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Novel Treatments for Cardiovascular Disease Prevention

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SUMMARY

The purpose of this review is to describe novel pharmacologic and nonpharmacologic preventive therapies, as well as new strategies to improve delivery of available therapies. Cardiovascular disease (CVD) is the leading cause of death worldwide, and prevention plays a critical role in curbing the global epidemic. Despite available treatment for tobacco addiction, platelet inhibition, blood pressure, and lipid lowering for reduction of atherosclerotic disease, significant gaps in treatment of total CVD remain. We review a range of new preventive treatment options, including drugs for tobacco cessation, platelet/thrombotic inhibition, lipid- and blood pressure-lowering; nonpharmacologic options such as left atrial appendage closure devices and caloric restriction; and strategies such as fixed-dose combination drugs, laboratory screening for drug tailoring, and community-based prevention programs. CVD preventive research continues to evolve and provide clinicians and patients with novel pharmacologic and nonpharmacologic therapies, including new preventive strategies.

Keywords

Cardiovascular disease; Novel; Prevention; Treatment

Background

Cardiovascular disease (CVD) is the leading cause of death worldwide [1]. Previously thought to affect primarily high-income countries, CVD now leads to more death and disability in low-and middle-income countries (LMIC). The pattern of the CVD epidemic in many LMIC is different from the classic “rise and fall” pattern in high-income countries, as described by Mirzaei et al. [2]. Instead, the “rise only” and “flat” patterns, with variable magnitude and timing, suggest that falling age-adjusted CVD mortality rates in LMIC, are far from certain. CVD prevention will play a critical role in curbing the epidemic in both settings. Absolute risk assessment and subsequent risk factor control comprises the cornerstone of a modern, individual-level preventive strategy with many inexpensive,

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Concept/design (MDH, DB); data analysis/interpretation (MDH/DB); drafting article (MDH/DB); critical revision of article (MDH/DB); approval of article (MDH/DB).

Conflicts of Interest

We have no conflicts of interest to disclose.

effective therapies available, such as nicotine replacement, aspirin, antihypertensive medications, and lipid-lowering therapies. Gaps in prevention remain, however. We review new pharmacologic and nonpharmacologic treatments for CVD prevention, as well as new strategies to improve delivery of available therapies.

New Pharmacologic Treatments for CVD Prevention (Table 1)[1]

Smoking Cessation Therapy

Tobacco cessation is the most important preventive measure for tobacco users to reduce their absolute risk of a CVD-associated morbidity and mortality. Varenicline is a $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist approved by the US Food and Drug Administration (FDA) in 2006 to aid smoking cessation [3]. A 12-week course of varenicline 1 mg twice daily has demonstrated a 13.5% and 5.8% absolute increase in smoking cessation among “healthy smokers” at 52 weeks compared to placebo and buproprion SR 150 mg twice daily, respectively [4]. A similar 12% absolute increase in smoking cessation was also seen among participants with stable coronary heart disease using varenicline for 12 weeks compared to placebo [5]. There were no differences in cardiovascular events, cardiovascular mortality, all-cause mortality, or serious adverse events between the 2 groups in this study, though it was not sufficiently powered to detect a difference in clinical outcomes. Lower doses of varenicline have not been shown to improve quit rates at 1 year [6]. Since its approval, the FDA has required varenicline’s manufacturer, Pfizer, to issue a “Boxed Warning” statement about the risks of mood and behavior changes that can be associated with varenicline, particularly in people with a history of psychiatric illness [7].

Antiplatelet Agents

Antiplatelet agents continue to evolve beyond aspirin, dipyridamole, ticlodipine, and clopidogrel for patients with coronary artery disease (CAD) and stroke to the next generation of drugs such as prasugrel, ticagrelor, and cangrelor. Prasugrel is a thienopyridine that is an irreversible ADP P2Y12 antagonist. In the phase III TRITON-38 clinical trial, prasugrel demonstrated a 2.2% absolute reduction in the primary composite endpoint of death, nonfatal myocardial infarction, and nonfatal stroke compared to clopidogrel in acute coronary syndrome (ACS) patients being managed with percutaneous coronary intervention (PCI) [8]. Median follow-up was 14.5 months. This reduction was counterbalanced by an absolute increase in major Thrombolysis in Myocardial Infarction (TIMI) bleeding and life threatening bleeding by 0.6% and 0.5%, respectively. The FDA approved prasugrel in 2009 based on the overall benefit compared to clopidogrel, which was largely driven by a reduction in nonfatal myocardial infarction [9]. However, due to the excess bleeding associated with prasugrel, the FDA required prasugrel’s manufacturer, Eli Lilly-Daiichi Sankyo, to issue a “Boxed Warning” for patients with a high bleeding risk (bleeding history, age >75 years, body weight <60 kg, and history of TIA or stroke) and those likely to undergo urgent coronary artery bypass graft (CABG) surgery [10].

