

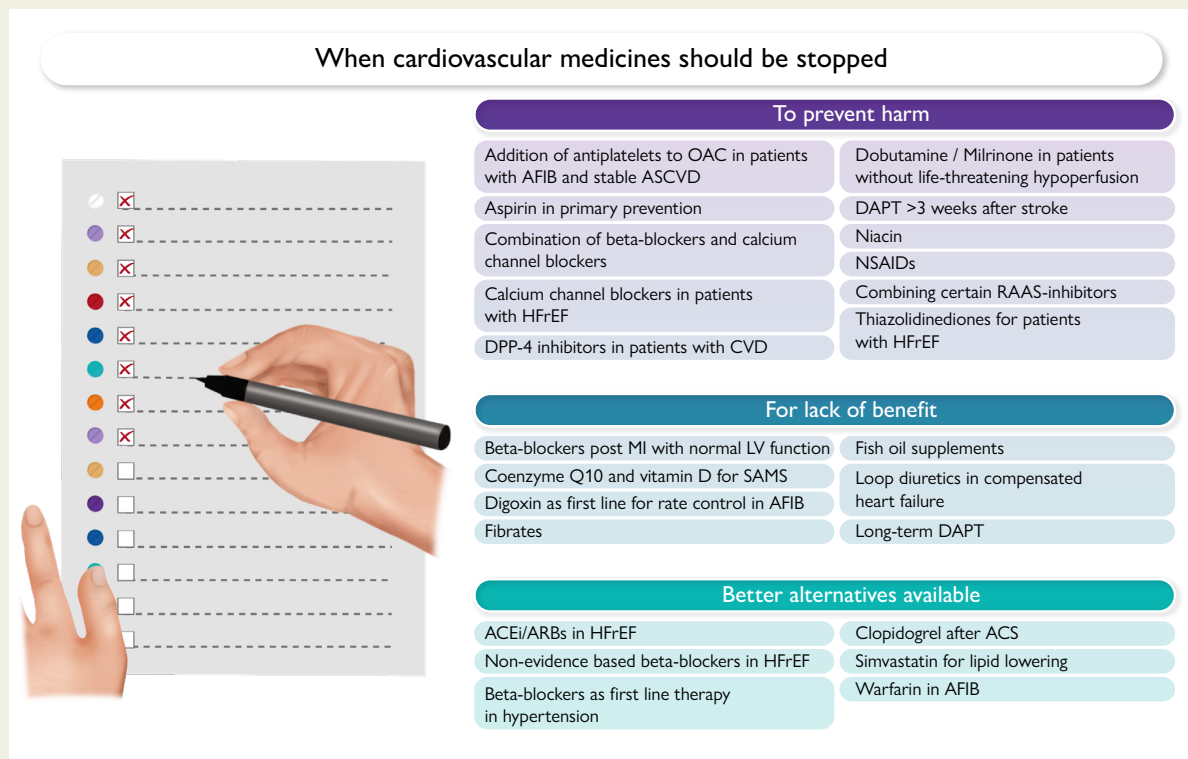
When cardiovascular medicines should be discontinued

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Graphical Abstract



Cardiovascular medicines that should either be deprescribed to prevent harm or for a lack of benefit or be switched to better alternatives. OAC, oral anticoagulation; AFIB, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; HFrEF, heart failure with reduced ejection fraction; DPP-4, dipeptidyl peptidase-4; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; NSAID, non-steroidal anti-inflammatory drug; RAAS, renin-angiotensin-aldosterone system; AMI, acute myocardial infarction; SAMS, statin-associated muscle symptoms; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ACS, acute coronary syndrome.

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Abstract

An integral component of the practice of medicine is focused on the initiation of medications, based on clinical practice guidelines and underlying trial evidence, which usually test the addition of novel medications intended for life-long use in short-term clinical trials. Much less attention is given to the question of medication discontinuation, especially after a lengthy period of treatment, during which patients age gets older and diseases may either progress or new diseases may emerge. Given the paucity of data, clinical practice guidelines offer little to no guidance on when and how to de-prescribe cardiovascular medications. Such decisions are often left to the discretion of clinicians, who, together with their patients, express concern of potential adverse effects of medication discontinuation. Even in the absence of adverse effects, the continuation of medications without any proven effect may cause harm due to drug–drug interactions, the emergence of polypharmacy, and additional preventable spending to already strained health systems. Herein, several cardiovascular medications or medication classes are discussed that in the opinion of this author group should generally be discontinued, either for the prevention of potential harm, for a lack of benefit, or for the availability of better alternatives.

Keywords Cardiovascular medicines • Polypharmacy • Deprescribing

Clinical practice guidelines issued by professional societies offer evidence-based recommendations for clinicians and systems to guide clinical decision-making. Nonetheless, it should be appreciated that a majority of the recommendations issued within clinical practice guidelines are not based on evidence from large, randomized clinical trials (RCTs).^{1,2} Even when there is RCT evidence available, many established medicines have been tested in prior decades in the context of historical care and often excluded the elderly and patients with multimorbidity and polypharmacy.^{3,4} Most major RCTs investigate the effects of initiating a new medication as opposed to the question of discontinuing certain treatments after a lengthy period of time, given that RCTs tend to have relatively short periods of follow-up. Decisions on when to stop medications are much less well defined and left to the discretion of clinicians. When patients come to clinics, the tendency is to add more and more medications and it is unusual to discontinue medications, exacerbated by ‘clinical inertia’ or the concept that if a patient is stable, do not stop treatments.⁵ In fact, continuing unnecessary medications may be harmful even if the specific drug is not harmful, since taking more medications in and of itself has drawbacks.

