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Improving the Design of Future PCI Trials for Stable Coronary Artery Disease

Brief title: Design of Future PCI Trials in Stable CAD

Guillaume Marquis-Gravel, MD, MSc,^a David J. Moliterno, MD,^b Darrel P. Francis, MA, MD,^c Peter Jüni, MD, PhD,^d Yves D. Rosenberg, MD, MPH,^e Bimmer E. Claessen, MD, PhD,^f Robert J Mentz, MD,^{a,g} Roxana Mehran, MD,^{f,h} Donald E. Cutlip, MD,ⁱ Cynthia Chauhan, MSW,^j Susan Quella, RN, BSN, OCN,^j Faiez Zannad, MD,^k Shaun G. Goodman, MD, MSc.^l

- a. Duke Clinical Research Institute, Durham, NC, USA
- b. Gill Heart Institute and Division of Cardiovascular Medicine, University of Kentucky, Lexington, Kentucky, USA
- c. Department of Cardiology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom
- d. Department of Medicine and Institute of Health Policy, Management and Evaluation, Applied Health Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
- e. National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA
- f. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA
- g. Department of Population Health Sciences, Duke University School of Medicine, Durham, North Carolina, USA
- h. Clinical Trials Center, Cardiovascular Research Foundation, New York, New York, USA
- i. Baim Institute for Clinical Research, Boston, Massachusetts, USA
- j. Patient-partner, USA
- k. Clinical Investigation Center 1433, French Clinical Research Infrastructure Network, Investigation Network Initiative-Cardiovascular and Renal Clinical Trialists, Centre Hospitalier Regional et Universitaire de Nancy, Vandoeuvre les Nancy, France
- l. Terrence Donnelly Heart Centre, St Michael's Hospital, University of Toronto and Canadian Heart Research Centre, Toronto, Ontario; and Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada

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Address for correspondence: Dr. Shaun G. Goodman, St. Michael's Hospital, Room 6-034 Donnelly Wing, Toronto, Ontario M5B 1W8, Canada. Fax: (416) 864-5407; Phone number: (416) 864-5722; E-mail: shaun.goodman@unityhealth.to

Twitter handle: @G_MarquisGravel

Tweet: Improving the Design of Future #PCI Trials for Stable #CAD: expert and #patient opinions on important methodological considerations #cardiotwitter @CVCTForum

Unstructured abstract

The role of percutaneous coronary interventions (PCI) in addition to medical therapy for patients with stable coronary artery disease (CAD) continues to be debated in routine clinical practice, despite more than two decades of randomized controlled trials. The residual uncertainty arises from particular challenges facing revascularization trials. Which endpoint do doctors care about, and which do patients care about? Which participants should be enrolled? What background medical therapy should we use? When is placebo control relevant? In this manuscript, we discuss how these questions can be approached, and the merits and disadvantages of possible options. Engaging multiple stakeholders, including patients, researchers, regulators, and funders to ensure the design elements are methodologically valid and clinically meaningful should be an aspirational goal in the development of future trials.

Condensed abstract

The role of percutaneous coronary interventions (PCI) in stable coronary artery disease (CAD) continues to be debated, partly because of dispute over which endpoint should be the focus, what trial population is relevant, what background medical therapy should be used, and whether placebo control is needed. In this manuscript, we discuss how these questions can be approached, and the merits and disadvantages of possible options.

Key words

Coronary artery disease, percutaneous coronary intervention, randomized controlled trials, methods

Abbreviations

CAD = coronary artery disease

DAPT = dual antiplatelet therapy

MI = myocardial infarction

PCI = percutaneous coronary intervention

QOL = quality of life

RCT = randomized controlled trial

Coronary artery disease (CAD) is a leading cause of mortality, morbidity, and disability globally.(1) After more than two decades of randomized controlled trials (RCT), there is however no clear consensus regarding whether revascularization should be offered in patients with stable CAD.(2-5) While revascularization techniques and devices have steadily improved, more effective medical therapies have also been developed.(6-11) Collectively, the major contemporary trials defining the current treatment practices in patients with stable CAD suggest that, compared with medical management, percutaneous coronary intervention (PCI): 1) is not associated with improved rates of death and/or total MI; 2) is associated with lower rates of unplanned revascularization and of spontaneous MI; 3) improves health status of symptomatic patients (Table 1).(5,12-20) Despite the lack of clear benefit in terms of mortality or of total MI identified in RCTs, more than 700,000 PCIs were performed in stable patients between 2009 to 2014 in the United States, among whom approximately one-fourth was apparently asymptomatic, a population for which no benefit is expected.(21) This observed mismatch between the evidence and what is actually done in clinical practice highlights the persistent perceived community equipoise regarding the indication for PCI in stable CAD.(2)

