontologic considerations in cardiovascular pharmacology and therapeutics. In:, Sinsh BN, Dzau VJ, Vanhoutte PM, Woosley RL, eds. *Cardiovascular Pharmacology and Therapeutics.* New York, NY: Churchill-Livingstone; 1994:1131.

25–50%, and any maintenance infusion should be initiated at a rate of 0.5–2.5 mg/min, with the patient monitored closely for adverse effects. The dose of lidocaine should also be reduced if the patient is receiving β-blockers[119] or cimetidine, because these drugs reduce the metabolism of lidocaine.

Other Antiarrhythmic Drugs

The use of antiarrhythmic drugs in the elderly is extensively discussed elsewhere.[79,120] In the CAST I trial, encainide and flecainide significantly increased mortality in survivors of MI with asymptomatic or mildly symptomatic ventricular arrhythmias, when compared with placebo.[121] In the CAST II, moricizine insignificantly increased mortality, when compared with placebo.[122] Akiyama et al[123] found that older age increased the likelihood of adverse events, including death, in patients treated with encainide, flecainide, or moricizine in these 2 studies.

In a retrospective analysis of the effect of empirical antiarrhythmic treatment in 209 cardiac arrest patients who were resuscitated outside of the hospital, Moosvi et al[124] found that the 2-year mortality was significantly lower in patients treated with no antiarrhythmic drug than in patients treated with quinidine or procainamide. Hallstrom et al[75] showed an increased incidence of death or recurrent cardiac arrest in patients treated with quinidine or procainamide versus no antiarrhythmic drug.

In a prospective study of 406 elderly subjects (mean age 82 years) with heart disease (58% with prior MI) and asymptomatic complex ventricular arrhythmias, the incidence of sudden cardiac death, total cardiac death, and total mortality were not significantly different in patients treated with quinidine or procainamide or with no antiarrhythmic drug.[125] In this study, quinidine or procainamide did not reduce mortality in comparison with no antiarrhythmic drug in elderly patients with presence versus absence of ventricular tachycardia, ischemic or nonischemic heart disease, and abnormal or normal LV ejection fraction. The incidence of adverse events causing drug cessation in elderly patients in this study was 48% for quinidine and 55% for procainamide.

A meta-analysis of 6 double-blind studies of 808 patients with chronic atrial fibrillation who underwent direct current cardioversion to sinus rhythm demonstrated that the 1-year mortality was significantly higher in patients treated with quinidine than in patients treated with no antiarrhythmic drug.[126] In the Stroke Prevention in Atrial Fibrillation Study, arrhythmic death and cardiac mortality were also significantly increased in patients receiving antiarrhythmic drugs when compared with those not receiving antiarrhythmic drugs, especially in patients with a history of CHF.[127]

Teo et al[63] analyzed 59 randomized controlled trials, comprising 23,229 patients, which investigated the use of class I antiarrhythmic drugs after MI. Patients receiving class I antiarrhythmic drugs had a significantly higher mortality than did patients receiving no antiarrhythmic drugs. None of

TABLE 6. Important Drug-Disease Interactions in Geriatric Patients

Underlying Disease	Drugs	Adverse Effect
Congestive heart failure	β blockers, verapamil	Acute cardiac decompensation
Cardiac conduction disorders	Tricyclic antidepressants	Heart block
Hypertension	NSAIDs	Increased blood pressure
Peripheral vascular disease	β blockers	Intermittent claudication
Chronic obstructive pulmonary disease	β blockers	Bronchoconstriction
Chronic renal impairment	NSAIDs, contrast agents, aminoglycosides, ACE inhibitors	Acute renal failure
Diabetes mellitus	Diuretics	Hyperglycemia
Prostatic hypertrophy	Drugs with antimuscarinic side effects	Urinary retention
Depression	β blockers, centrally acting antihypertensives	Precipitation or exacerbation of depression
Hypokalemia	Digoxin	Cardiac arrhythmias
Peptic ulcer disease	Anticoagulants, salicylates	GI hemorrhage

NSAIDs, nonsteroidal anti-inflammatory drugs; GI, gastrointestinal.

