

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Long-Term Use of Cardiovascular Drugs Challenges for Research and for Patient Care



Xavier Rossello, MD,*† Stuart J. Pocock, PhD,*‡ Desmond G. Julian, MD§

ABSTRACT

Little is known about the benefits and risks of the long-term use of cardiovascular drugs. Evidence from randomized clinical trials (RCTs) rarely goes beyond a few years of follow-up, but patients are often given continuous treatment with multiple drugs well into old age. We focus on 4 commonly used cardiovascular drug classes: aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors given to patients after myocardial infarction. However, the issues raised apply more broadly to all long-term medications across cardiovascular diseases and the whole of medicine. The evidence and limitations of RCTs are addressed, as well as current practice in pre-licensing trials, the increasing problems of polypharmacy (especially in the elderly), the lack of trial evidence for withdrawal of drugs, the role of regulatory authorities and other stakeholders in this challenging situation, and the potential educational solutions for the medical profession. We conclude with a set of recommendations on how to improve the situation of long-term drug use. (J Am Coll Cardiol 2015;66:1273-85) © 2015 by the American College of Cardiology Foundation.

Worldwide, millions of patients with coronary heart disease (CHD) have been receiving cardiovascular drugs for decades, in the absence of any evidence from clinical trials to justify their use beyond 5 to 10 years (1-5). Although there is abundant evidence of the value of 4 groups of drugs (aspirin, beta-blockers, statins, and angiotensin-converting enzyme [ACE] inhibitors) in the prevention and treatment of CHD in the first few years after an acute coronary event (1-5), there is inadequate evidence for the continuation of these drugs beyond that time. Additional concerns have arisen with the introduction of the fixed-dose polypill as a potential life-long therapy.

Our attention was drawn to this issue by the personal experience of 1 of the investigators (6). He developed an episode of severe hypotension during exercise, and developed another of sinoatrial block,

which led to syncope after being on a beta-blocker for >15 years, cough from an ACE inhibitor after being on ramipril for 10 years, and aspirin-induced gastrointestinal bleeding after being on the drug for 20 years. We suspect such risks are not uncommon. The 2 episodes due to the beta-blocker could have been fatal if immediate help had not been available, and the death would not have been attributed to the drug.

Therefore, we feel it is important to challenge the assumption that the efficacy and safety of drugs given in the relatively short term remain the same over the long term and into old age.

In the following sections, Aspirin, Statins, Beta-Blockers, and Angiotensin-Converting Enzyme Inhibitors After Myocardial Infarction and The Knowledge Gap in Long-Term Use of Cardiovascular Drugs, we summarize the evidence and the gaps of knowledge with the regard to the use of aspirin,

From the *Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain; †Hatter Cardiovascular Institute, University College London, London, United Kingdom; ‡London School of Hygiene and Tropical Medicine, London, United Kingdom; and the §Netherhall Gardens, London, United Kingdom. Dr. Rossello has received support from a Spanish Society of Cardiology research fellowship grant. Dr. Pocock has received research grants from Amgen, AstraZeneca, Biosensors, Boston Scientific, GlaxoSmithKline, Janssen, and The Medicines Company. Dr. Julian has reported that he has no relationships relevant to the contents of this paper to disclose.

[Listen to this manuscript's audio summary by JACC Editor-in-Chief Dr. Valentin Fuster.](#)

Manuscript received June 28, 2015; accepted July 7, 2015.



ABBREVIATIONS AND ACRONYMS

ACC	= American College of Cardiology
ACE	= angiotensin-converting enzyme
ACS	= acute coronary syndrome
AHA	= American Heart Association
ARB	= angiotensin receptor blocker
CHD	= coronary heart disease
EMA	= European Medicines Agency
FDA	= Food and Drug Administration
MI	= myocardial infarction
PCI	= percutaneous coronary intervention
RCT	= randomized clinical trial
STEMI	= ST-segment elevation myocardial infarction

statins, ACE inhibitors, and beta-blockers after myocardial infarction (MI). The section on Problems With Current Practice in Pre-Licensing Trials explains how the regulatory environment influences the current practice of pre-licensing trials. We then tackle the increasing problems of polypharmacy, especially in the elderly, in the Problems of Polypharmacy section; of the long-term use of cardiovascular drugs in Long-Term Use of Medications and Aging; and the lack of trial evidence for withdrawal of drugs in the Deprescribing section. We propose a potential randomized trial in the section called An Example Randomized Clinical Trial for Withdrawal of Beta-Blockers. The section on Responsibilities of Regulators and Other Stakeholders considers the responsibilities of the regulating authorities and other stakeholders facing this challenge and the potential educational solutions for the medical profession. The Recommendations section provides a concluding set of recommenda-

tions to improve the situation. The **Central Illustration** depicts the content of the review.

ASPIRIN, STATINS, BETA-BLOCKERS, AND ANGIOTENSIN-CONVERTING INHIBITORS AFTER MI

CHD is a chronic condition that includes patients with and without previous MIs. Secondary prevention interventions reduce the risk for new cardiovascular events in patients with established CHD. By way of example, we report the biological effects and the main evidence regarding the 4 drugs most commonly used in cardiology: aspirin, statins, beta-blockers, and ACE inhibitors. We also summarize the guidelines' recommendations for each drug (**Table 1** [7-9]).

Aspirin decreases platelet aggregation and prevents formation of coronary thrombus. Aspirin reduces the risk of both re-infarction and vascular death in post-MI patients (10). According to the guidelines (7), aspirin should be prescribed indefinitely after MI. Despite the strong evidence supporting the absolute risk reduction of thrombotic events with the use of aspirin in secondary prevention, the tradeoff between the benefits and the risk of bleeding events is less clear in some particular settings, such as in the elderly.

Statins are effective in reducing low-density lipoprotein cholesterol. After an ST-segment elevation myocardial infarction (STEMI), statins lower the risk of cardiovascular death, recurrent MI, stroke, and the need for coronary revascularization (11,12). The

American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend that high-dose statin therapy should be initiated or continued in all patients with STEMI with no contraindication to its use. It is implied that continuation is long-term. Statins are also widely used for primary prevention, and although they seem to be cost-effective therapy, concerns have arisen regarding an increase in geriatric-specific adverse effects (13) and the potential of the increased incidence of diabetes (14).

Beta-blockers prevent the action of endogenous catecholamines, and consequently, lower heart rate and blood pressure. Beta-blocker treatment after MI is associated with reduced mortality and morbidity (5). Patients with MI complicated by heart failure, left ventricular dysfunction, or ventricular arrhythmias receive the greatest benefit of this therapy (7). The value (or not) of long-term duration of routine beta-blocker therapy after uncomplicated MI has not been investigated. In the AHA/ACC Foundation secondary prevention guidelines (15), beta-blocker therapy is recommended to last for 3 years in all patients with normal left ventricular function who have had a MI. It is unclear what should happen beyond 3 years.