The difficulty translating RCT evidence into clinical practice partly results from challenges specific to the conduct of trials in patients with stable CAD. In November 2018, a group of cross-sector stakeholders including representatives from academia, regulators, funding agencies, and patient advocates convened in Washington, D.C., for a workshop during the 15th Global CardioVascular Clinical Trialists Forum, to discuss methodological considerations in the conduct of RCTs evaluating the role of PCI among patients with stable CAD (list of participants available in the Online Appendix). In this manuscript, we present methodological perspectives on clinical trial conduct in this space, with a focus on the choice of patient-oriented study

endpoints, heterogeneity of study populations, concomitant medical therapy, and appropriate control groups (Central Illustration).

Key challenges encountered in previous trials

High proportions of screening failure, slow recruitment, and low event rates have made the conduct of major trials evaluating PCI in stable CAD challenging (Figure 1).(22) These issues may result from the unwillingness of physicians and/or patients to accept clinical equipoise between medical and invasive management of stable CAD, leading to slow recruitment, over-representation of low-risk patients, and underestimation of the effect size of PCI (Figure 2).(23) Trial participants also often tend to have a healthier distribution than the spectrum of patients seen in clinical practice, translating into lower-than-expected event rates.(24) With continuous improvements in the management of concomitant cardiovascular risk factors, sample size calculations based on data generated from previous studies can further lead to overly optimistic event rate estimations during study planning. These issues have often resulted in major protocol amendments. For instance, due to a lower than anticipated event rate, the primary end point of the ISCHEMIA trial (a composite of cardiovascular death or nonfatal MI) was “reverted” to a 5-component composite (expanded to also include hospitalization for unstable angina, hospitalization for heart failure, or resuscitated cardiac arrest) during the course of the trial, in accordance with a pre-specified adaptive design.(22,25) In the BARI 2D trial, a 1.5-year follow-up period extension was required due to slow recruitment.(16)

To address these challenges, pre-trial population characterization of potential sites can be enabled by electronic health records and registries to ensure that only study sites with a high recruitment potential are activated.(26) These technologies can also be leveraged locally to

identify high-risk populations (e.g. high-risk non-invasive ischemic stress test, cardiovascular comorbidities, etc.) based on algorithmic computable phenotypes applied to electronic health records,(27) and automatically compute the number of patients potentially eligible within each center and reasons for exclusion, in order to better understand individual site's approach to participating in the RCT. Also, rigorous adaptive study designs involving pre-specified protocol modifications based on periodic blinded event rate appraisals (adaptive randomization, sample size, and follow-up times), represent a desirable alternative to traditional study protocols that are more reactive in their approach. This has been the object of a recent US Food and Drug Administration guidance document.(28)

Post-trial crossovers also represent a potential challenge in the interpretation of study findings. For example, in the ORBITA trial, participants were unblinded after the study period, and the majority of those randomized to the placebo procedure underwent PCI, contrary to previous trials.(14) In theory, post-trial crossover should not impact the observed effect size and internal validity, but some have argued that this high proportion could be viewed as a failure of medical therapy to be tolerated and/or to control symptoms properly. After unblinding, participants took the decision to undergo PCI based on an informed shared decision-making process with their providers, taking into account the prevailing clinical equipoise at this time, the result of the coronary angiogram, and their personal preferences. For this reason, whether the study results would have been different with a longer follow-up period remains speculative. In future trials, clear documentation of the reasons for post-trial crossover and/or planning follow-up times long enough to reasonably capture crossovers related to treatment failure are mitigation strategies to be considered.

