Facing the challenge of polypharmacy when prescribing for older people with cardiovascular disease. A review by the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

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Abstract

Population ageing has resulted in an increasing number of older people living with chronic diseases (multimorbidity) requiring five or more medications daily (polypharmacy). Ageing produces important changes in the cardiovascular system and represents the most potent single cardiovascular risk factor. Cardiovascular diseases (CVD) constitute the greatest burden for older people, their caregivers, and healthcare systems.

Cardiovascular pharmacotherapy in older people is complex because age-related changes in body composition, organ function, homeostatic mechanisms and comorbidities modify the pharmacokinetic and pharmacodynamic properties of many commonly used cardiovascular and non-cardiovascular drugs. Additionally, polypharmacy increases the risk of adverse drug reactions and drug-interactions, which in turn can lead to increased morbi-mortality and healthcare costs. Unfortunately, evidence of drug efficacy and safety in older people with multimorbidity and polypharmacy is limited because these individuals are frequently under-represented/excluded from clinical trials. Moreover, clinical guidelines are largely written with a single-disease focus and only occasionally address the issue of coordination of care, when and how to discontinue treatments, if required, or how to prioritize recommendations for patients with multimorbidity and polypharmacy.

This review analyses the main challenges confronting healthcare professionals when prescribing in older people with CVD, multimorbidity and polypharmacy. Our goal is to provide information that can contribute to improve drug prescribing, efficacy, and safety, as well as drug adherence and clinical outcomes.

Key words: older people, pharmacokinetic and pharmacodynamic changes, polypharmacy, inappropriate prescribing, adverse drug reactions, drug-drug and drug-disease interactions

Abbreviations

AADs: antiarrhythmic drugs. ACEIs: angiotensin-converting enzyme inhibitors. ADRs: adverse drug reactions. AF: atrial fibrillation. AH: atrial-His interval. AKI: acute kidney injury. aPTT: activated partial thromboplastin time. ARBs: angiotensin receptor blockers. AV: atrio-ventricular. AVB: atrio-ventricular block. BCR-ABL: Bcr-Abl tyrosine-kinase. BP: blood pressure. BPH: benign prostatic hypertrophy. BTK: Brunton Tyrosine Kinase. CAD: coronary artery disease. CAM: complementary/alternative medicines. CCBs: calcium channel blockers. CKD: chronic kidney disease. CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation. C_{max}: peak plasma levels. CNS: central nervous system. COPD: chronic obstructive pulmonary disease. COX: cyclo-oxygenase. CPGs: clinical practice guidelines. CrCl: creatinine clearance. CV: cardiovascular. CVD: cardiovascular diseases. CYP: cytochrome P450. DBP: diastolic blood pressure. DDIs: drug-disease interactions. DOACs: direct acting oral anticoagulants. DVT: deep vein thrombosis. ED: emergency department. eGFR: estimated glomerular filtration rate. eNOS: endothelial nitric oxide synthase. GERD: gastroesophageal reflux disease. GI: gastrointestinal. GPs: general practitioners. HbA1c: glycosylated hemoglobin. HCTZ: hydrochlorothiazide. HCN4: hyperpolarization-activated cyclic nucleotide-gated channel 4. HCV: hepatitis C virus. HER2: human epidermal growth factor receptor 2. HF: heart failure. HFpEF: heart failure with preserved ejection fraction. HFrEF: heart failure with reduced ejection fraction. HIF1: hypoxia inducible factor. HIV: human immunodeficiency virus. HMPs: herbal medicinal products. HTN: hypertension. HV: His bundle-ventricular interval. I_{CaL}: L-type calcium current. IHD: ischemic heart disease. IL: interleukin. INR: International Normalized Ratio. i.v.: intravenous. KDIGO: Kidney Disease: Improving Global Outcomes. LMWH: low-molecular weight heparins. LV: left ventricular. LVEDP: left ventricular end-diastolic pressure. MDRD: Modification of Diet in Renal Disease. NADPH: nicotinamide adenine dinucleotide phosphate. NaSSAs: Noradrenergic and specific serotonergic antidepressants. NO: nitric oxide. NSAIDs: nonsteroidal anti-inflammatory drugs. NYHA: New York heart association class. OTC: over the counter. PD/PK: pharmacodynamic/pharmacokinetics. PDE: phosphodiesterase inhibitors. PE: pulmonary embolism. PGH/F: prostaglandins H and F. P-gp: P glycoprotein. Pi3K: phosphoinositide 3-kinase. PIM: potentially inappropriate medication. PPI: proton pump inhibitors. PR: interval of the electrocardiogram. PVOD: pulmonary veno-occlusive disease. QoL: quality of life. RAAS: renin-angiotensin-aldosterone system. RBF: renal blood flow. RCTs. randomized clinical trials. SBP: systolic blood pressure. SERCA2a: sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase 2a. SIADH: syndrome of inappropriate antidiuretic hormone release. SIRT1: silent information regulator 1. SNRIs: serotonin-norepinephrine reuptake inhibitors. SSRIs: selective serotonin reuptake inhibitors. TIA: transient ischemic attack. TCAs: tricyclic antidepressants. TGF: transforming growth factor. TNFα: tumor necrosis factor alfa. TxA2: thromboxane A2. t½: half-life. UFH: unfractionated heparin. Vd: volume of distribution. VEGF: vascular endothelial growth factor. VEGFR: VEGF receptor. VKAs: vitamin K antagonists. VKORC1: Vitamin K epOxide Reductase Complex subunit 1. VO_2max, maximum oxygen consumptions. VSMC: vascular smooth muscle cells. VTE: venous thromboembolism. wtTTR: wild-type transthyretin.

Introduction

The progressive rise in life expectancy over the last century has resulted in an unprecedented increase in the number of older people, defined as those aged ≥65 years, and nowadays individuals aged >75 years represent the most rapidly growing population in Western countries. In 2030, the European Union population aged ≥65 years is expected to increase up to 23% and up to 20% in the U.S.A.[1] These demographic changes are leading to a progressive increase in the number of older people living with ≥2 chronic conditions simultaneously (multimorbidity) and complex health states (also termed geriatric syndromes), requiring multiple medications (polypharmacy). Specifically, the advances in prevention and treatment of cardiovascular diseases (CVD) have led to a decline in cardiovascular morbidity and mortality, so that many patients currently survive a heart attack or stroke and suffer from heart failure (HF) of different etiologies. The main characteristics of older people with CVD are summarized in **Table 1**.

In this review, we sought to analyse the main challenges that practitioners face when prescribing for older people with CVD, as well as identifying ways of reducing the risk of inappropriate polypharmacy. We also addressed the important issue of patient-centred treatments and the identification of major knowledge gaps to improve cardiovascular therapy in this growing patient population.

Advanced age - A potent cardiovascular risk factor

Aging produces multiple structural and functional changes in the cardiovascular system that can increase the susceptibility of aging individuals to develop CVDs which represent the most prevalent conditions in older people (**Table S1**).[2,3] The prevalence of CVD increases from 65-70% in persons aged 60-79 to 79-86% in those aged ≥80 years. Of interest, several cardiovascular syndromes such as isolated systolic hypertension, HF with preserved ejection fraction, and calcific/degenerative aortic stenosis are most prevalent in older people.[2-4] Among 46.3 million Medicare old beneficiaries the prevalence of hypertension, hypercholesterolemia, ischemic heart disease (IHD), diabetes, and HF was 61%, 48%, 38%, 28% and 17%, respectively. Of interest, 27% of patients with hypertension and about 65% of those with HF had ≥5 concomitant chronic health conditions.[5]

Because of the high prevalence of CVD in older people, cardiovascular drugs are among the most frequently used drugs in this population. In the National Social Life, Health and Aging Project home medication survey, among the 20 most commonly prescribed drugs in older people were antiplatelet agents (aspirin, clopidogrel), statins (atorvastatin, simvastatin), glucose-lowering agents (metformin), β-blockers (metoprolol, atenolol), angiotensin-converting enzyme inhibitors

(ACEIs: lisinopril), angiotensin receptor blockers (ARBs: valsartan), diuretics (hydrochlorothiazide), calcium channel blockers (amlodipine) and anticoagulants.[6,7]

Multimorbidity

The majority of older patients with CVD present other non-CVD pathoologies.[4,5,7-10] Therefore, old patients should be screened for CV and non-CV comorbidities and, when present, non-CVD should be treated with suitable medications that can improve symptoms and outcomes, but do not exacerbate their CVD. Interestingly, disease states in the same patient are interrelated in a sense that disease in one organ facilitates the development and progression of the disease in another organ, which can substantially impact the prognosis and treatment of each condition. Hypertension produces damage in the heart, vessels, kidneys, and central nervous system; diabetes can result in heart disease, stroke, chronic kidney disease (CKD) and nerve and eye damage; patients with CKD exhibit an elevated cardiovascular risk manifesting as ischemic heart disease, HF, arrhythmias, and sudden cardiac death; increased risk for CVD and accelerated atherosclerosis are reported in almost all rheumatologic conditions; and anticancer drug-induced cardiotoxicity represents a major cause of morbidity and mortality among cancer survivors. These interrelationships are the basis for new subspecialties (cardio-renal, cardio-rheumathology, cardio-oncology).

