

A Conceptual Framework for Addressing Residual Atherosclerotic Cardiovascular Disease Risk in the Era of Precision Medicine

Running Title: *Patel et al.; Framework for Addressing Residual ASCVD Risk*

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Until recently, therapies to mitigate atherosclerotic cardiovascular disease (ASCVD) risk have been limited to lifestyle interventions, blood pressure lowering medications, high intensity statin therapy, antiplatelet agents, and in select patients, coronary artery revascularization. Despite administration of these evidence-based therapies, substantial residual risk for cardiovascular events persists, particularly among individuals with known ASCVD. Moreover, the current guideline-based approach does not adequately account for patient-specific, causal pathways that lead to ASCVD progression and complications. In the past few years, multiple new pharmacological agents, targeting conceptually distinct pathophysiological targets, have been shown in large and well-conducted clinical trials to lower cardiovascular risk among patients with established ASCVD receiving guideline directed medical care. These evidenced-based therapies reduce event rates, and in some cases all-cause and cardiovascular mortality; these benefits confirm important new disease targets and challenge the adequacy of the current “standard of care” for secondary prevention.

After years of treating our patients following an acute coronary syndrome (ACS) event with the same core group of medications that have been proven to be safe, beneficial, and cost-effective, a diverse array of potentially beneficial options to address residual risk are now available. The near simultaneous development of these new approaches to secondary prevention disrupts existing paradigms regarding assessment and treatment of residual risk. For example, consider a hypothetical patient with obesity, hypertension, type 2 diabetes mellitus, and hyperlipidemia who had a non-ST elevation myocardial infarction and received an intracoronary drug eluting stent. This patient would likely be given instructions on healthy lifestyle practices and prescribed current guideline directed medical therapy including low-dose aspirin, P2Y12 inhibitor, high intensity statin, beta-blocker, ACE inhibitor and metformin. In addition, we must

now consider a new evidence base of available treatment options to lower residual ASCVD risk even further by targeting causal pathways. Based on recent trial data, an evidence-based case could be made for the addition of ezetimibe, a PCSK9 inhibitor, canakinumab, an SGLT2 inhibitor, a GLP-1 agonist, and after 12 months from the ASCVD event, extended duration dual antiplatelet therapy or low dose rivaroxaban and aspirin. How are clinicians supposed to choose from this portfolio of options?

Clearly there is now an abundance --perhaps even an excess-- of therapies to target residual risk in patients with ASCVD and clinicians will need new strategies to navigate through the various treatment options and guide selection of the one or several choices best suited for the individual patient. Although the move towards precision cardiovascular medicine is still in its infancy, we will need to accelerate translational efforts so that as clinicians we can make sensible choices among the many options for reducing residual risk.

Here, we propose an approach for considering residual risk in light of these important new data (**Figure**). We propose five broad residual risk targets: lipoproteins, inflammation, metabolism, platelets, and coagulation. This conceptual framework builds on prior constructs that have considered soluble biomarkers like LDL and hs-CRP as residual risk targets (1,2). The approach recognizes distinct ASCVD pathophysiological pathways and identifies therapies to combat these targets and mitigate residual risk. We propose potential precision medicine tools (which in many cases are highly speculative) that may provide insights into pathophysiological mechanisms underlying an individual's residual risk and may potentially help guide selection of one of the newer agents. We suggest that the precision cardiovascular care toolbox should include clinical history and physical exam findings, lifestyle information (eventually including wearable device physiological data), genetics, biomarkers, data-derived risk scores, and in some

cases on-treatment responses to an initial trial of a targeted therapy (3,4). And of course, long-term safety and economic implications will remain paramount as we focus on residual risk. Indeed, until the precision medicine toolkit is operationalized, we believe that safety and cost should be the primary considerations for selection among the potential treatment options, particularly those with similar treatment effects.

Targeting residual risk with new strategies will be met with enormous challenges. There is a lack of data as to who will benefit most from specific residual risk reduction strategies. Although there are data supporting some precision medicine tools, such as LDL-C, hs-CRP, and the DAPT risk score, most treatments do not have validated surrogate markers to evaluate treatment response. Even for those therapies with a putative marker, we have little or no evidence to support that initiating or titrating therapy to the biomarker target improves outcomes. As the most sobering example, in 2018 we still do not know whether LDL cholesterol levels should be used as a treatment target for LDL-lowering therapies.

