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Deprescribing in Older Adults With Cardiovascular Disease

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Abstract

Deprescribing, an integral component of a continuum of good prescribing practices, is the process of medication withdrawal or dose reduction to correct or prevent medication-related complications, improve outcomes, and reduce costs. Deprescribing is particularly applicable to the commonly encountered multimorbid older adult with cardiovascular disease and concomitant geriatric conditions such as polypharmacy, frailty, and cognitive dysfunction–a combination rarely addressed in current clinical practice guidelines. Triggers to deprescribe include present or expected adverse drug reactions, unnecessary polypharmacy, and the need to align medications with goals of care when life expectancy is reduced. Using a framework to deprescribe, this review addresses the rationale, evidence, and strategies for deprescribing cardiovascular and some noncardiovascular medications.

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APPENDIX For supplemental Materials and tables, please see the online version of this paper.

Keywords

deprescribing; geriatrics; medications; multimorbidity; multiple chronic conditions; older adults; polypharmacy

The aims of drug therapy are to forestall or treat disease, improve quality of life, and increase longevity. Balancing those central aims are the associated risks and burdens of drug therapy–particularly common in multimorbid older adults with cardiovascular disease(s) and geriatric conditions such as polypharmacy, frailty, and cognitive dysfunction. Furthermore, the limited inclusion of older adults in clinical trials (1), known heterogeneity in treatment efficacy and safety (2), and an evolutionary shift toward a less-is-more attitude regarding medication use (3) has prompted a need to re-examine the balance between benefits and risks at the level of the individual patient. However, this requires assessments in areas other than the medical/surgical domain, such as patients' values and goals of care, cognitive and physical function, multimorbidity, and medication burden (4). Although further developed in other countries, this re-equilibration of medication use is gathering momentum in the United States under the auspices of an emerging focus called "deprescribing," most relevant to older adults but applicable across the lifespan (5).

Deprescribing, a top priority in patient safety (6), is the process of medication withdrawal or dose reduction under health care supervision to reduce unnecessary or potentially harmful medication use with the goal of improving outcomes (5,7). The primary aim of this review is to communicate fundamental concepts of medication deprescribing to the cardiovascular clinical team (cardiovascular physicians, pharmacists, nurses, nurse practitioners, physician assistants) (8). Bridging the knowledge gap will lead to more meaningful collaborations between the cardiovascular team and clinical partners (primary care, geriatrics, palliative care) and will advance the view that discussions surrounding deprescribing are considered an integral component of routine cardiovascular care.

DEFINITION OF DEPRESCRIBING

Common definitions of deprescribing have included in their description a process of medication removal or dose reduction (5,7,9). A notable key feature of a proactive approach to deprescribing is the explicit focus on the relative benefits and harms. These are tied to a holistic review of a patient's medication list, clinical situation, and life circumstances. Therefore, a comprehensive definition of deprescribing should include: 1) an organized process of medication removal or dose reduction; 2) oversight of the deprescribing process by an appropriate member of the health care team; 3) a goal of improving 1 or more specific outcomes; and 4) consideration of an individual's overall physiological status, stage of life, and goals of care. This can apply both to a broad-based review of a patient's medications to identify potential candidates for deprescribing, and to a specific focus on one class of medications.

RATIONALE FOR DEPRESCRIBING

Most clinical practice guidelines (including cardiovascular guidelines), along with the evidence-base from which they are derived, have either incompletely addressed or omitted addressing care of older adults with multiple chronic conditions or multimorbidity. The presence of multimorbidity, in addition to the index cardiovascular disease (CVD), enhances the difficulty of disease-based care. This is due in part to competing risks (2) and recommendations (e.g., therapeutic competition between guidelines or increased risk for adverse events due to coexisting illnesses) that render assessments of efficacy and safety of pharmacological therapies difficult.

Guidelines have greatly aided the standardization of care. They have even addressed concerns of medical undertreatment (10). However, strict guideline adherence in older adults have had unintended consequences–increased medication burden often leading to decreased functional capacity and quality of life (11). Proposed mechanisms include the direct action of individual agents, worsening polypharmacy (increasing the possibility of interactions between medications, diseases, and patients), and increased treatment burden (12,13). Guidelines additionally do not consider the potential for competing recommendations across conditions, known as “therapeutic competition” (e.g., nonsteroidal anti-inflammatory agents for arthritis, which can worsen hypertension, coronary artery disease, or heart failure) (14).

Current cardiovascular guidelines rarely discuss treatment duration for cardiovascular pharmacological therapies. Some medications are appropriately time-limited (e.g., antiplatelet agents such as clopidogrel, prasugrel, or ticagrelor post-coronary stent implantation). However, many cardiovascular medications do not have a time limitation and are routinely administered over many years. Rossello et al. (15) noted the lack of long-term (≥10 years) efficacy and safety data for commonly used cardiovascular medications. In fact, the average duration of follow-up in 30 secondary prevention trials examining 4 core cardiovascular medications (i.e., aspirin, beta-blockers, statins, and angiotensinconverting enzyme inhibitors) was around 3 years. Because long-term benefits and risks of many cardiovascular medications are unknown, especially in older adults with multimorbidity, medication appropriateness should be tailored and determined within the context of each patient’s clinical milieu, function, life expectancy, health priorities, and outcome goals (16,17).