Adapted from Parker BM, Cusack BJ. Pharmacology and appropriate prescribing. In: Reuben DB, Yoshikawa TT, Besdine RW, eds. *Geriatric Review Syllabus: A Core Curriculum in Geriatric Medicine.* 3rd ed. Iowa: Kendall/Hunt Publishers, Am Geriatric Soc, 1966:33.

TABLE 7. Selected Clinically Significant Drug–Drug Interactions in Geriatric Patients

Primary Drugs	Interacting Drugs	Mechanism of Interaction	Possible Effects
Augmented drug effects			
Antidiabetic sulfonylureas (tolbutamide, chlorpropamide)	Chloramphenicol, warfarin	IM	Hypoglycemia
	Phenylbutazone	IM, DP, IE	
	Quinidine	OM	
Azathioprine	Allopurinol	IM	Bone marrow suppression
Carbamazepine	Diltiazem, verapamil	IM	Increase serum carbamazepine concentration and risk of toxicity (eg, nausea, ataxia, nystagmus)
Cyclosporine	Diltiazem, verapamil	IM	Increase serum cyclosporine concentration and risk of toxicity (eg, hepato- and nephrotoxicity)
Digoxin	Amiodarone, diuretics, quinidine, verapamil	OM	Increase serum digoxin concentration and risk of toxicity (eg, nausea, confusion, cardiotoxicity)
Disopyramide	Diltiazem, verapamil	OM	Bradycardia
Lidocaine	β blockers, cimetidine	HBF	Increase serum lidocaine concentration and risk of toxicity (eg, sedation, seizures, cardiotoxicity
Methotrexate	Aspirin, indomethacin, phenylbutazone	DP, IE	Bone marrow suppression
	Probenecid	IE	
	Sulfisoxazole	DP	
Procainamide	Diltiazem, verapamil	OM	Bradycardia
Propranolol	Cimetidine	HBF	Bradycardia
	Diltiazem, verapamil	OM	Bradycardia, hypotension
Phenytoin	Amiodarone, chloramphenicol, cimetidine, fluconazole, isoniazid, phenylbutazone	IM	Increase serum phenytoin concentration and risk of toxicity (eg, nystagmus, sedation)
	Valproic acid, warfarin	DP, IM	
Quinidine	Diltiazem, verapamil	IM	Increase serum quinidine concentration and risk of toxicity (eg, nausea, cinchonism, arrhythmias)
Warfarin	Aspirin, indomethacin	DP	Hemorrhage
	Amiodarone, cimetidine, metronidazole	IM	
	Phenylbutazone, sulfonamides	DP, IM	
Decreased drug effects			
All medications	Cholestyramine	IA	Delay or reduce absorption of other drugs. Administer other drugs 1–2 h before or 4–6 h after cholestyramine
Antidiabetic sulfonylureas (tolbutamide, chlorpropamide)	β blockers (nonselective)	IIS, MCM, IIR	Decrease hypoglycemic effects
	Corticosteroids, thiazide diuretics	OM	
Digoxin	Sucralfate	IA	Reduce absorption of digoxin. Administer sucralfate at least 2 h apart from digoxin
Lincomycin	Kaolin-pectin	IA	Decrease drug bioavailability
Phenytoin	Calcium, sucralfate	IA	Decrease serum phenytoin concentration and anticonvulsant effect
	Rifampin	SM	
Prednisone	Barbiturates	SM	Decreased steroid effects
Quinidine	Barbiturates, rifampin	SM	Decrease antiarrhythmic effect
Tetracycline	Antacids-iron	IA	Decrease drug bioavailability
Warfarin	Barbiturates, carbamazepine, glutethimide, rifampin	SM	Loss of anticoagulant control
	Vitamin K	SP	
Other drug effects			
ACE inhibitors	Potassium-sparing diuretics, potassium-containing medications	RAP	Hyperkalemia
HMG-CoA reductase inhibitors	Cyclosporine, gemfibrozil, niacin	Unknown	Rhabdomyolysis, acute renal failure
	Erythromycin	IM	

