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Review article

New therapeutic options for reducing atherosclerotic cardiovascular disease residual risk

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Abstract Adults with atherosclerotic cardiovascular disease (ASCVD) bear a significant risk of recurrent ASCVD events, particularly those classified as very high risk, despite current standard-of-care therapies. While addressing lifestyle modification efforts to reduce this "residual risk" must remain the foundation of ASCVD risk reduction efforts, there is significant interest in the development of newer therapies that may provide further benefit. Important domains for targeting therapies include those directed at lipid, inflammatory, metabolic, and thrombotic residual risk. With respect to therapies addressing lipid targets, ezetimibe and PCSK9 monoclonal antibody therapies have been shown to reduce ASCVD risk beyond statin therapy. Inclisiran, currently approved in the European Union, also lowers LDL-C, with cardiovascular outcome data pending as to whether it will provide further ASCVD risk reduction. Further, therapies to lower lipoprotein(a) are in development that hold promise for reducing lipoprotein(a)-associated residual risk. Also, of interest has been whether targeting inflammation will reduce ASCVD risk. While canakinumab did demonstrate proof of concept in being the first such therapy to selectively reduce inflammation resulting in ASCVD event reduction, cost and fatal infections precluded its further development. Moreover, clinical trials of colchicine have also shown benefit, but recommendations are yet to adopt this as a therapeutic option to reduce ASCVD risk. Metabolic agents include icosapent ethyl, SGLT2 inhibitors, and GLP1 receptor agonists that now have evidence for reducing cardiovascular outcomes. Finally, in high risk individuals, antithrombotic therapy with rivaroxiban or dual antiplatelet agents have shown benefit. The potential remains great for the development and use of newer therapies to address residual ASCVD risk.

Key words atherosclerotic cardiovascular disease, residual risk, dyslipidema, inflammation, thrombosis, metabolic

Persons with atherosclerotic cardiovascular disease (ASCVD), including history of acute coronary syndrome, myocardial infarction, ischemic stroke, or peripheral arterial disease, remain at substantial risk of recurrent events and mortality despite evidence-based standard of care therapies, a concept known as "residual risk". In the Atherothrombosis in Metabolic Syndrome and with Low HDL/High Triglycerides: Impact on Global Health Outcomes (Aim-HIGH) cohort of more than 3000 subjects with prior ASCVD, overall 16% of subjects, despite on statin therapy, suffered a recurrent ASCVD event over a mean follow-up of 4.2 years, translating into an annual event rate of approximately 4%1. The best predictors of residual risk in these statin-treated subjects with ASCVD included, male sex, hemoglobin A1c, alcohol use (inversely), family history of cardiovascular disease, homocysteine, history of carotid artery disease, and lipoprotein(a). A more recent analysis of the Marketscan database of over 27,000 adults with prior ASCVD[2] showed 1539 recurrent ASCVD events (5.7%) to occur over a median follow-up of 2 years. Over half (53%) of such ASCVD patients were classified as "very high risk" and had event rates 3-fold greater than those not at very high risk (53.1 vs. 17.0 per 1,000 person years), and of those who were very high risk with a history of multiple major ASCVD conditions (26% of those classified as very high risk), recurrent ASCVD event rates were even higher (89.8 per 1,000 person years). Current US guidelines[3] classify those with prior ASCVD as very high risk if they have multiple major ASCVD conditions (recent acute coronary syndrome, myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease) or one such major event and multiple high risk conditions (such as age 65 years or greater, diabetes, cigarette smoking, chronic kidney disease, or hypertension). It has been suggested that multiple cardioprotective standard of care therapies, including statins, beta blockers, ACE inhibitors / angiotensin receptor blockers, and aspirin, if given together, can reduce ASCVD risk by as much as 75%[4,5]. Of interest, while recent trials of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have provided statistically significant reductions in ASCVD outcomes beyond statin therapy, the absolute risk reductions are modest—1.5% in the Fourier trial[6] involving evolocumab and 1.6% in Odyssey Outcomes[7] involving alirocumab, with still nearly 10% of patients in these trials suffering recurrent ASCVD events despite treatment with a PCSK9 inhibitor.

