

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

# Medical Therapy for Long-Term Prevention of Atherothrombosis Following an Acute Coronary Syndrome



## JACC State-of-the-Art Review

Guglielmo Gallone, MD,<sup>a,b</sup> Luca Baldetti, MD,<sup>a</sup> Matteo Pagnesi, MD,<sup>a</sup> Azeem Latib, MD,<sup>c</sup> Antonio Colombo, MD,<sup>d</sup> Peter Libby, MD,<sup>e</sup> Francesco Giannini, MD<sup>d</sup>

### ABSTRACT

Following an acute coronary syndrome (ACS), heightened predisposition to atherothrombotic events may persist for years. Advances in understanding the pathobiology that underlies this elevated risk furnish a mechanistic basis for devising long-term secondary prevention strategies. Recent progress in ACS pathophysiology has challenged the focus on single “vulnerable plaques” and shifted toward a more holistic consideration of the “vulnerable patient,” thus highlighting the primacy of medical therapy in secondary prevention. Despite current guideline-directed medical therapy, a consistent proportion of post-ACS patients experience recurrent atherothrombosis due to unaddressed “residual risk”: contemporary clinical trials underline the pivotal role of platelets, coagulation, cholesterol, and systemic inflammation and provide a perspective on a personalized, targeted approach. Emerging data sheds new light on heretofore unrecognized residual risk factors. This review aims to summarize evolving evidence relative to secondary prevention of atherothrombosis, with a focus on recent advances that promise to transform the management of the post-ACS patient. (J Am Coll Cardiol 2018;72:2886-903) © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation.

Following an acute coronary syndrome (ACS), patients have a high risk of subsequent ischemic events (1-5): each episode associates with an increase in mortality (6-9). A heightened predisposition to atherothrombotic events may persist for years (10-13), suggesting that the pathobiology of recurrent events post-ACS differs from that of stable coronary artery disease (CAD) patients who have not sustained a previous ischemic event. This observation furnishes a mechanistic basis for a long-term secondary prevention strategy in this high-risk population.

In particular, despite the expectation of improved clinical outcomes with the advent of percutaneous coronary intervention (PCI), current evidence does not uniformly support the superiority of coronary revascularization (aside from culprit lesion intervention in ACS) over medical therapy (14-19).

The recent progress in intracoronary imaging technology has revealed an enormously complex picture of ACS pathophysiology that challenges the prevailing concept of the “vulnerable plaque,” stimulating a shift toward a more holistic consideration of the “vulnerable patient” beyond revascularization



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From the <sup>a</sup>Unit of Cardiovascular Interventions, IRCCS San Raffaele Scientific Institute, Milan, Italy; <sup>b</sup>Division of Cardiology, Department of Medical Sciences, Città della Scienza e della Salute Hospital, University of Turin, Turin, Italy; <sup>c</sup>Department of Cardiology, Montefiore Medical Center, New York, New York; <sup>d</sup>Interventional Cardiology Unit, GVM Care & Research Maria Cecilia Hospital, Cotignola, Italy; and the <sup>e</sup>Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts. Dr. Libby has served as an unpaid consultant for Amgen, AstraZeneca, Esperion Therapeutics, Ionis Pharmaceuticals, Sanofi-Regeneron, and XBiotech, Inc.; has served on the scientific advisory board of Corvidia Therapeutics, Olatec Therapeutics, and Medimmune; and has received laboratory funding from Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 8, 2018; revised manuscript received August 21, 2018, accepted September 4, 2018.

of flow-limiting lesions (20,21). This perspective highlights the importance of optimal medical management and risk factor control that targets the atherosclerotic burden as a whole as well as the thrombotic milieu in secondary prevention. Indeed, numerous clinical studies have demonstrated that such noninvasive interventions can ameliorate risk more consistently than invasive revascularization (22-25).

Despite current guideline-directed medical therapy (GDMT), a consistent proportion of post-ACS patients experience recurrent atherothrombosis, representing “residual risk.” This recognition offers an opportunity to improve outcomes even beyond current GDMT in patients post-ACS (26). Thus, the constantly expanding understanding of ACS pathophysiology and its translation to the clinical scenario provide insight both into the underlying mechanisms of residual risk and new therapeutic targets.

Contemporary clinical trials that have evaluated more aggressive lipid-lowering and antithrombotic interventions than currently recommended GDMT have convincingly demonstrated benefit (27-29), recent studies of novel anticoagulant agents offer new opportunities to address the thrombotic milieu beyond plaques themselves, and the CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) has established inflammation as a new therapeutic target to reduce cardiovascular events in a subset of the secondary prevention population (30).

This review aims to summarize current views relating to the pathophysiology, clinical outcomes, and therapeutic strategies toward long-term prevention of atherothrombotic events following ACS. The goal is to emphasize a focus on emerging therapies that promise to transform clinical management of the higher-risk post-ACS stable CAD patient in the near-term.

## AVOIDING RECURRENT ISCHEMIC EVENTS: CURRENT GUIDANCE AND FUTURE PERSPECTIVE

Current optimal medical management to reduce ischemic event recurrence includes antiplatelet and lipid-lowering agents. These therapies target the principal pathophysiological pathways traditionally implicated in plaque disruption and arterial thrombosis. This review will not consider other well-established secondary prevention treatments, including pharmacological interventions (i.e., beta-blockers, renin-angiotensin system inhibitors, and aldosterone receptor antagonists) that have long

demonstrated an undisputed reduction in mortality, that do not directly target atherothrombosis, but should furnish the foundation of secondary prevention strategies. Lifestyle measures also doubtless have a fundamental role in secondary prevention, but have less robust databases, and involve behavioral and societal measures that, despite their primordial importance, exceed the scope of the current review.

Table 1 summarizes the main recommendations from the European Society of Cardiology and the American College of Cardiology/American Heart Association guidelines (31-37). Despite their differences, the following discussion has relevance for both. Specifically, this review focuses upon aspects of patient management not addressed or that have only weak recommendation in the current guidelines and principally include:

1. The long-term management of antithrombotic (antiplatelet and anticoagulation) therapy.
2. Platelet function and genetic testing to guide antiplatelet therapy.
3. The optimal strategy to guide lipid-lowering therapy.
4. The use of new lipid-lowering agents.
5. The use of C-reactive protein (CRP) to guide statin and ezetimibe therapies.
6. The use of biological anti-inflammatory agents.

Before addressing these issues, we will summarize the current views on the post-ACS setting that underlie the therapeutic strategies to prevent recurrent atherothrombosis.