ACE inhibitors act by blocking the renin-angiotensin system, and have been shown to reduce fatal and nonfatal cardiovascular events in patients with STEMI (16). However, although the clinical benefit is well established in high-risk subgroups, such as patients with anterior MI, ejection fractions of <40%, heart failure, previous MI, or tachycardia (7), the role of routine long-term ACE inhibitor therapy in low-risk patients after STEMI is less certain (4,17,18). Current ACC/AHA guidelines declare that ACE inhibitors are reasonable for all STEMI patients, with no contraindications to their use.

Once initiated, there is no clear evidence for how long these 4 drugs should be prescribed. Additional concerns have arisen with the introduction of the fixed-dose polypill as potential life-long therapy in post-MI patients (19,20). Although we concentrate on post-MI patients, including those with STEMI and non-STEMI, these problems and the uncertainties regarding long-term drug use may also apply to other cardiac diseases (e.g., heart failure, atrial fibrillation) and in the primary prevention setting.

THE KNOWLEDGE GAP IN LONG-TERM USE OF CARDIOVASCULAR DRUGS

Clinicians or those writing guidelines have given little consideration to the use of drugs over decades, and trialists have used "long-term" to mean "not very short-term." Thus, in a recent publication of a

randomized clinical trial (RCT) in post-MI patients, PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) (21), the expression “long-term use” in the title referred to a median 33 months of follow-up. Even more disturbingly, a recent real-world Swedish registry in post-MI patients (22) defined a long-term perspective as 1 year of follow-up. Beyond these terminology issues, these studies reflect the proportion of post-MI patients taking cardiovascular drugs. In the RCT, the percentages of patients taking medications 1 to 3 years after a MI were as follows: aspirin, 100%; statin, 93%; beta-blocker, 82%; and ACE inhibitor or angiotensin receptor blocker (ARB), 80%. In the registry, the percentages of patients on medications at 1-year of follow-up were: aspirin, 82%; statin, 73%; beta-blocker, 80%; and ACE inhibitor or ARB, 75%. However, our use of long-term relates to much longer periods; real-world, post-MI patients may well stay on such drugs for decades, although there is no direct evidence that this is beneficial.

Current treatment of survivors of acute MI is based on the results of large RCTs and subsequent meta-analyses. These have demonstrated that aspirin, beta-blockers, ACE inhibitors, and statins improve prognosis after an acute MI. Although RCTs provide the highest level of evidence for assessing the efficacy and safety of a drug, there are some limitations with regard to the extrapolation of their results to the seriously long-term usage of these drugs.

The key limitation is a gap of knowledge between the short-term evidence and the long-term use of these drugs. Although the average follow-up in RCTs is limited, these medications are often administered open-endedly over many years. Table 2 (11,12,17,23-49) shows an overview of some landmark RCTs that demonstrated the efficacy of aspirin, statins, beta-blockers, and ACE inhibitors in post-MI (and stable CHD) patients. A good example of this problem is a meta-analysis published in 2010 on the use of statins as primary and secondary prevention, in which the median follow-up across 26 trials was 4.9 years (2). A more extreme case is seen with beta-blockers after MI; a meta-analysis published in 1999 (5) had a mean follow-up across 82 RCTs of only 1.4 years.

A second gap between evidence and real-world practice is that the recommended long-term use of these drugs is based implicitly on a constant relative hazard assumption, meaning that the benefits continue (and stay constant) over the long-term, when no data exist to confirm or refute this presumption. It is important to consider how the

CENTRAL ILLUSTRATION Long-Term Use of Cardiovascular Drugs: Challenges for Research and for Patient Care

CONCERNS WITH CURRENT LONG-TERM USE OF CARDIOVASCULAR DISEASE DRUGS

-  **Unclear guidelines for drug use after myocardial infarction**
 - Health care providers/physicians need better guidance for long-term use of Aspirin, Statin, Beta-blockers and ACE inhibitors
 - Once initiated, no evidence for how long these drugs should be prescribed
-  **Knowledge gap regarding long-term use**
 - RCTs provide relatively short-term follow-up
 - RCTs prior to primary PCI are outdated
 - Efficacy/safety trade-off may change, especially in the elderly
-  **Problems with pre-licensing RCTs**
 - Successful drugs are added to standard of care, increasing polypharmacy
 - Lack of head-to-head trials
-  **Problems with polypharmacy**
 - Patients often on multiple drugs, long-term
 - Deprescribing policies need objective evidence
-  **Long-term medication in the elderly**
 - Aging, co-morbidities and frailty affect drug safety and efficacy
 - Older patients under-represented in RCTs
-  **Lack of drug withdrawal trials**
 - A need to investigate drug withdrawal as alternative to long-term continuation of drugs

Rossello, X. et al. J Am Coll Cardiol. 2015; 66(11):1273-85.

Summary of our concerns regarding current long-term use of cardiovascular drugs. ACE = angiotensin-converting enzyme; PCI = percutaneous coronary intervention; RCTs = randomized clinical trials.

absolute risk changes over time. Many trials started follow-up in the post-acute phase of acute coronary syndrome (ACS), when the risk is high, and therefore, the benefit may be greatest. Survivors several years after an MI may be a relatively low-risk cohort, so absolute benefits may be relatively small. In the truly long term, the risks of major cardiac events and death increases with age, but whether these medications benefit elderly patients long after the initial MI remains without assurance by RCTs.

In a pre-reperfusion era meta-analysis (16), ACE inhibitors started in the acute phase of MI showed an early absolute benefit of 5 lives saved per 1,000 patients treated in the first month. Even more importantly, this meta-analysis showed that most of this benefit was markedly reduced over the subsequent 3 years.

TABLE 1 Summary of ACC/AHA Guidelines Regarding Use of Aspirin, Statins, Beta-Blockers, and ACE Inhibitors*