While appropriate polypharmacy, defined as the concurrent use of five or more prescription and over-the-counter medications may have beneficial effects,⁶ it also carries risk of adverse events⁷ and may have an adverse effect on medication adherence, especially in those taking a large number of medications and in the elderly.⁸ Inappropriate polypharmacy is common and includes the prescription of ineffective or even harmful medications.⁹ It is estimated that approximately one in five prescription medications in the elderly is inappropriate.¹⁰ Deprescribing describes the process of stopping or tapering inappropriate medications in order to reduce polypharmacy and its attendant harm.⁹ In addition, deprescribing medications may help to prevent unnecessary expense in strained health systems.

Below, we have summarized and discussed examples of cardiovascular medications that either should be discontinued when encountered to prevent harm or should at least be re-evaluated given a lack of benefit or availability of better choices (Table 1). The list is non-exhaustive and represents the opinions of the author group. For all of these agents, there may be circumstances in which exceptions can be made when these agents may be useful despite an unfavourable risk profile for their use in general.

Medications to stop to prevent harm

Primum non nocere represents one of the most important ethical principles in all of medicine and should guide our actions in daily clinical

practice, although this should be modified to ‘use treatments that have greater benefit than harm.’ Therefore, it is our duty to regularly review patient’s prescription lists to scan for medications that cause more harm than good or are outright harming patients. Below, we have provided a non-exhaustive list of medications that should be deprescribed when encountered in the clinical settings discussed.

Antiplatelet therapy in patients on oral anticoagulants with stable cardiovascular disease

Oral anticoagulation is the cornerstone in the prevention of thromboembolic events in patients with atrial fibrillation,¹¹ while single antiplatelet therapy, usually with low-dose aspirin, is recommended for secondary prevention in patients with stable ischaemic heart disease for the prevention of serious adverse events.^{12,13} After an acute coronary syndrome (ACS) and/or undergoing percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) is recommended to prevent recurrent adverse cardiac events.¹⁴ If such patients also have atrial fibrillation, current clinical practice guidelines suggest a short period of triple therapy consisting of a direct oral anticoagulant (DOAC), a P2Y₁₂ inhibitor and aspirin, followed by a dual antithrombotic therapy consisting of DOAC and one antiplatelet agent for up to 1 year, followed by oral anticoagulation therapy alone.^{11,13,14}

Of interest, registry and claims data suggest that a considerable portion of patients with atrial fibrillation and stable ischaemic heart disease receive aspirin on top of oral anticoagulation.¹⁵ In the ORBIT-AF registry, one-third of patients receiving inappropriate aspirin therapy did not even have a history of atherosclerotic cardiovascular disease (ASCVD). Such patients did not experience a lower rate of ischaemic events but were at increased risk of major bleeding in registry analyses^{16,17,18} and dedicated RCTs.¹⁹ The most compelling trial randomized 2236 patients with stable coronary disease and atrial fibrillation to rivaroxaban alone or rivaroxaban with single antiplatelet therapy.¹⁹ Not surprising, add-on antiplatelet therapy increased major bleeding by nearly 70%. But antiplatelet therapy also increased the composite of death and thrombotic events by 36%, and death was increased by 80%. Thus, when confronted with a patient taking oral anticoagulation for atrial fibrillation, clinicians should carefully assess co-medication and the indication for concomitant antiplatelet therapy, which should generally be deprescribed in patients latest 1 year after ACS or PCI.

Low-dose aspirin in primary prevention of atherosclerotic cardiovascular disease

Low-dose aspirin is recommended in all patients with ASCVD to reduce atherosclerotic events.^{20,21} In patients without ASCVD who are

Table 1 Cardiovascular medicines that should be deprescribed as they either inflict harm, for a lack of benefit, or for availability of better alternatives

Rationale	Substance	Indication	Results
Harm	Antiplatelet therapy in patients with AFIB and stable ASCVD on OAC	Reduction of ischaemic events	Increased bleeding risk without reduction in ischaemic events.
	Aspirin in primary ASCVD prevention	Reduction of ischaemic events	Moderate reduction in cardiovascular events, significant increase in bleeding events
	Combining beta-blockers and calcium channel blockers	Heart rate control	Combined negative chronotropic effects potentially resulting in harmful adverse events
	Calcium channel blockers in patients with heart failure	Angina relief and heart rate control	Negative inotropic effects potentially resulting in harmful adverse events
	DPP-4 inhibitors in established CVD	Type 2 diabetes	No effects on cardiovascular events, increased risk of heart failure events observed with saxagliptin.
	Dobutamine or milrinone in patients without life-threatening hypoperfusion	Improvement in cardiac output and hypoperfusion, reduction in mortality	Increase in mortality.
	DAPT > 3 weeks after stroke	Reduction of ischaemic events	Increase in bleeding risk, lack of benefits on ischaemic events.
	Niacin	CVD risk reduction	Increase in adverse events, no cardiovascular benefits
	NSAIDs	Pain	Increased risk of major vascular events (myocardial infarction, stroke) as well as heart failure-associated events and mortality
	Combining ACE inhibitors and ARBs or ACE inhibitors and ARNi	Heart failure	No additive effects on mortality, high risk of angiooedema and other adverse effects
Thiazolidinediones in patients with heart failure	Type 2 diabetes	Increased risk of heart failure events, no cardiovascular benefits.	
Lack of benefit	Beta-blockers > 1 year after reperfused MI	CVD risk reduction	Equipoise, ongoing trials, one recent neutral trial
	Coenzyme Q10 and vitamin D	SAMS	No evidence for SAMS prevention, lack of high-quality data.
	Digoxin as a first-line rate control drug in atrial fibrillation	Heart rate control in AFIB	More adverse effects, narrow therapeutic range, necessity for digoxin plasma level measurements?
	Fibrates for CVD risk reduction	Hypertriglyceridaemia, atherogenic lipid profile, CVD risk reduction	No effects on cardiovascular events in contemporary trials, especially as add-on to statin therapy, despite beneficial effects on triglyceride levels
	Fish oil supplements for CVD risk reduction	CVD risk reduction	No effects on cardiovascular events in contemporary trials testing 'over-the-counter' fish oil supplements
	Loop diuretics in patients with compensated heart failure	Maintenance of euvoalaemia	Potential adverse neurohormonal and kidney effects, safety of discontinuation
	Fixed duration of DAPT after PCI	Reduction of ischaemic events	Novel evidence suggests feasibility, efficacy, and safety of tailored approach based on ischaemic and bleeding risk and presence of comorbidities