Ticagrelor is a cyclopentyl- triazolo-pyrimidine that is a reversible and direct-acting oral P2Y12 antagonist that does not require hepatic conversion to an active form, unlike clopidogrel and prasugrel. In the phase III PLATO clinical trial, twice daily ticagrelor demonstrated a 1.9% absolute reduction in the primary composite endpoint of vascular death, nonfatal myocardial infarction and nonfatal stroke compared to clopidogrel in ACS patients. Median follow-up was 9.1 months. Unlike prasugrel, ticagrelor did not demonstrate an increase in major TIMI or fatal hemorrhage compared to clopidogrel, though there was a

[1]Treatments introduced over the past five (5) years.

0.6% absolute increase in non-CABG major TIMI bleeding. The FDA approved the use of ticagrelor in patients with ACS in July 2010 [11].

Cangrelor is a nonthienopyridine adenosine triphosphate analog that is a reversible, direct-acting intravenous P2Y12 antagonist that has a half-life of 3 to 6 min. In two phase III clinical trials, Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI [12] and CHAMPION PLATFORM [13], peri-PCI adminstration of cangrelor did not reduce cardiovascular events. In CHAMPION PCI, cangrelor at the time of PCI did not demonstrate a difference in the primary composite endpoint of death, nonfatal myocardial infarction, or ischemia-driven revascularization compared to clopidogrel at 48 h in patients with establish coronary heart disease, stable/unstable angina, or non-ST-elevation myocardial infarction. In CHAMPION PLATFORM, cangrelor at the time of PCI did not demonstrate a decrease in the primary composite endpoint of death, nonfatal myocardial infarction, or ischemia-drive revascularlization compared to placebo at 48 h, with background aspirin and clopidogrel therapy.

Antithrombotic Agents

Hirudin, argatroban, and bivalirudin are intravenous, direct thrombin (IIa) inhibitors that have been approved for treatment of heparin-induced thrombocytopenia (HIT), adjunctive treatment for patients with HIT (or at risk for HIT) who are undergoing PCI (argatroban), or as an alternative to unfractionated heparin for patients undergoing PCI (bivalirudin) [14]. Dabigatran is an oral, reversible, and direct thrombin inhibitor that has been evaluated as an alternative to warfarin for the prevention of stroke in patients with nonvalvular atrial fibrillation (AF). In the phase III RE-LY clinical trial, dabigatran 150 mg daily demonstrated a 0.58% absolute reduction in the primary composite endpoint rate of stroke or systolic embolism compared to warfarin with similar bleeding rates [15]. Median follow-up was 2 years.

Rivaroxaban is an oral direct Xa inhibitor that is being evaluated for patients with ACS and nonvalvular AF. In the phase II ATLAS ACS TIMI-46 clinical trial, rivoraxaban demonstrated a dose-dependent increase in the primary safety endpoint of bleeding compared to placebo in patients with stabilized ACS at 6 months (hazard ratios [HRs] 2.21 [95% CI 1.25–3.91] for 5 mg, 3.35 [2.31–4.87] for 10 mg, 3.60 [2.32–5.58] for 15 mg, and 5.06 [3.45–7.42] for 20 mg doses; $P < 0.0001$) [16]. Rivoraxaban demonstrated a nonsignificant 1.4% absolute decrease in the primary composite efficacy endpoint of death, nonfatal myocardial infarction, and nonfatal stroke compared to placebo. A phase III clinical trial has been planned to evaluate the efficacy and safety of low-dose add-on rivaroxaban for ACS patients. The phase III ROCKET AF clinical trial is also evaluating the efficacy and safety of rivaroxaban in patients with nonvalvular AF with a primary composite endpoint of all-cause stroke and noncentral nervous system systemic embolism [17]. Apixaban is another oral direct Xa inhibitor that is in early testing stages for the prevention of stroke/systemic embolic in patients with nonvalvular AF and for the management of ACS.