Multimorbidity complicates the clinical picture, diagnosis and decision-making, promotes "fragmented" care, contributes to a decline in functional status and quality of life (QoL), and increases frailty, healthcare resource utilization (outpatient visits, hospitalizations) and mortality.[4,8] Furthermore, it increases drug treatment complexity (polypharmacy) and the risk of adverse drug reactions (ADRs), drug-drug interactions (DDI), and drug-disease interactions. Indeed, over one fifth of older people with multimorbidity receive medications that may adversely affect a coexisting condition. Non-steroidal anti-inflammatory drugs (NSAIDs) and some anti-cancer drugs can worsen HF (i.e., anthracyclines, carfilzomib, cyclophosphamide, docetaxel, sunitinib, trastuzumab) and hypertension (i.e., vascular endothelial growth factor-VEGF inhibitors, ponatinib)[11], and the administration of β-blockers in patients with HF, hypertension or atrial fibrillation worsens chronic obstructive lung disease.[12] Thus, effects on coexisting conditions should be considered when prescribing medications in old patient with CVD and multimorbidity.

Thus, the progressive aging of the population has naturally resulted in a growing number of older people with CVD and multimorbidity, with CVD representing the greatest burden for the patient, their caregivers and health systems worldwide.[2]

Multidisciplinary team approach

Healthcare systems and clinical practice guidelines (CPGs) are mainly oriented towards single-disease rather than multimorbidity.[4] However, application of multiple disease-specific CPGs in patients with CVD and multimorbidity without integration may lead to contradictory recommendations and be impractical, or even harmful, and misaligned with patients' preferences and values.[7,8,10] Additionally, these patients are treated simultaneously by several specialists, which can lead to discrepancies in goals of care, drugs prescribed, and overall medical management.[10] In these circumstances, a holistic patient care requires a multidisciplinary team for a successful comprehensive geriatric assessment and coordinated management of multimorbidity.[13] The coordinated team work between the cardiologist, and other medical specialists, nurses, pharmacists, social workers, family and caregivers, plays a key role to establish the goals of cardiovascular pharmacotherapy according to patient´s preferences and values.[7,10] The multidisciplinary team approach assists in the decision-making, enables personalized treatment strategies, evaluates the complexity, feasibility and adherence to treatment, select drugs and doses to optimize benefits, minimize harm, improve QoL and outcomes, and coordinates care across transitions (i.e., between emergency departments, in-/out-patient units, skilled nursing facilities) when the older people is more vulnerable. The multidisciplinary team approach improves the quality of care for patients with chronic CVD.[10,13]

Goals of care

The main challenge when treating old people with CVD and multimorbidity is to provide the optimal care, but older adults may have goals different from outcomes measured in randomized clinical trials (RCTs) performed in younger adults. Main goals of care are to preserve QoL, maintain daily functional capacity (including cognitive and physical function) and independence, symptom control, and reduce the burden of treatment and hospitalizations, while life extension may be of less interest.[7,8] However, prioritizing the goals in this population is challenging as disease-specific CPGs are often not applicable for very elderly patients (age ≥ 80 years) and even with the same pattern of multimorbidity, older adults are heterogeneous in terms of illness severity, functional status, prognosis and treatment options.[7,8] Therefore, old people with CVD and multimorbidity may benefit from the switch from a disease-specific approach to a patient-centred care to ensure that receive optimal care and drug prescription to maximize efficacy and safety and minimize harms of pharmacotherapy.[7,8,10] When treatment goals are different for patients, family, caregivers and

physicians, collaborative goal setting is useful for personalising care and adapting it to a patient's goals, values and resources. Thus, decisions regarding optimal cardiovascular drug treatment in older adults need to be individualized taking into consideration patient's overall health context, functional status, life expectancy and personal preferences.

Age-related changes in the pharmacokinetics and pharmacodynamics of cardiovascular drugs

Treatment in older people is complicated by age-associated changes in body composition, organ structure and function, homeostatic mechanisms, and comorbidities that affect the pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics (the relationship between drug concentration at the site of action and drug effect) of many cardiovascular drugs.

1. Pharmacokinetic changes (**Table 2**).

Oral drug absorption may be delayed in the older individuals, but full drug absorption can be achieved because most drugs are absorbed by passive diffusion.[14-16] However, the reduced activity of some gut wall transporters and of first-pass metabolism can modify the bioavailability of selected drugs administered orally. The activation of prodrugs, as in the case of ACEIs and dabigatran, can be initially reduced but this reduction is not clinically relevant during chronic treatment.

In older people body fat mass increases, while total body water and lean body mass decrease.[15] Thus, the volume of distribution (Vd) and half-life of lipophilic drugs may increase, while the Vd of hydrophilic drugs decreases, leading to a more rapid increase in plasma concentrations. Because plasma albumin levels decrease, the free-active fraction of drugs highly bound to albumin available for passive diffusion to their target sites might probably increase. However, changes in plasma protein binding may have limited clinical relevance, because the effect of protein binding on free plasma concentration is rapidly counterbalanced by its effects on clearance.

The biotransformation of some cardiovascular drugs (**Table S2**) occurs mainly in the liver and age-related changes in hepatic function may account for the differences observed in drug metabolism in older people. Hepatic clearance depends on the liver capacity to metabolize a drug (expression/activity of drug metabolizing enzymes), hepatic blood flow and plasma protein binding.[16] Drugs with high hepatic extraction ratios, such as diltiazem, lidocaine, metoprolol, morphine, nifedipine, propranolol, and verapamil, are rapidly metabolized and their clearance depends primarily on the hepatic blood flow, which decreases which age; thus, dose adjustments may be required to minimize the risk of ADRs.[15,16] Conversely, drugs like warfarin, with a low intrinsic clearance, are slowly metabolized and the rate of elimination is mainly dependent on the

hepatic metabolizing activity and free drug fraction. Hepatic metabolism via cytochrome P450 (CYP)-mediated phase I reactions (oxidization, reduction, hydrolysis) leading to active metabolites decreases, while phase II conjugation reactions leading to inactive metabolites are relatively unaffected by age.[14,15] Some cardiovascular drugs are metabolized by specific CYPs isoforms (mainly CYP3A4, 2D6 and 2C19) and CYP inhibitors/inducers increase/reduce their effects, respectively, leading to important DDIs.

Aging is associated with a reduction in renal mass, blood flow, estimated glomerular filtration rate (eGFR) and tubular secretion/reabsorption, and an increase in renal diseases impairing renal function. These changes reduce the clearance and increase the exposure and risk of ADRs of renally-cleared drugs (**Table S2**). Accurate determination of eGFR is critical to adjust dose requirements of these drugs.[17] Equations based on serum creatinine measurement (Cockcroft–Gault, MDRD and CKD-EPI) are widely used and the CKD-EPI equation was recommended for estimating eGFR in adults of any age.[18] However, because of reduced muscle mass, exercise, and meat intake, in older people serum creatinine levels may be within the reference limits, while renal function is reduced. Thus, these equations can misclassify kidney disease by one stage in >30% of the participants.[17] To overcome these problems, equations based on cystatin C alone or in combination with creatinine were developed. CKD-EPI$_{Cr\text{-}cys}$ is more accurate than all creatinine-based equations in older patients across a wide spectrum of eGFR, but it is not recommended, probably because it is not yet generally available.[17,19] Unfortunately, there are no specific guideline recommendations based on age, possibly because few studies have compared the different formulas in old and particularly in very elderly frail patients.