Continued

Table 1 Continued

Rationale	Substance	Indication	Results
Better alternatives available	ACEi/ARBs in HFrEF	HF risk reduction	Better outcome data for sacubitril/valsartan
	Choice of beta-blocker in HFrEF	Cardiovascular risk reduction	Bisoprolol, carvedilol, and metoprolol succinate shown to reduce mortality and HF readmission rates
	Beta-blockers as first-line therapy in hypertension	Cardiovascular risk reduction	Less pronounced effects on stroke incidence compared with other established antihypertensives
	Clopidogrel after ACS	Reduction of MACE	Better outcome data for prasugrel and ticagrelor
	Simvastatin for lipid lowering	ASCVD primary and secondary prevention	Better efficacy and effectiveness for rosuvastatin and atorvastatin
	Warfarin in AFIB	Reduction of thromboembolic events	Better outcome data for DOACs (dabigatran, rivaroxaban, apixaban, edoxaban)

AFIB, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; OAC, oral anticoagulation; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; DAPT, dual antiplatelet therapy; NSAID, non-steroidal anti-inflammatory drugs; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor blocker neprilysin inhibitor; MI, myocardial infarction; HFrEF, heart failure with reduced ejection fraction; HF, heart failure; PCI, percutaneous coronary intervention; SAMS, statin-associated muscle symptoms; DOAC, direct oral anticoagulant; ACS, acute coronary syndrome; MACE, major adverse cardiovascular event.

deemed at cardiovascular risk, aspirin therapy was consistently associated with a reduction in non-fatal ischaemic events but an increase in non-fatal bleeding events along trials.^{22,23} Similar results were observed in patients with diabetes mellitus.²⁴ Especially in the elderly, bleeding risks seem to outweigh cardiovascular benefits.²⁵ Contemporary clinical practice guidelines suggest that in patients with diabetes, aspirin may be considered,²⁶ while in those at low or moderate cardiovascular risk, aspirin is contraindicated given the risk of harm.^{20,27}

Combining beta-blockers and calcium channel blockers

While the combination of a beta-blocker and a dihydropyridine calcium channel blocker conveys additional effects in blood pressure management, the combination of beta-blockers and non-dihydropyridine calcium channel blockers for arrhythmia or hypertension treatment should generally be avoided, as the combined negative chronotropic effects may result in serious adverse events. In selected patients such as those with compensated heart failure with reduced ejection fraction (HFrEF) and atrial fibrillation with uncontrolled rapid ventricular response, a careful combination of low-dose non-dihydropyridine calcium channel blockers and beta-blockers may be used, especially if left ventricular function is thought to be depressed due to ongoing tachycardia.²⁸ It has to be noted that the data underlying the contraindication for non-dihydropyridine calcium channel blockers in HFrEF are somewhat outdated and did not primarily address rate control in atrial fibrillation.²⁹

Calcium channel blockers in patients with heart failure with reduced ejection fraction

Non-dihydropyridine calcium channel blockers such as diltiazem and verapamil are commonly used in the treatment of angina and arrhythmias. Given their negative inotropic effects, current clinical practice

guidelines recommend against the use of calcium channel blockers in patients with HFrEF.^{30–32}

Use of dipeptidyl peptidase-4 inhibitors in patients with diabetes and established cardiovascular disease

Dipeptidyl peptidase-4 (DPP-4) inhibitors prevent breakdown of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide, thereby increasing the secretion of insulin, suppressing glucagon release, and normalizing blood glucose levels. Randomized controlled cardiovascular outcome trials for five DPP-4 inhibitors have proved the cardiovascular safety of DPP-4 inhibitors but failed to demonstrate cardiovascular benefits.²⁶ Treatment with the DPP-4 inhibitor saxagliptin was associated with a significantly increased risk for heart failure hospitalization when compared with placebo and should therefore not be used in patients with or at risk of heart failure.³³ Given the striking cardiovascular benefits demonstrated for treatment with GLP-1 receptor agonists and sodium–glucose cotransporter-2 (SGLT-2) inhibitors, preference should be given to drugs of those two classes and patients with established cardiovascular disease on DPP-4 inhibitors should be switched accordingly.²⁶ GLP-1 receptor agonists, which work on the same pathway, should not be added to DPP-4 inhibitors, but rather should replace these drugs.

Dobutamine or milrinone for patients with decompensated heart failure but without life-threatening hypoperfusion

Positive inotropes, while they may provide temporary improvement in cardiac output, have been proved to provide more harm than benefit in the absence of life-threatening hypoperfusion. In the OPTIME-CHF trial, for example, for patients hospitalized with decompensated heart failure, milrinone increased death, myocardial infarction, atrial fibrillation, hypotension, and ventricular tachycardia two- to three-fold,³⁴

concerning findings confirmed in other trials and registries.^{35,36} Every large randomized trial of inotropic therapy has shown greater harm than benefit, regardless of the duration.³⁷ The use of 'home' inotropes, thus, is not justified and should generally be avoided, given the described harm and if administered in patients awaiting transplantation an implantable cardioverter defibrillator should be in place. Unfortunately, sometimes they are used since a patient then may be a higher priority on the heart transplant listing system.