Key methodological considerations in future trials

Endpoint selection

Appropriate endpoint selection represents a critical topic for future RCTs conducted in the stable CAD population. Focusing on health status outcomes such as symptoms, functional status, and QOL has been advocated in a 2013 American Heart Association scientific statement.(29) Some trials have suggested possible improvements of health status with PCI when evaluated as a secondary endpoint, but they were not powered to evaluate these outcomes.(12,14) The recent ISCHEMIA trial was the first trial to evaluate angina-related health status as a key secondary endpoint, using the Seattle Angina Questionnaire summary score.(20)

Learning from past narratives in other therapeutic areas, providers' perspectives on the desirable benefits of therapies are often misaligned with patients' expectations.(30,31) Patients are at the forefront of their own life trajectories, hence the importance of involving a broad representativeness of individuals affected by the condition among the study team early in the design phase of future trials, in order to inform the selection of meaningful, truly patient-oriented endpoints.(32-34) Importance of early patient engagement in RCT development has been put forward in the United States by the Patient-Centered Outcomes Research Institute (PCORI), a funding agency dedicated to support research guided by patients. For their research to be funded, information supporting the patient-centered nature of the study endpoint needs to be provided based on direct patient input (e.g. surveys, meetings, etc.).(35,36) For example, in the first PCORI-funded randomized controlled trial, the ADAPTABLE trial, patient partners were involved in the development of the research question.(37) Similarly, the Canadian Institute of Health Research's Strategy for Patient-Oriented Research offers patient-oriented clinical trial

funding opportunities.(38) As funding agencies continue adopting incentives supporting patient-centeredness of clinical research, patient engagement in protocol development and endpoint selection will gain further momentum in cardiovascular outcomes RCTs. Within this construct, conducting a national or multinational survey should be an urgent priority to inform the choice of endpoints aligned with patients' preferences in future RCTs on stable CAD.

Angina burden, patient satisfaction, QOL, functional status, and treatment side effects, all represent promising potential patient-oriented endpoints to be considered in future PCI trials in stable CAD.(39,40) However, while these endpoints reflect patients' experience of the disease, they are more vulnerable to ascertainment bias compared with more objective clinical outcomes. Selecting an endpoint that is clinically meaningful and patient-centered, and that simultaneously can be measured validly and reliably, demands thoughtful consideration. A major limitation of tools currently employed to evaluate functional status of CAD patients, such as the SAQ, is that they are prone to recall bias and may not capture the day-to-day longitudinal experience of the patient.(41)

Ubiquity of mobile devices now enables the development of novel endpoints derived from data collected continuously in participants daily lives. Longitudinal, real-time endpoint collection can be conducted remotely by the means of mobile health applications as part of "site-less" randomized trials, in which even recruitment can be achieved seamlessly within patients' own living environment.(26) These methods are immune to recall bias, and create efficiencies by allowing participants to be followed remotely without burdensome study visits.(42) Angina can be reported in a digital diary capturing the intensity and temporality of symptoms in real-time, as is being undertaken in the ORBITA-2 trial.(43) Adverse events could also potentially be

monitored through digital diaries, including the nature and frequency of study drug side effects, and causes and time of drug discontinuation.

Biosensors and wearables can also enable seamless collection of digital biomarkers during participants' daily activities, such as activity level, making measurements more responsive to participant's status changes over time.(26,44,45) For example, the NOVA-SKIN study (NCT02591758) is currently developing a novel "vitality index" for patients with chronic angina by the use of a biometric vest worn during participants' daily lives to collect heart rate and activity.(44,45) However, standardization, acceptability, and validity of these novel endpoints generated from real world data need to be established to produce real world evidence,(26,46) and how angina frequency and intensity should be combined into an accepted endpoint remains to be delineated through a multi-stakeholder consensus.

Alternative endpoint modelling strategies to the traditional frequentist approach should also be considered in future trials, such as Bayesian analyses, as has been done in the health status substudy of the ISCHEMIA trial.(20) Bayesian analyses allow to conduct unlimited interim analyses without compromising statistical significance, which could translate into smaller sample sizes, shorter study durations, and globally more efficient study conduct. Bayesian analyses are also well-suited to provide non-binary answers to research questions addressing the continuum of symptom improvement.

