



Clinical pharmacology relevant to older adults with cardiovascular disease

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1 Introduction

Although older adults are generally among the highest users of cardiovascular medications, they are typically underrepresented or excluded from most efficacy and safety trials. Drug developers are usually reluctant to include many senior adults in randomized controlled clinical trials in part due to their high prevalence of multiple comorbidities, frailty, and polypharmacy; and to age-related pharmacokinetic and pharmacodynamic complexities. Consequently, there is often insufficient high quality evidence-based data to inform pharmacologic management of common cardiovascular conditions on older adults. In the absence of data, clinicians often rely on conceptual principles regarding metabolism and drug-drug interactions to minimize adverse drug events, but this is often not well-substantiated or standardized. A related challenge is poor cardiovascular medication adherence among older adults, and its detrimental impact on their health outcomes. In this brief review we highlight some aspects of these topics.

2 Pharmacokinetics and pharmacodynamics of old age

Pharmacokinetics refers to the processing of a drug by the body after its administration, a concept which encom-

passes absorption, distribution, metabolism and excretion (ADME). Table 1 highlights some of the age-related physiologic changes can affect pharmacokinetics.^[1] Most cardiovascular medications are given orally and a number of gastrointestinal changes can theoretically affect absorption. Fortunately, most oral cardiac medications are absorbed via passive diffusion which is not affected by age. One exception is the absorption of oral furosemide which can be impeded in older adults with heart failure (usually when fluid in the intestinal mucosa inhibits absorption) and which thereby leads to increased time required to reach maximal plasma concentration. Similarly, numerous changes in body composition could affect cardiovascular drug distribution. While in most cases, such susceptibilities have little clinical impact, it is pertinent when it affects volume of distribution and thereby changes the proper loading dose of a cardiac medication. For example, a loading dose for digoxin should be based on lean body weight, known to decrease with age, due to digoxin's extensive distribution to peripheral tissues including skeletal muscle.

Age-related changes in metabolism are more typical. Aging of the liver (i.e., decreased liver mass and decreased hepatic blood flow) often entails decreased phase I oxidative metabolism by CYP3a4 isoenzymes. The clearance of many HMG COA reductase inhibitors (atorvastatin, simvastatin, lovastatin) depends on this pathway and hence metabolism slows with age. Therefore older adults requiring these medications often benefit from lower daily dosages. The clearance of high hepatic extraction ratio cardiac drugs given parenterally such as labetalol, lidocaine, propranolol, and verapamil is also reduced and older patients also often benefit from decreases in their daily doses. Hepatic phase II

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Table 1. Physiologic changes in the older adult that may impact pharmacokinetics.

Gastrointestinal	Body composition	Liver	Renal
Decreased gastric acid	Decreased total body water	Decreased size	Decreased blood flow and glomerular filtration rate
Decreased gastric blood flow	Decreased lean body mass	Decreased blood flow	Decreased blood flow
Decreased gastric motility	Increased total body fat		Increased filtration rate
	Changes in plasma proteins and p-glycoprotein		Decreased tubular secretory function

metabolism is generally thought to be preserved with advancing age. There is some limited data suggesting that frailty may reduce the conjugation and clearance of substrates such as paracetamol and metoclopramide.

Changes in renal metabolism also occur with age (see Table 1). By age 80, glomerular filtration rate (GFR) may be one-half to two thirds that seen in younger adults aged 25–40 years.^[2] Unfortunately, this reduction in estimated GFR can be masked by overestimation of renal function when laboratory report results from the Modified Diet in Renal Disease (MDRD) formula when a serum creatinine test is ordered. The preferred estimating equation of GFR for dosing primarily renally cleared medications is the Cockcroft-Gault

$$\text{For men: } \frac{(140 - \text{age}) \times (\text{weight in kilograms})}{(\text{Serum creatinine}) \times (72)}$$