Dual antiplatelet therapy exceeding three weeks in patients with ischaemic stroke

Current clinical practice guidelines recommend initiation of DAPT consisting of aspirin and clopidogrel in patients with minor non-cardioembolic ischaemic stroke or high-risk transient ischaemic attacks (TIA) within 24 h of symptom onset and continuation for 21 days to reduce the risk of recurrent ischaemic stroke for up to 90 days.³⁸ This recommendation is based on the results of two major RCTs.^{39,40} In a post-hoc time-course analysis of the CHANCE trial, the benefits of reducing recurrent strokes outweighed the bleeding risk associated with DAPT, especially within the first 3 weeks of treatment, after which bleeding risks outweighed the ischaemic benefits.⁴¹ Two additional, large RCTs compared the effects of long-term DAPT after ischaemic stroke or high-risk TIA.^{42,43} In both trials, a DAPT strategy failed to reduce the occurrence of recurrent stroke while significantly increasing the risk of bleeding and in one trial even death. Based on these results, DAPT should be limited to the first 21–30 days and deprescribed in patients taking it long term.⁴⁴

Niacin

Niacin exhibits a dual mechanism targeting both the liver and adipose tissue and results in a decrease of both low-density lipoprotein-cholesterol (LDL-C) and triglycerides and an increase in high-density lipoprotein-cholesterol (HDL-C).^{45,46} Two large RCTs tested the effects of niacin, one of them a combination with laropiprant, on cardiovascular outcomes in patients with established vascular disease.^{47,48} While treatment with niacin resulted in significant improvements in the lipid profile, no beneficial effects on cardiovascular outcomes were noted. Niacin treatment increased the frequency of serious adverse effects involving seven organ system categories.⁴⁹ This resulted in a dramatic reduction of prescriptions in the USA⁵⁰ and a suspension of approval by the European Medicines Agency.⁵¹ Given the unfavourable risk/benefit ratio and the availability of safer and more effective lipid-lowering drugs, there is currently no indication for the use of niacin in patients with cardiovascular disease.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are available both as over-the-counter and prescription medicines and are among the most widely used drugs in the world to treat pain and reduce inflammation.⁵² While not cardiovascular medicines *per se*, their cardiovascular effects warrant discussion in this paper. Two main types of NSAIDs are available, non-selective NSAIDs such as diclofenac and ibuprofen that inhibit both cyclooxygenase (COX)-1 and COX-2 and selective COX-2 inhibitors such as rofecoxib. While the latter was shown to exhibit fewer adverse gastrointestinal effects, a statistically increased risk in major vascular events led to the worldwide withdrawal of the drug.⁵³ Large meta-analyses could later confirm that also several non-selective NSAIDs exhibit elevated risk of major vascular events.^{54,55} Therefore, the use of NSAIDs in the general population should be selective and

minimized in patients with established coronary artery disease, given the increased risk of recurrent events.⁵⁵

In addition, NSAIDs inhibit the prostaglandin secretion in the kidneys, thereby causing sodium and water retention as well as renal vasoconstriction, all effects potentially detrimental for patients with HFrEF as well as heart failure with preserved ejection fraction. Several observational studies have suggested worsening of heart failure translating into increased morbidity and mortality associated with NSAID treatment in patients with HFrEF which should therefore be avoided and deprescribed.^{31,32,56,57}

Combinations of inhibitors of the renin-angiotensin-aldosterone system

Current clinical practice guidelines for the management of HFrEF recommend the use of angiotensin receptor-neprilysin inhibitors (ARNi) in all patients with HFrEF and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) only when ARNi treatment was deemed not feasible. In addition, a mineralocorticoid receptor antagonist should be added on top of ACE inhibitor, ARNi or ARB in all patients, given its pronounced beneficial effects on death and hospitalizations in large 'add-on' outcome trials.^{58,59} The former practice of adding an ARB to existing ACE inhibitor therapy, especially along with mineralocorticoid receptor antagonists, is now outdated as in clinical trials, such a practice did not substantially improve mortality^{60,61} and was associated with more adverse events.⁶²

Thiazolidinediones in patients with heart failure

Thiazolidinediones, also known as glitazones, are a class of antidiabetic medications acting as agonists of peroxisome proliferator-activated receptor (PPAR)- γ . Members of this medication class were consistently shown to be associated with an increased risk of heart failure hospitalizations.^{63,64} Therefore, thiazolidinediones should not be used in patients at risk of and with a history of heart failure. Despite evidence that pioglitazone may exert beneficial effects on the combined endpoint of cardiovascular death, myocardial infarction, or stroke in patients with type 2 diabetes and increased risk of macrovascular events,^{65,66} given the observed risk of heart failure events associated with thiazolidinedione treatment and the consistent cardiovascular benefits of SGLT-2 inhibitors and GLP-1 receptor agonists, preference should be given to the latter in patients with cardiovascular disease.^{26,67,68} Given its availability as a generic medication, pioglitazone remains a potentially useful alternative in patients without heart failure, especially when GLP-1 receptor agonists and SGLT-2 inhibitors are not reimbursed or if additional glucose control is needed.²⁶ SGLT-2 inhibitors are particularly beneficial for patients with heart failure.

Medications to stop for a lack of benefit

Inappropriate polypharmacy needs to be avoided in order to reduce the risk of drug–drug interactions, adverse drug reactions as well as unnecessary expenses in already strained health systems. This is particularly important for medications known to cause harm, but extends to medications that lack beneficial effects as in the context of polypharmacy, it may in fact lead to harm. Below, we have provided a non-exhaustive list of medications that should be deprescribed when

encountered in the clinical settings discussed for a lack of apparent benefit.