ETHICAL BASIS FOR DEPRESCRIBING

Acts of prescribing and deprescribing can be considered in the context of 4 ethical principles: beneficence, nonmalfeasance, autonomy, and justice. These principles may be helpful when the appropriateness of deprescribing is unclear. Beneficence refers to how clinicians should act in the best interest of the patient, typically by determining whether an intervention can fulfill the goals of medicine by providing benefit such as symptom control. Nonmalfeasance (“first, do no harm”) means that clinicians must evaluate potential medication risks in relation to potential benefits. Although typically understood as adverse side effects, harms also include burden related to administration and/or cost. Autonomy, considered as individual self-determination in defining preferences for treatment and desired

health outcomes, is key. Incorporating patients' health care beliefs, values, and goals for care, particularly as they may change over time, is essential. Justice, the ethical principle governing the fair and equitable distribution of burdens and benefits to all members of society, is an important consideration with regard to the economic cost of inappropriate, nonbeneficial, or potentially harmful medications, including the cost of harm associated with their use. Deprescribing is concordant with these ethical principles when serving patient-centered interests (18).

TRIGGERS TO DEPRESCRIBE

There are numerous clinical scenarios where the cardiovascular clinical team should consider deprescribing. Based on current evidence, we grouped common triggers to deprescribe into 4 easily recognizable categories.

ADVERSE DRUG REACTIONS.

Adverse drug reactions (ADRs) commonly occur in older adults and are often underdiagnosed. ADRs occur in up to 35% of older outpatients and 44% of older hospitalized patients, and account for one-tenth of all emergency department visits (19). Moreover, patients taking ≥7 medications have an approximately 80% risk of an ADR. The occurrence of an ADR is a natural time to discontinue a medication.

ADRs often have varied presentations. They may present asymptomatically (e.g., abnormal laboratory value), symptomatically (e.g., shortness of breath), or may be misattributed to a "normal process of aging" or symptoms of an underlying chronic disease (20,21). Medication-related harm in older adults may arise from use of medications that are associated with increased risk of harm in older adults (selected examples from the Beers criteria are shown in Table 1). Moreover, medications that are considered typically appropriate for older adults can also cause harm. Because medication adverse reactions are often misinterpreted as arising from an underlying disease or aging, any new unexplained symptoms should prompt a careful evaluation for a potential pharmacological basis.

An ADR may present as cardiovascular conditions (heart failure, elevated blood pressure, syncope, death) or noncardiovascular conditions (falls, gastrointestinal bleeding, dementia) (Table 2, Online Table 1). A contemporaneous example of a future ADR trigger presenting as a noncardiovascular condition is aspirin use for primary prevention. Multiple large randomized studies (2 in adults ≥70 years of age) have recently shown an increased risk of bleeding with minimal or no benefits in cardiovascular event reduction (22). This new knowledge may necessitate aspirin deprescribing for primary prevention. ADR may also present as hospitalization(s), permanent disability, or intervention to prevent permanent disability (23). Harm may also occur when medication use potentiates drug-drug interactions or when dosed inappropriately in patients with renal insufficiency (Table 3) (24,25). Notably, a meta-analysis of 13 trials in older adults, some that included deprescribing, demonstrated that preemptive interventions significantly reduced the risk of ADRs by 21% versus control subjects (23).

POLYPHARMACY.

Polypharmacy is defined as long-term use of ≥5 medications, which is particularly common in multimorbid older adults (26). Overall polypharmacy prevalence among older adults increased from 24% in 2000 to 39% in 2012 (27) with a mean number of 7.2 medications in a community sample of ambulatory heart failure patients (11). Moreover, polypharmacy is associated with a higher risk of ADRs (6), reductions in physical and cognitive function, worsening of nutritional status, and increases in health care costs (28). Polypharmacy can be perpetuated by prescribing in the absence of an ongoing indication, which often occurs when a disease or symptom control medication is ineffective, or symptoms have resolved, but the medication is continued (e.g., nitrates after revascularization or resolution of angina).

PRESCRIBING CASCADES.

Prescribing cascades are common, but not unique to older adults. They are a sequence of events that starts with the prescription of a drug, followed by an ADR that is misinterpreted as a new medical condition, leading to additional medication prescriptions to treat the drug-induced adverse event (29). One example is lower extremity edema, occasionally seen as a side effect of amlodipine. Instead of discontinuing amlodipine, a diuretic is prescribed with potassium supplementation. Other examples of prescribing cascades are the intensification of antihypertensive agents and heart failure medications among patients taking drugs known to increase blood pressure or exacerbate heart failure (24,25) (Table 2). Detecting prescribing cascades helps identify medications that can be discontinued in order to prevent future ADRs and reduce medication burden.