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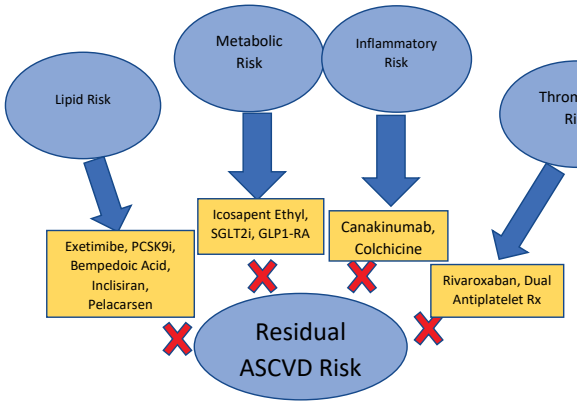

Figure 1. Domains for targeting atherosclerotic residual cardiovascular disease risk

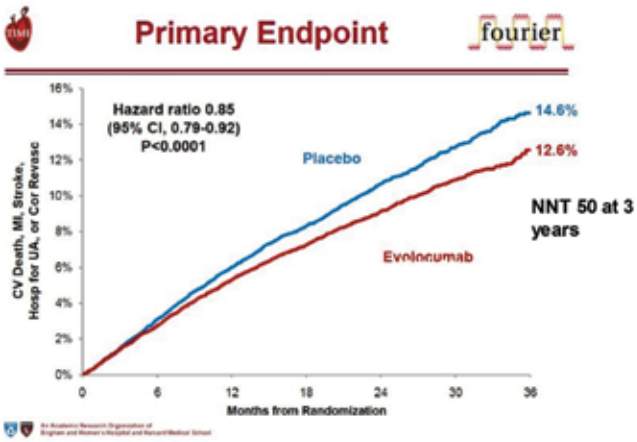

Figure 3. Evolocumab provides further 15% ASCVD reduction beyond statin therapy in FOURIER trial (from Sabatine et al.)

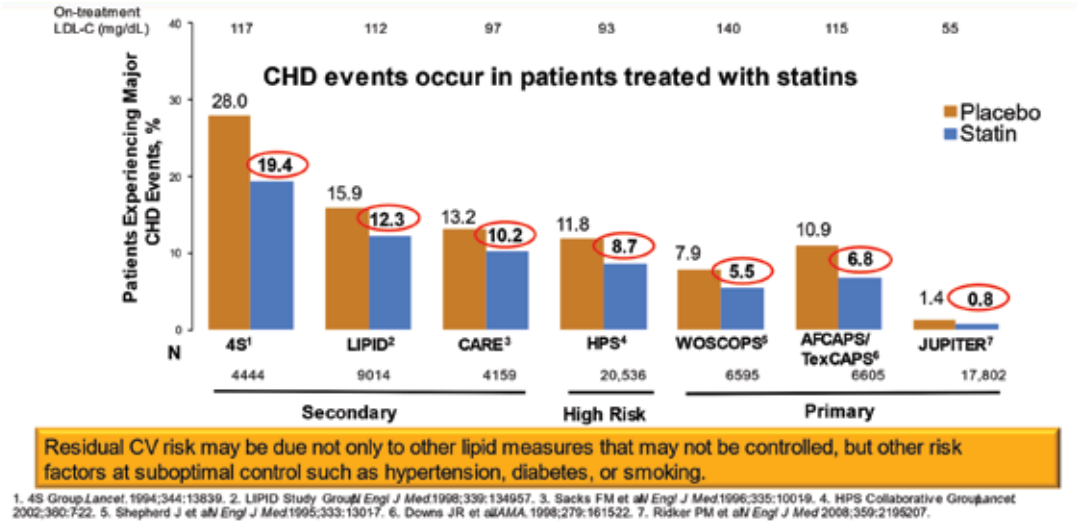

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Figure 2. Despite ASCVD benefit with statin monotherapy, substanial residual cv risk remains

At the foundation of addressing ASCVD residual risk is to address lifestyle-related factors that may help explain such risk. Besides complete smoking cessation and avoidance of environmental tobacco smoke, recent lifestyle management guidelines recommend consuming a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats along with at least moderate intensity physical activity of 150 minutes (or 75 minutes vigorous activity) per week, along with recommendations for resistance training[8].