Finally, some have argued that incorporating periprocedural MIs as endpoints have little value from a patient's perspective as compared with spontaneous MIs, because patients' experiences of both types of events are markedly different. The latter are diagnosed solely based on biochemical or imaging criteria, do not require the presence of manifest symptoms,(47-49) and have variable impacts on subsequent mortality across heterogeneous definitions.(50-53) In

addition, including periprocedural MIs as a component of the primary endpoint may attenuate the observed magnitude of the treatment effect, as was observed in the ISCHEMIA (based on observation of the crossing Kaplan-Meier curves of spontaneous and periprocedural MIs) and the FAME 2 (based on a landmark analysis at 8 days) trials.(5,12) In these trials, rates of total MIs were similar between both study groups, but directionality of the treatment effect on spontaneous and periprocedural MIs was opposite. If inclusion of periprocedural MI as a component of the primary endpoint is justified solely on the basis of its potential repercussions on future mortality, this practice should be questioned if mortality is already a component of the primary endpoint, as periprocedural MIs that do not subsequently lead to death is of little significance from a patient's perspective. Only once the impact on mortality of the different types of MI have been determined and agreed upon will they be well suited as "surrogate" endpoints.

Trial population

The nature of the conclusions drawn from a trial directly relates to the characterization of the study population, but patients with stable CAD do not represent a homogeneous group in terms of extent of CAD, severity of objective ischemia, amount of affected myocardium, left ventricular function, symptom burden, adherence to medical therapy, and concomitant cardiovascular risk factors. These factors all contribute to define the underlying risks and expected benefits from revascularization. Selecting narrow eligibility criteria results in the constitution of a more homogeneous study sample, yet the findings may only be applicable to a small fraction of the patients encountered in routine clinical practice (Figure 1).(54) Most of the trials evaluating PCI for stable CAD had more than 10 eligibility criteria, attenuating the

applicability of findings to real-world populations, and limiting the facility with which practicing clinicians can apply newly-generated evidence (Table 2).

To streamline the translation of study findings into clinical practice, many have called for transitioning from explanatory studies, designed to detect treatment effects of revascularization in an idealized setting, to more pragmatic studies conducted in a setting as similar as possible to usual practice.(55-58) Explanatory designs remain well-suited for early phase trials aiming to demonstrate a promising treatment effect in a carefully selected population, but pragmatic eligibility criteria representing patients who would normally be considered to receive the treatment in clinical practice are desirable for studies aiming to impact routine clinical care.(56) Engaging clinicians through national surveys, involving patient-partners, and examining data from real-world national registries to inform development of eligibility criteria embracing clinical needs should be considered to further enhance the applicability of study findings.(1,26,59) Despite the initial costs incurred, patient and clinician engagement in the early design phase of trials has been shown to spur recruitment rates, and to be cost-effective in the long term.(60-62)

Harnessing national registries to identify, enroll, and randomize participants, collect baseline characteristics, and capture endpoints through linkage with other data sources (electronic health records, claims data, etc.) has the potential to create efficiencies by “dual-purposing” structured data from pre-existing data sources, while simultaneously improving the external validity of the findings.(26,63) For example, the SWEDEHEART registry was leveraged in multiple trials to enroll the majority of eligible patients presenting to study sites in clinical practice, ensuring the constitution of a study population representative of the patients receiving the intervention in a routine setting.(64,65) Some randomized, registry-based trials

have also been conducted in other countries, including the United States.(66-68) Creation of large, valid, and reliable outpatient registries is however necessary to address the population of patients with stable CAD, as most of them are not treated as inpatients, and would therefore not be enrolled in national registries such as NCDR's CathPCI and Chest Pain MI registries. These registries could be adapted by expanding their inclusion criteria to individuals with CAD followed on an outpatient basis, and to include additional patient-reported endpoints such as health status, similarly to what is being done in NCDR's TVT Registry, which includes Kansas City Cardiomyopathy Questionnaire at follow-up after TAVR.(69) These registries could also be leveraged to conduct registry-based randomized trials, as has been done with the SAFE-PCI trial.(70) An alternative strategy would be to create common data models with standardized data element definitions to facilitate research across health systems exploiting various EHR platforms, such as is currently being done in multiple observational and interventional trials within the PCORnet in the US.(71)