Lipid-Lowering Agents

Pitavastatin is a potent statin introduced relatively recently in Japan, South Korea, and Thailand. It has comparable lipid-lowering effects to atorvastatin. The open-label, noninferiority JAPAN ACS clinical trial demonstrated a similar regression in plaque volume between 4 mg of pitavastatin and 20 mg of atorvastatin during a median follow-up of 9.3 months [18]. Interestingly, there was no significant correlation between LDL lowering and plaque volume regression. The study was not powered to evaluate clinical outcomes.

Mipomersen is a second-generation antisense oligonucleotide designed to inhibit apolipoprotein B100 (apoB) synthesis through mRNA binding in patients with homozygous familial hypercholesterolemia. Multiple phase II studies have demonstrated a dose-dependent decrease in apoB and LDL cholesterol, but adverse events (subcutaneous injection site erythema, elevated hepatic transaminases) are common [19,20]. In a 2010 phase III randomized, double-blind, placebo controlled clinical trial, mipomersen reduced baseline LDL cholesterol by an additional 21.4% compared to placebo [21]. This 26-week study included only 51 patients with a history of homozygous familial hypercholesterolemia and aggressive lipid-lowering therapy and was not powered to evaluate differences in clinical outcomes.

Low HDL cholesterol concentrations have been associated with increased CVD, and compounds to increase HDL concentrations are being developed [22].

Nicotinic acid, a well-established drug for treating mixed hyperlipidemia, is currently one of the most potent drugs for increasing HDL cholesterol. However, about a third of patients suffer predominantly cutaneous side effects making compliance very poor. These side effects are due to stimulation of prostaglandin D2. A recently launched preparation of nicotinic acid combined with a prostaglandin D2 DP-1 blocker laropriprant appears to decrease the incidence of side effects of flushing and itching.

Cholesteryl ester transfer protein (CETP) is involved in reverse cholesterol transport. It channels atherogenic cholesteryl esters from HDL to apolipoprotein B containing lipoproteins LDL and VLDL. Inhibition of CETP results in marked increases in HDL concentrations, and several pharmaceutical companies are exploiting this property. One CETP inhibitor, torcetrapib, was associated with increased cardiovascular mortality despite increasing HDL cholesterol. This was traced to off-label effects resulting from increased mineralocorticoid activity. Two other CETP inhibitors anacetrapib and dalcetrapib are currently in phase III trials. Anacetrapib demonstrated a 40% decrease in LDL and 138% increase in HDL at 24 weeks in a recent phase II clinical trial of 1,623 participants [23].

Activation of the nuclear receptors LXR (liver X receptor) and FXR (farsenoid X receptor) promotes reverse cholesterol transport by increasing cholesterol efflux from the macrophages into HDL. LXR and FXR agonists are in development, but nonselective compounds appear to result in increased serum triglycerides and LDL cholesterol.

Thyroid hormone mimetics lower serum cholesterol, improve reverse cholesterol transport, decrease lipoprotein (a) and decrease body fat in animal models. As expected they have profound metabolic effects and preliminary results with selective compounds suggest that in the short term adverse events are minimal [24].

Acyl coenzyme A (CoA) cholesterol acyltransferase inhibitors, such as pactimibe and avasimibe and the squalene synthase inhibitor lapaquist, have been dropped from further development due to side effects. Inhibition of microsomal triglyceride transfer protein decreases serum lipids, and the compound lomitapide is currently under development.

The thrust of drug development to prevent atherosclerosis is now moving towards reducing inflammation to prevent plaque. Experimental approaches include CC-chemokine ligand 5 (CCL5), CXC-chemokine ligand 4 inhibitors, and soluble epoxide hydrolase inhibitors [25,26]. However, inhibition of lipoprotein-associated phosphatase A2 (Lp-PLA_2) appears to be a more established and promising approach [27]. Lp-PLA_2 circulates with LDL, but its precise role in atherosclerosis is not entirely clear. It is produced by inflammatory cells and is upregulated in apoptotic macrophages in plaque. It may have a role in generation of lysophosphatidylcholine from oxidized LDL. Epidemiological studies show an association

with increased cardiovascular risk. Initial studies of inhibitors of Lp-PLA_2 (darapladib and varespladib) show decreased Lp-PLA_2 and a more stable plaque with decreased inflammatory cells and a reduced necrotic core [28]. Further phase III clinical studies in patients with ACS and in chronic coronary disease are in progress.