## ATHEROTHROMBOTIC RESIDUAL RISK: WHAT DO WE KNOW

**LESSONS FROM PATHOPHYSIOLOGY.** The traditional understanding of the mechanisms leading to ACS centers on the rupture of a thin-capped atherosclerotic plaque with a large lipid or necrotic core—the so-called “vulnerable plaque”—which results in the exposure of prothrombotic material and further propagation of pro-thrombotic mediators, that may ultimately form a flow-limiting thrombus (38). A consistent body of evidence has occasioned a reassessment of this view, providing a much more complex picture of the processes involved in ACS (21,39). Intravascular ultrasound virtual histology, infrared spectroscopy, and optical coherence tomography have revealed subclinical plaque ruptures in

## ABBREVIATIONS AND ACRONYMS

<b>ACS</b>	= acute coronary syndrome
<b>CAD</b>	= coronary artery disease
<b>CRP</b>	= C-reactive protein
<b>DAPT</b>	= dual antiplatelet therapy
<b>GDMT</b>	= guideline-directed medical therapy
<b>LDL-C</b>	= low-density lipoprotein cholesterol
<b>MACE</b>	= major adverse cardiac events
<b>MI</b>	= myocardial infarction
<b>PCI</b>	= percutaneous coronary intervention
<b>RCT</b>	= randomized controlled trial

**TABLE 1 ESC and ACC/AHA Recommendations of Medical Therapy for the Prevention of Recurrent Atherothrombosis**

ESC Guidelines 2015,* 2016,† 2017‡§		ACC/AHA Guidelines 2013,   2014,¶ 2016#	
Recommendation	Class**	Recommendation	Class††
<b>Antithrombotic Therapy</b>			
Aspirin at a dose of 75–100 mg/day is recommended indefinitely	I	Aspirin at a dose of 75–100 mg/day is recommended indefinitely	I
DAPT with a P2Y <sub>12</sub> inhibitor, preferably ticagrelor or prasugrel, in addition to aspirin is recommended in all patients	I	DAPT with a P2Y <sub>12</sub> inhibitor, preferably ticagrelor or prasugrel, in addition to aspirin is recommended in all patients‡‡	I
DAPT is recommended for 12-month unless high bleeding risk (PRECISE-DAPT score ≥25)	I	DAPT is recommended for 12-month (in patients with DES implantation and high bleeding risk [e.g., oral anticoagulant agent use, intracranial surgery, overt bleeding event], discontinuation of DAPT after 6 months may be reasonable [Class IIb])	I
Continuation of DAPT for longer than 12 months may be considered in patients tolerating DAPT without bleeding complication§§	IIb	Continuation of DAPT for longer than 12 months may be reasonable in patients tolerating DAPT without bleeding complication and without high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant agent use), who did not undergo CABG following ACS	IIb
In MI patients at low bleeding risk and high ischemic risk, low-dose rivaroxaban may be considered in those receiving aspirin and clopidogrel	IIb		
<b>Lipid-Lowering Therapy</b>			
High-dose statins early after admission are indicated in all ACS patients without contraindication or history of intolerance, regardless of initial LDL-C values	I	High-intensity statin therapy should be initiated or continued as first-line therapy in patients younger than 75 years of age, unless contraindicated	I
An LDL-C goal of 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% from baseline values in patients with a baseline LDL-C between 1.8 and 3.6 mmol/L (70–139 mg/dL) is recommended	I	No recommendations are made for or against specific LDL-C or non-HDL-C targets	-
Ezetimibe in combination with statins should be considered in patients not reaching the target despite maximally tolerated statin dose	IIa	Addition of nonstatin cholesterol-lowering drug(s) may be considered in patients receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response, if the benefits outweigh the potential for adverse effects.	IIb
If the LDL-C target is not reached with the highest tolerable statin dose and/or ezetimibe, PCSK9 inhibitors may be considered	IIb		
<p>*2015 ESC NSTEMI-ACS guidelines. †2016 ESC/EAS dyslipidaemia guidelines. ‡2017 ESC STEMI guidelines. §2017 ESC/EACTS focused update on DAPT.   2013 ACC/AHA blood cholesterol guidelines. ¶2014 ACC/AHA NSTEMI-ACS guidelines. #2016 ACC/AHA focused update on DAPT duration. **ESC clinical practice guidelines recommendation classification system. ††ACC/AHA clinical practice guidelines recommendation classification system. ‡‡In medically managed patients, prasugrel is not indicated. §§In medically managed patients, DAPT continuation is limited to those with an index MI.</p> <p>ACC = American College of Cardiology; ACS = acute coronary syndrome; AHA = American Heart Association; CABG = coronary artery bypass graft; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; ESC = European Society of Cardiology; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NSTEMI-ACS = non-ST-segment elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction.</p>			

4% to 79% of CAD patients (21) and that 75% of “vulnerable plaques” evolve to display characteristics associated with stability within 12 months, probably due to cycles of rupture and healing (40). Indeed, fibrous plaques that produce substantial lumen narrowing often show morphological evidence of previous rupture and healing (41–43). Many plaque ruptures may not cause a persistent and/or occlusive thrombus, and therefore do not manifest clinically. Thus, plaque disruption may occur in both “stable” coronary disease and ACS. So-called “stable” lesions that cause flow-limiting stenoses may commonly arise from smooth muscle proliferation and elaboration of extracellular matrix triggered by previous subclinical plaque rupture and thrombosis. Indeed, thrombin and platelet products released locally at the site of plaque disruption, such as platelet-derived growth factor and transforming growth factor beta, can promote a “healing” response that involves collagen deposition, reinforcing the fibrous skeleton

of the plaque, thickening the fibrous cap, and resisting rupture. In ACS, the disruption crosses the threshold to clinical manifestation because of formation and persistence of a thrombus sufficient to cause distal ischemia (44). Such flow-limiting thrombi may be the exception rather than the rule following plaque disruption.

Accordingly, plaque rupture per se does not suffice to trigger occlusive thrombus formation: a local prothrombotic milieu in the “solid state” of the plaque, and an unfavorable balance between thrombotic and fibrinolytic properties in the “fluid phase” of blood as well as platelet hyper-reactivity likely determine the destiny of a disrupted plaque to cause an occlusive thrombosis and ACS (1,10,21,39,44). These key concepts help to understand why an invasive lesion-based approach (with the exception of culprit lesion revascularization in ST-segment elevation myocardial infarction) does not consistently confer improved outcomes, and why a

**TABLE 2** Studies Reporting Outcomes of Post-ACS Stable CAD Compared With CAD Patients Without a History of Prior ACS

Study (Ref. #), Enrollment Period; Follow-Up (Months)	Study Description	SCAD Subgroups Compared in Each Study	Post-ACS SCAD Patients, n Without-Prior-ACS SCAD Patients, n	Atherothrombotic Outcomes in Post-ACS Versus Without-Prior-ACS SCAD Patients
REACH (2), 2003-2004; 48	Prospective registry enrolling patients at risk or with atherothrombosis	Post-ACS stable CAD definition includes patients MI/stroke-free for at least 1 yr prior to enrollment Without-prior-ACS SCAD definition includes patients without prior MI/stroke	15,740 15,264	MACE HR: 1.41 (1.32-1.51)
ARCTIC-INTERRUPTION (48), 2009-2011; 17 (IQR: 15-18)	RCT in which patients were randomized 1 yr after DES implantation to interrupt or to continue thienopyridine for follow-up duration	Post-ACS SCAD definition includes patients ACS/stroke-free for at least 1 yr prior to randomization Without-prior-ACS SCAD definition includes patients without prior ACS	323 (156 DAPT, 167 ASA) 936 (479 DAPT, 457 ASA)	Death, MI, ST, stroke, or urgent revascularization 4.3% vs. 3.1% ST or any urgent revascularization 2.0% vs. 1.3%
DAPT (4), 2009-2011; 18	RCT in which patients were randomized 1 yr after DES implantation to interrupt or to continue thienopyridine for further 18 months	Post-ACS stable CAD definition includes patients MI/stroke-free for at least 1 yr prior to enrollment Without-prior-ACS SCAD definition includes patients without prior MI	5,340 6,308	MACE 5.9% vs. 4.3% (p = 0.02) MI 3.8% vs. 2.4% (p = 0.01) ST 1.2% vs. 0.6% (p = 0.04) Stroke 0.8% vs. 0.8% (p = NS)
CORONOR (49), 2010-2011; 60	Prospective registry enrolling patients with stable CAD (>1 yr from last MI or coronary revascularization)	Post-ACS stable CAD definition includes patients MI-free for at least 1 yr prior to enrollment Without-prior-ACS SCAD definition includes patients without prior MI	2,554 1,540	MI 4.5% vs. 3.5%
COMPASS (50), 2013-2016; 23	RCT in which patients with stable atherosclerotic vascular disease were randomized to receive rivaroxaban plus ASA, rivaroxaban twice daily, or ASA for follow-up duration	Post-ACS stable CAD definition includes patients MI-free for at least 2 yrs prior to randomization Without-prior-ACS SCAD definition includes patients without prior MI	5,199 (2,659 ASA + rivaroxaban, 2,540 ASA) 9,825 (4,436 ASA + rivaroxaban, 5,389 ASA)	MACE 5.2% vs. 4.4%