Finally, ensuring genders, racial minorities, and socio-economic classes are well-represented in study populations is necessary to maximize generalizability of study findings to real-life populations. In the most recent PCI trials, women represented only a quarter of study populations, and race/ethnicity were inconsistently reported.(12,14,72) Capping randomization at pre-specified proportions of males and of Caucasian/white, aligning with demographics of the country in which the study is conducted, could be done in future trials.

Background medical therapy

Maximization of, and adherence to, background medical therapies represent other important considerations in the conduct of RCTs for stable CAD. Whether participants should be

treated as much as possible like they would be in routine clinical practice, or conversely with efforts to comply closely with guidelines recommendations, exceeding what is usually done in clinical practice, remains another source of debate due to concerns regarding feasibility, external validity, and ethical acceptability. Excluding participants based on low expected adherence to background therapy and encouraging strict adherence to maximally tolerated co-interventions by all participants maximizes internal consistency and is desirable for participants' health, but potentially creates barriers to the translation of the findings into resource-limited routine clinical practice.(57,58)

In addition to representing a threat to external validity, maximizing adherence in RCTs is logistically challenging on many fronts. Up-titration of concomitant pharmacological therapies requires additional human resources, and participants from different jurisdictions may not have access to the same drugs owing to variability in local regulatory approval delays or reimbursement considerations. Also, optimal medical therapy encompasses a wide array of pharmacological and lifestyle interventions that are challenging to implement, resulting in heterogeneous background therapies used across trials (Table 3). Physical exercise, weight management, smoking cessation, environmental modifications, treatment of concomitant risk factors, and anti-anginal therapies are evidence-based interventions recommended by practice guidelines to improve symptoms and/or outcomes in patients with established CAD,(73-75) but they have not been approached consistently across trials. Prescribing these interventions to study participants is feasible, but intervening actively to address all the recommended lifestyle interventions to comply with standard of care within a multinational clinical trial may be unrealistic, and is not pragmatic. Limiting the number of components included in the definition

of “optimal medical therapy” thus represents a trade-off to improve both feasibility and generalizability, but concerted efforts to ensure consistency across trials is crucial.

Co-interventions, the provision of care other than the randomly allocated interventions as part of routine clinical practice, also have the potential to bias a trial’s results if provided unequally across study groups.⁽⁷⁶⁾ Participants randomized to a placebo group may have more clinically-driven intensification of their anti-anginal treatment compared with those randomized to a potentially effective investigational treatment (for example, PCI), which will in turn results in bias towards the null.⁽⁷⁷⁾ Conversely, in unblinded trials, dual antiplatelet therapy (DAPT) duration among patients randomized to the PCI group will likely be longer than for those randomized to medical therapy. This could result in an overestimation of the treatment effect afforded by PCI, as attempts to decipher the relative role of PCI vs. DAPT are challenging. Careful collection of data on co-interventions at baseline and during follow-up can help understanding the potential extent of performance bias. If changes in co-interventions were minimal after randomization and were similar between groups during the entire course of the trial, then the risk of performance bias is low.⁽⁷⁷⁾ For example, in the ORBITA trial, the investigators documented the use of anti-anginal drugs at each stage, and reported a similar number of anti-anginal drugs at different time-points.⁽¹⁴⁾ In future trials, pre-specified adjusted sensitivity analyses including co-interventions as covariates could be considered to determine whether observed results could be partially explained by potential differences in co-interventions.

Also, the apparent challenge of unequal co-interventions across study groups can be converted into an advantage by incorporating changes in anti-anginal drugs into the primary endpoint. Echoing endpoint modelling approaches adopted in oncology trials, progression-free

survival and time to treatment failure could be considered as novel alternatives in stable CAD trials evaluating medical or invasive management approaches. When adapted to the stable CAD arena, the concept of progression-free survival could be measured as the interval between randomization and either clinically-indicated escalation in anti-anginal medical therapy, anginal symptom progression, drug discontinuation due to side effects, clinically indicated PCI, or death. Although these concepts are not necessarily intertwined, they collectively capture the failure to achieve a proper state of patient's well-being.