Blood Pressure Lowering Agents

The direct renin inhibitor, aliskiren, was approved for the treatment of hypertension by the FDA in 2007 [29]. Data from monotherapy and combination therapy trials were pooled to demonstrate systolic blood pressure reduction up to 15 mmHg over 6–8 weeks with aliskiren 600 mg daily [30]. Side effects were similar to irbesartan. Aliskiren 300 mg demonstrated regression of left ventricular mass (approximately 5 g/m^2, or 5%), similar to losartan 100 mg, over 9 months in participants with left ventricular hypertrophy [31]. When combined with losartan, aliskiren demonstrated a 20% relative decrease in urinary albumin-to-creatinine ratio of diabetic patients with underlying nephropathy [32]. Aliskiren has also been shown to reduce N-terminal pro-BNP levels compared to placebo over 3 months in patients with NYHA II and III heart failure [33].

Nonpharmacologic Treatments for CVD Prevention

WATCHMAN® Left Atrial Occlusion Device

The WATCHMAN® (Aritrech, Minneapolis, MN, USA) left atrial appendage occlusion device, developed by Atritech, Inc., demonstrated noninferiority with warfarin for the prevention of stroke, cardiovascular death, and systemic embolism in 707 patients with nonvalvular AF over 18 months in the PROTECT AF trial [34]. Participants in the intervention arm required a short course of warfarin following implantation (45 days) but experienced three additional safety events per 100 patient-years. In 2009, the FDA determined the WATCHMAN® device to be “approvable with conditions”, including 5-year follow-up of PROTECT AF participants, physician training to certify WATCHMAN® implantation, and postapproval surveillance of 2,000 additional patients [35].

Caloric Restriction

Caloric restriction has demonstrated improvements in life expectancy in animal models, but there are limited data on the impact of long-term caloric restriction in aging and in CVD prevention in humans. In volunteers, long-term caloric restriction led to significant reductions in weight, blood pressure, blood cholesterol, and inflammatory markers, thereby reducing cardiovascular risk [36]. The NIH-funded, phase II CALERIE trial is currently evaluating the effects of two years of 25% caloric restriction in nonobese participants [36]. Secondary endpoints include differences in cardiovascular risk factors between intervention and control participants.

New Strategies to Improve Delivery of Available Therapies

Pharmacologic

Combination therapies—such as Augmentin (amoxicillin + clavulanic acid) to treat resistant bacteria and Zestoretic (lisinopril + hydrochlorothiazide) to treat hypertension—have been used for many years. Bangalore et al. performed a meta-analysis of all fixed-dose combination therapies and estimated that noncompliance is reduced by 25%, compared to individual therapies [37]. Prevention of CVD with polypill therapy gained global attention when first proposed by Wald and Law in 2003, in part because of the 80% reduction in CVD events predicted by the authors [38]. The first published phase II primary CVD prevention study of a polypill was the The Indian Polycap Study, which evaluated the safety and efficacy of aspirin, atenolol, hydrochlorothiazide, ramipiril, and simvastatin on

cardiovascular risk factors [39]. At 12 weeks, reductions on blood pressure, heart rate, and urinary 11-dehydrothromboxane B2 were similar in participants receiving the Polycap compared to those receiving the hydrochlorothiazide/ramipril, atenolol, and aspirin alone. However, LDL cholesterol lowering was less in the Polycap group (0.7 mm/L) compared to simvastatin alone (0.83 mm/L), and overall dropout was 15%. While the appropriateness of the polypill for primary CVD prevention has been called into question [40,41], its use for secondary CVD prevention is less controversial. Several trials of secondary prevention are currently underway but results will likely not by available for another 3–5 years [42].

Laboratory Screening

Inadequate antiplatelet blockade leads to increased cardiovascular events in patients with established CAD due to individual differences in drug metabolism, including bioconversion of clopidogrel into its active metabolite by cytochrome P450 CYP enzymes [43]. *Ex vivo* platelet function assays may provide clinicians with a tool to tailor antiplatelet therapy. Common assays include: light transmittance aggregometry (LTA), VerifyNow P2Y12® P2Y12 (Accumetrics, San Diego, CA, USA) (turbidimetric-based assay), Plateletworks (Helena Laboratory Corp., Beaumont, TX, USA), IMPACT-R (with or without ADP stimulation), PFA-100® (Siemens Healthcare Diagnostics, Barcelona, Spain), and Innovance PFA P2Y (Siemens Healthcare Diagnostics, Barcelona, Spain) [44]. Results from LTA, VerifyNow, and Plateletworks (aggregation tests) have demonstrated improvements in predicting composite major adverse clinical events (all-cause death, nonfatal myocardial infarction, stent thrombosis, and ischemic stroke) in patients undergoing elective PCI above other clinical predictors, whereas the other assays (shear-dependent tests) did not [44]. Forthcoming trials will prospectively evaluate using higher doses of clopidogrel (or prasugrel) in so-called “nonresponders” undergoing elective drug-eluting stent placement [45,46], as well as the overall effectiveness of platelet function testing compared to usual care [47].