This report reviews newer and emerging therapeutic targets that are focused on addressing residual ASCVD risk. We will focus on four domains for targeting therapies: those directed at lipid, inflammatory, metabolic, and thrombotic residual risk (Figure 1).

Therapies for Lipid Residual Risk

Over the past 3 decades, a wealth of primary and secondary prevention clinical trials of statin therapy have demonstrated overall 25-40% reductions in the risk of ASCVD events[9], establishing them as the standard of care for patients with known ASCVD as well as those at higher risk of ASCVD according to recent guidelines[3]. However, significant "residual risk" remains (Figure 2). To address remaining "lipid" residual risk, there has been significant interest and exploration into non-statin therapies, including niacin and fibrates, cholesterol absorption inhibitors (ezetimibe), PCSK9 inhibitors, and more recent novel therapies such as silencing RNA (siRNA) therapies for low density lipoprotein-cholesterol and antisense oligonucleotide therapy for lipoprotein(a). Large-scale clinical trials of niacin[10,11] and cholesterol ester transferase protein (CETP) inhibitors[12] have largely been negative or with limited clinical benefit, resulting in a failure to prove the high density lipoprotein-cholesterol (HDL-C) hypothesis. Moreover, major trials of fibrate therapy[13] have also failed their primary endpoints, although we await the results of the PROMINENT trial involving pemafibrate due out within a few years[14].

The IMPROVE-IT trial[15] was the first landmark non-statin trial to demonstrate benefit, in this case with ezetimibe, a cholesterol absorption inhibitor, although the benefit demonstrated (on top of a background of 40 mg simvastatin therapy) was modest, with a relative risk reduction of only 6%. But given the high-risk population studied (acute coronary syndrome within 10 days) and the

long 7-year duration of the trial, there was a 2% absolute risk reduction resulting in a number needed to treat of 50. Ezetimibe therapy has thus been integrated into treatment of high risk persons beyond statin therapy by most national guidelines.

More recently, the FOURIER[6] and Odyssey Outcomes[7] trials of PCSK9 inhibitors further demonstrated improvement in cardiovascular outcomes beyond statin therapy (including some patients on ezetimibe), both showing a 15% relative risk reduction. FOURIER included a wide range of mostly stable ASCVD patients (Figure 3) while ODYSSEY OUTCOMES included persons within one year of their acute coronary syndrome. However, despite powerful PCSK9 therapy that lowers LDL-C 50-60% beyond statin therapy, 9.8% of patients in FOURIER and 9.5% of patients in ODYSSEY OUTCOMES still suffered subsequent ASCVD events. Nevertheless, these trials provide an additional therapeutic option beyond statins and ezetimibe to further reduce ASCVD residual risk. In particular, the FOURIER trial showed a linear trend for lower ASCVD event rates with the lower the LDL-C achieved down to at least 20 mg/dL, with no threshold below which there was any attenuation of benefit achieved[16]. In fact, the prior GLAGOV trial involving the effect of evolocumab on progression of atherosclerosis involving intravascular ultrasound also supported this, showing greater regression of atherosclerosis also down to an LDL-C level of 20 mg/dL with no threshold below which there was any attenuation of benefit[17].