AT END OF LIFE AND AS PART OF PALLIATIVE CARE

A discussion of deprescribing as a palliative care strategy should be routine in older adults with CVD and an anticipated life expectancy of ≤2 years (30). The concomitant presence of multimorbidity, frailty and/or cognitive impairment in addition to the index CVD(s) should also trigger this conversation, even if life expectancy is >2 years. The deprescribing conversation should focus on shifting goals of care to symptom management, and reduction of ADRs and treatment burden (16,17,30). Although the incremental benefit of deprescribing in addition to palliative care is not fully known in patients with limited life expectancy (31), data demonstrate that deprescribing is acceptable to patients and their families (32). One randomized trial showed evidence of improved quality of life with such an approach (33).

CLINICAL TRIALS OF DEPRESCRIBING

Deprescribing trials are increasing in number and differ from traditional prescribing trials designed to estimate the efficacy of starting a medication. First, the target populations in deprescribing trials often have a higher comorbidity burden and are closer to end of life. Second, deprescribing trials often include patients with mild or subclinical symptoms possibly related to medication use. Such trials may aid in a mechanistic understanding of the association between medication cessation and symptom improvement. Third, deprescribing trials can also be used to examine medication discontinuation safety, particularly when prescribing indications have changed because the underlying condition has improved either

naturally or as a result of therapy (e.g., nitrates for angina following coronary revascularization).

Six completed or ongoing deprescribing-related studies (33–37) are shown in Table 4 with the details of the search strategy noted in Online Table 2. Due to space constraints, we focus in the following text only on studies that are completed, included adults ≥70 years, and took place in a non-nursing home environment, as these are felt likely to be most applicable to the cardiovascular team. The mean age in 2 of the 6 studies was around 55 years (35,37) with the mean age in the rest >70 years. All but 1 was multicentered, recruited ≥295 participants, and focused on antihypertensive and/or lipid-lowering medication therapy (36). The deprescribing process, as well as the primary and secondary outcomes, varied substantially between studies.

Findings from an important, albeit small, deprescribing study of younger individuals with heart failure deserves mention. Halliday et al. (37) addressed the safety of heart failure medication withdrawal in a randomized clinical trial of patients with recovered (ejection fraction ≥50%) dilated cardiomyopathy. Although more work is needed, this trial demonstrated that approximately 40% of participants relapsed when their heart failure medications were withdrawn, implying that long-term administration of heart failure medications is often, but not always, necessary (37).

Kutner et al. (33) examined statin discontinuation in patients with a life expectancy ≤1 year. Most participants (58.7%) had a history of CVD and statin use (68.3%) for ≥5 years. The median survival was 7 months with no difference in the proportion of deaths at 60 days between groups discontinuing and continuing statins (23.8% vs. 20.3%; $p = 0.36$). Statin discontinuation improved quality of life (total McGill quality of life score $p = 0.04$), reduced medication burden ($p = 0.03$), and reduced medication costs by $3.37 per day (95% confidence interval: 2.83 to 3.91).

The DANTE (Discontinuation of Antihypertensive Treatment in Elderly People) study Leiden deprescribing trial used a parallel-group, unblinded clinical trial design. Participants with mild cognitive impairment were randomized to either discontinuation or continuation of antihypertensive medications (34). At baseline, 11.2% of participants had CVD, 45.8% had orthostatic hypotension, and 61.5% took at least 2 antihypertensive medications. Employing a deprescribing algorithm developed by the study investigators, physicians withdrew antihypertensive treatment until a maximum of a 20-mm Hg increase in systolic blood pressure occurred. Deprescribing antihypertensive medications did not improve cognitive, psychological, or general daily functioning at 16 weeks of follow-up, but also did not increase adverse events. These findings should be placed in the context of the recently published SPRINT (Systolic Blood Pressure Intervention Trial) MIND trial (38). This substudy of SPRINT found a nonsignificant reduction in all-cause probable dementia (primary outcome), but a statistically significant reduction in the secondary outcome of incident dementia or mild cognitive impairment (20.2 vs. 24.1 cases/1,000 person-years; hazard ratio: 0.85; 95% confidence interval: 0.74 to 0.97) with intensive blood pressure therapy. Additional research is needed to define optimal blood pressure for reducing cognitive decline in older adults with hypertension.

Systematic reviews of deprescribing that included, but did not focus on, cardiovascular conditions or medications offer further insight into outcomes. A subgroup analysis of a systematic review of randomized trials to reduce polypharmacy suggested a potential mortality reduction (39). Other deprescribing benefits have included reduction in falls and improvements in cognitive and psychomotor function (5). Many studies examined the possibility of harm with deprescribing; however, no harm was demonstrated.

ATTITUDES, BARRIERS, AND ENABLERS TO DEPRESCRIBING

Current evidence finds that most older adults would prefer to decrease their medication burden and are open to discussions of medication deprescribing (40). One approach to initiate discussions with patients regarding deprescribing could be the use of such statements as “Sometimes medications are continued when the benefits don’t seem to be outweighing the risks. I believe that is the case for medication X and would like to discuss how you would feel if we remove it.” See Online Appendix Section 1 for further details.

STEPS TO DEPRESCRIBE

The decision and subsequent action to deprescribe should be undertaken using a holistic approach through an informed and shared decision-making process. This discussion should include patients, families, and appropriate clinical health care personnel (41) (see the Framework for Deprescribing section later in the text). A suggested step-by-step protocol for deprescribing (based on Scott et al. [5]) for cardiovascular clinicians is described in the following section and shown in the Central Illustration.