Long-term beta-blocker treatment after reperfused myocardial infarction in patients with normal ejection fraction

The cardiovascular benefits of beta-blocker therapy in patients with stable HFrEF extend to patients with left ventricular dysfunction related to ACS and are therefore clearly recommended by current clinical practice guidelines.¹⁴ Whether beta-blocker therapy is beneficial in all post-ACS patients, including those with normal left ventricular function after undergoing coronary reperfusion, is less clear, as the majority of large, adequately powered, cardiovascular outcome trials investigating post-ACS beta-blocker treatment were conducted prior to the reperfusion era. CAPRICORN was a trial conducted in patients undergoing coronary reperfusion, but it only included patients with a reduced left ventricular function.⁶⁹ Several meta-analyses and registry studies yielded mixed results in post-ACS patients in the contemporary era.^{70,71} In a smaller, open-label trial, treatment with carvedilol when compared with placebo did not improve the occurrence of major adverse cardiovascular events in patients with ST-elevation myocardial infarction with preserved ejection fraction after undergoing successful PCI.⁷² A recent UK National Institute for Health and Care Excellence evidence review of data for the use of beta-blockers for more than 1 year after acute myocardial infarction (AMI) in patients without left ventricular dysfunction yielded zero relevant clinical studies relevant for their review.⁷³ The REDUCE-AMI trial was a registry-based, prospective, randomized, controlled, open-label trial randomizing 5020 patients with an AMI that underwent coronary angiography and had preserved left ventricular ejection fraction (at least 50%) to either long-term treatment with metoprolol or bisoprolol or no beta-blocker treatment.⁷⁴ After a median follow-up of 3.5 years, no significant difference in the primary endpoint of death from any cause or new myocardial infarction was noted between the two treatment arms, and there was no suggestion of an early benefit during the first several months after AMI.⁷⁵

Several additional large, prospective, randomized, controlled trials are currently ongoing randomizing patients after ACS with preserved ejection fraction to either beta-blocker therapy or placebo.¹⁴ Two trials are investigating the question of duration, by randomizing patients to beta-blocker withdrawal 6–12 months after the ACS or ongoing beta-blocker therapy.¹⁴ While evidence for beta-blocker therapy in all patients after ACS is lacking, the medication is usually well tolerated and likely not harmful. The results of REDUCE-AMI, however, support deprescription of routine beta-blocker use in low-risk patients (only 35% had ST-elevation myocardial infarction at presentation) with preserved ejection fraction post-AMI. The results of ongoing trials will provide further insight into this approach.

In this context, it is important to note that beta-blocker therapy should not be stopped abruptly, as this can cause adverse drug withdrawal events, but rather tapered.⁷⁶

Coenzyme Q10 and vitamin D for the prevention or treatment of statin-associated muscle symptoms

Statin therapy represents the cornerstone of lipid-lowering therapy both for the treatment and prevention of ASCVD.^{45,77} Vast experience over several decades stemming from clinical trials, registries, observational studies, and clinical experience demonstrate good tolerability

and safety of statin treatment.⁷⁸ A common phenomenon, affecting up to a quarter of patients treated with statins, is the occurrence of muscle complaints usually termed statin-associated muscle symptoms (SAMS). While a series of n-of-1 trials could not find any effect of statins on muscle symptoms,⁷⁹ it remains the leading cause of statin discontinuation⁸⁰ with broad effects on cardiovascular disease risk.⁸¹ Statin-induced coenzyme Q10 deficiency has been suggested to be involved in the pathophysiology of SAMS, and while statin treatment reduces circulating levels of coenzyme Q10, evidence on its effects on intramuscular levels is scarce.^{82,83} Several smaller RCTs have failed to demonstrate any significant benefit of coenzyme Q10 supplementation in improving SAMS, thus discouraging the routine use of coenzyme Q10 supplementation in patients on statin therapy.^{84,85}

Patients with SAMS were further shown to exhibit lower levels of vitamin D.⁸⁶ Several smaller, non-blinded, non-randomized studies suggested that vitamin D supplementation may improve SAMS but no RCTs are available to date.⁸⁷ Thus, at this moment, routine vitamin D supplementation in patients with SAMS and vitamin D deficiency is not supported by high-quality evidence.

Digoxin as a first-line rate control drug in atrial fibrillation

Digoxin is one of the oldest cardiac medications still in use. Given its positive inotropic effects, it was widely used as a heart failure medication before the arrival of novel, highly effective therapies. Today, its use is mostly limited to rate control in patients with atrial fibrillation and rapid ventricular response given its parasympathomimetic effects on the atrioventricular node. The narrow therapeutic range makes the occurrence of adverse drug reactions common and may necessitate repeat measurements of serum digoxin levels, to ensure exposure to digoxin levels low enough to avoid adverse effects but within therapeutic range to ensure desired drug effects.^{88,89} While some observational studies suggested an association between digoxin use and elevated mortality, this association was not seen in randomized controlled trials and was likely driven by higher serum digoxin levels.^{88,90,91} Yet another limiting factor in the widespread use of digoxin is that it does not control exercise increase in heart rate, when compared with beta-blockers and calcium channel blockers.⁹² Data directly comparing rate control agents are limited but given its overall favourable risk/benefit ratio, preference should be given to beta-blockers and, in patients with preserved ejection fraction, non-dihydropyridine calcium channel blockers. We believe that digoxin should therefore generally be deprescribed in patients with atrial fibrillation if beta-blockers or calcium channel blockers have not been tried yet and the use of digoxin be limited to add-on therapy or alternative if other agents are not preferred, not tolerated, or contraindicated.^{11,93} It needs to be mentioned that a small randomized trial from 1993 suggested that withdrawal of digoxin in patients with stable HFrEF on ACE inhibitor treatment is not safe.⁹⁴ Whether this is still true in the current era of goal-directed quadruple therapy is not known.