The atherothrombotic risk of post-ACS stable CAD patients remains persistently higher than that of CAD patients without a history of prior ACS. All obtainable atherothrombotic outcomes are presented. When available, the associated significance level is specified. MACE denotes CVD, MI, or stroke.  
CAD = coronary artery disease; CVD = cardiovascular death; HR = hazard ratio; IQR = interquartile range; MACE = major adverse cardiovascular events; NS = not significant; RCT = randomized controlled trial; SCAD = stable coronary artery disease; ST = stent thrombosis; other abbreviations as in Table 1.

pharmacological approach, targeting the disease burden and the patient as a whole, may indeed confer greater benefit.

**LESSONS FROM CLINICAL STUDIES.** The risk of myocardial infarction (MI) after an ACS is greatest during the first 30 days and remains significantly elevated in the first year with reported rates of 5% and 5% to 7%, respectively (12,45-47). Patients who do not experience recurrent ischemic events for 1 year after an ACS comprise “post-ACS stable CAD” subjects. Yet, the risk of this population remains persistently higher than that of CAD patients without a history of prior ACS (1,2,4,48-50) (Table 2), and exhibit a stronger predisposition to atherothrombosis for years (1,10-13), suggesting that a distinct pathobiology may operate in patients who have already experienced an ACS.

While much information characterizes the short-term and medium-term prognosis of ACS patients, post-ACS stable CAD has received less extensive assessment. Registries and randomized controlled

trials (RCTs) have reported the outcomes of post-ACS stable CAD populations (Table 3). Three contemporary registries reporting real-world data relating to post-MI stable CAD patients from Sweden (n = 76,687) (12), Canada (n = 6,749) (51), and the United States (n = 13,492) (52) showed annualized major cardiovascular event (MACE) (cardiovascular death, MI, or stroke) rates of 6.7%, 6.7%, and 4.4%, which appeared consistent over the longer-term follow-up. Data from post-MI stable CAD populations derived from 2 contemporary trials (3,29) revealed annual rates in the placebo groups of 4.1% and 3.0% for the same outcome, somewhat lower than those of real-world registries.

In summary, post-ACS stable CAD patients appear to have a sustained and higher risk of recurrent atherothrombosis and subsequent death than individuals with CAD who have not sustained an ACS. The overall incomplete adoption of GDMT in practice (Table 3) likely contributes to these findings; yet, the high event rates reported in the

TABLE 3 Studies Reporting Outcomes of Post-ACS Stable CAD Populations			
Study (Ref. #) Enrollment Period	Description of the Post-ACS Stable CAD Population/ Subgroup*	Study Type	N (% of Total Study Enrollment)
Swedish registry (12), 2006-2011	All Swedish patients admitted to hospital with a diagnosis of MI and without MACE for 1 yr from index MI	Observational, retrospective registry	N = 76,687 (70.8%) (29.2% experienced MACE in the first year from MI)
Canadian registry (51), 2006-2010	All patients admitted to hospital with a diagnosis of MI and without MACE for 1 yr from index MI	Observational, retrospective registry	N = 6,749 (79.5%) (20.5% experienced MACE in the first year from MI)
U.S. insured patients HIRE registry (52), 2007-2010	Patients age 50-65 yrs and without prior stroke, admitted to hospital with a diagnosis of MI and without MACE for 1 yr from index MI	Observational, retrospective registry	N = 13,492 (100%)
DAPT study (3), 2009-2011	Patients with MI undergoing stent implantation and without MACE for 1 yr, randomized to further 18-month DAPT or placebo plus ASA	Randomized double-blind, placebo-controlled trial	N = 3,576 (30.7%) (69.3% underwent PCI for a reason other than MI) (Control group n = 1,771 [49.5%])
PEGASUS-TIMI 54 (29), 2010-2013	Patients with MI 1 to 3 yrs prior to enrolment (median 1.7 yr) and 1 additional risk factor, randomized to ticagrelor plus ASA or placebo plus ASA	Randomized double-blind, placebo-controlled trial	N = 21,162 (100%) (Control group n = 7,067 [33.4%])
Post-ACS stable CAD patients appear to have a sustained risk of recurrent atherothrombosis. The high event rates reported in GDMT-treated RCT populations suggest residual risk, despite current management. *Post-ACS stable CAD definition includes patients free of CVD/MI/stroke at 12 months from index ACS. Months are reported as means (SD) or median (interquartile range). MACE denotes CVD, MI, or stroke. BMS = bare metal stent; CI = confidence interval; GDMT = guideline-directed medical therapy; PCI = percutaneous coronary intervention; NA = not available; other abbreviations as in Tables 1 and 2.			

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optimally-treated RCT populations demonstrate the substantial residual risk that remains despite current management.

BREAKING DOWN THE CONTRIBUTORS TO RESIDUAL RISK

Many factors contribute to the residual risk of individuals with post-ACS stable CAD (Central Illustration).

MORE EFFECTIVE TARGETING OF KNOWN PATHOBIOLOGICAL PATHWAYS. Gaps in implementation of current GDMT hamper the benefits that better targeting of the known components of residual risk could confer. In this regard, contemporary clinical trials that have investigated more aggressive lipid-lowering and antithrombotic interventions than currently recommended standards have demonstrated considerable room for improvement in outcomes.

Time and intensity of dual antiplatelet therapy. Dual antiplatelet therapy (DAPT) was initially administered to patients to reduce the risk of stent thrombosis after PCI (53,54). With the use of second-generation drug-eluting stents, several studies demonstrated the noninferiority of 3 to 6 months versus 12 months DAPT following PCI in undifferentiated CAD populations (55-61). These studies, based by design on a stent-centered vision of DAPT

deployment, do underestimate the benefit of DAPT in reducing MI in specific high-risk subsets (e.g., post-ACS patients), where much of the hazard derives from recurrent MI with culprits unrelated to the lesion previously treated (50% to 80%) (3,4,49,62). Indeed, medically managed ACS patients undergoing 12-month DAPT had consistently reduced MACE (45,63,64), as did post-ACS stable CAD patients undergoing long-term DAPT (3,29,65,66). In the post-ACS with stable CAD population in the 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) study, treatment with ticagrelor in addition to aspirin yielded a 16% reduction in MACE (29), and a meta-analysis of 6 trials evaluating the efficacy of long-term DAPT in the post-ACS stable CAD setting showed similar results (Table 4) (66). Prolonged DAPT entailed an increased risk of major (but not fatal) bleeding. The observed reduction in ischemic events may be particularly relevant in patients with high atherosclerotic burden, at the cost of excess bleeding events (67,68). In this subset, despite the increased absolute risk of hemorrhagic events, the net ischemia-bleeding benefit leans toward long-term DAPT (67,68). Importantly, sustained DAPT studies excluded patients at higher bleeding risk based on several criteria (29,48,69-72); therefore,