Aspirin	
STEMI	After PCI, aspirin should be continued indefinitely (Class I, Level of Evidence: A)
NSTEMI	Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81 to 325 mg daily in all other patients (Class I, Level of Evidence: A)
SIHD	Treatment with aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications in patients with SIHD (Class I, Level of Evidence: A)
Statins	
STEMI	High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use (Class I, Level of Evidence: B)
NSTEMI	High-intensity statin therapy should be initiated or continued in all patients with NSTEMI-ACS and no contraindications to its use (Class I, Level of Evidence: B)
SIHD	In addition to therapeutic lifestyle changes, a moderate or high dose of a statin therapy should be prescribed, in the absence of contraindications or documented adverse effects (Class I, Level of Evidence: A)
Beta-blocker therapy	
STEMI	Oral beta-blockers should be initiated in the first 24 h in patients with STEMI who do not have any of the following: signs of heart failure; evidence of a low output state; increased risk for cardiogenic shock; or other contraindications to use of oral beta-blockers (PR interval >0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease) (Class I, Level of Evidence: B) Beta-blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use (Class I, Level of Evidence: B)
NSTEMI	Oral beta-blocker therapy should be initiated within the first 24 h in patients who do not have any of the following: 1) signs of HF; 2) evidence of low-output state; 3) increased risk for cardiogenic shock; or 4) other contraindications to beta-blockade (e.g., PR interval >0.24 s, second- or third-degree heart block without a cardiac pacemaker, active asthma, or reactive airway disease) (Class I, Level of Evidence: A) It is reasonable to continue beta-blocker therapy in patients with normal LV function with NSTEMI-ACS (Class IIa, Level of Evidence: C)
SIHD	Beta-blocker therapy should be started and continued for 3 yrs in all patients with normal LV function after MI or ACS (Class I, Level of Evidence: B) Beta-blocker therapy should be used in all patients with LV systolic dysfunction (EF <40%) with HF or previous MI, unless contraindicated (Class I, Level of Evidence: A) Beta-blockers may be considered as long-term therapy for all other patients with coronary or other vascular disease (Class IIb, Level of Evidence: C)
ACE inhibitors	
STEMI	An ACE inhibitor should be administered within the first 24 h to all patients with STEMI with an anterior location, HF, or EF ≤40%, unless contraindicated (Class I, Level of Evidence: A) ACE inhibitors are reasonable for all patients with STEMI and no contraindications to their use (Class IIa, Level of Evidence: A)
NSTEMI	ACE inhibitors should be started and continued indefinitely in all patients with LVEF <0.40 and in those with hypertension, diabetes mellitus, or stable CKD, unless contraindicated (Class I, Level of Evidence: A) ACE inhibitors may be reasonable in all other patients with cardiac or other vascular disease (Class IIb, Level of Evidence: C)
SIHD	ACE inhibitors should be prescribed in all patients with SIHD who also have hypertension, diabetes mellitus, LVEF ≤40%, or CKD, unless contraindicated (Class I, Level of Evidence: A) Treatment with an ACE inhibitor is reasonable in patients with both SIHD and other vascular disease (Class IIa, Level of Evidence: B)
<p>Each statement is presented with the class of recommendation and level of evidence in brackets. *Recommendations from O'Gara et al. (7), Fihn et al. (8), and Amsterdam et al. (9). ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; AHA = American Heart Association; CKD = chronic kidney disease; EF = ejection fraction; HF = heart failure; LV = left ventricle/ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI-ACS = non-ST-segment elevation acute coronary syndrome; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease; STEMI = ST-segment elevation myocardial infarction.</p>	

In STEMI patients who undergo primary percutaneous coronary intervention (PCI), risks change rapidly over time; cardiac mortality is high (>7%) during the first month, but subsequently falls to <1.5% year. Also, the cause of death after STEMI is mainly cardiac in the first 5 years, but noncardiac mortality becomes more important later (50).

A third limitation of evidence from RCTs is the change in practice over time. Many trials were performed in the fibrinolytic era, whereas current widespread use of primary PCI (reperfusion therapy) has had an impact on long-term prognosis, and may well affect the value of post-MI medications. For instance, the evidence regarding beta-blocker use after MI is mostly derived from trials conducted in the pre-reperfusion era. In 1 meta-analysis (5) cited in the 2013 ACC/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, the median publication date of the 82 beta-blocker RCTs included was 1982. Moreover, most of these trials were performed

before the implementation of other secondary prevention therapies, such as statins and ACE inhibitors. Thus, controversy exists over the role of beta-blockers after primary PCI. In the absence of relevant RCTs, observational studies are contradictory; 1 that showed treatment with beta-blockers after successful primary PCI was associated with reduced 6-month mortality (51), whereas another demonstrated no reduction of a composite of cardiovascular events with the use of beta-blockers after MI (52).

The universal definition of MI has changed 3 times between 2000 and 2012 (53-55), which is a further complication, making a lower risk cohort progressively eligible for RCTs in real-world practice, when these patients would not have been included in RCTs using previous definitions.

Another limitation is the difficulty in extrapolating RCT results to the real world. For example, the average age of patients included in MI trials tends to be younger than the typical MI patient; there is often

TABLE 2 Summary of the Main RCTs Regarding Use of Aspirin, Statins, Beta-Blockers, and ACE Inhibitors in Secondary Prevention

Study (Ref. #)	Year Published	No. of Participants	Mean Follow-Up (yrs)	Age Range (yrs)	Mean Age (yrs)	Eligible Population	Placebo-Controlled	Drug
Aspirin								
Cardiff-I (23)	1974	1,239	1	NR	55	Post-MI	Yes	Aspirin
CDP-A (24)	1976	1,529	1.8	NR	56	Post-MI	Yes	Aspirin
Cardiff-II (25)	1979	1,682	1	NR	56	Post-MI	Yes	Aspirin
PARIS (26)	1980	1,216	3.4	30-74	56	Post-MI	Yes	Aspirin and persantine
AMIS (27)	1980	4,524	>3	30-69	55	Post-MI	Yes	Aspirin
Statins								
4S (12)	1994	4,444	5.4	35-70	NR	History of angina or MI	Yes	Simvastatin
CARE (11)	1996	4,159	5	21-75	59	Post-MI	Yes	Pravastatin
LIPID (28)	1998	9,014	6.1	31-75	62	Post-MI or UA	Yes	Pravastatin
GISSI-P (29)	2000	4,271	2	19-90	60	Post-MI	Yes	Pravastatin
LIPS (30)	2002	1,677	3.9	18-80	60	Post-PCI	Yes	Fluvastatin
ALLIANCE (31)	2004	2,442	4.5	≥18	61	CHD	Yes	Atorvastatin
PROVE IT (32)	2004	4,162	2	≥18	58	Post-ACS	No	Pravastatin and atorvastatin
A to Z (33)	2004	4,497	2	21-80	61	Post-ACS	No	Simvastatin (low vs. high dose)
TNT (34)	2005	10,001	4.9	35-75	61	CHD	No	Atorvastatin (low vs. high dose)
IDEAL (35)	2005	8,888	4.8	≤80	62	Post-MI	No	Atorvastatin and Simvastatin
SEARCH (36)	2010	12,064	6.7	18-80	64	Post-MI	No	Simvastatin (low vs. high dose)
Beta-blockers								
Multicenter International (37)	1975	3,038	Up to 3	≤70	55	Post-MI	Yes	Practolol
Julian et al. (38)	1982	1,456	1	30-69	55	Post-MI	Yes	Sotalol
EIS (39)	1984	1,741	1	35-69	54	Post-MI	Yes	Oxprenolol
Salathia et al. (40)	1985	800	1	NR	NR	Suspected MI	Yes	Metoprolol
LIT (41)	1987	2,395	1.6	45-74	58	Post-MI	Yes	Metoprolol
CAPRICORN (42)	2001	1,959	1.3	≥18	63	Post-MI with LV dysfunction	Yes	Carvedilol
ACE inhibitors								
SAVE (43)	1992	2,231	3.5	21-80	59	Post-MI and LV dysfunction	Yes	Captopril
TRACE (44)	1995	1,749	2-4.2	≥18	67	Post-MI and LV dysfunction	Yes	Trandolapril
AIRE (45)	1993	2,006	1.3	≥18	65	Post-MI with HF	Yes	Ramipril
ISIS-4 (46)	1995	58,050	1.3	NR	NR	Suspected MI	Yes	Captopril, mononitrate, and magnesium sulfate
QUIET (47)	2001	1,725	2.25	18-75	58	Post-PCI or atherectomy	Yes	Quinapril
CAMELOT (48)	2004	1,997	2	30-79	57	CHD	No	Enalapril and amlodipine
EUROPA (49)	2003	12,218	4.2	≥18	60	SIHD without HF	Yes	Perindopril
PEACE (17)	2004	8,290	4.8	≥50	64	SIHD and preserved LV function	Yes	Trandolapril