Fibrates for cardiovascular risk reduction

While elevated triglycerides were shown to be associated with increased cardiovascular risk, the concept of triglyceride lowering to reduce cardiovascular events remains controversial at best.⁹⁵ Therefore, current clinical practice guidelines do not specify triglyceride targets or indications for the initiation of triglyceride-lowering treatment for cardiovascular risk reduction.⁴⁵ Fibrates act as agonists of PPAR- α , and treatment results in a reduction in circulating triglycerides accompanied

by a more modest reduction in LDL-C and total cholesterol and by a modest increase in HDL-C.⁹⁶ While some trials showed cardiovascular benefits associated with fibrate therapy, only few trials investigated the effects of fibrates as an add-on therapy to statins, the gold-standard medication, and meta-analyses suggested an overall lack of cardiovascular benefits.⁹⁷ Subgroup analyses of RCTs hinted at cardiovascular benefits of fibrate therapy in patients with an atherogenic lipid profile, evidenced by low HDL-C and elevated triglycerides.⁹⁸ The PROMINENT trial therefore tested the effects of treatment with pemafibrate in patients with diabetes at high cardiovascular disease risk and evidence of an atherogenic lipid profile, with a majority receiving statins.⁹⁹ While pemafibrate successfully improved the lipid profile, it was not associated with a reduction in cardiovascular events but did result in a higher incidence of venous thromboembolism and renal events.⁹⁹ The U.S. Food and Drug Administration (FDA) has recently determined that the benefits of fenofibrate treatment in combination with statins no longer outweigh the risks¹⁰⁰ and that approval should be withdrawn.¹⁰¹ Novel approaches to triglyceride lowering currently in development include the inhibition of apolipoprotein C-III and angiotensin-like 3 protein.¹⁰² In the meantime, fibrate therapy should be avoided except for the prevention of acute pancreatitis in patients with uncontrolled, very high levels of triglycerides.

Fish oil supplements for cardiovascular risk reduction

Non-prescription fish oil supplements are among the most popular dietary supplements worldwide with a market size of several billion USD.¹⁰³ They usually contain low doses of the polyunsaturated omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both long-chain omega-3 fatty acids. Data from the National Health and Nutrition Examination Survey, a cross-sectional, population-based survey, suggested that the main motivation for the intake of omega-3 supplements was to increase one's heart health and lower serum cholesterol levels.¹⁰⁴ Despite multiple studies demonstrating the effects of omega-3 fatty acids on lipoprotein metabolism, inflammation, membrane stabilization, oxidation, atherogenesis, and plaque composition and progression, results from clinical trials remain controversial and mostly neutral, especially for low-dose compounds usually sold over-the-counter.¹⁰⁵ Results from the open-label GISSI trial in the late 1990s suggested beneficial effects on mortality, especially sudden cardiac death, but no effect on non-fatal cardiovascular events with the use of low-dose omega-3 supplements.¹⁰⁶ More recent, high-quality, randomized, placebo-controlled trials failed to demonstrate a clinical benefit with the use of low-dose omega-3 supplements in both primary and secondary prevention scenarios and are thus not recommended by current clinical practice guidelines.^{13,107–109} One large randomized controlled trial in a mixed primary and secondary prevention cohort on statin therapy with elevated triglyceride levels demonstrated striking benefits on ischaemic events with the use of a prescription omega-3 fatty acid formulation consisting of 4 g of EPA without DHA, a dose approximately 5–10 higher than most available over-the-counter supplements.¹¹⁰ Currently available evidence does not support the intake of over-the-counter omega-3 fatty acids with the intention of improving cardiovascular health.

Loop diuretics in patients with compensated heart failure and euvolaemia

Although loop diuretics represent the cornerstone in the treatment of symptomatic volume overload in acute *de novo* and *decompensated*

heart failure, there are some caveats and cautionary aspects to their use as maintenance therapy.³¹ After such an acute event, a majority of patients are subsequently discharged on maintenance diuretic therapy to reduce signs and/or symptoms of congestion and prevent worsening of heart failure, despite a paucity of good quality evidence. The goal of diuretic treatment in the stable setting is to maintain euvolaemia using the lowest diuretic dose possible. To achieve the latter, good surveillance with frequent visits and dose titrations is necessary, which in daily clinical practice may not be feasible. There is ongoing debate as to whether diuretic therapy should be discontinued in patients reaching euvolaemia, given the potential of adverse neurohormonal and renal haemodynamic effects,¹¹¹ known to contribute to the pathophysiology of heart failure. In addition, diuretic therapy was associated with increased mortality in observational studies,^{112,113} an observation at least partly confounded by disease severity.^{114,115} Current clinical practice guidelines offer little to no guidance regarding diuretic adjustments. Two small studies suggested that reducing furosemide doses in stable outpatients was safe, improved glomerular filtration rates, and did not affect symptoms.^{116,117} The ReBIC-1 trial ($n = 188$) compared a strategy of furosemide withdrawal with diuretic maintenance in outpatients with stable HFrEF. Furosemide withdrawal was not associated with worsening clinical symptoms or furosemide reuse,¹¹⁸ suggesting that diuretic discontinuation should be considered in stable outpatients without signs of fluid retention to avoid negative effects of polypharmacy and diuretic treatment itself. Moreover, use of spironolactone and SGLT-2 inhibitors may prove sufficient volume control that many loop diuretics may not be necessary for many patients.

Duration of dual antiplatelet therapy

Current clinical practice guidelines recommend a default strategy of DAPT for 12 months in patients after ACS and 6 months in patients with stable coronary disease undergoing PCI.^{13,14} Given a plethora of RCTs investigating a variety of DAPT combinations and choices of single antiplatelet therapy as well as different durations in various clinical scenarios, clinicians now are able to tailor the antiplatelet strategy to their patients and their respective bleeding and ischaemic risk, mode of presentation, and comorbidities based on high-quality evidence.