**TABLE 3** Continued

Follow-Up, Months	Treatments	Annualized Cardiovascular Outcomes in Post-ACS Stable CAD Patients		
		MACE/yr	MI/yr	Stroke/yr
36	Index MI revascularization 48.0% Index MI (Day 0) → Day 366: Statin 78.2% → 73% ASA 91.4% → 82.4% Clopidogrel 68.6% → 25.2%	6.7%	3.1%	1.2%
61 (19-79)	Index MI revascularization 53.4% Statin 77.2% Antiplatelet other than ASA 69.4% (ASA NA)	Annualized rates: • from 0 to 24 months: 6.7% • from 25 to 60 months: 3.9%	Annualized rates: • from 0 to 24 months: 3.3% • from 25 to 60 months: NA	Annualized rates: • from 0 to 24 months: 1.0% • from 25 to 60 months: NA
24 (NA)	NA	4.4%	2.6%	0.9%
18	Index MI revascularization 100% ASA 100% Thienopyridine 50.5%	3.2% (Control group 4.1%)	2.5% (Control group 3.5%)	0.5% (Control group NA)
33 (28-37)	ASA 99.9% Statins 92.6% Ticagrelor (any dose) 66.6%	2.7% (Control group 3.0%)	1.6% (Control group 1.8%)	0.6% (Control group 0.7%)

the optimal subset of real-world patients who would derive net clinical benefit from this strategy remains undefined.

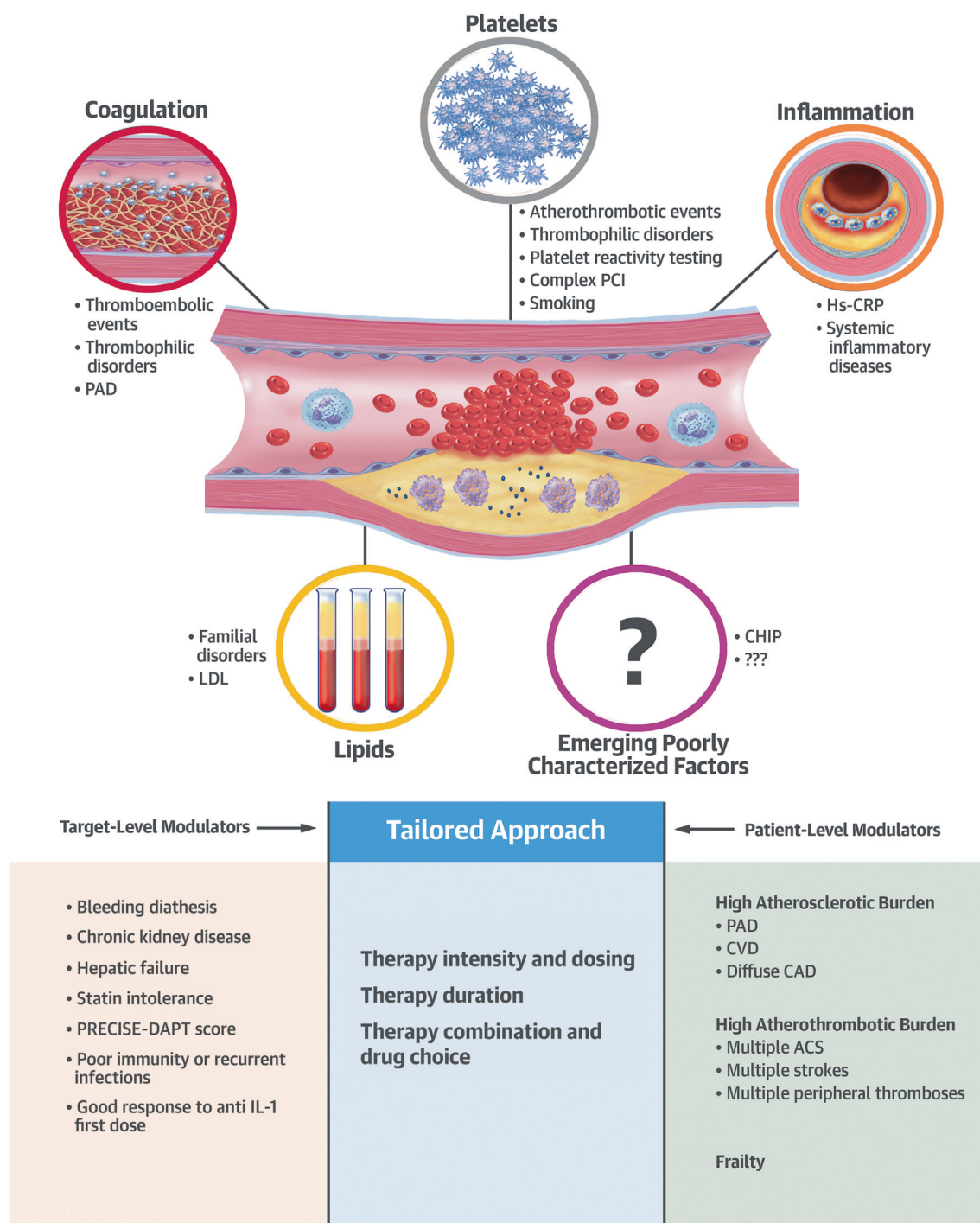
In this regard, several risk stratification scores to estimate ischemia-bleeding net benefit for patient selection have undergone retrospective evaluation and validation in broad selected and unselected, in-trial and real-world populations (5,73-75). Of these tools, the PRECISE-DAPT (predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy) score (75) which includes 5 simple items measurable at the time of PCI/ACS presentation, demonstrated the best performance and applicability in predicting out-of-hospital long-term bleeding outcomes. Specifically, longer DAPT duration exerted a significant anti-ischemic benefit in the group with a score below 25 and was associated with increased bleeding only in high-risk patients (score  $\geq 25$ ) (75).

While awaiting prospective validation of the PRECISE-DAPT SCORE, the secondary ACS prevention setting seems nevertheless to identify a high-risk cluster of patients who could benefit from long-term DAPT irrespective of the initial management strategy: in particular, patients with a high atherosclerotic burden (e.g., with peripheral artery disease, cerebrovascular disease, or diffuse coronary disease) and a low bleeding risk (PRECISE-DAPT  $< 25$  and no

bleeding events) may gain the greatest benefit from a long-term DAPT strategy.