High-sensitivity C-reactive protein (hsCRP) is independently associated with coronary heart disease and CVD events and moderately improves risk prediction, particularly for intermediate risk patients [48]. The JUPITER trial evaluated the role of rosuvastatin in CVD primary prevention in patients with LDL < 130 mg/dL and hsCRP > 2.0 mg/L [49]. Based on the results (reduction of 0.59 vascular events per 100 person-years compared to placebo), the FDA expanded rosuvastatin’s indication to include the prevention of CVD in men >50 years old and women >60 years old who have an elevated hsCRP and at least one traditional risk factor [50], a decision deemed controversial by some [51].

Community-based Prevention Programs

Community-based primary preventive efforts have received widespread attention and support since the North Karelia project. Less heralded were similar improvements in cardiovascular risk factors in Kuopio, another county in Finland that did not participate in the formal community-wide primary prevention program [52]. A 2011 meta-analysis by Ebrahim et al. demonstrated no difference in total and coronary heart disease mortality in 10 trials with clinical event endpoints of community-based primary CVD prevention [53]. However, community-based primary prevention programs may demonstrate effectiveness in high-risk individuals or when local CVD-related mortality rates are rising rather than falling (as was the case in Finland from 1972–1992). In India, Prabhakaran et al. demonstrated reductions in tobacco consumption, blood pressure, cholesterol, and glucose across 10 Indian industrial intervention sites compared to controls [54], which may provide support for wider evaluation of such efforts in low- and middle-income countries.

Conclusions

CVD preventive research continues to evolve and provide clinicians and patients with novel pharmacologic and nonpharmacologic therapies and strategies to decrease the incidence, prevalence, and subsequent burden of CVD.

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Table 1

List of novel therapies for CVD prevention, proposed mechanism of action, target disease/population, and current stage of clinical trial investigation (clinicaltrials.gov)

Name	Proposed mechanism of action	Target disease/population	Current stage of clinical trial
Smoking Cessation Therapy			
Varenicline	$\alpha 4\beta 2$ nicotinic receptor partial agonist	Smokers, including with established CVD	IV
Antiplatelet Agents			
Prasugrel	Irreversible ADP P2Y12 antagonist	ACS managed with PCI	IV
Ticagrelor	Reversible ADP P2Y12 antagonist	ACS	III (completed)
Cangrelor	Reversible ADP P2Y12 antagonist (intravenous)	ACS managed with PCI	III (completed)
Antithrombotic Agents			
Dabigatran	Direct ILa inhibitor	Nonvalvular AF	IV
Rivaroxaban	Direct Xa inhibitor	ACS and nonvalvular AF	III
Apixaban	Direct Xa inhibitor	ACS and nonvalvular AF	III
Lipid-Lowering Agents			
Pitavastatin	HMG CoA inhibitor (statin)	Post-ACS	III
Mipomersen	Antisense inhibitor of apoB synthesis	Homozygous familial hypercholesterolemia	III
Nicotinic acid + laropriprant	D2 receptor antagonist to reduce flushing associated with nicotinic acid	Primary hypercholesterolemia; mixed dyslipidemia	III
Anacetrapib	Cholesterol ester transfer protein inhibitor	Low HDL	III
Dalcetrapib	Cholesterol ester transfer protein inhibitor	Low HDL	III
Lomitapide	Inhibition of microsomal triglyceride transfer protein	Homozygous familial hypercholesterolemia	III
Darapladib	LP-PLA_2 inhibitor	Stable cardiovascular disease; ACS	III
Varespladib	LP-PLA_2 inhibitor	ACS	III
Blood Pressure-Lowering Agents			
Aliskiren	Direct renin inhibitor	Hypertension	IV
Nonpharmacologic Therapy for Nonvalvular Atrial Fibrillation			
WATCHMAN® left atrial appendage occlusion device	Percutaneous occlusion of left atrial appendage	Nonvalvular atrial fibrillation	III
Miscellaneous			
Caloric restriction	Decreased atherosclerosis	Primary CVD prevention	II

ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.