Placebo procedures and blinding

Value of blinded placebo-controlled trials for stable CAD

Compared with no intervention, placebo administration improves patient-reported outcomes like angina.(78,79) This effect is inflated with placebo procedures (vs. placebo drugs),(80) and when clinicians' expectations about the treatment effect are high.(81) The power of suggestion in stable angina can be illustrated by the FAME-2 trial experience, in which patients with an FFR >0.80 were not randomized, but were enrolled into a registry. Among those, the proportion with CCS class II-IV angina was decreased by 77% thirty days after patients were told they had no flow-limiting lesion. This finding mirrored a similar observation made a decade earlier in the DEFER trial.(82)

Several case studies exemplify the importance of placebo procedures, sometimes called sham operations, in the evaluation of new treatment strategies for angina. Transmyocardial laser revascularization was previously believed to ameliorate symptoms, improve exercise parameters, and decrease risks of clinical events compared with medical therapy alone.(83-88) Those beliefs were based on consistently positive unblinded RCTs, ultimately leading to the incorporation of

transmyocardial laser revascularization into practice guidelines,(89-91) until two sham-controlled RCTs proved otherwise.(92,93) The authors of one of the latter studies appropriately concluded that “all other clinical trials in this field should be viewed with caution and skepticism, unless proper attention is taken to account for placebo effects of the experimental laser therapies.”(93) Similarly, surgical internal mammary artery ligation was believed to be effective to improve angina based on unblinded experiments,(94) until two sham-controlled studies demonstrated the absence of clinical benefit.(95,96) While proper randomization with an unpredictable and concealed allocation sequence ensures similarity of patient characteristics and management at trial baseline, blinding of participants and study personnel is required to achieve similar patient management after the trial begins. Even apparently hard events adjudicated by a blinded endpoint committee, such as hospitalization for revascularization, are susceptible to the impact of unblinding, because blinding of the adjudication committee cannot retrospectively inject blinding into decisions that were made by unblinded individuals. Since the importance of placebo controls is well-established in trials of pharmacologic interventions, placebo-controlled trials of invasive procedures are desirable to obtain unbiased estimates of symptomatic effect size, as long as ethical standards are respected and patient safety remains at the center of the investigator’s concerns.

Feasibility of placebo-controlled trials for stable CAD

Implementation of invasive placebo procedures requires considerable additional efforts compared with unblinded trials of the same sample size. Two contemporary RCTs have demonstrated the feasibility of placebo-controlled trials in patients with stable CAD: the Coronary Sinus Reducer for Treatment of Refractory Angina (COSIRA),(97) and the ORBITA

trials.(14) In the COSIRA trial, 104 participants with refractory angina were randomized to coronary sinus reducing device implantation or to placebo procedure.(97) Participants were offered either conscious sedation or headsets during the procedure to maintain blinding. All underwent percutaneous coronary sinus angiography through a 6-French diagnostic catheter, but only those randomized to the treatment arm received a coronary sinus reducing device. The operators spent a similar amount of procedural time regardless of the treatment assignment. Mean CCS class improved significantly in both groups at six months, and 42% of those in the placebo control group improved their functional class, capturing the apparent placebo effect of the procedure, the natural evolution of the disease, and/or regression to the mean. The proportion of participants who improved their CCS class by ≥ 2 levels (primary endpoint) was however significantly higher among those in the treatment group (35% vs. 15%; $p=0.02$), suggesting that device implantation led to symptom improvement beyond the placebo effect.(97)

The ORBITA study was the first placebo-controlled randomized trial to assess the efficacy of PCI in patients with stable ischemic heart disease. Among 200 participants with angina and single-vessel disease suitable for PCI, 105 were randomized to PCI, and 95 to a placebo procedure. All patients were sedated and wore headphones playing music during the procedure. Additional efforts were taken to ensure all staff members not directly involved in the procedure were unaware of the treatment assignment. The primary endpoint of exercise time improved similarly at 6 weeks in both groups. The ongoing SHam-controlled INtErvention to Improve QOL in CTOs (SHINE-CTO) trial (NCT02784418), ORBITA-2 (NCT03742050) and Clinical Efficacy of Permanent Internal Mammary Artery Occlusion in Stable Coronary Artery Disease (NCT03710070) trials will provide further insights regarding the feasibility of sham-controlled designs for PCI trials.