2. Pharmacodynamic changes

Cardiovascular drugs may exert different effects in older compared with younger individuals because ageing produces important changes in cardiovascular structure and function, as discussed previously,[2,3,12,20] (**Table S1**) and comorbidities can affect the pharmacokinetics and pharmacodynamics (due to changes in receptor number and affinity, signal transduction pathways, cellular responses, and homeostatic compensatory mechanisms) of different agents. **Table 3.**

Polypharmacy

Polypharmacy, defined as the concurrent use of ≥5 prescribed and non-prescribed medications [over the counter (OTC), vitamins, dietary supplements, herbal preparations] is a growing problem in older people. Multimorbidity, physical and mental health conditions, multiple prescribers, prescribing “cascades” and clinical practice guidelines (CPGs) are common causes of

polypharmacy.[21-24] Importantly, inappropriate polypharmacy, i.e. the use of potentially excessive, inappropriate, unnecessary, ineffective or harmful medications,[25] carries important negative consequences in older people that are summarized in **Figure 1.**

Up to 90% of community-dwelling adults ≥65 years use at least one medication, 30-50% are exposed to polypharmacy and 10-20% use ≥10 medications (excessive polypharmacy) and most older people will receive polypharmacy during their remaining lifespan.[22,24,26] Cardiovascular drugs are the most widely used and the most frequent cause of ADRs in ambulatory older people.[6,7,22] The prevalence of polypharmacy increases in nursing home residents, with up to 91%, 74% and 65% taking more than 5, 9, and 10 medications, respectively.[27] Polypharmacy and ADRs increase during hospitalization and correlate with longer hospital stay and mortality.[28,29]

Almost two-thirds of older people use OTCs (mainly NSAIDs), but only 5% of OTCs used prior to hospitalization appeared in patient charts.[6] Additionally, more than 60% of patients with CVD combine complementary/alternative and prescription medications and one-half use dietary supplements potentially interacting with warfarin, amiodarone or digoxin.[6,30] However, patients did not notify the use and because physicians may not routinely ask patients about the use of unconventional medications serious ADRs can be missed and not prevented.

However, because increasing numbers of older people live longer with CVD and the number of available cardiovascular drugs increases, polypharmacy may be just clinically appropriate when all drugs are prescribed in accordance with the best available evidence.[25] Therefore, the assumption that polypharmacy is always harmful, and indicative of suboptimal care needs to be reconsidered in the clinical context of the conditions for which drugs are prescribed.

Age-related changes in drug pharmacokinetics/pharmacodynamics, multimorbidity, and polypharmacy increase the risk of ADRs that decrease patient's QoL and drug adherence, and worsens geriatric syndromes and increases morbidity and mortality.[14,22-24,28] The risk of ADRs increases with the number of medicines taken, i.e. from 13% in individuals taking 2 medicines, to 58% when taking 5, and ~100% when taking ≥8 medications.[6,23,24] Patients taking drugs for which regular monitoring is recommended (i.e., antiplatelets, antiarrhythmics, digoxin, glucose-lowering drugs, diuretics, ACEIs, ARBs, warfarin) are at increased risk of ADRs.[7,23,24] In a meta-analysis of 42 trials, the prevalence of ADR-related hospitalizations among adults ≥60 years was 8.7% and cardiovascular drugs associated with admission included β-blockers, anticoagulants, digoxin, ACEIs, calcium channel blockers, and oral glucose-lowering drugs.[29] Thus, monitoring antithrombotic, antihypertensive and glucose-lowering drugs can reduce drug-related admissions to hospital. Importantly, more than 80% of serious ADRs are type A reactions, i.e. dose-dependent, predictable, and potentially avoidable. Thus, as a rule, pharmacological treatment should be started

at a low dose that should be gradually titrated upwards, based on the clinical response and ADRs. The most important ADRs in older people treated with cardiovascular drugs are summarized in **Table 4**.

The term prescribing "cascades" refer to the sequence of events that take place when an ADR is misinterpreted as a new medical condition, leading to the administration of additional, potentially avoidable, medications contributing further to polypharmacy (e.g., NSAIDs used OTC to treat pain, a common cold or statin-induced myalgia increase blood pressure leading to the prescription of antihypertensive agents).[31] Thus, before adding a new drug, prescribers should keep in mind that any new symptom in older people should be considered a possible ADR until proven otherwise.

Polypharmacy also increases the risk pharmacokinetic (modifications in drug exposure) or pharmacodynamic (modifications in response leading to additive, synergistic or antagonistic effects) DDIs and drug-disease interactions.[22,24,28,32] The incidence of DDIs increases with the number of medications (10.9% when 2-4 drugs are used, 80.8% if ≥10 drugs are used). In a meta-analysis of 31 trials, the median DDI prevalence rate for hospital admissions and hospital visits were 22.2% and 8.9%, respectively.[33] The most commonly potential serious DDIs and drug-disease interactions with cardiovascular drugs are shown in **Tables S3** and **S4**, respectively. Thus, before prescribing a new drug in older people, it is necessary to review the medications already prescribed and consider the possible interactions that the new drug might produce.

Inappropriate polypharmacy

Improving prescribing for older people is an essential part of medical care and a priority for all health-care systems. Inappropriate polypharmacy is a common practice and includes the prescription of medications when there is no evidence-based indication or the indication has expired, fail to achieve the therapeutic goals, cause inacceptable ADRs when safer and/or more effective drugs are available or the patient is not willing or able to take the medicines as intended.[25,34]

The problem of prescribing potentially inappropriate medications (PIM): optimizing cardiovascular drug therapy avoiding the use of PIM can improve clinical outcomes and reduce ADRs. Inappropriate treatments can lead to over-prescribing (more drugs than necessary), misprescribing (drug use can be improved by changing the dose and frequency) and under-prescribing (not prescribing all agents that are needed or using lower doses than required). Failing to identify and achieve expected therapeutic objectives, trigger unacceptable ADRs when safer and/or more effective drugs could be used and failing to identify adherence issues.[25,34]

Approximately 14%-27% of older people in the general population, 29-45% of nursing home residents and 44%-85% of hospitalized patients are prescribed at least one PIM.[35,36] Most (59%) of the PIM at hospital discharge were first prescribed in the intensive care unit and 20% on the wards.[37] Prescription of PIM is particularly frequent in individuals with multimorbidity, disability, polypharmacy, poor functional or mental status, renal impairment and when multiple prescribers are involved, and is a common cause of preventable ADRs, frailty, falls, cognitive impairment, hospitalizations, and wasteful utilization of resources.[25,35,36] Common PIMs include NSAIDs, class I and III antiarrhythmics, calcium channel blockers, sulfonylureas, and antithrombotic agents.[34,35,37] Several tools can help to identify PIM and/or potential prescription omissions in older people, including the Beers', STOPP/START, EURO-FORTA and the Medication Appropriateness Index.[34,35,38] ACOVE-3 and GPGPA tools are useful in determining need for medication continuation in vulnerable older adults who are closer to the end of life. However, no one validated tool assesses all aspects of PIM or has been shown to be superior in improving patient-related outcomes and decreasing polypharmacy risks, and it remains unclear if they reduce hospital admissions.[23,35,38] A simple and effective approach to systematically identify PIM is to match each of the patient's conditions with their medications".