**Platelet function and genetic testing to guide antiplatelet therapy.** Tailored antiplatelet therapies guided by platelet function testing (PFT) have a solid pathophysiological rationale and derive further support from evidence that high and low platelet reactivity on P2Y inhibitor treatment predicts ischemic and bleeding outcomes, respectively (76,77). Yet, all RCT evaluating strategies based on initial intensification of P2Y inhibitor therapy (higher clopidogrel dose, switch to prasugrel) (78,79) or therapy adjustment following repeated platelet function monitoring (80-82) in stable CAD or in ACS patients with high on-treatment platelet reactivity failed to demonstrate any benefit, leading major guidelines not to recommend PFT for tailoring DAPT (33,36). The recent CREATIVE (Clopidogrel Response Evaluation and Anti-Platelet Intervention in High Thrombotic Risk PCI Patients) trial reopened this debate by demonstrating improved outcomes with a PFT-guided tailored approach. Briefly, this single-center RCT enrolled post-PCI East Asian patients with high on-treatment platelet reactivity, and compared conventional therapy (clopidogrel 75 mg plus aspirin) with either double-dose clopidogrel or adjunctive cilostazol. The primary outcome of all-cause death, MI, target vessel revascularizations, and



**CENTRAL ILLUSTRATION** Residual Risk Reduction in Acute Coronary Syndrome Secondary Prevention: Multifaceted Approach

Gallone, G. et al. J Am Coll Cardiol. 2018;72(23):2886-903.

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cerebrovascular events at 18 months post-PCI occurred in 14.4%, 10.6% (not significant vs. conventional therapy), and 8.5% (significant vs. conventional therapy) patients, respectively. The study found no significant difference in major bleeding across groups (83). These findings require confirmation in larger, multicenter RCTs and across ethnic groups. Nonetheless, as a selective reversible phosphodiesterase type 3 inhibitor unaffected by genetic polymorphisms (84,85) and with better platelet inhibition results than high-dose clopidogrel in high on-treatment platelet reactivity patients (84,86), cilostazol might improve outcomes in patients with low responsiveness to clopidogrel through a tailored PFT-guided approach.

Of note, a pure PFT-guided de-escalation strategy with a stage-adapted treatment approach in the early phase of ACS, with the possibility of switching from prasugrel to clopidogrel, was associated with an improved net clinical benefit (MACE or bleeding grade 2 or higher according to Bleeding Academic Research Consortium criteria) outcome (87); whether this strategy may be useful to direct long-term DAPT in the stable CAD setting remains untested.

Other applications of functional testing that may confer clinical benefit in CAD patients for whom clinical evidence is lacking include: assessment of (non)compliance with treatment; de-escalation or escalation treatment when deemed necessary after an unwanted/unexpected event (88); PFT-guided single antiplatelet therapy when clopidogrel instead of aspirin is considered, either because of concomitant anticoagulation therapy (33,89,90), or as an off-label indication (27% of patients on single antiplatelet therapy were treated with clopidogrel in a wide prospective stable CAD registry reflecting modern practice) (91,92).

Finally, genetic variation surely influences the response to antiplatelet agents, in particular clopidogrel (93), and point-of-care genetic testing might optimize P2Y treatment (94). Yet, differences in genotype explain only 6% to 12% of the variability of in-clopidogrel platelet reactivity (95,96), clopidogrel

pharmacogenetics do not consistently predict clinical outcomes (97), and so far, no RCT has demonstrated clinical benefit with this approach. On these bases, genetic testing does not currently constitute a promising strategy to tailor antiplatelet therapy.

**Anticoagulation therapy.** The inhibition of coagulation factors in addition to antiplatelet therapy following ACS can improve cardiovascular outcomes. Yet, the benefit was often outweighed by the substantial increase in major and intracranial bleeding events, other unwanted effects, and clinical impracticality (98). With the wide adoption of DAPT, the interest in anticoagulant therapy for CAD waned until the introduction of new oral anticoagulants agents. These agents generally provide effective anticoagulation along with reduced risk of fatal and intracranial bleeding compared with warfarin in several clinical conditions and without the requirement of regular monitoring.

In the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 51) trial, the addition of low dose of rivaroxaban (2.5 mg twice daily), a selective direct factor Xa inhibitor, afforded a 16% reduction in MACE over placebo (93% of the patients were treated with DAPT) in patients with a recent ACS at a mean follow-up of 13 months (99). Because of the observed increase in major and intracranial bleeding, these results may have relatively limited clinical application.

Conversely, the findings of the recent COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial reopen the debate relating to the use of anticoagulation in the long-term prevention of both the occurrence and the recurrence of ACS (50,100). In patients with stable atherosclerotic vascular disease, the combination of rivaroxaban (2.5 mg twice daily) plus aspirin reduced MACE 24% more than aspirin alone at a mean follow-up of 23 months, at the expense of increased major, but not intracranial or fatal bleeding. In the study population, 61.8% of patients had a previous MI, of which 95.5%

## CENTRAL ILLUSTRATION Continued

**(Top)** Selected targets of medical therapy after an ACS, each with some clinically relevant factors that may affect residual risk. The complex interplay of target-level and patient-level features in each individual warrants an individualized approach **(bottom)** in terms of therapy intensity, duration, and drug combination. We should strive to craft a specific personalized management strategy for each patient aiming to optimize residual risk reduction versus drug-related harm. A consideration of individual target-level therapy modulators **(left bottom)** and patient-level modulators **(right bottom)** may help maximize net clinical benefit in accordance with current guideline-directed medical therapy. Of note, a portion of the residual risk may be due to still unknown and unaddressed pathophysiological factors **(pink circle)**. ACS = acute coronary syndrome; APS = antiphospholipid syndrome; CAD = coronary artery disease; CHIP = clonal hematopoiesis of indeterminate potential; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; PAD = peripheral artery disease.