This table is based on the most comprehensive published meta-analyses (1-5), and includes randomized clinical trials (RCTs) with >1,000 patients and >1-year follow-up.
 4S = Scandinavian Simvastatin Survival Study; A to Z = Combined use of low-molecular-weight heparin with the glycoprotein IIb/IIIa inhibitor tirofiban and efficacy of early aggressive simvastatin therapy; AIRE = Acute Infarction Ramipril Efficacy; ALLIANCE = Aggressive Lipid-Lowering Initiation Abates New Cardiac Events study; AMIS = Aspirin Myocardial Infarction Study; CAMELOT = Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; CAPRICORN = Carvedilol Post-Infarct Survival Control in LV Dysfunction; CARE = Cholesterol and Recurrent Event; CHD = coronary heart disease; CDP-A = Coronary Drug Project Aspirin Study; EIS = European Infarction Study; EUROPA = European trial On reduction of cardiac events with Perindopril in stable coronary Artery disease; GISSI-P = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione; IDEAL = Incremental Decrease in End Points Through Aggressive Lipid Lowering; ISIS-4 = Fourth International Study of Infarct Survival; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease; LIPS = Lescol Intervention Prevention Study; LIT = Lopressor Intervention Trial; NR = not reported; PARIS = Persantine-Aspirin Reinfarction Study; PEACE = Prevention of Events with Angiotensin Converting Enzyme Inhibition; PROVE IT = Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction; QUIET = Quinapril Ischemic Event Trial; SAVE = Survival and Ventricular Enlargement Trial; SEARCH = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; TNT = Treating to New Targets; TRACE = Trandolapril Cardiac Evaluation; UA = unstable angina; other abbreviations as in Table 1.

a systematic exclusion and under-recruitment of elderly patients in cardiovascular RCTs (56). This issue will be covered in the section on Deprescribing. Also, the net benefit of some medications may be neutralized with the appearance of age-related adverse effects and comorbidities (drug-disease and drug-drug interactions), which are not well studied in RCTs. This issue is discussed in the section on Long-Term Use of Medications and Aging.

In principle, we need RCTs of post-MI medications to be extended into truly long-term follow-up. However, in practice, to achieve trials with >5 years follow-up is a major challenge, not just because of increased noncompliance and loss to follow-up, but also due to the increased costs of organizing and monitoring long-term follow-up. Thus, to fill the evidence gaps on long-term effectiveness and safety issues regarding cardiovascular drug use, and despite

the inherent problems with potential selection bias, there is also a need for quality, large-scale registries.

PROBLEMS WITH CURRENT PRACTICE IN PRE-LICENSING TRIALS

The RCTs that the pharmaceutical industry undertakes are aimed at getting their products licensed by regulators, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These regulators often require placebo-controlled trials based on a background of current standard therapy. Therefore, new cardiovascular medications are commonly tested on a background of guideline-recommended therapies that include “standard of care.” This process leads to polypharmacy because newly licensed prescription drugs are continually introduced, whereas older drugs are not commonly reassessed, and therefore, stay in use. The incremental problems of polypharmacy are emphasized, particularly in elderly patients.

There is a lack of head-to-head trials in CHD patients that would offer the opportunity to replace an old drug with a newer one, rather than continually adding drugs to the armamentarium. An example of a head-to-head trial in post-MI patients was VALIANT (Valsartan in Acute Myocardial Infarction Trial) (57). This 3-arm trial randomized patients after an acute MI that was complicated by heart failure or low ejection fraction to additional therapy with valsartan, valsartan plus captopril, or captopril. Valsartan appeared to be as effective as captopril for overall survival. However, combining valsartan with captopril increased the rate of adverse events without improving survival, demonstrating that the constant addition of drugs is not always beneficial.

RCTs of ivabradine in both stable CHD and heart failure patients (58-60) were all placebo-controlled studies, thus adding ivabradine on top of a beta-blocker in many patients. Thus, the opportunity for a head-to-head ivabradine versus beta-blocker comparison was missed, which is disadvantageous because 1 prime feature of both drugs is a reduction in heart rate.

We cannot expect the industry to promote these head-to-head trials in such a regulatory environment, because they understandably want the most straightforward trial progress to achieve drug licensing. However, we encourage regulators to take a broader vision of patient care, recognizing the dangers of polypharmacy; this could entail a thorough review of the merits and hazards of the current overall drug regime each time a new drug is added to the armamentarium (see Responsibilities of Regulators and

Other Stakeholders). Regulators might also insist on more pre-licensing head-to-head trials as an integral part of enhancing public health needs alongside commercial interests.

PROBLEMS OF POLYPHARMACY

The decision to prescribe a drug is often on the basis of a single disease-oriented approach and its associated guideline recommendations for that specific drug. This paradigm of care, which is focused on a specific drug-disease link instead of holistic (whole patient) care, promotes the use of multiple medications by a patient, a condition known as polypharmacy. This becomes more complicated because polypharmacy is increased by the presence of comorbidities, such as hypertension, chronic obstructive pulmonary disease, or diabetes, each of which has its own guideline-recommended drugs.

An American survey of prescribing patterns in the ambulatory adult population (61) reported the highest prevalence of medication use in women older than 65 years of age, 12% of whom took at least 10 medications and 23% of whom took at least 5 prescription drugs. This trend is increasing dramatically among older adults in the United States (62), and cardiovascular drugs represent the most used pharmacological group in polypharmacy cohorts (63,64). Among the 20 most commonly used prescriptions in the United States, 2 are antiplatelet agents (aspirin in first place and clopidogrel in 18th place), 2 are statins (atorvastatin in third place and simvastatin in seventh place), 2 are beta-blockers (metoprolol in sixth place and atenolol in eighth place), and 2 are renin-angiotensin system inhibitors (lisinopril in fifth place and valsartan in 14th place) (64). Moreover, cardiovascular drugs are the most frequent cause of adverse drug events in ambulatory older patients (65).