IM indicates inhibition of drug metabolism; DP, displacement of protein binding; IE, inhibition of renal excretion; OM, other mechanisms (pharmacodynamic effects of drugs on tissue responses); HBF, decreased hepatic blood flow; IA, inhibition of drug absorption; IIS, inhibition of insulin secretion; MCM, modification of carbohydrate metabolism; IIR, increased peripheral insulin resistance; SM, stimulation of drug metabolism; SP, increased hepatic synthesis of procoagulant factors; RAP, reduction of aldosterone production.

Adapted from Bressler R. Adverse drug reactions. In: Bressler R, Katz MD, eds. *Geriatric Pharmacology.* New York, NY: McGraw Hill; 1993:54.

the 59 trials demonstrated that a class I antiarrhythmic drug decreased mortality in postinfarction patients. Therefore, it is currently not recommended that class I antiarrhythmic drugs be used for the treatment of ventricular tachycardia or complex ventricular arrhythmias associated with heart disease.

Amiodarone is very effective in suppressing ventricular tachycardia and complex ventricular arrhythmias. However, there are conflicting data about the effect of amiodarone on mortality.[128–135] The Veterans Administration Cooperative Study comparing amiodarone versus placebo in heart failure patients with malignant ventricular arrhythmias recently showed that amiodarone was very effective in decreasing ventricular tachycardia and complex ventricular arrhythmias, but it did not affect mortality.[134]

In the Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT), 2521 patients (mean age 60 years) with NYHA class II or III heart failure, a LV ejection fraction of 35% or less, and a mean QRS duration on the resting ECG of 120 milliseconds, were randomized to placebo, amiodarone, or an ICD.[135] At 46-month median follow-up when compared with placebo, amiodarone insignificantly increased mortality by 6%.[135] At 46-month median follow-up when compared with placebo, ICD therapy significantly reduced all-cause mortality by 23%.[135]

The incidence of adverse effects from amiodarone has been reported to approach 90% after 5 years of treatment.[136] In the Cardiac Arrest in Seattle: Conventional Versus Amiodarone Drug Evaluation study, the incidence of pulmonary toxicity was 10% at 2 years in patients receiving an amiodarone dose of 158 mg daily.[137] Based on these data, one should reserve the use of amiodarone for the treatment of life-threatening ventricular tachyarrhythmias or in patients who cannot tolerate or who do not respond to β-blocker therapy.

Amiodarone is also the most effective drug for treating refractory atrial fibrillation in terms of converting atrial fibrillation to sinus rhythm and slowing a rapid ventricular rate. However, because of the high incidence of adverse effects caused by amiodarone, amiodarone should be used in low doses in patients with atrial fibrillation when life-threatening atrial fibrillation is refractory to other therapy.[138]

Lipid-Lowering Drugs

The safety of lipid-lowering drugs, specifically 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (statins), was demonstrated in the Cholesterol Reduction in Seniors Program (CRISP)[139] Furthermore, a meta-analysis of 14 randomized trials of statins from 90,056 participants confirmed the safety and efficacy of statins.[140]

In the Scandinavian Simvastatin Survival Study,[141] 4444 men and women with coronary artery disease were treated with double-blind simvastatin or placebo. At 5.4 years follow-up, patients treated with simvastatin had a 35% decrease in serum low-density lipoprotein (LDL) cholesterol, a 25% reduction in serum total cholesterol, an 8% increase in serum high-density lipoprotein (HDL) cholesterol, a 34% decrease in major coronary events, a 42% reduction in coronary deaths, and a 30% decrease in total mortality. In patients 65–70 years old, simvastatin reduced all-cause mortality 35%, coronary artery disease mortality 43%, major coronary events 34%, nonfatal MI 33%, any atherosclerosis-related end point 34%, and coronary revascularization 41%.[142] The absolute risk reduction for both all-cause mortality and coronary artery disease mortality was approximately twice as great in persons 65–70 years old, when compared with persons younger than 65 years old.[142]