Deprescribing: this is the process of withdrawing drugs in an attempt to reduce polypharmacy and ADRs, and improve outcomes, taking into account multimorbidity, care goals, and patient´s values, and preferences.[23,39] The finding that it is feasible to reduce medication burden in older people without significant ADRs and apparently improving QoL should encourage physicians to consider deprescribing as an integral component of good prescribing practice.[7,39] However, discontinuation of some cardiovascular drugs (i.e., β-blockers, clonidine, digoxin, antiplatelets, statins) can be associated with withdrawal adverse effects and therefore deprescribing requires careful planning. The lack of data on the appropriate duration of cardiovascular medications, including time to benefit or harm, and on their effectiveness in older adults with multimorbidity are major barriers for deprescribing in patients with CVD.

Prescribing all beneficial medications that are needed – The problem of over and underprescribing in clinical practice. Older people often do not receive all necessary cardiovascular medications recommended by international guidelines or are prescribed at inadequate doses or duration. Drug underuse has been seen for aspirin and beta-blockers post-myocardial infarction, ACEIs in HF or anticoagulants in individuals with atrial fibrillation.[8,10,40] Reasons for underprescribing include limited evidence of clinical benefit in older people, fear of ADRs, costs issues, inadequate attempts to reduce polypharmacy or increase adherence to other medications and/or prioritize benefits of active over preventative therapies.[40]

Drug adherence - A key issue. Approximately 30-75% of older people do not take the medications they are supposed to be taking, 50% of prescriptions are known to be incorrectly taken by the patient and 33–69% of drug-related hospital admissions can be attributed to patients not taking the medications as prescribed.[26] Non-adherence increases with polypharmacy, multimorbidity, physical or cognitive impairment, poor patient education and treatment cost and complexity,[26,41] and is associated with poor QoL and increases hospitalizations, mortality and medical costs.[7,8] Thus, assessment of adherence should be a routine part of care. Because barriers to medication adherence are multifactorial, no single strategy is optimal for all patients and a combination of strategies should always be used to improve drug adherence.[41] Simplification of complex treatments using long-acting formulations, medications that can treat several conditions simultaneously (i.e., β-blockers in patients with hypertension, angina, HF and atrial fibrillation) and clearly written/oral instructions have been shown to be simple strategies to improve adherence.[41] Regular monitoring of drug efficacy and safety is critical to prevent ADRs and improve QoL and clinical outcomes. However, up to two-thirds of patients receiving cardiovascular drugs that require laboratory-based monitoring (i.e., renin-angiotensin-aldosterone system inhibitors, digoxin, glucose-lowering drugs, warfarin), are not regularly monitored.[21]

The importance of periodic systematic medication reviews: Careful planning of drug regimens to meet the complex needs of older people appear to help optimizing medicines use and improve clinical outcomes.[18,42,43] Structured periodic reviews of all medications, matching each medication to the patient's comorbidities and goals of care is of importance, as shown in **Figure 2**. A careful medication review has been shown to be particularly important in patients with hepatic and/or renal impairment, in those who develop new symptoms, ADRs or DDIs, and at times of transitioning from hospital to home or long-term care facilities.[21,44,45] Transition of care is also commonly associated with medication changes that cause confusion and ADRs and this needs be taking into account. At hospital discharge, 41% of patients received 5-8 medications, 37% received ≥9 and 44% received at least one PIM (mainly due to lack of indication).[45] A review of all medications at this time appears to allow the identification and avoidance of PIM and can prevent potential ADRs.

Prescribing in older people - A clinical challenge

Drug prescription in older people with CVD and multimorbidity or frailty is a complex process and represents the main challenge facing health-care systems worldwide.[8,9] Importantly, these patients are frequently under-represented/excluded in RCTs and when recruited, they differ significantly from real-world older patients.[8] Furthermore, RCTs mainly focus on the reduction of 'hard' clinical outcomes (myocardial infarction, stroke, revascularizations, admissions, mortality) and pay less

attention to symptom relief, preservation of physical and cognitive function and QoL, which might be of greater concern among older people than prolonging survival and offer limited information regarding ARDs that may limit quality of life and DDIs. Thus, the benefit-risk balance of drugs in the prevention/treatment of CVD in older people with multimorbidity is limited and based on the extrapolation of results from studies performed in younger people. Indeed, ~25% of new drug approvals lack dosing recommendations for older people[46] and only 45% of newly developed drugs in the period 2010–2018 included reports on efficacy/safety in older people.[8]

CPGs incorporate scientific evidence derived from RCTs in health decision making through the formulation of recommendations that have enhanced day-to-day cardiology patient management. However, they are mainly configured for individual diseases rather than for patients with multimorbidity. This disease-specific approach assumes that benefits and risks of cardiovascular drugs remain constant over time and rarely considers the time to benefit and time to harm of therapy, when or how to deprescribe or how to prioritize recommendations for patients with multimorbidity and polypharmacy.[8,47] Dumbreck et al.[48] analysed 12 CPGs and found that potentially serious DDIs were common: 133 and 111 for drugs recommended for the treatment of type 2 diabetes and HF, respectively, and 19% involved one of the 2-4 drugs recommended as first line treatment. This is not a surprise because treatment of one comorbidity may have a negative impact on another comorbidity (see Table S4); polypharmacy increases the risk of ADRs and DDIs; and the attempt to reach recommended targets may lead to ADRs, i.e. blood pressure lowering increases instability and falls in older people.

Current literature suggests that despite the relatively limited information available, a successful practical approach in older people with CVD is to take therapeutic decisions based not on chronological age alone but on a comprehensive individual geriatric risk assessment, taking in consideration health habits, cardiovascular risk factors, multimorbidity, physical/cognitive status, life expectancy, time to benefit or harm and goals of care.[7,8,23,43,49,50] Then clinicians must prioritize which long-term medications for the prevention/treatment of CVD are most likely to produce benefit and least likely to harm the patient, and use their best clinical judgment in their attempts to adhere to prescribing guidelines.[21,25,38] This patient-centred care approach allows a more comprehensive assessment of the individual's health status (personalized pharmacotherapy).[7-9] General steps/actions that should be taken into consideration when prescribing in older people with CVD and multimorbidity are summarized in **Figure 3**.

Optimal prescribing in older people with CVD and limited life expectancy remains an unmet need due to lack of evidence-based data. Many patients with limited life expectancy, multimorbidity, functional impairments and frailty can start or continue to receive some recommended drugs for

secondary prevention and treatment of chronic diseases until death, increasing the likelihood of ADRs and potentially adding morbidity to the last phase of life.[50] Because this may not be the best way to optimize care, the concept of time to benefit (or to harm) of cardiovascular drugs with respect to symptoms, QoL, morbidity and mortality must also be incorporated into the therapeutic decisions.[7,50] CPGs rarely mention the time to benefit or harm of therapy, but recommend preventive interventions in older adults when the estimated life expectancy is greater than the time to benefit of the drug is achieved. In older patients with a short life expectancy or with advanced diseases (cancer, dementia) in which the goals of care are just palliative, treatment of CVD until death and/or use of secondary prevention medications that take several years to provide benefits may no longer be beneficial or appropriate, particularly when they can produce ADRs early in treatment (eg, myalgia-statins, hypoglycemia-glucose-lowering drugs).[49,50] In these patients, alternative goals of care include the preservation of functional independence and QoL and the alleviation of distressing symptoms (i.e., pain, dyspnea, edema, anxiety, depressed mood), although some forms of prophylaxis can be appropriate if consistent with the goals of care. CPGs are needed to inform decision-making around deprescribing long-term medications in patients with limited life-expectancy.-Therefore, when reviewing the need for existing or new medications, we must keep in mind the remaining life expectancy, time to benefit, and goals of care for the individual elderly patient.