In a Scottish primary care population (66), 21.5% of adults received at least 4 medications, and 4.6% received ≥ 10 medications. These prevalences increased with age (36.0% and 7.4%, respectively, in those ages 60 to 69 years, and 70.4% and 18.6%, respectively, in those ages 80 years or older). Cardiovascular conditions (e.g., heart failure, ischemic heart disease, and atrial fibrillation) were associated with the highest levels of prescribing, which is consistent with clinical guidelines advocating their treatment with multiple drug classes.

Polypharmacy increases health care costs and the risks of noncompliance and of adverse drug reactions, which is enhanced by both drug-drug and drug-disease interactions (67).

Fixed-dose combination therapy (the polypill) has recently been shown to improve adherence in post-MI patients (19). Its future availability may expose more patients to polypharmacy. The SECURE (Secondary Prevention of Cardiovascular Disease in the Elderly) trial is an RCT of the efficacy of the polypill in post-MI patients, which is about to start recruitment, but it will be more difficult to assess the impact of long-term treatment with a polypill on the risk of adverse events.

There are also concerns regarding the benefit and/or risk tradeoff for aspirin and statins in primary prevention. In this setting, it has been argued that some AHA/ACC risk scores may overestimate an individual's cardiovascular risk (68), especially among older people (69). This could result in an excess of people exposed to drug side effects and more health care spending. This overestimation may lead to unnecessary harms, such as bleeding with aspirin, and less cost-effectiveness (reduced absolute benefit) of primary prevention interventions, such as statins (13).

LONG-TERM USE OF MEDICATIONS AND AGING

At present, 13% of the American population is ages 65 years or older, and this will rise to approximately 20% by 2030 (67). People ages 85 years and older are the most rapidly growing segment of the U.S. population and will include 18% of those ages 65 years or older by 2040. In the United Kingdom, people ages 65 years and older will account for 23% of the population by 2035 (70). The fastest increase is occurring among the very old (age 85 years and older); between 1985 and 2010, this population more than doubled. Aging is often accompanied by both comorbidities and frailty, and consequently leads to potentially excessive polypharmacy.

Physiological aging changes both the pharmacokinetics and pharmacodynamics of cardiovascular drugs (70). Pharmacokinetic changes include a reduction in renal and hepatic clearance and increased body fat, leading to altered distribution, metabolism, and elimination of cardiovascular drugs (particularly beta-blockers and ACE inhibitors). Pharmacokinetic changes also increase the risk of statin-related adverse events in older adults, including cognitive impairment, falls, neuropathy, and muscle damage (13). The pharmacodynamics of cardiovascular drugs are affected by age-related changes in end-organ responsiveness (67,71). Therefore, alterations to both sinus node activity and atrioventricular conduction in the elderly may lead to increased sensitivity to the bradycardic effect of beta-blockers.

In addition, the elderly experience more comorbidities, and the drugs used to treat them increase the risk of drug-disease and drug-drug interactions (Table 3). As a drug-disease interaction, beta-blocker treatment can cause intermittent claudication in patients with peripheral vascular disease and bronchoconstriction in the presence of chronic obstructive pulmonary disease. A drug-drug interaction can occur when ACE inhibitors and potassium-sparing diuretics cause hyperkalemia, or when simultaneous use of statins and other lipid-lowering agents, such as gemfibrozil and niacin, result in rhabdomyolysis and acute renal failure. ACE inhibitors may interact with co-trimoxazole, increasing the risk of sudden death (72). In the same way, ACE inhibitors and aspirin may interact with common medications, such as nonsteroidal anti-inflammatory drugs, resulting in hyperkalemia and peptic ulceration, respectively (73).

In making treatment decisions in the elderly, clinicians should take into account the limited external validity of RCTs (74)—can the results of a particular treatment after MI be reasonably applied to the elderly

TABLE 3 Common Side Effects and Interactions of Aspirin, Statins, Beta-Blockers, and ACE Inhibitors in the Elderly

Drug Class	Side Effects in Older Patients	Drug-Disease Interactions	Drug-Drug Interactions
Aspirin	Gastrointestinal bleeding, dyspepsia, tinnitus, skin reactions	Asthma (bronchospasm) Gastrointestinal bleeding history, dehydration, and hypertension (bleeding)	Anticoagulants, antiplatelets and antithrombins (bleeding) NSAIDs (peptic ulcer)
Statins	Myalgias, confusion, renal insufficiency, liver toxicity	Hypothyroidism, CKD, diabetes mellitus (statin-induced myopathy)	Fibrates (myopathy) Amiodarone, erythromycin, diltiazem, azole antifungals, fibric acids (P450 system interactions)
Beta-blockers	Confusion, fatigue, bronchospasm, conduction block, claudication, depression, incontinence, hypoglycemia	COPD (bronchospasm) PAD (intermittent claudication) Raynaud syndrome (increased symptoms) CHF (acute decompensation) Conduction disease (heart block)	Sulfonylureas (hypoglycemia) Calcium-channel blockers (chronotropic incompetence)
ACE inhibitors	Falls, dizziness, hypotension, hyperkalemia, fatigue, acute kidney injury, cough	CKD (hyperkalemia and renal failure)	Diuretics (hypotension) NSAIDs (renal failure)

COPD = chronic obstructive pulmonary disease; NSAID = nonsteroidal anti-inflammatory drug; PAD = peripheral artery disease; other abbreviations as in Table 1.

in routine practice? Older people are often underrepresented in RCTs as a consequence of exclusion criteria and under-recruitment (56). In routine practice, the median age of patients presenting with a first MI is 70 years, and patients ages 75 years or older account for 36% of all MIs (67). However, only 7% of all patients enrolled in ACS trials between 1966 and 2000 were 75 years of age or older (75). Moreover, because of the short duration of RCTs, too few patients are followed into older age; therefore, there is inadequate testing of drug efficacy and safety in the elderly. Some key studies fail to demonstrate benefit in the elderly. In a meta-analysis of post-MI patients who received an ACE inhibitor, no survival benefit was found in patients ages 75 years or older (16).

Most drug RCTs focus on the reduction of “hard” clinical outcomes, whereas less attention is paid to symptom relief and quality of life, which might be of greater concern among the elderly.

Better evidence is needed on the effectiveness and potential harms of drugs in older adults, who tend to have multiple chronic conditions and who are sometimes frail.

DEPRESCRIBING

Discontinuing drug treatments, or deprescribing, is the process of withdrawing drugs in an attempt to improve patients’ outcomes (76). Deprescribing involves establishing which drug does not have a current indication or may be causing a problem. In contrast to prescribing practices, the deprescribing process is not represented in guidelines and is usually based on clinical judgment. Although prescribing drugs is substantially based on evidence from RCTs, the rationale for discontinuation of drugs is inadequately addressed by RCTs, as discussed in the following section. This issue is crucial in older adults, who are the largest per capita consumers of prescription medications and the most vulnerable population for medication adverse effects and interactions, partly as consequence of polypharmacy.