In the Cholesterol and Recurrent Events Trial,[143] 4159 men and women 21–75 years old (1283 65–75 years old) with MI, serum total cholesterol levels <250 mg/dL, and serum LDL cholesterol levels ≥ 115 mg/dL were treated with double-blind pravastatin and placebo. At 5-year follow-up, patients treated with pravastatin had a 32% reduction in serum LDL-cholesterol, a 20% decrease in serum total cholesterol and a 5% increase in serum HDL cholesterol. Pravastatin reduced coronary artery disease death or nonfatal MI significantly by 39% in persons 65–75 years old, and insignificantly by 13% in persons younger than 65 years old.[143] Pravastatin decreased major coronary events significantly by 32% in persons 65–75 years old, and significantly by 19% in persons younger than 65 years old. It also reduced stroke significantly by 40% in persons 65–75 years old, and insignificantly by 20% in persons younger than 65 years old. Pravastatin decreased coronary revascularization significantly by 32% in persons 65–75 years old, and significantly by 25% in persons younger than 65 years old. For every 1000 persons treated with pravastatin for 5 years, 225 cardiovascular events would be prevented in persons 65–75 years old and 121 cardiovascular events would be prevented in persons younger than 65 years old.[143]

In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, a randomized, placebo-controlled study of 5804 men and 3000 women, pravastatin 40 mg/d was shown to lower LDL concentrations by 34% in subjects 70–82 years old. In this study, drug treatment reduced coronary heart disease death and nonfatal MI. No benefit on stroke prevention was seen, and there were more cancer diagnoses with pravastatin. However, incorporation of this latter finding in a meta-analysis showed no overall increase in cancer risk.[144]

The Long-Term Intervention with Pravastatin in Ischemic Disease study randomized 9014 persons with a history of MI or unstable angina who had initial serum total cholesterol levels of 155–271 mg/dL to pravastatin 40 mg daily or placebo.[145] At 8-year follow-up of 3514 persons who were 65–75 years old at the start of the study, pravastatin, when compared with placebo, significantly reduced all-cause mortality by 21%, death from CHD by 24%, fatal and nonfatal MI by 26%, death from cardiovascular disease by 26%, need for coronary artery bypass graft surgery by 26%, and need for coronary angioplasty by 34%.[145]

The Heart Protection Study randomized 20,536 men and women (5806 of whom were 70–80 years old) with prior MI (8510 persons), other CHD (4876 persons), and no CHD (7150 persons) and a serum total cholesterol level of 135 mg/dL or higher to simvastatin 40 mg daily or to placebo.[146] Of the 7150 persons without CHD, 25% had cerebrovascular disease, 38% had peripheral arterial disease (PAD), 56% had diabetes mellitus, and 3% had only treated hypertension

without atherosclerotic vascular disease or diabetes mellitus. At 5-year follow-up, simvastatin, when compared with placebo, significantly reduced all-cause mortality by 13%, any cardiovascular death by 17%, major coronary events by 27%, any stroke by 25%, coronary or noncoronary revascularization by 24%, and any major cardiovascular event by 24%.[146] These significant reductions in mortality and in cardiovascular events occurred regardless of initial levels of serum lipids, age, or gender. First major cardiovascular event was significantly reduced with simvastatin by 24% in persons younger than 65 years old, by 23% in persons 65–69 years old, and by 18% in persons who were 70–80 years old at the start of the study.[146] Five years of simvastatin treatment prevented MI, stroke, and revascularization in 70–100 persons per 1000 treated persons.[146]

Sixty-nine elderly patients (mean age 75 years old) with intermittent claudication due to PAD were randomized to simvastatin 40 mg daily or placebo.[147] When compared with placebo, simvastatin significantly increased treadmill exercise time until the onset of intermittent claudication by 24% 6 months after treatment and by 42% 1 year after treatment.