Conclusions

Appropriate prescription of safe and effective pharmacotherapy in older people with CVD and multimorbidity remains one of the greatest challenges in geriatric medicine. Aging produces cumulative changes in cardiovascular structure and function increasing the risk of developing CVD. Additionally, age-related changes in body composition, pharmacokinetics/pharmacodynamics can modify drug exposure and responsiveness to cardiovascular drugs in older adults as compared to younger patients. Thus, dose adjustments are required to minimize the risk of ADRs, and certain cardiovascular drugs should be administered with caution, avoided, or closely monitored when prescribed in older people. In accordance with disease-specific CPGs, older patients are treated with polypharmacy for primary/secondary prevention, symptom control, slow disease progression and improve outcomes. Nevertheless, better clinical evidence is needed regarding the efficacy and safety of cardiovascular drugs in older people with CVD and multimorbidity. There is an urgent need to develop appropriate and specific CPGs for this growing population based on RCTs (or consensus, until trial data become available), that discuss how the most common comorbidities impact the applicability of guideline recommendations and prioritize those treatments that optimize

benefits, improve physical and psychosocial function, QoL and outcomes, and minimize harms (ARDs and DDIs) in this population. Focus on the comprehensive assessment of risk and complexity of prescribing cardiovascular drugs is important to ensure that older people with CVD and multimorbidity receive the most effective and safest cardiovascular pharmacotherapy.

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Figure legends

Figure 1. Main characteristics of older people and the consequences of inappropriate polypharmacy.

Abbreviations. ADRs: adverse drug reaction. CAM: complementary/alternative medicines. CV: cardiovascular. DDIs: drug-disease interactions. ED: emergency department. HMPs: herbal medicinal products. OTC: over the counter. PD/PK: pharmacodynamics/pharmacokinetics. QoL: quality of life.

Figure 2. Main steps when prescribing in older people with cardiovascular diseases and polypharmacy.

* Use the Beers, STOPP/START (Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment) criteria and the Medication Appropriateness Index.

Abbreviations. ADRs: adverse drug reactions. CAM: complementary/alternative medicines. GPs: general practitioners. HMPs: herbal medicinal products. OTC: over the counter. QoL: quality of life.

Figure 3. The rational use of cardiovascular drugs in older patients with multimorbidity.

Abbreviations. ADRs: adverse drug reactions. CAM: complementary/alternative medicines. CV: cardiovascular, CVD: cardiovascular diseases. HMP: herbal medicinal products. OTC: over the counter. PD/PK: pharmacodynamic/pharmacokinetics. QoL: quality of life. RCTs: randomized clinical trial

Table 1. Characteristic of older people with cardiovascular diseases

1. Aging is associated with physiological changes in organ body structure and function and in homeostatic mechanisms
- This modifies the pharmacodynamic/pharmacokinetic properties of cardiovascular drugs

2. Vulnerability: greater propensity to get sick
- Many older people present ≥ 2 chronic medical or psychiatric conditions simultaneously (multimorbidity)
- Produces physical impairment, functional limitation and disability, frailty, impairs the quality of life and increases sedentary lifestyles
- Geriatric syndromes: cognitive impairment and delirium, falls, pressure ulcers, urinary incontinence, functional decline

3. Polypharmacy: older people use multiple medications (prescriptions, over the counter, alternative/herbal medications, vitamins, and supplements)
- Higher risk of inappropriate polypharmacy: overuse, underuse, misuse, unnecessary, inappropriate, or harmful drugs
- Higher risk of adverse drug reactions and drug-drug and drug-disease interactions

Table 2. Age-related changes in the pharmacokinetic parameters of cardiovascular drugs[12,14-16]

Parameter	Physiological change	Consequences
Absorption	• ↓ gastric acid production and emptying • ↓ splanchnic blood flow, motility and absorption surface • ↓ gut wall transporters and first pass metabolism	• Delayed absorption, but no changes in the amount absorbed • Antiacids and laxatives can ↓ drug absorption • ↓ the first-pass effect and ↑ the oral bioavailability of diltiazem, opioids, propranolol, simvastatin, verapamil
Distribution	• ↓ cardiac output and tissue perfusion • ↓ extracellular and total body water • ↓ total body and muscle mass • ↑ body fat (18-35% in men, 30-45% in women)	• ↓ Vd and ↑ plasma levels of hydrophilic drugs (digoxin, gentamycin, theophylline). ↓ the loading dose in the elderly • ↑ Vd and half-life of highly lipophilic drugs: amiodarone, benzodiazepines, dronedarone, lidocaine, opioids, verapamil, vitamin D3
Plasma protein binding	• ↓ plasma albumin • ↑ α1-acid glycoprotein	• ↑ free drug levels of highly albumin-bound drugs: amiodarone, diltiazem, dronedarone, propafenone, propranolol, verapamil, warfarin
Biotransformation	• Liver mass (20-30%) and hepatic blood flow (20-50%) • ↓ CYP450-mediated phase I reactions • Hepatic diseases (alcoholic liver disease, cirrhosis, carcinoma) are more common in elderly	• ↑ C_{max} and t½ of highly metabolized drugs (Suppl. Table 2) • ↓ the dose to minimize the risk of adverse effects in patients with HF, or hepatic diseases
~~Excretion~~	• ↓ renal mass and renal blood flow (30-35%) • ↓ eGFR and tubular secretion and reabsorption • ↑ renal diseases that decrease renal function: glomerulosclerosis, interstitial fibrosis, diabetes • ↑ comorbidities that ↓ RBF: HTN, vascular diseases, heart failure, diabetes	• ↑ C_{max} and half-life (exposure) of renally excreted drugs (Suppl Table 2) • Drug accumulation due to reduced renal excretion is the most important cause of ADRs and drug-drug interactions • Monitor the renal function • ↓ doses of drugs mainly eliminated by the kidneys

Abbreviations: ADRs: adverse drug reactions. CCBs: calcium channel blockers. CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation. C_{max}: peak plasma levels. eGFR: estimated glomerular filtration rate. HCTZ: hydrochlorothiazide. HTN: hypertension. RBF: renal blood flow. t½: half-life. Vd: volume of distribution

↑: increase. ↓: decrease.

Table 3. Aging-associated physiological changes that affect pharmacodynamics of cardiovascular drugs[12,20]

Physiological changes	Pharmacodynamic effects
Decreased cardiac reserve	• The heart is more susceptible to HF in patients treated with disopyramide or class IV AADs
Decreased LV compliance	• Decreased cardiac output with β-blockers
Increased arterial stiffness	• ↑ risk of hemodynamic lability from vasodilator drugs and diuretics
Degeneration of sino-atrial and atrio-ventricular nodal function	• ↑ risk of bradycardia and AV block in patients treated with digoxin or class II and IV AADs
Changes in cardiac ion channel expression/activity	• ↑ risk of intracardiac conduction block when treated with class I AADs • Decreased repolarization reserve: ↑risk of drug-induced proarrhythmia
Increased myocardial fibrosis	• Decreased intracardiac conduction velocity and the risk of conduction slowing
Decreased baroreceptor sensitivity	• ↑ risk of orthostatic hypotension, instability and falls with use of antihypertensives, nitrates, and vasodilators
Downregulation of β-adrenoreceptors	• ↓ response to β-agonists (bronchodilation) and antagonists (antihypertensive effects)
Reduced response to diuretics	• ↓ the active transport of the diuretic to their site of action in the lumen tubule
Increased sensitivity to hyponatremia	• Due to aging-related reduction of glomerular filtration rate, drugs, the SIAD or endocrinopathies
Increased sensitivity to anticoagulants	• ↑ the risk of bleeding (age explains up to 40% of the variance in warfarin dosing)
Increased sensitivity to drugs acting on the central nervous system	• ↓ P-gp activity at the blood-brain barrier leading to an accumulation of its substrates in the brain • ↓ chemoreceptor reflexes: ↑ respiratory depression by opioids • Some CV drugs (amiodarone, digoxin, lidocaine, metoprolol) can increase neurocognitive impairment in the elderly

Abbreviations. AADs: antiarrhythmic drugs. AV: atrio-ventricular. CCBs: calcium channel blockers. CV: cardiovascular. HF: heart failure. P-gp: P-glycoprotein. SIAD: Syndrome of Inappropriate Antidiuresis
↑: increase. ↓: decrease.