At present, deprescribing receives insufficient attention, and there is a great need for the deprescription process to be based on objective evidence rather than solely on subjective clinical judgment.

THE NEED FOR TRIALS ON WITHDRAWAL OF DRUGS

The possibility that cardiovascular drugs may have reduced efficacy over longer medication periods is an important issue that has received little attention. Likewise, the potential long-term harm of these drugs, enhanced by an accumulating polypharmacy,

especially in elderly patients, still needs to be addressed. Clinical trials aimed at investigation of the withdrawal of certain established medications are needed to cover both these long-term efficacy and safety issues (77).

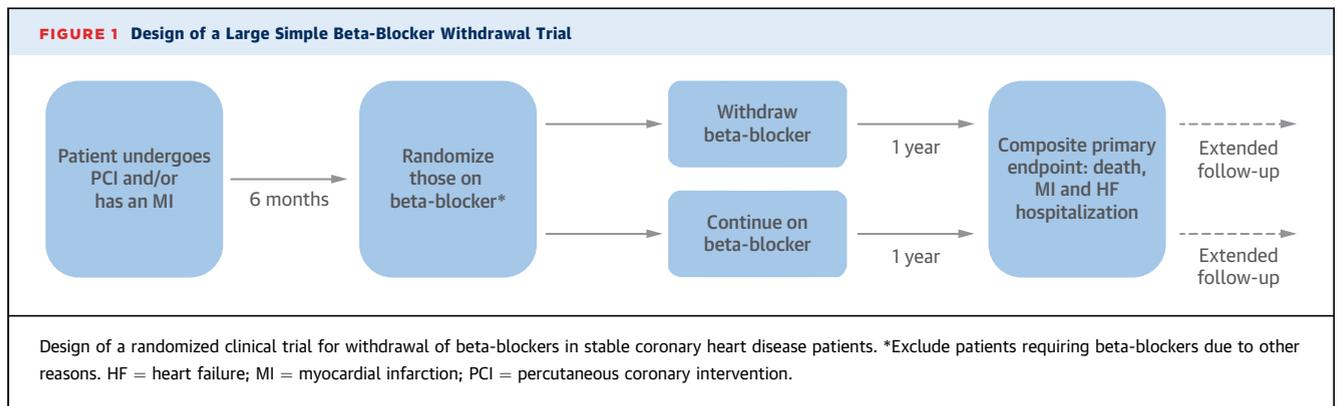
One major problem in undertaking such trials investigating withdrawal of a drug is the difficulty of funding them. Once a drug has achieved regulatory approval, company sponsors do not routinely plan any long-term efficacy and safety assessment. Also, it is clearly not in their commercial interests to investigate any timely withdrawal of their drugs. Thus, evidence is relegated to post-licensing surveillance, with its inevitable biases, absence of efficacy data, and inadequate detection of adverse effects. Consequently, the deprescribing process receives little help from current guidelines or clinical trials, and any decisions on withdrawal of drugs are largely ad-hoc and on the basis of individual clinical judgment.

The regrettable lack of drug withdrawal trials has to be improved to provide objective guidance on the long-term use and potential withdrawal of drugs. One notable exception concerns trials into the timing of withdrawal of dual antiplatelet therapy after PCI (78,79). Their challenge of counterbalancing the risks of ischemic events (stent thrombosis and MI) and bleeding events is a paradigm of the tradeoff between efficacy and safety assessment, and a good illustration of how to get trials of treatment withdrawal on the research agenda.

Limited observational data are available describing the clinical impact of drug withdrawal after MI (80). There is no good evidence base for the continuation of aspirin, statins, beta-blockers, and ACE inhibitors in the long term, and further investigation is needed.

Drug discontinuation is sometimes associated with a rebound phenomenon, which might complicate how to design a drug withdrawal trial. Thus, abrupt beta-blocker withdrawal may be associated with an increased risk for acute MI and sudden death (8). Consequently, the drug should be tapered down over a 1- to 3-week period. In the same way, abrupt statin withdrawal may lead to an inflammatory rebound process (80). Other publications have suggested a potential increased thrombotic risk following antiplatelet therapy withdrawal (81), whereas a hypertensive rebound phenomenon after ACE inhibitor withdrawal is more controversial.

We wish to encourage an active debate that will lead to action in the planning and execution of RCTs of withdrawal of cardiovascular drugs that are currently in long-term use. There are many questions to be posed. First, which drugs are ripe for such investigation? Here, we propose beta-blockers as a prime case



(see the following section). Next, at which point in follow-up after which initial disease event do we propose patients be randomized to drug withdrawal or continuation? Exactly which patients will be eligible and how will they be identified? In the longer term, patient management may take place more with primary care physicians than with cardiologists, so how to achieve reliable follow-up requires careful consideration. Another challenge is the choice of primary and secondary endpoints, covering both the efficacy and safety aspects of drug withdrawal and/or continuation.

AN EXAMPLE RCT FOR WITHDRAWAL OF BETA-BLOCKERS

The first RCTs of beta-blockade in secondary prevention after MI were published in the 1960s, and all such trials took place before primary PCI became routine practice. Beta-blocker therapy after successful primary PCI has not been studied in RCTs, but a non-randomized comparison shows that this therapy is associated with lower 6-month mortality (51). However, there is little evidence of continued efficacy and safety for the long-term use of beta-blockers in stable CHD (although it is common practice), and this problem should be addressed by a randomized controlled drug withdrawal study. The design essentials of such an RCT are discussed in the following (Figure 1).

First, the eligibility criteria should encompass a broad spectrum of patients with stable CHD, with special attention paid to those who have had a MI, which would form a pre-specified subanalysis. Patients who take beta-blockers due to the presence of documented arrhythmias, chronic heart failure, and refractory angina would need to be excluded, because withdrawal would be contrary to recommended guidelines and established patient benefit.

Second, randomization to continuation or withdrawal (using a tapering of dose according to good standard practice) would take place 6 months after a coronary event in post-MI patients or revascularization in stable patients, in the spirit of identifying patients at a routine post-procedure follow-up visit. Because of the need for tapering and screening for any side effects, assignment could not realistically be double-blinded.

Third, the composite primary endpoint could be all-cause death, MI, and hospitalization for heart failure over a 1-year follow-up, which could be powered for a noninferiority hypothesis, but also assessed for superiority. A potential further hypothesis could focus on specific subgroups (e.g., the elderly, post-MI patients) and also on longer term follow-up, if this could be maintained.

Secondary endpoints could include hospitalizations for ACS and repeat revascularization procedures. In addition, quality of life and angina symptoms could be obtained (perhaps by telephone interviews at 4 months and 1 year). Compliance data on beta-blocker use (or not) should also be collected during these interviews. Safety endpoints would include side effects and interactions attributable to beta-blocker therapy (e.g., atrioventricular block).