**TABLE 4 Efficacy of Long-Term DAPT in the Post-ACS Stable CAD Setting**

Trial (Ref. #), Year	Description of Post-ACS Stable CAD Population/Subgroup*	N (% of Total Trial Enrollment)	Investigated Thienopyridine Versus Control Arm	Hazard Ratio (95% CI) for					
				CVD/MI/Stroke	CVD	MI	Stroke	ST	Major Bleeding
<div><div><div>● Months from MI/ACS to DAPT initiation (or DAPT interruption in the control arm, §)</div><div>★ Months of Follow-up†</div><div>→ months</div></div></div>									
CHARISMA MI (64), 2006	Patients age ≥45 yrs with prior MI. Excluded patients with a prior indication for clopidogrel or at high bleeding risk	3,846 (24.6)	Clopidogrel vs. placebo	<div><div>CHARISMA MI</div><div><div>Index MI</div><div>23.6 (NA) 27.6 (NA)</div><div>months</div></div></div>					
				0.77 (0.61-0.98)	0.82 (0.57-1.18)	0.74 (0.53-1.03)	0.75 (0.48-1.19)	NA	1.17 (0.76-1.79)
PRODIGY (71), 2012	Patients age ≥18 yrs, with prior ACS treated with PCI. Excluded patients at high bleeding risk, planned surgery, or prior stroke in the last 6 months*	1,465 (74.4)	Clopidogrel vs. no therapy	<div><div>PRODIGY</div><div><div>Index ACS</div><div>6 (NA) 24 (NA,§)</div><div>months</div></div></div>					
				0.91 (0.65-1.28)	1.00 (0.61-1.64)	0.84 (0.53-1.33)	0.73 (0.38-1.44)	0.67 (0.30-1.48)	1.50 (0.53-4.20)
ARCTIC-Interruption (48), 2014	Patients ≥18 yrs, with prior ACS treated with PCI. Excluded patients at physician's discretion, those >15 months from prior randomization, STEMI presentations, with aspirin resistance, or at high bleeding risk	323 (25.7)	Clopidogrel or prasugrel vs. no therapy	<div><div>ARCTIC-Interruption</div><div><div>Index ACS</div><div>12 (NA) 17 (15-18)</div><div>months</div></div></div>					
				0.79 (0.18-3.51)	0.36 (0.01-8.69)	0.53 (0.05-5.85)	2.08 (0.19-22.99)	0.36 (0.01-8.69)	5.35 (0.26-110.58)
DAPT (69), 2014	Patients ≥18 yrs with prior MI treated with PCI. Excluded patients at high bleeding risk, planned surgery, or concomitant DES and BMS at index PCI	3,576 (30.7)	Clopidogrel or prasugrel vs. placebo	<div><div>DAPT</div><div><div>Index MI</div><div>12 (NA) 18 (NA)</div><div>months</div></div></div>					
				0.52 (0.38-0.72)	0.67 (0.31-1.44)	0.42 (0.29-0.62)	1.06 (0.49-2.32)	0.27 (0.13-0.57)	2.38 (1.27-4.43)
DES-LATE (55), 2014	Patients age ≥18 yrs with prior ACS treated with PCI. Excluded patients with antiplatelet drugs contraindication or long-term clopidogrel indication	3,063 (60.7)	Clopidogrel vs. no therapy	<div><div>DES-LATE</div><div><div>Index ACS</div><div>13.3 (12.1-16.1) 42.0 (24.7-50.7)</div><div>months</div></div></div>					
				0.85 (0.60-1.21)	1.00 (0.55-1.83)	0.69 (0.38-1.23)	1.00 (0.58-1.72)	0.81 (0.32-2.05)	1.27 (0.79-2.03)
PEGASUS-TIMI 54 (29), 2015	Patients age ≥50 yrs with prior MI 1-3 yrs before enrollment with 1 additional risk factor. Excluded patients with planned DAPT or anticoagulation, high bleeding risk, and prior stroke	21,162 (100)	Ticagrelor vs. placebo	<div><div>PEGASUS-TIMI 54</div><div><div>Index MI</div><div>20.4 (14.4-27.6) 33 (28-37)</div><div>months</div></div></div>					
				0.84 (0.76-0.94)	0.85 (0.71-1.00)	0.83 (0.72-0.95)	0.78 (0.62-0.98)	NA	2.50 (1.86-3.36)

Continued on the next page

TABLE 4 Continued

Trial (Ref. #), Year	Description of Post-ACS Stable CAD Population/Subgroup*	N (% of Total Trial Enrollment)	Hazard Ratio (95% CI) for					
			CVD/MI/Stroke	CVD	MI	Stroke	ST	Major Bleeding
POOLED ANALYSIS (66)		33,435						
<p>In post-ACS stable CAD patients, DAPT reduces ischemic events compared with aspirin alone. *Post-ACS stable CAD definition includes patients free of CVD/MI/stroke at 12 months from index ACS, except for PRODIGY, where patients were considered "stabilized" after one event-free month. †Difference in DAPT duration between study arms was equivalent to follow-up time in all the studies apart from PRODIGY, where randomization occurred 5 months prior to DAPT discontinuation in the control-arm, and DES-LATE, where difference in DAPT duration was 36 months. Months are reported as means (SD) or median (interquartile range). §DAPT interruption in the control arm.</p> <p>Abbreviations as in <a href="#">Tables 2 and 3</a>.</p>								

were in the post-MI stable CAD phase. In patients with a previous MI, rivaroxaban plus aspirin compared with aspirin alone showed a 26% reduction in the primary outcome and a 22% reduction in the net clinical benefit endpoint (the composite of the primary outcome, fatal bleeding, and symptomatic bleeding into a critical organ/area). Major bleeding increased only in the group of patients whose previous MI occurred at least 5 years prior to rivaroxaban initiation and in patients without previous MI, consistent with the evidence of lower bleeding risk in patients with more recent MI (3,65).

These results raise a number of considerations relating to the ideal combination of an antiplatelet with an anticoagulant agent versus DAPT in the post-MI stable CAD setting:

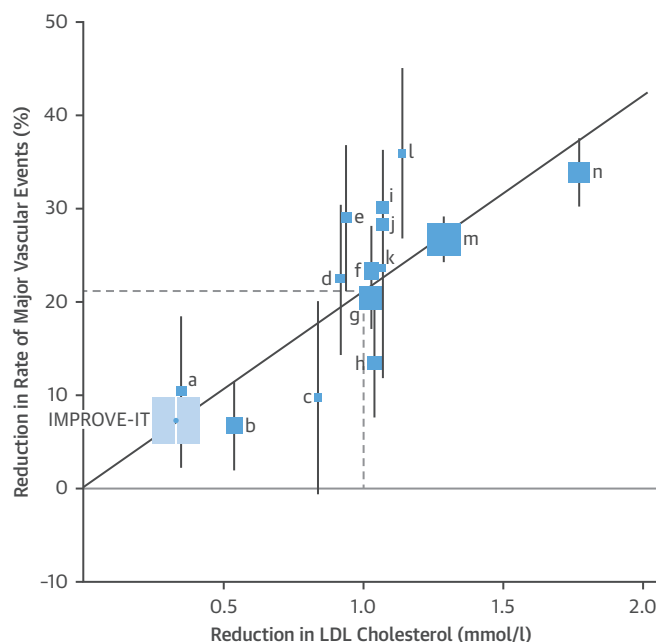
1. The magnitude of the observed event reduction seems greater than that of DAPT and comparable to that of statins (29).
2. The net clinical benefit appears to apply consistently across different durations of the post-MI stable phase, while prolonged DAPT has not yet undergone investigation.
3. The net clinical benefit appears to apply irrespective of previous antithrombotic therapy, as opposed to long-term DAPT, which offers no benefit in patients who have shown stability for 1 year or more on single antiplatelet therapy (101).
4. Patients who start rivaroxaban within 5 years from MI appear not to have increased major bleeding, as opposed to those treated with DAPT (29,66).

This observation requires cautious interpretation and more details regarding ischemia-bleeding net benefit. Indeed, the net clinical benefit endpoint in patients within 5 years from MI did not significantly favor rivaroxaban plus aspirin (50), and a previous study of antiplatelet (P2Y inhibitor) with low-dose rivaroxaban versus DAPT in the ACS setting demonstrated similar high bleeding risk in both arms (102).

Pending a direct comparison of antiplatelet plus anticoagulant agent versus DAPT regimens in the post-MI stable CAD setting, this approach appears very promising to reduce thrombotic risk further.

**Lipid-lowering therapy.** In 2005, the findings of a meta-analysis (103) of 14 trials that compared statin therapy with placebo (90,056 patients with a baseline median low-density lipoprotein cholesterol [LDL-C] value in the range of 3.79 to 4.96 mmol/l [146.6 to 191.8 mg/dl]) affirmed that the cardiovascular event reduction correlates with the absolute reduction of LDL-C, independent of the baseline LDL-C. Other trials compared more intensive versus standard statin therapy, later pooled in a meta-analysis (104) including 39,612 patients with baseline median LDL-C values of 2.09 to 2.64 mmol/l (80.8 to 102.1 mg/dl).