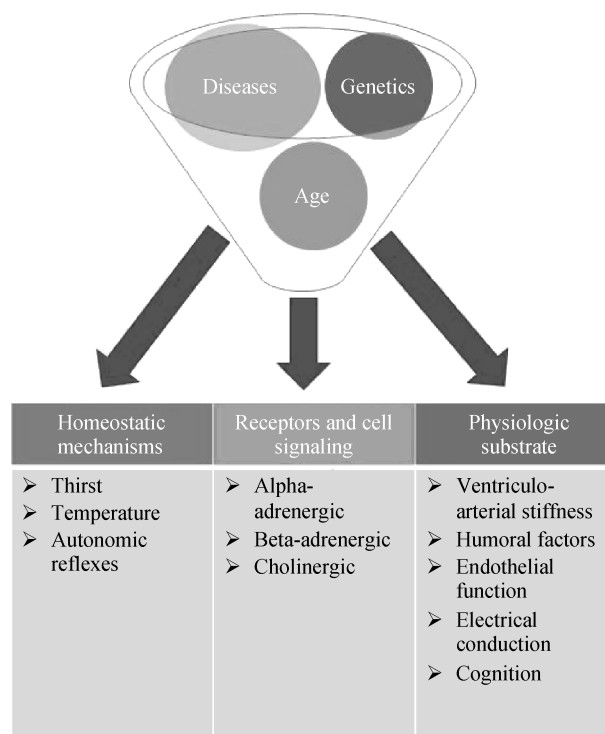
$$\text{For women: the above result} \times 0.85$$

Thus, the renal clearance of a number of medications such as digoxin, angiotensin enzyme inhibitors, *N*-acetyl procainamide, and the new antithrombotics (i.e., dabigatran, rivaroxaban, apixaban, and edoxaban) is reduced with age, and patients receiving renally metabolized medications also often benefit from lower daily doses.

Pharmacodynamics relates to the actions of the drug on the body. Figure 1 summarizes some of the age-related changes in homeostatic mechanisms, receptors and cell signaling, and physiological substrates.^[3] This can result in older adults having increased pharmacodynamic sensitivity to anticoagulants and the blood pressure reducing properties of calcium channel blockers. It is also important to note that decreased pharmacodynamic sensitivity can be seen with beta blockers such that higher doses are required to achieve lower heart rate goals.

3 Drug-drug and drug-disease interactions

Drug–drug interactions may be characterized as those that alter pharmacokinetics (i.e., clearance by hepatic metabolic enzymes or renal clearance) or pharmacodynamics, or those that have both pharmacokinetic and pharmacody-

**Figure 1. Factors that alter medication pharmacodynamics in older adults.**

amic interactions.^[4] Table 2 lists many of the cardiovascular drugs that have clinically important drug–drug interactions common among older adults.^[5,6] An example of a pharmacodynamic drug–drug interaction is that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can be associated with hyperkalemia in the presence of potassium supplements or potassium sparing diuretics. Examples of drug–drug interactions due to pharmacokinetic mechanisms include digoxin toxicity, which can be caused by amiodarone, macrolides, and verapamil). Warfarin is another common example. Clinically significant interactions can occur with warfarin via antibiotic-induced reduction in intestinal flora responsible for vitamin K synthesis (e.g., ciprofloxacin and cotrimoxazole), inhibition of the CYP450 enzyme group, especially CYP2C9 (e.g., amiodarone) or via a pharmacodynamic interaction (e.g., antiplatelet drugs and NSAIDs).

Drug–disease interactions are also more likely to occur in older patients (AGS 2012 Beers criteria).^[7] Some cardiac

Table 2. Clinically important cardiovascular drug-drug interactions in older adults.

Object	Interacting drug (s)	Effects
ACE-I/ARB	K+ supps, K+ sparing diuretics, SMX/TMP	↑ K+
Alpha-1 blockers	Loop diuretics	↑ Urinary incontinence
Peripheral*		
CCB	Clarithromycin, erythromycin	↑ Hypotension
Digoxin	Amiodarone, macrolides	↑ Digoxin toxicity
	verapamil	↑ Digoxin toxicity
Lithium	Loop diuretics	↑ Lithium toxicity
Warfarin	Amiodarone, ciprofloxacin	↑ Bleeding
	NSAIDs, SMX/TMP	

*Women only. ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker; CCB: calcium channel blockers; NSAIDs: nonsteroidal anti inflammatory drugs; SMX: sulfamethoxazole; TMP: trimethoprim.

medications (i.e., diltiazem and verapamil) can exacerbate chronic constipation, a frequent complaint of hospitalized, less active, and institutionalized elderly, heart failure (both diastolic and systolic) may be worsened by the use of non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, glitazones, dronedarone and cilostazol. Also of concern is that non-dihydropyridine calcium channel blockers (i.e., diltiazem and verapamil) can worsen systolic heart failure and that peripheral alpha blockers (i.e., prazosin, doxazosin, terazosin) may increase the risk of additional syncope episodes in those with a prior history.