Any drug withdrawal trial with a major adverse cardiac events-type primary endpoint needs to be as large as placebo-controlled trials of drug efficacy, which could be a problem. Hence, with a hazard ratio noninferiority margin of 1.3, to achieve 80% power, requires approximately 450 patients overall to reach the primary composite endpoint. Thus, the trial would need to recruit several thousand patients. Clearly, this would need to be a large, simple, pragmatic trial with limited data collection.

Can such a drug withdrawal RCT be funded and conducted? Is there the collective will to make such a

trial happen? Perhaps a smaller feasibility study is needed first to establish that such a trial is delineable.

However, the essential message is that without such trials of treatment withdrawal, there will continue to be no evidence base to determine which long-term therapies are beneficial to patients, and which are neutral or even harmful.

RESPONSIBILITIES OF REGULATORS AND OTHER STAKEHOLDERS

At present, regulatory authorities such as the FDA and EMA do not directly engage with many of the issues tackled in this review. Drugs are licensed on the basis of evidence of efficacy and safety from relatively short-term follow-ups in RCTs of selected populations. Post-licensing studies, whether RCTs or observational registries, are often requested to evaluate drug safety in more real-world populations, but they too are of limited duration.

Thus, concerns regarding long-term use of multiple cardiovascular (and other) drugs, especially in the elderly and patients with comorbidities, do not appear within the remit of regulators. So should their current focus on adding each individual new licensed drug on the basis of relatively short-term patient benefit on top of standard of care, now be expanded to the broader concept of “whole patient long-term care”? Were this increased responsibility to happen, regulators could then commission the types of RCTs and pharmacoepidemiological studies that would yield an evidence base that would be truly pertinent to real-world, long-term patient care.

The professional societies, such as the ACC/AHA and the European Society of Cardiology, have done an excellent job in producing very informative treatment guidelines that have enhanced day-to-day cardiology patient management. However, they have also not seriously grappled with the long-term use of multiple cardiovascular drugs, admittedly because of the lack of good evidence. Because of the importance of these issues, we encourage these societies to train working partners, and to begin research studies (and their funding) and other actions that could ultimately lead to evidence-based guidelines on long-term drug use. Of course, this would also require the research community in clinical cardiology to have a collective “wake-up call” in pursuing pertinent projects, both interventional and observational, on areas such as polypharmacy in the elderly.

Health care providers, such as the U.K. National Health Service, also need to consider how they can enhance more rigorous monitoring of individual

patients' long-term drug use. For instance, could they mandate that each patient on polypharmacy (e.g., ≥ 5 drugs) have regular (annual) reviews of their drug use by their primary treating physician, with a view to making sound decisions on whether any of them could be withdrawn. This would be particularly important in the elderly, where concerns about noncompliance also matter.

All treating physicians, both cardiologists and others (e.g., primary care) need to avoid the trap of routine repeat-prescribing over many years, regardless of whether this is in the patient's best interests. A better awareness of potential side effects, especially in the context of older age polypharmacy, is much needed. Also, those initiating drug use (e.g., cardiology consultants) may well be different from those handling long-term care (e.g., general practitioners). A closer dialogue across specialties is needed to ensure that a patient's total drug use, including deprescribing, is handled wisely.

Lastly, patients themselves should be encouraged to participate in decisions relating to their long-term therapy.

RECOMMENDATIONS

We conclude with a set of recommendations that relate both to a future research agenda and to improvements in patient care:

1. The gap in knowledge regarding the long-term efficacy and safety of cardiovascular drugs needs wider recognition.
2. The untested assumption that short-term drug benefit over a few years post-MI extends into long-term follow-up and older age needs to be challenged.
3. The trial evidence for beta-blockers, which began before the introduction of primary PCI, is outdated, meaning their role particularly needs to be questioned.
4. We need to encourage more RCTs to continue into long-term follow-up, and to reflect real-world practice, such as including increased numbers of older patients.
5. Regulatory placebo-controlled trials tend to lead to a growing plethora of approved drugs, so a new paradigm (e.g., more head-to-head trials) is needed.
6. The problems of polypharmacy need to be tackled.
7. Deprescribing should be considered more often, and requires more objective evidence for its practice.

8. RCTs that study withdrawal of long-term medication are needed; the case for a withdrawal trial of beta-blockers is particularly pertinent.
9. More research on the effectiveness and potential harms of cardiovascular drugs is needed in older patients, who often have comorbidities and are sometimes frail.
10. Regulators, professional societies, the cardiology research community, and health care providers all need to engage with these problems of long-term prescribing of multiple drugs.
11. Both cardiologists and primary care physicians should pay greater attention to each patient's long-term needs, for example, by regularly reviewing whether multiple long-term medications are truly of benefit.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Desmond G. Julian, University of Newcastle upon Tyne, Flat 1, 7 Netherhall Gardens, London NW35RN, United Kingdom. E-mail: DJ@desmondjulian.co.uk.

REFERENCES

1. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849-60.
2. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-81.
3. Domanski MJ, Exner DV, Borkowf CB, et al. Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction. A meta-analysis of randomized clinical trials. *J Am Coll Cardiol* 1999;33:598-604.
4. Al-Mallah MH, Tleyjeh IM, Abdel-Latif AA, et al. Angiotensin-converting enzyme inhibitors in coronary artery disease and preserved left ventricular systolic function: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2006;47:1576-83.
5. Freemantle N, Cleland J, Young P, et al. β Blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;318:1730-7.
6. Julian DG, Pocock SJ. Effects of long-term use of cardiovascular drugs. *Lancet* 2015;385:325.
7. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61:e78-140.
8. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;60:e44-164.
9. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64:e139-228.
10. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
11. Sacks FM, Pfeffer MA, Moye LA, et al., for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9.
12. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
13. Odden MC, Pletcher MJ, Coxson PG, et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States. *Ann Intern Med* 2015;162:533-41.
14. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735-42.
15. Smith SC Jr., Benjamin EJ, Bonow RO, et al. AHA/ACC secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Foundation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol* 2011;58:2432-46.
16. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. *Circulation* 1998;97:2202-12.
17. PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058-68.
18. Sorbets E, Labreuche J, Simon T, et al. Renin-angiotensin system antagonists and clinical outcomes in stable coronary artery disease without heart failure. *Eur Heart J* 2014;35:1760-8.
19. Castellano JM, Sanz G, Peñalvo JL, et al. A polypill strategy to improve adherence: results from the FOCUS project. *J Am Coll Cardiol* 2014;64:2071-82.
20. Working Group on the Summit on Combination Therapy for CVD. Combination pharmacotherapy to prevent cardiovascular disease: present status and challenges. *Eur Heart J* 2014;35:353-64.
21. Bonaca MP, Bhatt DL, Cohen M, et al., for the PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med* 2015;372:1791-800.
22. Jernberg T, Hasvold P, Henriksson M, et al. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J* 2015;36:1163-70.
23. Elwood PC, Cochrane AL, Burr ML, et al. A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction. *BMJ* 1974;1:436-40.
24. Coronary Drug Project Research Group. Aspirin in coronary heart disease. *J Chronic Dis* 1976;29:625-42.
25. Elwood PC, Sweetnam PM. Aspirin and secondary mortality after myocardial infarction. *Lancet* 1979;2:1313-5.
26. Persantine-Aspirin Reinfarction Study Research Group. Persantine and aspirin in coronary heart disease. *Circulation* 1980;62:449-61.
27. A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA* 1980;243:661-9.
28. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.
29. GISSI Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico). Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge? *Ital Heart J* 2000;1:810-20.
30. Serruys PWJC, de Feyter P, Macaya C, et al., for the Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of

- cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;287:3215-22.
31. Koren MJ, Hunninghake DB. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study. *J Am Coll Cardiol* 2004;44:1772-9.
 32. Cannon CP, Braunwald E, McCabe CH, et al., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.
 33. De Lemos JA, Blazing MA, Wiviott SD, et al., for the A to Z Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;292:1307-16.
 34. LaRosa JC, Grundy SM, Waters DD, et al., for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425-35.
 35. Pedersen TR, Faergeman O, Kastelein JJP, for the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 2005;294:2437-45.
 36. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet* 2010;376:1658-69.
 37. Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. A multicentre international study. *BMJ* 1975;3:735-40.
 38. Julian DG, Prescott RJ, Jackson FS, et al. Controlled trial of sotalol for one year after myocardial infarction. *Lancet* 1982;319:1142-7.
 39. European Infarction Study Group. European Infarction Study (E.I.S.): a secondary prevention study with slow release oxprenolol after myocardial infarction: morbidity and mortality. *Eur Heart J* 1984;5:189-202.
 40. Salathia KS, Barber JM, McIlmoyle EL, et al. Very early intervention with metoprolol in suspected acute myocardial infarction. *Eur Heart J* 1985;6:190-8.
 41. Lopressor Intervention Trial Research Group. The Lopressor Intervention Trial: multicentre study of metoprolol in survivors of acute myocardial infarction. *Eur Heart J* 1987;8:1056-64.
 42. CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;357:1385-90.
 43. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 1992;327:669-77.
 44. Køber L, Torp-Pedersen C, Carlsen JE, et al., for the Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670-6.
 45. Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821-8.
 46. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669-85.
 47. Pitt B, O'Neill B, Feldman R, et al., for the QUIET Study Group. The Quinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol* 2001;87:1058-63.
 48. Nissen SE, Tuzcu EM, Libby P, et al., for the CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA* 2004;292:2217-25.
 49. European trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782-8.
 50. Pedersen F, Butrymovich V, Kelbæk H, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. *J Am Coll Cardiol* 2014;64:2101-8.
 51. Kernis SJ, Harjai KJ, Stone GW, et al. Does beta-blocker therapy improve clinical outcomes of acute myocardial infarction after successful primary angioplasty? *J Am Coll Cardiol* 2004;43:1773-9.
 52. Bangalore S, Steg G, Deedwania P, et al., for the REACH Registry Investigators. β -Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA* 2012;308:1340-9.
 53. Antman E, Bassand JP, Klein W, et al. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-69.
 54. Thygesen K, Alpert JS, White HD, for the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol* 2007;50:2173-95.
 55. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60:1581-98.
 56. McMurdo MET, Roberts H, Parker S, et al., for the Age and Ageing Specialty Group, NIHR, Comprehensive Clinical Research Network. Improving recruitment of older people to research through good practice. *Age Ageing* 2011;40:659-65.
 57. Pfeffer MA, McMurray JJV, Velazquez EJ, et al., for the Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;349:1893-906.
 58. Fox K, Ford I, Steg PG, et al., for the SIGNIFY Investigators. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014;371:1091-9.
 59. Swedberg K, Komajda M, Böhm M, et al., for the SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;376:875-85.
 60. Fox K, Ford I, Steg PG, et al., for the BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372:807-16.
 61. Kaufman DW, Kelly JP, Rosenberg L, et al. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA* 2002;287:337-44.
 62. Charlesworth CJ, Smit E, Lee DSH, et al. Polypharmacy among adults aged 65 years and older in the United States: 1988-2010. *J Gerontol A Biol Sci Med Sci* 2015;70:989-95.
 63. Volpe M, Chin D, Paneni F. The challenge of polypharmacy in cardiovascular medicine. *Fundam Clin Pharmacol* 2010;24:9-17.
 64. Qato DM, Alexander GC, Conti RM, et al. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA* 2008;300:2867-78.
 65. Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA* 2003;289:1107-16.
 66. Payne RA, Avery AJ, Duerden M, et al. Prevalence of polypharmacy in a Scottish primary care population. *Eur J Clin Pharmacol* 2014;70:575-81.
 67. Fleg JL, Aronow WS, Frishman WH. Cardiovascular drug therapy in the elderly: benefits and challenges. *Nat Rev Cardiol* 2011;8:13-28.
 68. DeFilippis AP, Young R, Carrubba CJ, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 2015;162:266-75.
 69. Navar-Boggan AM, Peterson ED, D'Agostino RB, et al. One size may not fit all: using age- and sex-specific risk thresholds to guide statin therapy. *J Am Coll Cardiol* 2015;65:1633-9.
 70. Mukhtar O, Jackson SH. Drug therapies in older adults (part 1). *Clin Med* 2015;15:47-53.

- 71.** Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 2004;57:6-14.
- 72.** Fralick M, Macdonald EM, Gomes T, et al., for the Canadian Drug Safety and Effectiveness Research Network (CDSEEN). Co-trimoxazole and sudden death in patients receiving inhibitors of renin-angiotensin system: population based study. *BMJ* 2014;349:g6196.
- 73.** Seymour RM, Routledge PA. Important drug-drug interactions in the elderly. *Drugs Aging* 1998;12:485-94.
- 74.** Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet* 2005;365:82-93.
- 75.** Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA* 2001;286:708-13.
- 76.** Gnjidic D, Le Couteur DG, Hilmer SN. Discontinuing drug treatments. *BMJ* 2014;349:g7013.
- 77.** Pocock SJ, Gersh BJ. Do current clinical trials meet society's needs? A critical review of the evidence. *J Am Coll Cardiol* 2014;64:1615-28.
- 78.** Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. *J Am Coll Cardiol* 2015;65:1298-310.
- 79.** Mauri L, Kereiakes DJ, Yeh RW, et al., for the DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371:2155-66.
- 80.** Kim MC, Cho JY, Jeong HC, et al. Impact of postdischarge statin withdrawal on long-term outcomes in patients with acute myocardial infarction. *Am J Cardiol* 2015;115:1-7.
- 81.** Lordkipanidzé M, Diodati JG, Pharand C. Possibility of a rebound phenomenon following antiplatelet therapy withdrawal: a look at the clinical and pharmacological evidence. *Pharmacol Ther* 2009;123:178-86.

KEY WORDS cardiovascular medications, deprescribing, elderly, long-term treatment, polypharmacy, randomized clinical trials