While the PCSK9 monoclonal antibody therapies have the most clinical evidence for reducing ASCVD residual risk, several newer therapies, most of which are still in development, have significant promise for reducing lipid-associated residual risk. Bempedoic acid is an ATP citrate lyase inhibitor which acts in the same pathway as HMG Co-A reductase inhibitor, hence preventing the biosynthesis of cholesterol. It is current FDA approved and indicated in the US for persons with ASCVD or heterozygous familial hypercholesterolemia who may need further LDL-C lowering beyond statin therapy; it may be particular useful for those who are statin intolerant. As monotherapy it reduces LDL-C by approximately 15% and in combination with ezetimibe, approximately 35%. The CLEAR outcomes trial is pending and will demonstrate whether the addition of bempedoic acid beyond statin therapy provides further reduction in ASCVD outcomes[18]. Inclisiran is a small interfering double-stranded RNA which harnesses the natural process of RNAi, is distributed to liver due to GalNAc conjugation, resulting in inhibition of production of PCSK9 specifically, durably and potently. Clinical trials have shown inclisiran to produce a time averaged reduction in LDL-C of approximately 50% after IV injections at baseline, 3 months, and every 6 months later, making this "vaccine" like therapy a potential game changer in lipid management. Whether reducing PCSK9 and therefore LDL-C by this mechanism will result in further reduction in ASCVD outcomes beyond statin therapy is not yet determined, and cardiovascular outcomes trials are underway to examine this in high risk persons with known ASCVD[19]. Inclisiran is current approved in Europe, with approval pending in the United States. Finally, lipoprotein(a) is a significant genetic causal risk factor for ASCVD. Levels of lipoprotein(a) of 70 mg/dL (175 nmol/L) or higher are present in about 15% of the population[20]. Pelacarsen is an antisense oligonucleotide therapy that targets mRNA of lipoprotein(a), reduces lipoprotein(a) levels by up to 80%. A second agent, olpasiran, an si-RNA therapy, lowers lipoprotein(a) levels by up to 90% from early clinical trials[21]. Cardiovascular outcomes trials to examine whether lowering lipoprotein(a) beyond statin therapy with these therapies are in progress.

With recommendations and evidence to support lower LDL-C targets[22] to reduce residual risk, especially among our higher risk patients with ASCVD, the need for additional therapies beyond statins will continue to increase. US guidelines have supported the use of ezetimibe in those with ASCVD where LDL-C still remains at 70 mg/dL despite maximally tolerated statin therapy, and PCSK9i therapy in those at very high risk who still remain above this threshold[3]. European guidelines recommend an LDL-C target of <55 mg/dL for all those with ASCVD (and some primary prevention such as those with diabetes and multiple risk factors), with an option for an LDL-C target of <40 mg/dL with recurrent ASCVD events within 2 years[23]. Most recently, the Lipid Association of India has recommended even lower LDL-C targets of <30 mg/dL in certain extreme risk persons with ASCVD who have other high risk conditions[24].

Therapies for Inflammatory Residual Risk

Increased levels of inflammation, including hs-CRP and IL-6 have been shown to be associated with increased ASCVD risk through numerous studies[25]. Targeting inflammation to reduce ASCVD risk has been of great interest. The JUPITER trial[26] showed rosuvastatin to lower ASCVD events by 44% in persons with "normal" LDL-C who had elevated hs-CRP levels, and those who achieved the lowest levels of both hs-CRP and LDL-C had the lowest rates of ASCVD events[27]. However, since statins lower both LDL-C and hs-CRP, and the independent effect of lowering hs-CRP on ASCVD events was never demonstrated, this trial did not prove the inflammation hypothesis. CANTOS[28] was the first demonstration of proof-of-concept for lowering inflammation to reduce ASCVD events. In this trial, canakinumab, which lowers IL-6 by more than 40% and hs-CRP levels by more than 50%, was shown to reduce subsequent ASCVD events by 15% in those with prior CVD; however, the expense of this therapy as well as increased rate of fatal infections precluded it from receiving an indication nor recommendation in guidelines for lowering inflammation to reduce CVD. In the Cardiovascular Inflammation Reduction Trial (CIRT), administration of low dose methotrexate did not reduce cardiovascular outcomes and the trial was terminated early due to futility[29]. Finally, the COLCOT trial investigated the efficacy of colchicine in reducing cardiovascular outcomes in persons with a prior myocardial infarction. This resulted in a 23% relative risk reduction for the primary cardiovascular endpoint[30]. While both CANTOS and COLCOT show that selective

reduction of inflammation may further lower ASCVD risk, national guidelines have yet to adopt any anti-inflammatory therapy for reduction of ASCVD risk.