4 Medication non-adherence in older adults

Approximately 50% of elderly patients are non-adherent with one or more of their medications.^[8] Overall though, older patients are have been reported to be adherent to 70%-80% of all medications, i.e., rates that are similar to those seen in younger patients who take multiple medications. Nonetheless, since older adults are more likely to receive multiple prescriptions, poor adherence in relation to advancing age remains common. Some risk factors associated with non-adherence in older adults include cost, complexity of medical regimen, depression, visual/hearing impairments and cognitive impairment. Limited health literacy with poor understanding of the expected benefit of a given medication also often plays a major role. In other instances, older patients may have good understanding of the potential benefits of a drug, but they may not value or want to focus on that clinical endpoint (e.g., increased long-term survival might not be as valued as the goal for fewer pills, and/or unintended consequences of the medication). Side effects, particularly those that affect independence and quality of life, also exacerbate non-adherence.

The implications of poor adherence are underscored by a study of 31,455 elderly patients with median follow-up of 2.4 years following acute myocardial infarction (MI); patients with high adherence to statins ($\geq 80\%$ of days covered) had an 8% absolute risk reduction in death compared to patients with low adherence ($< 40\%$ of days covered). A similar, but less pronounced effect was observed for beta-blockers.^[9] Adherence with dual-antiplatelet therapy becomes crucial after deployment of a coronary stent. In a study of 500 patients who received a drug-eluting stent following acute MI, 13.6% stopped taking their prescribed theinopyridine drug within 30 days following discharge; increasing age was a strong predictor for discontinuing the drug.^[10] Compared to adherent patients, those who discontinued theinopyridines had a 10-fold higher likelihood of death within 11 months. Older patients with heart failure are also at high risk of medication non-adherence, which in turn is associated with increased hospital readmission rates. Administrative claims data from patients with hypertension and hyperlipidemia have shown that higher medication adherence is associated with fewer hospitalizations and lower health-related costs.^[11]

Several simple strategies help to improve medication adherence in older adults. These include prescribing generic drugs (i.e., a step that reduces costs), especially since many seniors have a limited or fixed income. Minimizing the number of overall prescriptions and dosing frequency also helps reinforce compliance. In general, once or twice daily medications are preferred over three to four times daily medications. Moreover, given the difficulty for many older adults to keep accurate track of dates, regimens that entail every other day dosing are less likely to be successful. For more active patients, diuretic dosage times can be adjusted so that they do not interfere with scheduled activities or sleep quality.

In some cases, it is useful to reduce the number of pills given at one time by dividing them between morning and dinner or evening doses. This is useful as long as the timing of administration does not diminish the efficacy of the medications involved. It is also often useful to associate medications with another daily activity (e.g., to take medications before a specific meal). The use of adherence aids is also helpful. Medication lists, medication calendars, or pill-boxes (especially the four-slot per day, 7-day boxes) are examples of such reminders. Furthermore, a growing list of high-tech prompts and dispensing devices are becoming available that augment adherence, many link the patient to family members or other caregivers who can better monitor compliance and reinforce optimal self-care.

Education is also critical, verbal and written information to patients about their medications has been demonstrated to

increase adherence. Similarly, a multidisciplinary intervention (education, social services, and close follow-up) helps improve adherence. In general, patient compliance improves when pills are matched to each individual patient's needs and goals, such that the patients (and the patient's family) have an understanding of the purpose and potential benefit of each medication

5 Conclusions

Overall, pharmacological challenges among older adults remain complex and problematic. Age-related pharmacokinetic and pharmacodynamic changes implicitly change the impact of medications, with effects compounded by common dynamics of multimorbidity, polypharmacy, frailty, and other dimensions of care. Thus, there is a predictable dimension of uncertainty when medications are prescribed, i.e., most medications have disproportionate potential to benefit older patients prone to disease, but to also engender unintended harm. Systematic underrepresentation of older adults in large clinical trials compounds this complexity as there is a dearth of data to guide pharmacological management in the largest consumers of most medications. Given such non-inclusion, clinicians and patients are often uncertain regarding dosing regimens and even the expected benefits of many common medications, patterns which commonly contribute to non-compliance, and missed opportunities to optimize care. In a time when pharmacological insights and products are accelerating throughout the world, the expansion of such advances to older adults still has many obstacles to overcome.

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