Double-blind RCTs show similar muscle complaints in statin-treated individuals and those receiving placebo (105-107). Yet, in daily practice, many patients (7% to 29% of treated patients, varying by statin and dose) attribute musculoskeletal or other complaints to statins, making them reluctant to adopt this highly

**FIGURE 1** The Linear Correlation Between the Reduction of LDL-C Levels and the Reduction in Major Vascular Events in the Main Trials Testing Lipid-Lowering Therapies

The hazard ratio for the reduction in major vascular events for each mmol/l of LDL-C reduction in the main lipid-lowering therapy trials are reported. Major vascular events are the composite of death from coronary heart disease, myocardial infarction, stroke, or revascularization >30 days after randomization. The **size of the box** is proportional to the number of endpoints in the study. **Letters from a to n** denote the following trials: **(a)** GISSI Prevenzione (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico); **(b)** ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial); **(c)** ALERT (Assessment of Lescol in Renal Transplantation); **(d)** LIPS (Lescol Intervention Prevention Study); **(e)** AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study); **(f)** CARE (Cholesterol and Recurrent Events); **(g)** LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease); **(h)** PROSPER (Prospective Study of Pravastatin in the Elderly at Risk); **(i)** ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm); **(j)** WOSCOPS (West of Scotland Coronary Prevention Study); **(k)** Post CABG (Post Coronary Artery Bypass Graft); **(l)** CARDS (Collaborative Atorvastatin Diabetes Study); **(m)** HPS2 (Heart Protection Study 2); and **(n)** 4S (Scandinavian Simvastatin Survival Study). LDL-C = low-density lipoprotein cholesterol. Reprinted with permission from Cannon *et al.* (27).

effective therapy (108). The availability of the cholesterol absorption inhibitor ezetimibe, and now of antibodies that neutralize proprotein convertase subtilisin kexin type 9 (PCSK9) offer alternatives to statins, although the studies that established the ability of these nonstatin LDL-lowering drugs to reduce events generally included patients already well-treated with statins (109).

IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) (27) compared ezetimibe in addition to statin against statin alone in

18,144 post-ACS patients with a mean baseline LDL-C of 2.43 mmol/l (93.8 mg/dl). The reduction in the Cholesterol Treatment Trialists endpoint of major vascular events (defined as the composite of death from coronary heart disease, MI, stroke, or coronary revascularization) strongly aligned across the studies: the event hazard ratios for 1 mmol/l (38.7 mg/dl) of LDL-C reduction in those comparing statins versus placebo (103), high-dose versus standard-dose statins (104), and ezetimibe plus statins versus statins (27) were 0.79, 0.78, and 0.80 respectively (Figure 1).

The milestone FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) trial achieved median LDL-C concentrations lower than in the previously mentioned trials (7). FOURIER compared the anti-PCSK9 antibody evolocumab plus statin to statin alone in 27,564 patients with atherosclerotic disease and a median baseline LDL-C of 2.4 mmol/l (92 mg/dl) at a median 2.2 years follow-up. A 22% reduction in MACE and no increase in systemic adverse events applied even in the lowest baseline LDL-C level quartile (where median LDL-C decreased from 1.89 to 0.57 mmol/l [74 to 22 mg/dl]) (110), providing compelling evidence that LDL-C lowering provides clinical benefit over an extremely wide range of LDL-C values. The ODYSSEY Outcome (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial affirmed this concept with alirocumab, although its design aimed for minimum LDL-C concentrations of 1.25 mmol (50 mg/dl) (111). The SPIRE trials with bococizumab also support event reduction with lower levels of LDL-C than generally achieved by statin alone (112). Thus, 2 classes of LDL-C-lowering agents (ezetimibe and PCSK9 inhibitors) that target pharmacodynamic mechanisms different from those of statin, effectively reduce cardiovascular risk.

These recent studies have important clinical implications:

1. An “as low as achievable with maximally tolerated therapy LDL-C value” strategy may reduce events beyond approaches in current guidelines that recommend a “target LDL-C value” (34) or “statin therapy intensity” (35) approaches.
2. A nonstatin agent combined with the maximally tolerated statin dose irrespective of baseline LDL-C levels can further reduce recurrent events.
3. These aggressive strategies may have particular importance in the secondary prevention setting in which the absolute risk decreases substantially for each LDL-C mmol/l stratum achieved.

**ADDRESSING NOVEL THERAPEUTIC TARGETS.** Based on laboratory evidence supporting the role of inflammation in atherothrombosis (113), clinical studies have demonstrated that inflammatory biomarkers, CRP in particular, predict the first occurrence and the recurrence of ACS (114,115). The magnitude of risk associated with CRP concentration (measured with a highly sensitive assay, hsCRP) rivals that of cholesterol and systolic blood pressure (116,117). CRP does not participate causally in atherothrombosis, but serves as a reliable overall gauge of inflammatory burden. Targeting inflammation therapeutically offers one potential novel approach to reduction of residual risk in secondary prevention.

Statin treatment reduces both CRP and LDL-C concentrations (118). The molecular mechanisms of the LDL-C-lowering independent effects of statins involves induction of the transcription factors Krüppel-like factors 2 and 4, and interference with the prenylation of small G proteins (119,120). In LDL-C-lowering trials, those patients achieving below median LDL-C and hsCRP derive the greatest clinical benefit, suggesting that the anti-inflammatory effects of statins contribute to event reduction (121-123). Following ACS, in the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22), trial, patients with a post-statin-treatment CRP below 2 mg/l had a 2.8% yearly rate of MI or coronary death, compared with 3.9% of patients with higher CRP levels ( $p = 0.006$ ). Analyses of the AtoZ trial and IMPROVE-IT trial showed similar patterns (123,124). Although these consistent analyses provide strong evidence that both LDL-C lowering and anti-inflammatory effects of the statins or statins combined with ezetimibe contribute to event reduction post-ACS, they cannot rigorously establish that a direct anti-inflammatory intervention would improve outcomes (26).

Imaging results also support the contribution of lowering inflammation as well as LDL-C to effects on the plaque itself. Intravascular ultrasound studies have shown that CRP reduction with statin therapy predicts plaque regression (125) and acquisition of characteristics of stabilization (126) independently of LDL-C levels. Fluorodeoxyglucose positron emission tomography has supported reduced intraplaque inflammation with statin therapy, although the interpretation of such studies requires caution (127,128). Despite this considerable body of evidence, and evidence from JUPITER regarding primary prevention, European and American guidelines have not yet embraced CRP-guided therapy due to lack of RCTs in the secondary prevention setting.

The CANTOS trial addressed this issue directly. This was the first clinical study to provide formal evidence that intervening on inflammation independently of LDL-C lowering could confer clinical benefit (30). The interleukin-1 $\beta$  inhibitor canakinumab at a dose of 150 mg every 3 months significantly reduced CRP levels (without affecting LDL-C levels) and resulted in a significant 15% lower rate of MACE in patients with prior MI and baseline CRP  $\geq 2$  mg/l. Participants who achieved CRP concentrations of  $< 2$  mg/l after a single dose of canakinumab had a 25% reduction in MACE and a 31% reduction in both cardiovascular and all-cause mortality. These results identify a subset of patients with residual inflammatory risk who respond to canakinumab, and for whom anti-inflammatory therapy may prove particularly clinically effective (129).