STEP 1: REVIEW AND MEDICATION RECONCILIATION.

Reconciliation includes all prescribed and over-the-counter medications, their indications, and nonadherence patterns (42). Reasons for nonadherence may provide insight into otherwise-overlooked adverse effects (e.g., diuretic discontinuation due to urinary incontinence), patient concerns, and/or health priorities that warrant discussion with a health care professional. To aid busy clinicians, medication reconciliation and medication therapy management programs (43) support the use of pharmacists and other team members to collect, review, and analyze medication lists to identify potential drug interactions and therapeutic duplication, and to inform clinicians of possible nonadherence and potential avenues to improve prescribing (44).

STEP 2: RISK ASSESSMENT OF ADVERSE EFFECTS OF INDIVIDUAL MEDICATIONS.

A fundamental tenet of deprescribing is to avoid future ADRs by paying close attention to current medication-related risks and patient-centric factors. Medication-related factors to consider include known ADRs, drug-drug or drug-disease interactions, and polypharmacy. Possible adverse effects must also be proactively investigated, because patients may not report them spontaneously. Potentially problematic medications have been identified by tools described later in the text (the Tools Used for Deprescribing section). Other risk assessment considerations include patient-related factors such as advancing chronological

and physiological age, cognitive impairment which predisposes to ADRs and complexity of dosing schedules (45).

STEP 3: ASSESS EACH DRUG'S ELIGIBILITY FOR DISCONTINUATION.

Medications used for symptom control in which the drug is ineffective and/or symptoms have resolved, those lacking in effectiveness, and medications without a current indication (e.g., long-term use of proton pump inhibitors) are potential candidates for deprescribing. For example, amiodarone in individuals with permanent atrial fibrillation may be discontinued if ventricular rates are otherwise well-controlled. Other medications that can be considered for removal are those that impose unacceptable treatment burden, such as due to burdens of monitoring, administration (e.g., multiple daily doses), or cost (46).

STEP 4: PRIORITIZE DRUG DISCONTINUATION.

Prioritization should stem from a discussion with the patient and family to determine the optimal sequence of discontinuation. Prioritization should also be based on the risk/benefit balance, ease of discontinuation, risk for adverse drug withdrawal events (Table 5), and patient preferences.

STEP 5: DISCONTINUE MEDICATION(S) AND IMPLEMENT MONITORING PROTOCOL.

Potential adverse effects and plans for monitoring should be discussed with the patient, akin to discussions about potential side effects and monitoring parameters that are expected upon drug initiation or up-titration. Medications should usually be discontinued 1 at a time so that any adverse effects or withdrawal symptoms can be attributed to discontinuation of a specific agent, with corrective action undertaken promptly. The rate of medication tapering should be cautiously undertaken in an evidence-based manner, if available, using individual clinical practice guidelines or drug monographs. Slow tapering over time may be prudent for some agents associated with increased risk for an adverse drug withdrawal event. These events may include a return of symptoms as a result of the withdrawal or a physiological withdrawal, such as rebound tachycardia after discontinuation of clonidine (47) (Table 5).

FRAMEWORK FOR DEPRESCRIBING

To overcome the barriers and clinical inertia to deprescribing, it is useful to have a framework to draw upon during discussions with patients, families, and colleagues. Two methods are the "domain management model" (4), described recently in the context of caring for older adults with heart failure but relevant across the spectrum of CVD, and the "5M model" (48). The 5Ms, a mnemonic to highlight meaningful care issues in older adults (Mind, Mobility, Medications, Multimorbidity, and Matters Most), is complementary to the domain management model (medical/ surgical, physical, cognitive, and social domains). Their complementary importance is in providing a framework for a holistic approach to patient care that necessitates the consideration of conditions and relevant contributing factors outside the index cardiovascular condition(s) being addressed (e.g., assessments of frailty, activities of daily living, fall risk, cognitive function [dementia, delirium, depression], and social environment) (see Table 6 for a real-world deprescribing example).

TOOLS USED FOR DEPRESCRIBING

Several tools, predominantly focused on care of older adults, are available to identify medications that may be appropriate for deprescribing (49). These tools have been divided into implicit and explicit tools. They attempt to address the polypharmacy burden, ADR risk, medication regimen optimization, and the decision-making required to implement the deprescribing process. Implicit tools apply a framework to evaluate drugs and include the ARMOR (Assess, Review, Minimize, Optimize, Reassess) tool (Online Table 3A) and the GPGP (Good Palliative-Geriatric Practice) algorithm (Online Table 3B).

Explicit tools are protocoled lists. They include the American Geriatrics Society (AGS) Beers criteria (already well-integrated into some electronic health systems) (Tables 1 to 3, Online Tables 1 and 4), STOPP (Screening Tool of Older Persons' Potentially Inappropriate Prescriptions) criteria (Online Table 3C), and internet tools (Online Section 2). The AGS Beers Criteria is an evidence-based, expert consensus list of medications that are often inappropriate in older adults due to excess risk of harms and/or limited benefits in this population (25). For this review, our primary focus has been on CVD medications. The STOPP criteria, relevant to deprescribing and identifying potentially inappropriate medications, include 65 indicators addressing drug-drug and drug-disease interactions, risks of falls, and medication class duplication. For persons approaching end of life, the STOPPFrail (STOPP in Frail Adults with Limited Life Expectancy) (50) tool is a particularly useful reference (Online Table 3D). Reviewing these before a coordinated cardiovascular and palliative care/hospice team discussion may be useful for consensus building surrounding specific medications and the approach to deprescribing.