Therapies for Metabolic Residual Risk

Since 2008 US FDA guidance has required all new diabetes therapies to show cardiovascular benefit. The advent of the sodium glucose lowering transport-2 inhibitors (SGLT2i) and glucagon like peptide-1 receptor agonists (GLP1-RA) in recent years have brought about a revolution not only in diabetes treatments, but more importantly cardiovascular risk reduction. The EMPA-REG trial[31] involving empagliflozin and CANVAS trial[32] involving canagliflozin were the first of the SGLT2i trials in persons with diabetes to show reductions in CVD outcomes and importantly showed significant reductions in heart failure incidence to be a major drive of the CVD reductions. Dapagliflozin in the DECLARE trial[33] also showed reductions in the composite of heart failure hospitalizations and CVD death (although not the co-primary cardiovascular composite outcome). Importantly, in persons with heart failure with reduced ejection fraction (HFrEF), both empagliflozin and dapagliflozin have been shown to reduce the composite heart failure endpoint[34,35]; empagliflozin also is the first SGLT2i to additionally benefit persons with heart failure with preserved ejection fraction (HFpEF)[36]. Moreover, SGLT2i therapies significantly benefit renal outcomes in persons with established chronic kidney disease[37,38], and thus are rapidly becoming standard of care therapies for such individuals. As for GLP1-RA therapies, liraglutide in the LEADER trial[39] showed cardiovascular event risk reductions in persons with diabetes, which included those with and without prior CVD. Semaglutide also benefitted persons with diabetes with significant reductions observed in the primary cardiovascular endpoints both in the SUSTAIN-6[40] and PIONEER-6[41] trials; in SUSTAIN-6 there was also a dramatic 39% reduction in stroke incidence, a secondary endpoint. Currently, both SGLT2i and GLP1-RA therapies indicated by several guidelines for the reduction of CVD events in persons with diabetes with either pre-existing CVD or multiple risk factors, irrespective of metformin use or initiation or target HbA1c level[42]. The recently released STEP 1 trial[43] involving a higher dosage of semaglutide (2.4 mg weekly) given to overweight and obese adults showed a dramatic a 15% reduction in weight, making this a significant advance in weight loss therapies. Of note, a cardiovascular outcomes trial involving this higher dosage of semaglutide given to persons with known ASCVD who also are overweight or obese is ongoing and will provide valuable data on the efficacy of this therapy in reducing CVD outcomes beyond that shown already among diabetes patients.

The other great advance this decade in metabolic therapies for reducing ASCVD risk is the demonstrated cardiovascular outcomes benefit of icosapent ethyl therapy, shown initially among Japanese patients in the JELIS trial[44] among patients in Japan, but much more broadly in the multinational REDUCE-IT trial (Figure 5)[45]. While specifically indicated for persons with moderate elevations

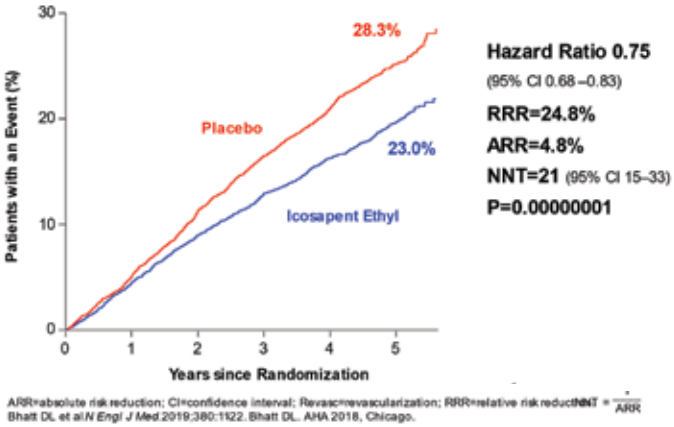

Figure 4. REDDUCE-IT Primary endpoint: Death, MI, stroke, coronary revasc, unstable angina