Observational data have also demonstrated that at 3-year follow-up in 1410 men and women (mean age 81 years old) with CHD and hypercholesterolemia, the use of statins significantly reduced CHD death or nonfatal MI by 50%,[148] stroke by 60%,[149] and CHF by 48%.[150] The lower the reduction in serum LDL cholesterol, the greater the reduction in coronary events[148] and in stroke.[149] At 29-month follow-up, statins also significantly reduced new coronary events by 37% and new stroke by 47% in 529 men and women (mean age 79 years old) with diabetes mellitus, prior MI, and hypercholesterolemia.[151] In addition, at 39-month follow-up of 660 men and women with PAD and hypercholesterolemia, statins significantly reduced new coronary events by 52% in those with prior MI and by 59% in those with no prior MI.[152]

On the basis of the available data showing increased risk of cardiovascular disease from abnormal lipoprotein patterns,[153] dietary therapy for older patients with dyslipidemia, regardless of age, in the absence of other serious life-limiting illnesses such as cancer, dementia or malnutrition, is recommended.[154] If hyperlipidemia persists after 3 months of dietary therapy, hypolipidemic drugs should be considered, depending on serum lipid levels, presence or absence of coronary artery disease, presence or absence of other coronary risk factors, and the patient's overall clinical status. This approach is consistent with the recent National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults recommendations in men ≥65 years old and women ≥75 years old.[155] In older men and women, the HMG-CoA reductase inhibitors would be the drugs of choice for treating a high serum LDL-cholesterol level.

Recent data have demonstrated that the serum LDL cholesterol should be reduced to <70 mg/dL in high-risk persons, regardless of age or gender.[156–158] The updated NCEP III guidelines state that in very high-risk patients, a serum LDL cholesterol level of less than 70 mg/dL is a reasonable clinical strategy.[159] When a high-risk person has hypertriglyceridemia or low serum HDL cholesterol, consideration can be given to combining a fibrate or nicotinic acid with an LDL cholesterol-lowering drug.[159] For moderately high-risk persons (2 or more risk factors and a 10-year risk

TABLE 8. Selected Clinically Significant Drug–Alcohol Interactions in Geriatric Patients

Primary Drugs	Interacting Drug	Possible Effects
Antidiabetic sulfonylureas	Alcohol	Disulfiram-like reactions (especially with chlorpropamide)
ACE inhibitors	Alcohol	Hypotension
Isoniazid	Alcohol	Decreased therapeutic effect of isoniazid, increased risk of hepatic toxicity
Nitrates	Alcohol	Hypotension
Phenytoin	Alcohol	Decreased serum phenytoin concentration and effectiveness (chronic use of alcohol);increased serum phenytoin concentration and risk of toxicity (acute intake of alcohol)
Rifampin	Alcohol	Decreased therapeutic effect of rifampin, increased risk of hepatic toxicity
Sedatives-hypnotics	Alcohol	Excessive sedation
Vitamins	Alcohol	Decreased absorption and storage of folic acid and thiamine
Warfarin	Alcohol	Increased anticoagulant activity (acute intoxication); decreased anticoagulant activity (chronic abuse)

Reproduced from Frishman WH, Cheng A, Aronow WS. Cardiovascular drug therapy in the elderly. In: Tresch DD, Aronow WS, eds. *Cardiovascular Disease in the Elderly Patient.* 2nd ed. New York, NY: Marcel Dekker Inc.; 1999:761.