DEPRESCRIBING WORKFLOW

The deprescribing process can be initiated anywhere (inpatient or outpatient) or by anyone on the health care team (including patients, or their surrogates). Building efficient communication lines between and within teams is the key to successful comanagement of cardiovascular and noncardiovascular medications (8,39). For example, if the cardiologist identifies a high-risk or overtly harmful noncardiovascular medication, then the cardiologist can: **1**) inform the primary care clinician and the patient to ensure that concerns are raised with the primary care clinician; or **2**) the cardiologist can stop or change the medication and communicate this to the patient and primary care clinician (or another prescriber). In either case, direct communication between all involved is paramount. Future research on the effectiveness of using pharmacists in collaborative practice protocols may enhance acceptance of deprescribing as part of routine cardiovascular care.

PAYMENT FOR DEPRESCRIBING

Although there are no specific billing codes for deprescribing, the time and complex decision-making involved in the process fulfill the criteria for higher level of care and medication risk management.

CONCLUSIONS

The continuum of good prescribing practices includes the deprescribing process. The cardiovascular clinical team must recognize, particularly in reference to older adults, that deprescribing is an important resource that can improve clinical care and enhance quality of life. Evidence to support cardiovascular medication deprescribing, tools to facilitate it, and models of care coordination between cardiovascular specialists and generalists are evolving. Further research (Table 7) will improve understanding of the deprescribing process and its impact on clinical care, patient-centered outcomes, and costs. The cardiovascular clinical community is on the threshold of an opportunity to improve medication safety and reduce ADRs, particularly among older adults, by implementing the principles of deprescribing into daily patient care as a key component of an appropriate prescribing spectrum.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

ADR	adverse drug reaction
CVD	cardiovascular disease
STOPP	Screening Tool of Older People’s Potentially Inappropriate Prescriptions

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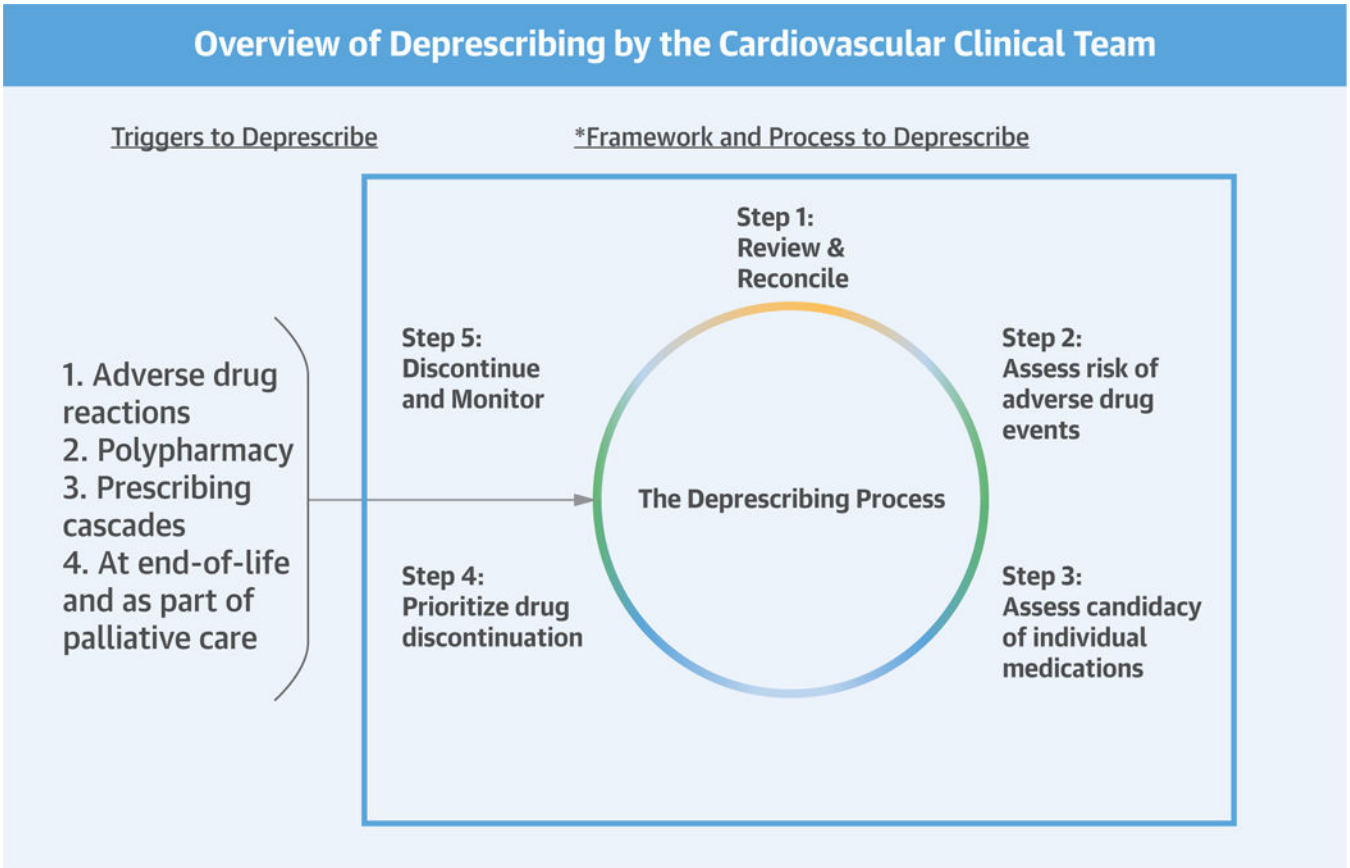
HIGHLIGHTS