Of note, participants in the placebo arm of CANTOS who received excellent GDMT and often revascularization had a 4.5% annual rate of MACE. This event rate illustrates the high residual risk in patients with above-median CRP despite statin therapy with well-controlled LDL-C. For comparison, the yearly MACE rates in the placebo arms of FOURIER and ODYSSEY, which did not select for residual inflammation, were 3.4% and 4.3%, respectively. Beyond “residual cholesterol risk,” these results endorse the existence of “residual inflammatory risk” and demonstrate the efficacy of directing a selective anti-inflammatory treatment to this subpopulation of ACS survivors. These findings point to a path of precision targeting of therapies to address residual risk in secondary prevention. Patients with residual inflammatory risk are not rare. In PROVE-IT and IMPROVE-IT, almost one-third of statin-treated patients had hsCRP  $> 2$  mg/l, about twice the number who have LDL-C  $> 1.75$  mmol (70 mg/dl) (130). Even in patients receiving anti-PCSK9 therapy, hsCRP predicts recurrent events. Moreover, more than one-third of patients meet the eligibility criteria for CANTOS despite achieving very low LDL-C concentrations on statin plus anti-PCSK9 therapy (131,132).

In the CANTOS trial, canakinumab also conferred a remarkable reduction in fatal lung cancer in exploratory analyses (133). There was also a small but statistically significant rise in fatal infection in CANTOS. This finding and the expense of this biological agent require better characterization of its clinical benefit trade-offs and cost-benefit analyses to ascertain the role of canakinumab in clinical practice (134). Nonetheless, the CANTOS findings, when considered in the context of the JUPITER, PROVE-IT, and IMPROVE-IT studies, indicate the potential for benefit of anti-inflammatory interventions in patients

with a persistent inflammatory residual risk, regardless of their LDL-C levels.

A number of other studies investigating colchicine (COLCOT [135], LoDoCo [136], and CLEAR\_SYNERGY [137]) and methotrexate (CIRT [138]) will amplify understanding of the role of anti-inflammatory drugs in the context of post-ACS stable CAD patients.

**ACHIEVING BEST CLINICAL PRACTICE: WHAT IS THE TRUE RESIDUAL RISK?** The concept of residual risk refers to patients who receive optimum GDMT and state-of-the-art revascularization as indicated. Addressing this risk requires several considerations:

1. The implementation of current treatment compliance and lifestyle measures in actual practice environments remains incomplete (139). A Swedish registry reported rates of lipid-lowering therapy and aspirin of 78.2% and 91.4%, which dropped to 73.0% and 82.4% after 2 years from the index event (12). The EUROASPIRE (European Action on Secondary and Primary Prevention by Intervention to Reduce Events) III and IV surveys that evaluated drug compliance in the European CAD population showed similar gaps (140,141). Of note, in both surveys, nearly one-half of the participants who smoked at the time of their coronary event (17.2% and 16.0%) continued to smoke, and only a small minority received counseling regarding evidence-based treatment for smoking cessation (14.3% and 18.4%) (140,142).
2. Clinicians should always aim to achieve the goals recommended by GDMT, as mere drug compliance does not ensure their attainment. In EUROASPIRE III and IV, amongst patients on lipid-lowering therapy, only one-half and one-fifth reached the recommended cholesterol goal, respectively.
3. The value of sometimes modest-appearing absolute risk reductions observed in clinical trials require consideration that magnitude may have far more relevance in daily practice: patients who do not reach GDMT goals due to risk-benefit considerations or drug side effects remain at higher residual hazard. These subsets might derive greater absolute risk reduction of tailored aggressive therapies than participants in highly structured clinical trials. For instance, addressing residual cholesterol risk by aggressive combination lipid-lowering therapy may have particular value in a patient who prematurely stops DAPT because of bleeding. Reducing the residual thrombotic risk by means of long-term DAPT may have special importance in a patient with statin intolerance and low bleeding risk. These conjectures require rigorous validation, but clinical trials seldom

capture such situations, which are commonly encountered in clinical practice.

4. When addressing residual risk from a health care system perspective, cost-effectiveness considerations merit careful concern in formulating the medical management of post-ACS stable CAD patients. In this regard, long-term DAPT yielded intermediate cost-effectiveness value in the overall PEGASUS-TIMI 54 population, with higher value observed in several high-risk subgroups (143). The addition of a nonstatin agent (ezetimibe or PCSK9 inhibitors) in statin-treated patients may prove cost-effective in very-high-risk and high-risk patients only, as estimated by 10-year absolute risk of atherosclerotic cardiovascular disease and depending on baseline LDL-C levels (144). Rivaroxaban plus aspirin may reduce the costs of hospitalization and procedures compared with aspirin as observed in COMPASS (145); moreover, pending formal cost-effectiveness analysis of the trial, initial estimates seem to suggest a high value for this strategy (146). Appropriate adoption of biological agents for this indication should aspire to a personalized approach, perhaps by using selected biomarkers to identify targeted subgroups who will derive the most benefit from these generally expensive therapies (129). Such approaches, yet to be precisely defined for most drugs and strategies, warrant consideration when tailoring prescription to the individual post-ACS stable CAD patient.

## CONCLUSIONS

Despite great strides in ACS secondary prevention over the last decades, this patient group retains a high risk of recurrent atherothrombotic events. Beyond the culprit lesion, accumulating evidence shows that increased risk likely results from a combination of predisposing factors and individual patient characteristics. These recognitions offer an opportunity to improve outcomes in secondary prevention using a personalized, targeted approach.

While conscientious adoption of GDMT provides a sure first step to address residual risk, the tailoring of clinical management to the individual patient pathobiology may provide a path to respond to this challenge. Thus, current evidence-based and GDMT furnishes the foundation to secondary prevention, but we must strive to seek new therapeutic targets and develop and rigorously evaluate new therapies. Indeed, the current recommendations for GDMT afford room to individualize existing treatments: a fine tuning of optimal antithrombotic duration, a PFT-guided approach to antiplatelet therapy,

the best coupling of antiplatelet with anticoagulant drugs with a long-term perspective, more aggressive lipid-lowering based on an “as-low-as-achievable with maximally tolerated therapy LDL-C value” approach, and novel direct anti-inflammatory agents may offer effective strategies to address the known faces of the atherothrombotic residual risk. The recent discovery that clonal hematopoiesis constitutes a potent completely heretofore unrecognized risk factor, independent of traditional factors, shows that we may have much yet to learn regarding pathobiology or residual risk, and raises the exciting perspective of entire new pathways to develop therapies (147).

Decades of research regarding the role of inflammation in the mechanisms leading to ACS have borne fruit by demonstrating clinical benefit of its therapeutic targeting, boding well for the future of anti-inflammatory therapies in the pipeline of atherothrombotic preventive drugs (148).

Despite great advances in our ACS understanding, we still lack pieces of the puzzle. In particular, the specific interplay of the individual predisposing factors to tip the balance of a ruptured plaque toward acute thrombosis remains largely speculative. The role of plaque erosion as a distinct mechanism of plaque disruption and the possibility of tailored preventive therapy following this form of ACS also merits consideration and clinical testing (149-153). The exploration of such possibilities promises to unveil new “faces” of residual risk and provide keys to its conquest.

**ACKNOWLEDGMENT** This paper is dedicated to the memory of Alessandro Gallone.

**ADDRESS FOR CORRESPONDENCE:** Dr. Antonio Colombo, Interventional Cardiovascular Unit, Villa Maria Cecilia Hospital, Via Corriera 1, 48010 Cotignola, Italy. E-mail: [colombo.antonio@hsr.it](mailto:colombo.antonio@hsr.it). Twitter: @SanRaffaeleMI, @BrighamWomens, @azeemlatib.

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**KEY WORDS** atherosclerosis, cholesterol, inflammation, post-MI stable coronary artery disease, residual risk, thrombosis