TABLE 9. Medications to Avoid in Older Patients

Medications	Prescribing Concerns
Disopyramide	Of all antiarrhythmics, disopyramide is the most potent negative inotrope and therefore may induce heart failure in the elderly. It is also strongly anticholinergic. When appropriate, other antiarrhythmic drugs should be used
Digoxin*	Because of decreased renal clearance of digoxin, doses in the elderly should rarely exceed 0.125 mg daily, except when treating atrial arrhythmias
Methyldopa* and methyldopa/HCTZ*	Methyldopa may cause bradycardia and exacerbate depression in the elderly. Alternate treatments for hypertension are generally preferred
Ticlopidine	Ticlopidine has been shown to be no better than aspirin in preventing clotting and is considerably more toxic. Avoid in the elderly

*Panelists believed that the severity of adverse reaction would be substantially greater when these drugs were recently started. In general, the greatest risk would be within about a 1-month period.

HCTZ indicates hydrochlorothiazide.

Adapted from Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med.* 1997; 57:1531–1536.

for CHD of 10–20%), the serum LDL cholesterol should be reduced to less than 100 mg/dL.[159] When LDL cholesterol-lowering drug therapy is used to treat high-risk persons or moderately high-risk persons, the serum LDL cholesterol should be reduced at least 30–40%.[159]

Anticoagulants

Anticoagulant therapy in the elderly is discussed extensively elsewhere.[79,160] Anticoagulants are effective in the prevention and treatment of many thromboembolic disorders, including venous thromboembolism and pulmonary embolism, acute MI, and embolism associated with prosthetic heart valves or atrial fibrillation. These conditions, necessitating the use of anticoagulants, are more common in elderly patients. In the report from the Sixty Plus Reinfarction Group, who evaluated the effects of oral anticoagulant therapy on total mortality after MI in patients over 60 years old, it was shown that active therapy lowered both mortality and reinfarction, when compared with placebo.[161] However, the treatment group also had more major bleeding complications.

The anticoagulant response to warfarin is increased with age.[162] Chronic diseases which increase the risk for bleeding during anticoagulant therapy are also more common in elderly patients. In addition, elderly patients are at higher risk for bleeding during anticoagulant therapy because of increased vascular or endothelial fragility.[163] Furthermore, older patients may be at increased risk for bleeding due to anticoagulant therapy because they may be taking other drugs which potentiate the anticoagulant effect. Drugs such as aspirin, cephalosporins, and penicillins increase the risk of bleeding in patients treated with heparin. Drugs such as allopurinol, amiodarone, aspirin, cimetidine, ciprofloxacin, clofibrate, cotrimoxazole, dextroproproxyphene, disulfiram, erythromycin, fluconazole, isoniazid, ketoconazole, meclofenamic acid, metronidazole, miconazole, norfloxacin, phenylbutazone, phenytoin, quinidine, sulfinpyrazone, sulindac, thyroxine, and trimethoprim-sulfamethoxazole potentiate the effect of warfarin, causing an increased prothrombin time and risk of bleeding.

ADVERSE EFFECTS OF DRUGS IN THE ELDERLY

Cardiovascular drugs are often associated with adverse effects that simulate common disorders of the elderly (Table 5). In addition, there are important drug–disease interactions (Table 6), drug–drug interactions (Table 7), and drug–alcohol interactions[164] (Table 8) that occur in older patients.

MEDICATIONS BEST TO AVOID IN THE ELDERLY

Careful selection of drugs and dosages of drugs in the elderly can minimize adverse outcomes while maximizing clinical improvement. In their first attempt to identify medications and doses of medication that may be best to avoid in the elderly, Beers and colleagues developed a set of explicit criteria after an extensive review of the literature and assistance from 13 well-recognized experts in geriatric medicine and pharmacology.[165] These criteria included 30 statements which described medications that should generally be avoided in nursing home residents, and statements which described doses, frequencies and duration of medications that should generally not be exceeded. Since the publication of the explicit criteria, several research studies have used these criteria to evaluate the appropriateness of medication prescribing in the elderly.[166–169] The most striking study of this type was performed by Willcox and colleagues[169] who reported a potentially inappropriate medication prescription in 23.5% of elderly residents in the community. Willcox and colleagues were criticized, however, for applying criteria which were designed for frail elderly patients in nursing homes to healthier elderly residents in the community, along with criteria that need to be updated.[170]