- Multimorbid older adults with CVD are disproportionately affected by medication-related issues.
- Deprescribing is an integral component of good prescribing practice.
- Incorporating deprescribing into routine cardiovascular care can reduce treatment burden and morbidity in older adults.



CENTRAL ILLUSTRATION. Overview of Deprescribing by the Cardiovascular Clinical Team

Deprescribing should incorporate a framework that includes the medical/surgical, physical, cognitive, and social domains. Steps 1 and 2 may be facilitated by using the deprescribing tools discussed in the text. See Table 6 for a real-world example. Based on Scott et al. (5) framework.

TABLE 1

Potentially Inappropriate Cardiovascular Medication Use in Older Adults

Cardiovascular Medication	Rationale
Central alpha agonists (e.g., clonidine)	Central nervous system effects, orthostatic hypotension, bradycardia
Dronedarone	Heart failure
Digoxin	More effective alternatives exist (avoid as 1st line)
Nifedipine, Immediate release	Hypotension, myocardial ischemia
Aspirin for primary prevention of cardiac events	Risk may exceed benefits for adults ≥70 yrs when used for primary prevention.
Dabigatran	Increased risk of gastrointestinal bleeding in older adults
Prasugrel	Increased risk of fatal and intracranial bleeding
Vasodilators	Syncope
Peripheral alpha-1 blockers (e.g., doxazosin, prazosin, terazosin)	Orthostatic hypotension

From the American Geriatrics Society Beers Criteria Update Expert Panel (25).

TABLE 2

Limited List of Drugs or Agents That May Exacerbate an Underlying Disease State in Older Adults

A. May Exacerbate Heart Failure	B. May Increase Blood Pressure
Antiarrhythmic medications	Calcineurin inhibitors
Class I: flecainide, disopyramide	Angiogenesis inhibitor (e.g., bevacizumab) and tyrosine kinase
Class III: sotalol	Inhibitors (e.g., sunitinib, sorafenib)
Other: dronedarone	Oral contraceptives
Antihypertensive medications	NSAIDs
Alpha 1-blocker (doxazosin)	Amphetamines
Dihydropyridine calcium channel	Alcohol
blockers: diltiazem,	Caffeine
verapamil, ni fedipine	Herbal supplements
C. May Increase Risk of Syncope, Falls/Fractures	**D. May Increase Risk of Gastrointestinal Bleeding**
Peripheral alpha-1 blockers (doxazosin, prazosin, terazosin)	Aspirin (>325 mg/day)

Drugs include potentially inappropriate cardiovascular medications, other common medications, and supplements. From Whelton et al. (24) and the American Geriatrics Society Beers Criteria Update Expert Panel (25).

NSAIDs = nonsteroidal anti-inflammatory drugs.

TABLE 3

Limited List of Potentially Inappropriate Cardiovascular Medications That Should Be Avoided in Older Adults

Topic	Rationale
Possible drug-drug interactions	
ACE inhibitors and triamterene	Hyperkalemia
Anticho linergics and anticholinergics*	Cognitive decline
Peripheral alpha-1 blockers and loop diuretics	Urinary incontinence in older women
Warfarin and amiodarone	Bleeding
Warfarin and NSAIDS	Bleeding
Loop diuretic agents and lithium	Increase risk of lithium toxicity
Dose reductions with renal insufficiency	
Triamterene, spironolactone	Hyperkalemia, hyponatremia
Direct acting oral anticoagulants	Bleeding
Low molecular weight heparins (enoxaparin, fondaparinux)	Bleeding
Colchicine	Gastrointestinal, neuromuscular, bone marrow toxicity

*See Online Table 3 for specific anticholinergics. From the American Geriatrics Society Beers Criteria Update Expert Panel (25).

ACE = angiotensin-converting enzyme; NSAIDs = nonsteroidal anti-inflammatory drugs.