Ethical considerations

There are certain ethical issues to be considered when planning trials involving placebo procedures. First, participants must accept that the risks conferred by a placebo procedure may extend beyond minimal risk. Among the 95 participants randomized to the placebo control arm in ORBITA, four required a PCI to mitigate complications related to the pressure-wire, and one experienced a periprocedural major bleeding event. No participant died because of a procedure-related complication, but clearly none of these complications would have occurred if participants did not undergo a placebo procedure. In the COSIRA trial, no serious periprocedural adverse events were reported in the placebo-control group. In both trials, the additional risk conferred by the placebo procedure extended beyond the procedural period itself, because all participants were prescribed continued DAPT to maintain blinding, leading to additional bleeding risks. Two participants randomized to a placebo procedure experienced a major bleeding event while on DAPT in ORBITA. Obtaining an unbiased assessment of treatment effect requires participants, investigators, and regulators to accept the potential risk of placebo procedure-related irreversible events as a trade-off to provide unbiased assessment of treatment effect. While placebo PCI procedures are associated with additional risks in comparison with no placebo, these risks are not disproportionate, are not higher than the investigational strategy currently used in clinical practice (i.e. PCI), and are carefully explained to patients before signing the informed consent. Also, if safety issues with placebo procedures are of concerns, independent data safety monitoring committees have the power to recommend stopping the trial.

The second major ethical consideration is that patients should only be enrolled into a placebo-controlled trial with a proper understanding that they may undergo either the real

intervention or a placebo intervention, and with an explanation of why this is being done. In one of the trials confirming the absence of treatment effect with surgical IMA ligation conducted in the 1950's, participants were not informed of the randomized placebo-controlled nature of the experiment.(95) They were all told that they would receive a promising intervention described in an “enthusiastic report published in the Reader’s Digest” by an investigator displaying a “reasonably optimistic attitude” about the treatment, despite the ongoing clinical equipoise.(95) All participants underwent surgical IMA isolation, but only those randomized to the treatment group actually underwent IMA ligation. Although this trial would be considered unethical by today’s standards, adherence to Good Clinical Practices requires a sustained commitment from investigators to ensure participants’ understanding of the implications of trial participation. Clinicians must take special precautions to ensure that no potentially overstated expectations are transmitted to participants.

Conclusion

Despite decades of RCTs, the role of revascularization in the treatment of stable CAD remains uncertain, related in part to operational challenges specific to the conduct of trials in this heterogeneous patient population. Methodologic considerations encompassing proper selection of endpoints and study populations, background medical therapy, and utilization of placebo procedures, need to be carefully crafted in rigorous adaptive designs according to the specific goals of the study (Table 4). The focus should now be on the development of novel, patient-oriented, technology-enabled endpoints. A shift to simpler, more pragmatic trials, as well as expanding and leveraging existing national registries to conduct registry-based randomized trials, should be advocated to catalyze the translation of study findings into daily clinical practice.

Engaging multiple stakeholders, including patients, researchers, regulators, and funders to ensure the design elements are methodologically valid and clinically meaningful should be an aspirational goal in the development of future trials.

Bullet points

- The role of revascularization for patients with stable coronary artery disease continues to be debated.
- This uncertainty partly results from methodologic challenges when conducting trials in this heterogeneous population.
- Multiple design elements can be optimized in future trials to facilitate translation into clinical practice.