Table 4. The main adverse drugs reactions produced in older people produced by commonly prescribed cardiovascular drugs[12,34]

Drugs	Main adverse drug effects
ACEIs/ARBs	• ACEIS: benazepril, captopril, enalapril, fosinopril, Lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril • ARBs: azilsartan, candesartan, eprosartan, irbesartan, losartan,olmesartan, telmisartan, valsartan • ↑ the risk of hyperkalemia, hypotension, falls, dizziness, fatigue, acute kidney injury, cough (ACEIs) • Start at low doses; high starting doses can precipitate hypotension or renal insufficiency. Monitor renal function at the beginning of treatment, especially in older people with renal artery stenosis. Potentially inappropriate prescriptions in people ≥75 years • Avoid the combination of ACEIs and ARBs or aliskiren because of the risk of hypotension and hyperkalemia
Alpha-adrenergic blockers:	• Treatment of hypertension and benign prostatic hyperplasia: doxazosin, prazosin, terazosin • Treatment of benign prostatic hyperplasia: alfuzosin, silodosin, tamsulosin • Postural hypotension*, especially in patients treated with diuretics or vasodilators. Avoid its use in patients with orthostatic hypotension or micturition syncope. Dizziness, fatigue, somnolence, dry mouth. • Doses used for treatment of BPH are less likely to cause hypotension than those required to treat hypertension • Not recommended as routine treatment for hypertension; alternative agents have superior risk/benefit profile
Antianginal drugs	• β-blockers, calcium channel blockers, nitrates, ranolazine,
Nitrates*	• Increased risk of orthostatic hypotension* in the elderly. Start at low doses and titrated in small increments. Headache, flushing, reflex tachycardia
Ivabradine	• Headache, dizziness, visual disturbances, bradycardia, atrial fibrillation, heart block. Avoid if low heart rate or rhythm disorders, severe hepatic disease
Ranolazine	• Dizziness, nausea, constipation. Avoid in liver diseases
Trimetazidine	• Nausea, headache, movement disorders. Avoid in patients with Parkinson disease, tremor and movement disorders, severe renal impairment
Antiarrhythmics	• Increase the risk of bradycardia and AVB (with class II and IV AADs or digoxin), intracardiac conduction block (class I AADs), HF in patients with poor LV function (disopyramide, sotalol and class IV AADs), orthostatic hypotension and falls (AADs with vasodilator properties: procainamide, quinidine, sotalol) and urinary retention (class IA)

	• Age reduces hepatic blood flow and CYP450 activity increasing the plasma levels and half-lives of AADs metabolized by the liver (CYP2D6: flecainide, metoprolol, mexiletine, propafenone, vernakalant; CYP3A4: amiodarone, diltiazem, dronedarone, lidocaine, quinidine, verapamil) • In patients with renal dysfunction reduce the dose of digoxin, disopyramide, flecainide, procainamide, sotalol • Higher risk of proarrhythmia in patients with structural heart disease (not amiodarone)
Adenosine	• Higher risk of bradycardia and AVB, facial flushing, dyspnea, dizziness and chest pressure
Amiodarone	• Presents a long half-life (>30 days) and multiple drug interactions (is a potent inhibitor of CYP3A4, CYP2C9, and P-gp), and ADRs. • Because of the high incidence of adverse effect, it is not recommended as first-line therapy for AF, unless in patients with structural heart disease if rhythm control is preferred over rate control. Monitor eye, hepatic, thyroid and pulmonary function. Maintenance should be max 200 mg/day
Disopyramide	• Avoid its use because of its negative inotropism and anticholinergic effects. It may induce HF and its anticholinergic effect may worsen symptoms of prostatism in older people
Disopyramide	• The dose should be individualized according to the corrected QTc interval and renal function. Avoid in patients with severe renal impairment (CrCl <20 mL/min)
Dronedarone	• Avoid in patients with permanent AF or severe or recently decompensated HF
Lidocaine	• Tremor, dysarthria, altered levels of consciousness, delirium, and seizures. Reduce the dose in debilitated patients and patients with cardiac and/or liver disease
Propafenone and sotalol	• Both exhibit β-blocker activity and can exacerbate bronchospasm
Anticoagulants	• Low molecular weight heparins, fondaparinx, thrombin inhibitors (argatroban, bivaluridin), unfractiones heparin, vitamin K antagonists (warfarin) • ↑ risk of bleeding, particularly in combination of antiplatelets, fibrinolytics and NSAIDs • Bleeding risk increases with age. Check for expired indications (temporary loss of mobility) • Ensure patient adherence to dosing and monitoring regimen. Check if patient is unfit for anticoagulation for cognitive reasons
Direct oral anticoagulants	• Apixaban, dabigatran, edoxaban, rivaroxaban • Renal impairment can ↑ risk of bleeding in elderly. Periodic monitoring of renal function is required. Avoid in patients if eGFR <15 mL/min/1.73 m^2 (dabigatran if eGFR <30 mL/min/1.73 m^2 • Dabigatran and rivaroxaban: ↑ risk of gastrointestinal bleeding in ≥75 years with AF or VTE. With caution

Low-molecular weight heparins	• Bemiparin, dalteparin, enoxaparin, nadroparin, tinzaparin • ↑ risk of bleeding. Avoid their use in severe renal failure
Unfractiones heparin	• Patients >60 years of age may have higher serum levels and longer aPTT as compared to younger patients. Dose-adjustment in unfractionated heparin dose may be required. • Low molecular weight heparins: reduce the dose or replace by UFH if eGFR <30 mL/min
Warfarin	• ↑ risk for GI and intracranial bleeding. Reduce the dose in the elderly with close periodic monitoring of the INR. • Warfarin presents multiple drug interactions with other drugs, foods, and supplements. Patients newly prescribed warfarin should receive education about diet and drugs that increase the risk of bleeding • Potentially inappropriate prescriptions in people ≥75 years for uncomplicated DVT for longer than 6 months and uncomplicated PE for longer than 12 months
Antiplatelets	• Adenosine reuptake inhibitors (dipyridamole), aspirin, glycoprotein IIB/IIIA inhibitors (abciximab, eptifibatide, tirofiban), protease-activated receptor-1 (PAR-1) antagonists (vorapaxar), P2Y12 platelet receptor antagonists (cangrelor, clopidogrel, prasugrel, ticagrelor, ticlopidine) • ↑ risk of bleeding, particularly in combination of anticoagulants, fibrinolytics and NSAIDs • Consider PPI in those with additional GI risk factors
Glycoprotein IIb/IIIa inhibitors	• Thrombocytopenia, intracerebral bleeding
Dipyridamole	• Hypotension*, dizziness, headache, rash, diarrhea, nausea. More effective alternatives are available. With caution in patients with coronary artery disease.
P2Y12 platelet receptor antagonists	• Prasugrel: avoid in ≥75 years and with history of TIA or stroke (↑ risk of fatal and intracranial bleeding). Reduce the dose to 5 mg in patients weighing less than 60 kg • Ticagrelor: avoid in patients with a history of prior intracranial bleeding
Vorapaxar	• Avoid in patients with a history of intracranial bleeding, stroke or TIA
Aspirin and other NSAIDs	• Dyspepsia, GI bleeding, peptic ulcer, impaired BP control, nephrotoxicity, and hyperkalemia. They can worsen renal function in patients with CKD or taking nephrotoxic drugs and can worsen or precipitate HF. • Lower doses of aspirin are recommended (<100 mg/day). Doses >160 mg/day increase the risk of bleeding, without evidence for increased efficacy. With caution for primary prevention of CV disease in patients ≥70 years due to increased risk of bleeding. Lack of evidence of benefit in adults ≥80 years. • Use with caution for short periods of time (stop during intercurrent illness)