TABLE 4

RCTs of Deprescribing-Related Interventions Focused on Cardiovascular Medication Classes

First Author (Ref. #)	Acronym	Sample Size	Setting/Age	Inclusion Criteria	Medication Class
Kutner et al. (33)	None	381	Palliative care research cooperative group member sites (U.S., Canada, Australia); 74 yrs (mean)	1 month ≥ life expectancy ≤1 yr, recent deterioration in functional status and statin use for primary or secondary CAD prevention, with no active CVD	Statins
Moonen et al. (34)	DANTE Study Leiden	356	General practices (the Netherlands); 81 yrs (mean)	Age ≥75 yrs with mild cognitive impairment	Anti-HTN agents
Luymes et al. (35)	ECSTATIC	1,067	Primary care clinics (the Netherlands); 54–55 yrs (mean)	Patients with low cardiovascular risk (ages 40–70 yrs, using statins and/or anti-HTN medications without an appropriate indication)	Lipid-lowering (predominantly statins), anti-HTN agents
Gulla et al. (36)	COSMOS*	295	Nursing homes (Norway); 86–88 yrs (mean)	Nursing home units with LTC patients. Age ≥65 yrs and current use of anti-HTN medications	Anti-HTN agents
Halliday et al. (37)	TRED-HF	51	Singsingle center (United Kingdom); 54–56 yrs (median)	Previous diagnosis of DCM with LVEF ≤40%, no current symptoms of HF; current HF therapy; normal LVEDVi; NT-pro-BNP <250 ng/l	Heart failure medications
Ongoing study	RETREAT-FRAIL	~1,100	Nursing homes (France); ≥80 yrs	Ongoing study	Anti-HTN agents

Deprescribing Process	Primary Outcome	Secondary Outcomes	Conclusions
Not provided	Proportion of deaths at 60 days	Number of non-statin medications, death, cardiovascular events, performance status, QOL, symptoms, and cost savings	Statin discontinuation was safe and did not increase mortality. Several secondary benefits: improvements in QOL, less non-statin medication use, decrease in medication costs
Deprescribing algorithm	Change in the overall cognition compound score	Chachanges in scores on cognitive domains, Geriatric Depression Scale-15, Apathy Scale, Groningen Activity Restriction Scale (functional status), and Cantril Ladder (QOL).	Deprescribing anti-HTN medications Did not improve cognitive, psychological, or general daily functioning, and did not increase the risk for adverse events
Nurse prompting of physician to discuss prescribing with patients, followed by use of a guideline if deprescribing attempted	Difference in the increase in predicted (10-yr) CVD risk between control and per-protocol population	Systolic and diastolic blood pressures, cholesterol	The The predicted CVD risk increased by 2.0% in the per protocol group compared with 1.9% in the usual care group, and this was within the noninferiority margin
Systematic medication review whereby physician received support from peers (collegial mentoring)	Number of anti-HTN drugs	Systolic blood pressure, pulse	Decreased number of anti-HTN medications. No sustained difference in pulse or systolic pressure
Random treatment assignment; supervised, step-wise reduction in medications over 16 weeks	Relapse of DCM within 6 months	Coccomposite safety outcomes (cardiovascular mortality, major adverse cardiovascular events, and unplanned cardiovascular hospital admission) and the occurrence of sustained atrial or ventricular arrhythmias; other individual outcomes	Approximately 40% of patients deemed recovered from DCM will relapse following treatment withdrawal. Current recommendation is to continue treatment indefinitely

Deprescribing Process	Primary Outcome	Secondary Outcomes	Conclusions
Unknown	All-cause mortality during a follow-up period of 24 months minimum to 48 months maximum	Unknown	Ongoing study

Included are published or ongoing randomized controlled trials (RCTs) of deprescribing-related interventions that are focused on cardiovascular medication classes from September 1965 to the present. “Deprescribing-related” refers to a spectrum of deprescribing studies (individual medications, medication groups, specific protocols or algorithms, tools, etc.).

* Multicenter, cluster-randomized, controlled trial.

CAD = coronary artery disease; CVD = cardiovascular disease; DCM = dilated cardiomyopathy; HF = heart failure; HTN = hypertension; LTC = long-term care; LVEF = left ventricular ejection fraction; LVEDVi = left ventricular end-diastolic volume indexed; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; QOL = quality of life.

TABLE 5

Examples of Cardiovascular Medications and Commonly Associated Events Resulting From Drug Withdrawal

Drug Withdrawn	Adverse Drug Withdrawal Event
Alpha 1-blocker	Increase in blood pressure
Angiotensin-converting enzyme inhibitor	Increase in blood pressure
Antianginal	Chest pain
Beta-blockers	Chest pain, tachycardia
Digoxin	Tachycardia
Diuretic agents	Increased vascular congestion

From Bain et al. (47).