in triglycerides (who also have either prior ASCVD or diabetes and multiple risk factors), the benefits of icosapent ethyl (pure EPA) appear to be independent of their triglyceride-lowering effect, involving antioxidant, anti-inflammatory and membrane stabilizing effects, hence their consideration here more generally as a metabolic agent. In the REDDUCE-IT trial, beyond statin therapy, icosapent ethyl therapy was shown to be associated with a further 25% relative risk reduction of the primary composite endpoint, with every secondary endpoint in hierarchical analysis met, with the exception of total mortality. The failure of other clinical trials of omega-3 fatty acid therapies, including combination EPA-DHA therapies, such as the recent STRENGTH trial[46] underscores the point that the REDUCE-IT trial implications should not be extended beyond icosapent ethyl. Only prescription icosapent ethyl therapy is indicated for cardiovascular event risk reduction and guidelines specify their use for persons with pre-existing ASCVD or diabetes with multiple risk factors and triglycerides of 135-499 mg/dl beyond statin therapy. Dietary supplement omega 3 fatty acid supplements often have impurities such as saturated and other fats, are oxidized, and none have been shown to reduce cardiovascular events.

Therapies for Thrombotic Residual Risk

Recent recommendations[47] have brought into question the appropriateness of aspirin therapy for primary prevention of cardiovascular disease due to questionable net clinical benefit from bleeding risks that largely counterbalance any cardiovascular benefits However, in patients with known ASCVD, effective antithrombotic therapy is standard of care, but despite aspirin therapy, events still occur, demonstrating significant thrombotic residual risk and thus the need for intensification of thrombotic therapy. Two trials of low dose rivaroxaban therapy have shown cardiovascular benefit. In the ATLAS ACS 2-TIMI 51 trial involving rivaroxaban 2.5mg or 5 mg added to other antiplatelet therapy (93% on dual antiplatelet therapy) a 16% relative risk reduction in major adverse cardiovascular events47 was shown, although this was offset by a 1.5% absolute risk increase in major bleeding. COMPASS, however, showed low-dose rivaroxaban therapy plus aspirin vs aspirin alone to have a

24% reduction in the primary outcome, with a 22% reduction in the net clinical benefit endpoint which was a composite of the primary outcome and fatal or symptomatic bleeding[48].

In addition, while the use of dual antiplatelet therapy (DAPT) for 1 year post-PCI has been a standard of care, its benefits from longer term treatment have only recently been demonstrated. In the PEGASUS TIMI-55 trial the additional of ticagrelor to aspirin in patients with a prior myocardial infarction showed a 16% reduction in MACE[49], and a subsequent meta-analysis of several trials in the post-ACS setting has shown similar benefits, but the benefits appear to be substantially counterbalanced by major bleeding. Further, among patients with diabetes and stable CAD with a history of PCI or bypass surgery, THEMIS-PCI showed from ticagrelor a reduction in the composite MACE endpoint, but also a significantly higher occurrence of major bleeding[50].

Conclusions

Despite currently approved standard of care therapies for persons with ASCVD, substantial residual risk exists, especially in those defined as "very high risk" according to current guidelines. While firmly entrenched into the guidelines for those with ASCVD, these therapies are still significantly underutilized, such as high intensity statins (51) and call for more aggressive efforts to address issues with clinical inertia. The advent of newer lipid, anti-inflammatory, metabolic, and antithrombotic therapies hold promise for further reducing this residual risk; however, costs and/or guideline restrictions to use in only those at highest risk (or not at all in the case of anti-inflammatory therapies) have limited their availability and overall impact on cardiovascular events globally. The hopeful demonstration of newer therapies in development with pending cardiovascular outcomes trials will hopefully add to the clinician's armamentarium of therapies to address ASCVD residual risk. Moreover, a greater emphasis and resources devoted towards lifestyle modification efforts remains central for population-wide cardiovascular risk reduction efforts.

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