Cardiovascular medicines with better available choices

The last decade was witness to the emergence of several, sometimes revolutionary, novel therapies in the field of antithrombotic therapy, heart failure as well as antidiabetic and cholesterol-lowering medications. With it, cost considerations have again become a focus, with the need to limit access to some of the novel and more effective drugs due to cost in certain countries. Nevertheless, herein we focus on the best available evidence that should guide clinicians in optimizing medication regimes for their patients, acknowledging that access to such therapies may be limited in some countries and health systems.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in heart failure with reduced ejection fraction

The treatment of HFrEF is based on 4(–5) main pillars, including beta-blockade and renin-angiotensin-aldosterone system inhibition.^{31,32} Angiotensin-converting enzyme inhibitors have long been a cornerstone in the treatment of HFrEF. In the PARADIGM-HF trial, the

ARNi sacubitril/valsartan was superior to the ACE inhibitor enalapril in reducing the risk of death and heart failure hospitalizations in patients with symptomatic HFrEF.¹¹⁹ Therefore, current clinical practice guidelines issued by the American College of Cardiology / American Heart Association (ACC/AHA) recommend replacing ACE inhibitors with an ARNi and suggest the use of ACE inhibitors or ARBs only if ARNi treatment is not feasible or not tolerated.³¹ The ESC guidelines recommend ARNi treatment as a replacement for ACE inhibitors.³²

Choice of beta-blockers in heart failure with reduced ejection fraction

Chronic beta-blockade represents another pillar in the treatment of HFrEF, with three beta-blockers (bisoprolol, carvedilol, and metoprolol succinate) shown to reduce mortality and heart failure hospitalizations, and preference should be given to those agents.¹³ Other formulations have shown to result in inferior outcomes, as seen in a clinical trial with metoprolol tartate.¹²⁰

Beta-blockers as first-line therapy in hypertension

Most clinical practice guidelines for the management of hypertension recommend the use of ACE inhibitors or ARBs in combination with a calcium channel blocker or a diuretic as the first-line therapy in patients with hypertension without comorbidities.^{121,122} While beta-blocker treatment was associated with significant reductions of the risk of stroke, heart failure, and major cardiovascular events when compared with placebo, in comparison with other blood pressure-lowering drugs, beta-blocker treatment was consistently less effective in controlling blood pressure and preventing stroke.¹²³ Therefore, most contemporary guidelines recommend beta-blocker treatment as part of the first-line therapy only when there is another specific indication, such as angina or heart failure. In the 2023 guidelines for the management of arterial hypertension issued by the European Society of Hypertension, beta-blocker treatment was upgraded to a first-line therapy irrespective of the presence of comorbidities, given the high prevalence of comorbid conditions.¹²⁴ We agree with the authors of a recent opinion paper that express concern over this 'convenience-based' recommendation, especially in patients without relevant comorbidities.¹²⁵

Clopidogrel after an acute coronary syndrome

Patients experiencing an ACS undergoing PCI require DAPT consisting of aspirin and a P2Y₁₂ inhibitor.^{14,21} Given the results of two pivotal trials, ticagrelor or prasugrel should be preferred over clopidogrel to reduce ischaemic adverse events.^{126,127} The latest European guidelines acknowledge that prasugrel and ticagrelor may not be readily available in every health system and therefore recommend clopidogrel as an alternative in such cases.¹⁴

Simvastatin for low-density lipoprotein-cholesterol lowering

In patients with ASCVD, an LDL-C reduction of at least 50% is recommended by current clinical practice guidelines.^{45,77} To achieve this, the use of a high-intensity statin (atorvastatin or rosuvastatin) is preferred given their improved efficacy, effectiveness, and better safety profile when compared with medium-intensity statins such as simvastatin, which at higher doses has increased risk of muscle toxicity with no

advantage over the more effective statins. For this reason, there is essentially no longer a role for simvastatin.

Warfarin in atrial fibrillation

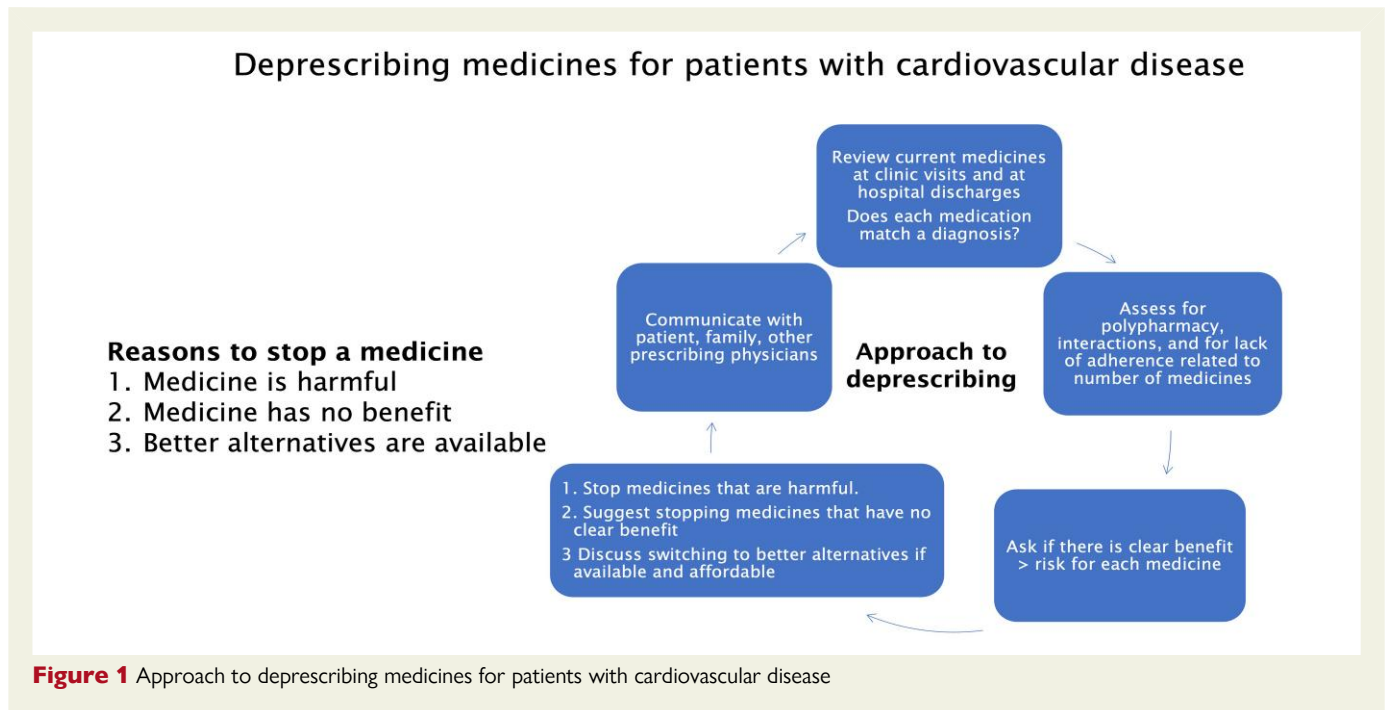
Oral anticoagulation is recommended for stroke prevention in patients with non-valvular atrial fibrillation.^{11,93} Based on the results of four pivotal cardiovascular outcome trials, DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) are recommended in preference over warfarin, given an overall 19% significant risk reduction in stroke/systemic embolism, an 8% reduction in death, and a 55% reduction in intracranial bleeding but no significant difference in major bleeding.¹²⁸ Patients eligible for DOAC treatment currently treated with warfarin should therefore be switched to DOAC therapy, unless they have mechanical valve prostheses, despite some conflicting data from the FRAIL-AF trial.¹²⁹ Availability of DOACs in generic form in the near future will enable widespread access across healthcare systems.