TABLE 6

An Illustrative Case of Deprescribing in an Asymptomatic Woman

Medical Domain	Other Domains	Deprescribing Process	Follow-Up
Medical condition/multimorbidity overview: 74-year-old woman presents for routine cardiology clinic follow-up 6 months after single-vessel percutaneous coronary intervention and history of poorly controlled hypertension. She was extremely obese in the past and had lost substantial amount of weight over the past few years. Currently, essentially asymptomatic.	Mobility/physical domain: walks 2–3 miles/ day on treadmill with resistive exercises. Normal instrumental activities of daily living and activities of daily living. Mind/cognitive domain: normal. Social domain: retired, lives with husband at home. Matters most/goals of care: her primary concern is to avoid cardiovascular events (heart attack, stroke)	Step 1: All medications were reviewed and reconciled. Step 2: Individual medication risk of adverse effects were assessed. She was on 4 anti-HTN medications with systolic BP <120 mm Hg. Concern was regarding future adverse drug reactions. Also, the use of amlodipine and HCTZ can possibly be considered a prescription cascade.*	Hydrochlorothiazide and amlodipine were safely removed with dose reduction of the beta-blocker and angiotensin receptor blocker. At the end of 5 months with BP checks every 2–3 weeks, the systolic BP range was between 120 mm Hg and 125 mm Hg. Her BP regimen at the end of 6 months was losartan (50 mg), atenolol (25 mg).
Non-CV comorbidities; diabetes mellitus, prior stroke without sequelae, mild chronic obstructive pulmonary disease, sleep apnea. On exam: well appearing. Pulse: 55 beats/ min, BP: 110/50 mm Hg, BMI: 25 Normal physical exam. 1+ pedal edema; no orthostatic hypotension noted.		Step 3: Assess candidacy for individual medication discontinuation or dose reduction. All 4 anti-HTN medications were candidates for removal or dose reduction along with clopidogrel (in 6 more months) and supplements.	The patient was advised to regularly check her BP going forward. She acknowledged the option to discontinue clopidogrel after a full year after coronary artery stenting but continue aspirin lifelong.
Tests: ECG: normal; Echocardiogram: ejection fraction 60% to 65%, otherwise normal. Medications: Aspirin (81 mg), clopidogrel (75 mg), atorvastatin (40 mg)		Step 4: Prioritize drug discontinuation or dose reduction. Based on her concomitant conditions, it was decided to attempt to discontinue hydrochlorothiazide and amlodipine with dose reduction of atenolol and losartan. Vitamins and supplements discontinuation were discussed.	She agreed to discontinue vitamin E, and co-enzyme Q10, but wished to stay on the single daily multivitamin tablet.
Losartan (100 mg), atenolol (100 mg), HCTZ (25 mg), amlodipine (5 mg) Alendronate (70 mg weekly), vitamin E, multivitamin, co-enzyme Q 10. Number CV medications: 7 Total number of medications: 11		Step 5: Discontinue and implement monitoring protocol. After a discussion regarding balancing the benefits of intensive BP treatment with associated risks and setting a systolic BP goal of 120–125 mm Hg, the deprescribing process was implemented over a period of 6 months.	Overall, goal concordance was achieved between patient, family, and the health care team.

The patient had low blood pressure and was living independently in the community; her life expectancy was estimated to be >10 years. **Primary deprescribing trigger:** Avoid future anticipated adverse drug reactions, such as falls, syncope, renal insufficiency due to intensive blood pressure treatment, while decreasing her cardiovascular event risk. **Secondary deprescribing trigger:** Reduce polypharmacy; avoiding prescribing cascades.

*See text regarding prescribing cascades.

BMI = body mass index; BP = blood pressure; CV = cardiovascular; ECG = electrocardiogram; HCTZ = hydrochlorothiazide; HTN = hypertension.

TABLE 7

Deprescribing Research Agenda

	Problem	Proposed Solution
1	Existing data not currently leveraged for deprescribing research	• Increase use of existing large datasets for deprescribing research • Assess newer causal inference statistical methods to develop “target trial emulation” in observational studies for emulating deprescribing RCTs *
2	Few RCTs of cardiovascular medication deprescribing	• Increase awareness of need for RCTs of deprescribing • Initiate and expand deprescribing research consortiums • Initiate RCTs of cardiovascular medication deprescribing • Initiate RCTs of the incremental benefit of deprescribing in palliative care
3	Barrbarriers to deprescribing by the cardiovascular team	• Increase research for optimal and cost-effective use of pharmacists for deprescribing • Increase research of physician, patient/family attitudes toward deprescribing • Increase research of patient decision aids • Improve training in geriatrics and deprescribing • Increase research of collaborative practice protocols between health care team members • Increase research of deprescribing in patients with cognitive dysfunction • Increase research that addresses difficulty of deprescribing due to time constraints in a busy cardiology clinic visit • Increase comparative effectiveness research of currently available tools to deprescribe • Assess the utility of the use of social workers to initiate a scripted goals of care discussion • Improve knowledge of deprescribing integrated into regular care, especially in specific settings (e.g., skilled nursing facilities, hospitals) • Consider studies of pharmaco-genetic testing or use of cardiovascular imaging to improve the personalization of the deprescribing process • Increase research on efficacy of non-pharmacological alternatives to medications
4	Lack of cost and cost-effectiveness studies of deprescribing	• Increase awareness of ICD codes developed or amended for medication therapy management with possible subcode for deprescribing †‡ • Perform cost-effectiveness analyses of deprescribing
5	Lack of measures to assess the quality of deprescribing process	• Initiate discussions and subsequently establish quality measures for goal-concordant deprescribing

*Hernán MA (51).

†Centers for Medicare and Medicaid Services (52).

‡Centers for Medicare and Medicaid Services (53).

ICD = International Classification of Diseases; RCT = randomized clinical trial.