Acknowledging the limitation of this first set of criteria, Beers updated and expanded it to encompass elderly patients who are in the ambulatory setting, along with medications that should be avoided in elderly patients known to have certain conditions.[171] With the assistance of 6 nationally recognized experts in geriatric medicine and pharmacology, a set of 63 criteria was developed using the first set of criteria plus a more recent literature review. Of the 63 criteria, 28 criteria described medications or categories of medication that were considered to be potentially inappropriate when used by all older patients, 35 criteria described medications or categories of medications that were considered to be potentially inappropriate when used by elderly patients with any of 15 known medical conditions such as heart failure, diabetes, hypertension, asthma, and arrhythmias. The 6 panelists further rated these criteria for importance. The panelists considered a criterion to be severe when an adverse outcome was both likely to occur and, if it did occur, would likely lead to a clinically significant event.[171] Table 9 lists the cardiac medications that were recognized by the expert panel as having the highest severity of potential problems occurring from their use and the reasons for their avoidance. Table 10 lists medications that were identified by the expert panel as having the highest severity of potential problems and the

TABLE 10. Medications to Avoid in Older Patients With Specific Diseases and Conditions

Diseases/Conditions	Medications	Prescribing Concerns
Heart failure	Disopyramide	Negative inotrope; may worsen heart failure
Hypertension	Diet pills; amphetamines	May elevate blood pressure
Blood-clotting disorders, limited to those receiving anticoagulant	Aspirin, NSAIDS, dipyridamole, and ticlopidine	May cause bleeding in those using anticoagulants therapy
Syncope or falls	Long-acting benzodiazepine drugs	May contribute to falls
Arrhythmias	Tricyclic antidepressant drugs*	May induce arrhythmias

*Panelists believed that the severity of adverse reaction would be substantially greater when these drugs were recently started. In general, the greatest risk would be within about a 1-month period.

Adapted from Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med.* 1997;157:1531–1536.

reasons for their avoidance in the elderly when certain cardiac-related conditions exist.

Although these criteria serve as useful tools for assessing the quality of prescribing to the elderly, they do not identify all cases of potentially inappropriate prescribing. In fact, these criteria may identify appropriate prescribing as inappropriate at times. The latter case may particularly be likely when physicians and pharmacists carefully adjust medication regimens for specific needs of individual patients.[171]

PRUDENT USE OF MEDICATION IN THE ELDERLY

Although the elderly make up only 14% of our population, they receive more than 30% of all prescribed medication.[172] The increased exposure of medications in the elderly may lead to higher incidence of adverse drug reactions and drug–drug interactions in this population.[173]

Physiologic changes with aging may also alter the elimination of drugs that can contribute to adverse outcomes with medication usage. With these concerns in mind, several authors have suggested some steps which clinicians may employ to ensure safe prescribing.[172,174,175] These suggestions include the following:

- Acquire a full history of the patient's habits and medication use.
- Evaluate the need for drug therapy. Consider alternative nondrug approaches when appropriate.
- Know the pharmacology of the drugs prescribed.
- Start with low dose of medication and titrate up slowly.
- Titrate medication dosage according to the patient's response.
- Minimize the number of medications used.
- Educate patients regarding proper usage of medications.
- Be aware of medication cost, which may have an impact on compliance.
- Provide patient with a portable prescription record.
- Review the treatment plan regularly and discontinue medications no longer needed.

With proper monitoring and adequate understanding of the effects of medications in the elderly, the use of medication can be a positive experience for both the elderly patient and the clinician.

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