The critical importance of assessing the dynamic and changing relationship of risk vs. benefit over time

As clinicians, it is our duty to ensure our patients are being treated with state-of-the-art evidence-based medicine in order to reduce morbidity and mortality and improve quality of life. Of equal or even higher importance is preventing unnecessary harm to our patients by drugs or interventions unequivocally proven to do so, by deprescribing such medications when encountering them (*Graphical Abstract*). Stopping medications with no proven health benefit represents an important opportunity to address and prevent polypharmacy, a clinically challenging situation associated with risk of adverse drug reactions and interactions ultimately causing increased morbidity and mortality and increasing costs.⁴

Reducing healthcare expenditures on ineffective but expensive drugs in turn may allow reimbursement of other expensive and effective therapies. Every clinician needs to monitor and scan his/her patient's prescriptions and laboratory studies on a regular basis to identify drugs that could be discontinued. Specific protocols for structured periodic reviews of all medications and deprescription of inappropriate medications have been published and shown to be effective.^{4,9}

Figure 1 illustrates an approach to deprescribing, which begins with understanding reasons to stop medications, and includes a systematic approach to reviewing opportunities to stop medications, assessing for when deprescribing may be especially important, assessing the risk and benefit of each medication, taking action to stop or switch medications, and clear communication with patients and other providers regarding decisions. The reviews should include all medications, including over-the-counter medications and supplements, and all medication needs to be matched to the patient's comorbidities and personal goals. Reviews should be undertaken on a regular basis, such as at all clinical visits and hospitalizations, but especially in the setting of new or existing hepatic or renal impairment and the occurrence of symptoms or adverse drug reactions both during and after discharge from hospital or intra-hospital transfer, critical phases associated with medication changes, and the occurrence of adverse effects.^{130,131} This requires time, expertise, and commitment of all members of the patient care and rehabilitation teams, including nursing staff,¹³² pharmacists, and other family members as appropriate. In each and every



decision on prescribing and deprescribing, patient views must be considered and are paramount. For example, patients and clinicians may not weigh the importance of clinical endpoints equally¹³³ and patient-centred outcomes provide important insights into patient's perspectives which may help for informed decision-making.¹³⁴ A patient may prefer a treatment with a weaker effect on a hard endpoint over a life-prolonging treatment causing burdensome side effects. Patients with advanced heart failure for example often express preference for quality over length of life, highlighting the potential discrepancy between clinician's and patients' expectations.¹³⁵ Further, treating clinicians and affected patients may perceive the severity of side effects differently, such as fatigue or erectile dysfunction. Incorporating patient views is becoming increasingly complex when the choice is not just between different medications or a specific medication and no medication, but a choice between a medical treatment based on the combination of several medicines and a single intervention with distinct benefits and risks, such as in the case of stable angina.^{136,137} Still, it is the clinician's job to educate the patient on the indication as well as expected benefits and side effects of each medication that is being prescribed or deprescribed. Further, false information needs to be carefully but firmly addressed and doubts dispelled.

N-of-1 trials involve crossover design experiments within individual patients and thereby may provide quantifiable, personalized data to facilitate shared decision-making in polypharmacy.¹³⁸ Caution should be exercised when withdrawing certain medicines to avoid adverse drug withdrawal events.¹³⁹

At the end of life, patients with cardiovascular disease are often highly symptomatic, institutionalized, and not receiving proper palliative care¹⁴⁰ highlighted by ongoing exposure to polypharmacy.¹⁴¹ Reasons for deprescription in this setting are manifold and include the risk of adverse effects, declining efficacy, and most importantly perceived life expectancy, changing goals of care, values, and patient's preferences.^{142–144} Clinicians should therefore continuously re-evaluate patient's preferences and have greater focus on improving quality of life rather than length of life.¹⁴⁵

A major barrier to drug deprescription is ultimately the lack of high-quality evidence around this topic, including the process and timing of deprescription itself, the correct strategy (partial vs. complete discontinuation, switching), lack of clinical data on medication efficacy and safety in elderly patients and patients with multimorbidity, lack of reliable information on drug–drug interactions, and heterogeneity of therapeutic responses fuelling the inherent weakness of risk/benefit ratio estimates. The widely unregulated over-the-counter market and clinician's and patient's belief represent additional major barriers in optimizing medication prescription.¹⁴⁶

Several RCTs have investigated the feasibility, safety, and effectiveness of deprescribing cardiovascular medicines mostly in older adults experiencing polypharmacy.^{143,147} While most deprescribing interventions proved to be safe, caution should be exercised to not deprescribe medications clearly shown to be beneficial.¹⁴⁸

We advocate that clinical practice guideline committees should include regular structured medication review and deprescribing in their mandates and that adequate research funding should be provided investigating scalable strategies. As every effective and life-saving medicine also exhibits some harmful effects, it is our responsibility in treating our patients to ensure that expected benefits continue to outweigh the risk.

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Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

No data were generated or analysed for or in support of this paper.

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