	• Patients at increased risk for GI bleeding (>75 years, peptic ulcer disease, history of GI bleeding, use of anticoagulants, SSRIs or glucocorticoids) should be treated concomitantly with misoprostol or a PPI.
Beta-blockers	• Cardioselective: acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nebivolol • Non-selective: carteolol, carvedilol, nadolol, penbutolol, propranolol, sotalol, or timolol • Elderly present a decreased sensitivity to β-blockers. • Bradycardia, AVB, confusion, fatigue, bronchospasm, claudication, depression, incontinence, decreased antihypertensive effects. They can limit maximum heart rate and exercise performance. Not lipophilic drugs (atenolol, nadolol) may produce fewer central nervous system effects • May cause acute cardiac decompensation in elderly with HF, intermittent claudication in patients with peripheral vascular disease (use carvedilol, nevibolol), bronchoconstriction in patients with asthma/COPD (use with caution β1-cardioselective drugs) and exacerbate the symptoms of depression (use hydrophilic drugs:-atenolol and nadolol) • They can suppress hypoglycemic symptoms in diabetic patients
Calcium channel blockers	• Dihydropyridines: amlodipine, felodipine, lacidipine, lercanidipine, nicardipine, nifedipine • Non-dihydropyridines: diltiazem, verapamil • Greater antihypertensive effects due to a decreased baroreceptor response and age-related increase in drug exposure • Dihydropyridines: peripheral edema, reflex tachycardia, headache/flushing, hypotension* and falls. Avoid immediate release nifedipine because of the risk of hypotension and myocardial ischemia • Non-dihydropyridines: bradycardia, AVB, hypotension, constipation and falls* and increase the risk of HF. Potentially inappropriate prescription of verapamil in people ≥75 years with chronic constipation; treat constipation.
Central acting antihypertensive drugs	• Clonidine, moxonidine, rilmenidine, guanfacine • They may precipitate or exacerbate depression, bradycardia, and orthostatic hypotension*. They are not recommended in the elderly unless intolerance or lack of efficacy of other antihypertensives
Colchicine	• Increased risk of colchicine toxicity if eGFR < 10 ml/min/1.73m^2
Digoxin	• Age reduces its Vd and renal clearance leading to higher serum levels and risk of adverse effects: nausea, confusion, delirium, ataxia, dizziness, drowsiness, bradycardia, AVB, tachyarrhythmias. Risk factors of toxicity: hypokalemia, hypomagnesemia, hypercalcemia, stages 4-5 CKD, hypoxia, acidosis, hypothyroidism, and myocardial ischemia. • Not recommended as first-line therapy for AF or HF because there are safer/more effective alternatives. No benefit in HFpEF • Maintenance doses <0.125 mg/day for any indication in people ≥75 years without renal impairment. Serum plasma levels >1.0 ng/ml have no additional benefit and may increase toxicity, particularly in women.

Diuretics: thiazides, loop diuretics	• Thiazides: bendroflumethiazide, chlorthalidone, hydrochlorothiazide, indapamide, metolazone, xipamide. • Loop diuretics: bumetanide, furosemide, torasemide • Excessive diuresis can cause hypovolemia, postural hypotension*, falls, poor sleep, nocturia, dehydration, electrolyte (hypokalemia, hyponatremia) and metabolic disturbances (hyperglycemia, hyperuricemia) and prerenal azotemia. With caution in patients with poor mobility, urinary incontinence, AKI and electrolyte disturbances. Avoid excessive diuresis in elderly patients with HFpEF. Monitor renal function and electrolytes (hypokalemia). • Thiazides: potentially inappropriate in elderly with history of gout (diabetes, hyperlipidemia) or eGFR <30 mL/min. • Loop diuretics: reduced diuretic response because of impaired tubular secretion. Potentially inappropriate in people ≥75 years for ankle edema (without clinical signs of HF) or as first-line therapy of hypertension. Advise patients to stop during intercurrent illness
Endothelin receptor antagonists	• Ambrisentan, bosentan, and macitentan • Increase in hepatic aminotransferases, decrease in hemoglobin and hematocrit, fluid retention, PVOD • Headache, hypotension, edema, anemia, ↑ liver aminotransferases
Glucose-lowering drugs	• Aggressive glycemic control ↑ the risk of hypoglycemia, dizziness, confusion, and falls. Establish individual HbA1C targets balancing any benefits vs hypoglycemia risk • Avoid sitagliptin, sulfonylureas and thiazolidinediones in patients with HF.
Long-acting sulfonylureas	• Avoid chlorpropamide, glibenclamide or glybutide because of ↑ risk of prolonged hypoglycemia in older people. Chlorpropamide causes SIADH
Insulin	• Avoid sliding-scale insulin regimens because they increase the risk of hypoglycemia
Metformin	• Start metformin with close monitoring of renal function: Avoid metformin if eGFR < 30 ml/min/1.73 m^2, any type of metabolic acidosis or acute conditions that may alter renal function (dehydration, severe infection, shock)
Iron	• Use low-dose oral iron therapy in vulnerable elderly
Mineralocorticoid receptor antagonists	• Eplerenone, Spironolactone • Hyperkalemia. Risk factors: CKD (eGFR <30mL/min), dose >25 mg daily, treatment with ACEI/ARBs, amiloride, triamterene, potassium supplements. Monitor serum potassium levels • Avoid spironolactone and eplerenone in patients with serum creatinine >2.5 mg/dL, or serum potassium >5.0 (spironolactone) or >5.5 mmol/L (eplerenone) at initiation. • Eplerenone does not confer benefits for patients > 75 years of age with HF post-myocardial infarction

Peripheral vasodilators:** Cilostazol, Naftidrofuryl, Pentoxyfylline	• Rarely effective and indicated long-term. Increase the risk of orthostatic hypotension* and falls in the elderly • Headache, flushing, dizziness, palpitations, chest pain, feeling sick, skin rash • Avoid cilostazol en patients with HF
Phosphodiesterase type 5 inhibitors	• Sildenafil, Taladafil, Vardenafil • Headache, flushing, epistaxis, nasal congestion
Potassium	• Risk of hyperkalemia. Risk factors: i.v. administration, CKD, co-treatment with ACEI/ARBs, spironolactone, amiloride, triamterene, trimethoprim
Prostacyclin analogues and prostacyclin receptor agonists	• Prostacyclin analogues: beraprost, epoprostenol, iloprost and treprostinil • Prostacyclin (IP) receptor agonists: selexipag • Headache, flushing, jaw pain, leg pain and diarrhea. Epoprostenol: pump malfunction, local site infection, catheter obstruction and sepsis. Abrupt interruption of the epoprostenol infusion may lead to a PH rebound with symptomatic deterioration and even death
Proton pump inhibitors	• Esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole • Potentially inappropriate medications. They increase the risk of *Clostridium difficile* infection, osteoporotic-related fractures, community-acquired pneumonia, vitamin B12 deficiency, kidney disease, and dementia, • Use the minimum dose required to treat symptoms. If used for longer than 12 weeks, the clinical rationale for continued use should support an underlying chronic disease (e.g., GERD) or risk factors (e.g., chronic NSAID use)
QT prolonging drugs	• The combination of QT prolonging drugs increases the risk of torsades de pointes. Avoid or use with close ECG monitoring
Ranolazine	• Dizziness, asthenia, headache, dyspepsia and constipation are more frequent in older patients
Sodium nitroprusside	• Avoid in patients with compensatory hypertension (e.g., aortic coarctation, arteriovenous shunting) or acute HF associated with reduced peripheral vascular resistance
Sacubitril-valsartan	• More symptomatic hypotension* and angioedema but less increases in the creatinine and potassium levels than valsartan
Soluble guanylate cyclase stimulators	• Riociguat, vericiguat • Hypotension*, bleeding, headache, anemia. It may worsen the cardiovascular status of patients with PVOP
Statins	• Atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, simvastatin • Myalgias may decrease physical activity and precipitate falls in oldest-old. Confusion, increase in hepatic enzymes.