Comparative effectiveness trials among these new therapies will be extremely difficult. The number of potential permutations and drug combinations is staggering, and given the progressive decline in ASCVD event rates, sample size requirements will be very large, perhaps even prohibitive. Moreover, identifying comparator and control groups will present a dilemma given the number of potential options. Thus, the design of robust clinical trials will be arduous and the pharmaceutical industry will likely not be incentivized to support such an endeavor. Observational comparative effectiveness studies have been proposed as an alternative or complement to randomized trials, but we have strong concerns that the inherent limitations of observational studies, even when performed with the most robust methodologies, will preclude identifying optimal drug combinations. Novel, adaptive trial designs testing precision medicine-

targeted therapies, which have been pioneered in oncology, may provide a path forward for the necessary studies in precision cardiovascular medicine (5).

These are remarkable times for researchers, clinicians, and most importantly our patients. The surprising and unprecedented recent successes from randomized clinical trials testing new therapies to lower residual risk have forced a reexamination of the underlying pathophysiological basis of atherosclerotic cardiovascular disease and opened the doors for precision medicine in targeting specific causal pathways.

Disclosures

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References

1. Morrow DA, de Lemos JA, Sabatine MS, Wiviott SD, Blazing MA, Shui A, Rifai N, Califf RM, Braunwald E. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation*. 2006;114:281-288.
2. Bohula EA, Giugliano RP, Cannon CP, Zhou J, Murphy SA, White JA, Tereshakovec AM, Blazing MA, Braunwald E. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. *Circulation*. 2015;132:1224-1233.
3. Shah SH, Arnett D, Houser SR, Ginsburg GS, MacRae C, Mital S, Loscalzo J, Hall JL. Opportunities for the Cardiovascular Community in the Precision Medicine Initiative. *Circulation*. 2016;133:226-231.
4. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ; CANTOS Trial Group. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet*. 2018;391:319-328.
5. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *N Engl J Med*. 2017;377:62-70.



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Figure Legend

Figure. A Proposed Conceptual Framework for Addressing Residual Atherosclerotic Cardiovascular Disease Risk in the Era of Precision Medicine

We propose five broad residual risk targets for secondary prevention of atherosclerotic cardiovascular disease and identify therapies either shown to be effective in large randomized trials (blue), or available for clinical use but not yet demonstrated to lower ASCVD risk (green).

Precision medicine tools are proposed for each category (in many cases highly speculative) that could be used to guide selection among the potential therapies. Abbreviations - PCSK9:

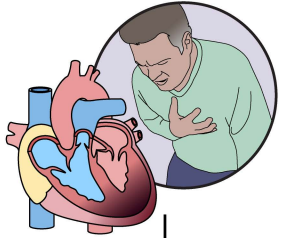
proprotein convertase subtilisin/kexin 9; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglycerides; Lp(a): lipoprotein (a); hs-CRP: high-sensitivity C-reactive protein;

DM: diabetes mellitus; Hb A1c: glycated hemoglobin; HOMA-IR: homeostatic model assessment for insulin resistance; BMI: body mass index; DAPT: Dual Antiplatelet Therapy;

PARIS: Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients; PRECISE

DAPT: PREdicting bleeding Complications In patients undergoing Stent implantation and

subsequent Dual Anti Platelet Therapy; VTE: venous thromboembolism.



Lifestyle interventions, guideline-directed medical therapy

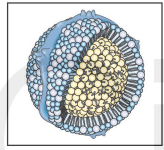


Residual risk target

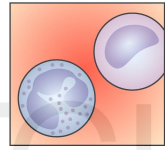
Residual risk-lowering therapies

Precision medicine toolbox

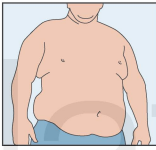
Lipoproteins



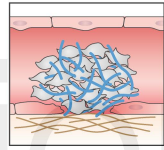
Inflammation



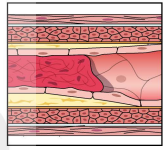
Metabolism



Platelets



Coagulation



Ezetimibe
PCSK9 inhibitor
Omega-3 fatty acids

Canakinumab
Methotrexate
Colchicine

SGLT2 inhibitor
GLP-1 agonist

Extended DAPT
Low dose ticagrelor

Low dose rivaroxaban

Standard lipids (e.g., LDL, HDL, TG), advanced lipid testing, Lp(a), HDL efflux capacity, genetic risk scores, atherosclerosis imaging

hs-CRP; biomarkers of inflammation, T cell and immune dysregulation, and clonal hematopoiesis; systemic inflammatory disease (e.g., psoriasis)

Prevalent type 2 DM, Hb A1c, HOMA-IR, BMI, visceral adiposity, liver fat

Antiplatelet risk scores (e.g., DAPT, PARIS, PRECISE-DAPT), platelet function testing, pharmacogenomics

PVD, prior VTE, thrombophilia, bleeding risk scores, coagulation biomarkers

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