* Patients need to be educated about postural hypotension. ** Other vasodilators: also include alpha-adrenergic blockers, nitrates and calcium channel blockers

Abbreviations. AADs: antiarrhythmic drugs. ADRs: adverse drug effects. AF: atrial fibrillation. ACEIs: angiotensin converting enzyme inhibitors. AKI: acute kidney injury. aPTT: activated partial thromboplastin time. ARBs: angiotensin receptor blockers. AVB: atrio-ventricular block. BP: blood pressure. BPH: benign prostatic hyperplasia. CKD: chronic kidney disease. CNS: central nervous system. COPD: chronic obstructive pulmonary disease. CrCl: creatinine clearance. CV: cardiovascular. CYP: cytochrome P450. DOACs: direct acting oral anticoagulants. DVT: deep vein thrombosis. eGFR: estimated glomerular filtration rate. GI: gastrointestinal. GERD: gastroesophageal reflux disease. HF: heart failure. HFpEF: heart failure with preserved ejection fraction. INR: International Normalized Ratio. i.v.: intravenous. LMWH: low-molecular weight heparins. NSAIDs: nonsteroidal anti-inflammatory drugs. NYHA: New York heart association class. P-gp: P glycoprotein. PK: pharmacokinetics. PPI: proton pump inhibitor. PVOD: pulmonary veno-occlusive disease. SIADH: syndrome of inappropriate antidiuretic hormone release. TIA: transient ischemic attack. UFH: unfractionated heparin. Vd: volume of distribution. VTE: venous thromboembolism.

Figure 1. Main characteristics of older patients and consequences of inappropriate polypharmacy

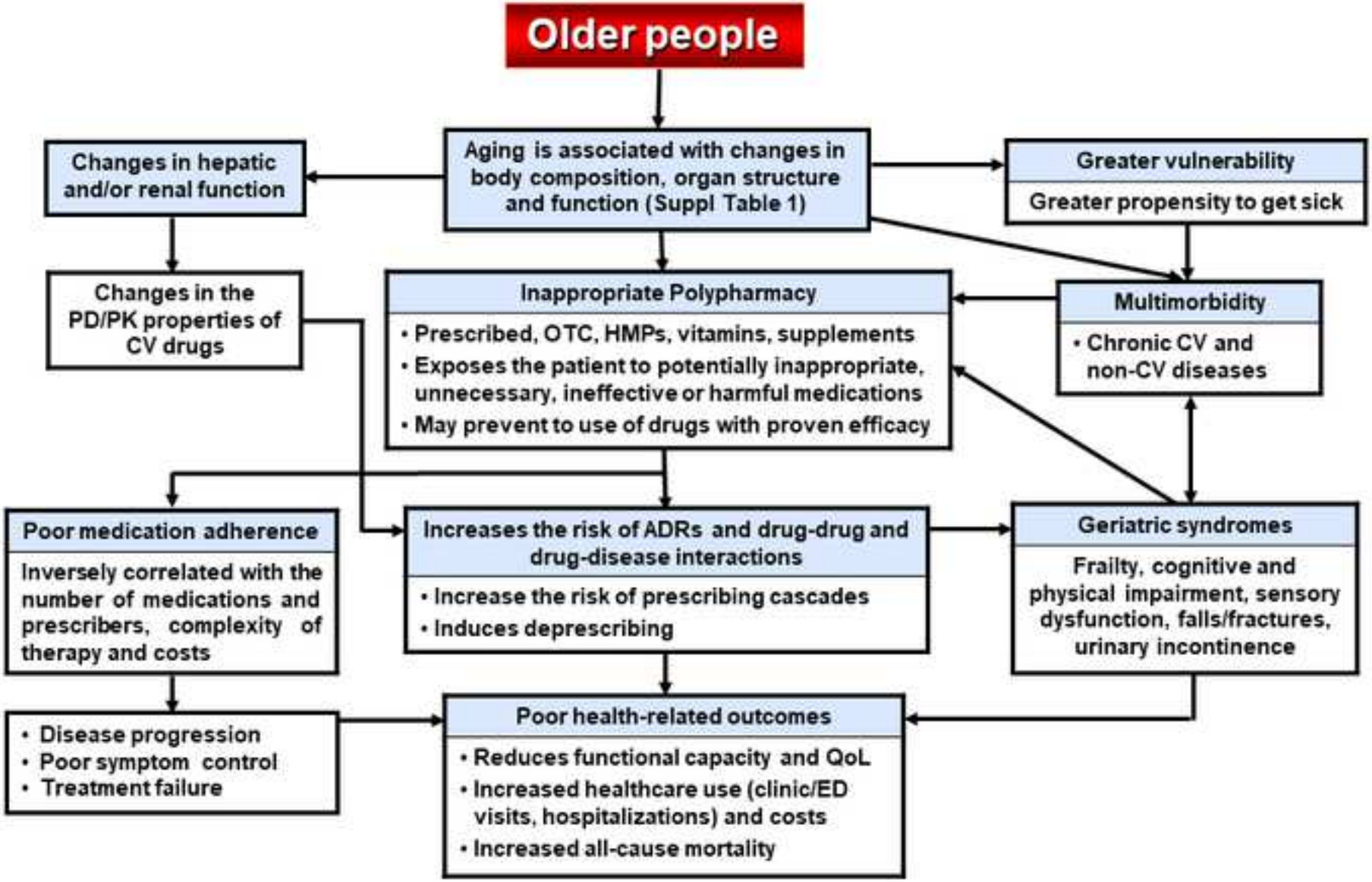

Figure 2. Facing the challenge of polypharmacy when prescribing for older people with cardiovascular disease

Identify all medications that the patient is currently using ("trust but verify")
• Prescribed, OTC, HMPs, CAM and dietary supplements
Assess patients' co-morbidities, cognition, functional status, and social support
• Review records: clinics, hospital, skilled nursing, assisted living, nursing homes • Screen for diet and nutritional state
Define overall care goals
• Based on functional status, QoL, estimated life expectancy and patients' preferences • Primary/secondary prevention, acute/chronic treatment, symptom control/management
Match each medication with patients' condition and goals of care
• Confirm that all prescribed drugs are indicated and effective* • Consider to deprescribe ineffective, unnecessary, or repeated medications • Replace any drug by a potentially safer and more effective alternative
Consider the need of new medications
• Confirm whether all recommended drugs are prescribed • Consider underlying causes to treat and the risk/benefit ratio
Document adherence and response to therapy
• Assess whether the patient follows the treatment correctly: dosage, frequency, route of administration and duration • Simplify the treatment: once daily, easy to swallow, medications with dual indications
Identify drug-related ADRs and drug-drug/-drug interactions
• Any new symptom/cognitive change should be considered an ADR until proven otherwise • Evaluate the cause and severity and discontinue culprit drugs • Assess liver and kidney function and adjust the dose accordingly
Provide drug information to patients and caregivers
• Simple verbal/written instructions for every medication • Explain the goals of treatment and the reasons to discontinue/initiate a new medication
Improve communication between health care providers
• Information should be readily available to all caregivers • Adopt a multidisciplinary care approach including GPs, pharmacists, nurses, dietitians, and other health care providers • Communication between hospital and community care providers is essential

Figure 3. The rational use of cardiovascular drugs in older people with cardiovascular diseases and multimorbidity

Elderly are a very heterogeneous population
• They cannot be defined by chronologic age, but should rather be stratified based on their comorbidities and frailty
Cardiologists should be trained on
• Age-related changes in CV structure and function • Pathophysiological mechanisms of CVD in the elderly • How to perform a geriatric risk assessment • How to manage multimorbidity in older people with CVD
Understand how aging affect the PD/PK of the CV medications
• Be familiar with drug efficacy and safety in elderly: if in doubt, do not prescribe
Avoid prescribing prior to diagnosis and treating symptoms rather than the underlying cause
• Define the goals (primary/secondary prevention, symptom control, slow disease progression) at every patient visit • More conservative goals if short life expectancy • Old-old people: QoL and morbidity more important than mortality
When possible, simplify the treatment
• Minimize dose frequency and reduce pill burden • Deprescribe medications under close monitoring and previous discussion with the patient • Whenever possible, use non-pharmacological treatments
Consider periodic medication reviews (see Figure 2)
• Particularly in patients with hepatic/renal impairment, ADRs or DDIs and at the time of care transition
Perform a patient's centered approach
• Tailor drug treatment to patient´s values and preferences
Improve communication and coordination of care
• Multiple clinicians are involved in the treatment of these patients

ADRs: adverse drug reactions. CV: cardiovascular. CVD: cardiovascular disease. DDIs: drug-drug interactions. PD/PK ; pharmacodynamic/pharmacokinetic. QoL: quality of life.

Supplementary files

Word count

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