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Figure legends

Figure 1

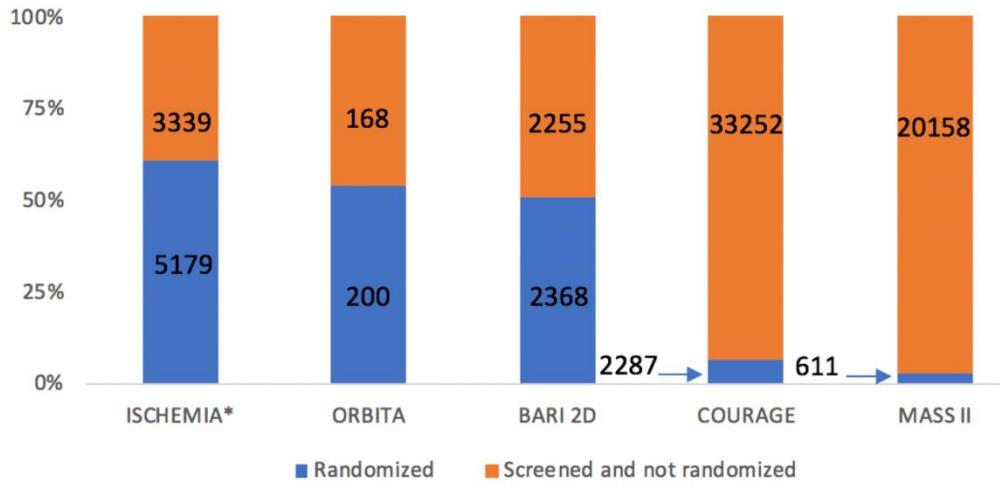


Figure 1. Enrollment rates in major randomized controlled trials of PCI in stable CAD. High proportions of screening failure and slow recruitment have made the conduct of major trials evaluating PCI in stable CAD challenging.

CAD = coronary artery disease; PCI = percutaneous coronary intervention.

**The number of patients screened in ISCHEMIA is not available. The number presented in the orange box represents the patients enrolled but not randomized.*

Figure 2 a

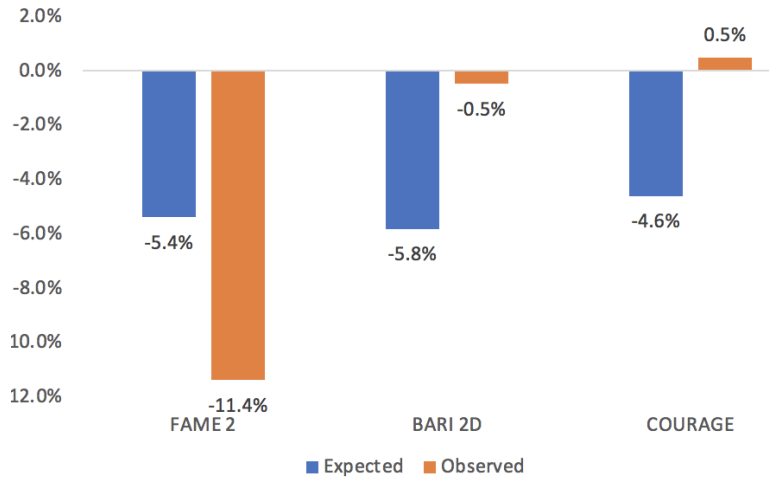


Figure 2 b

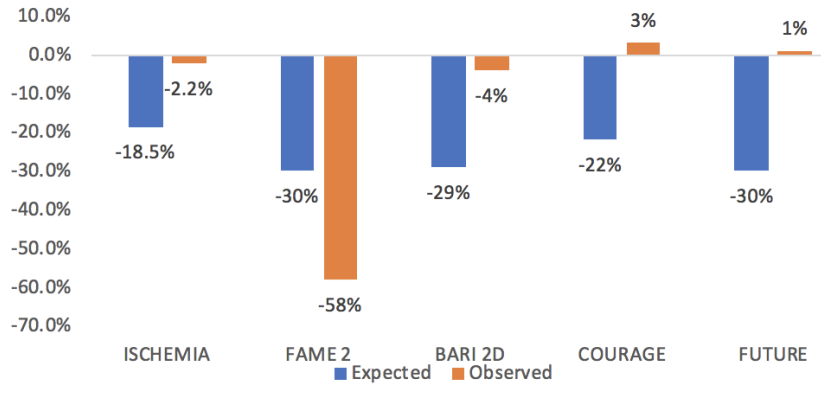
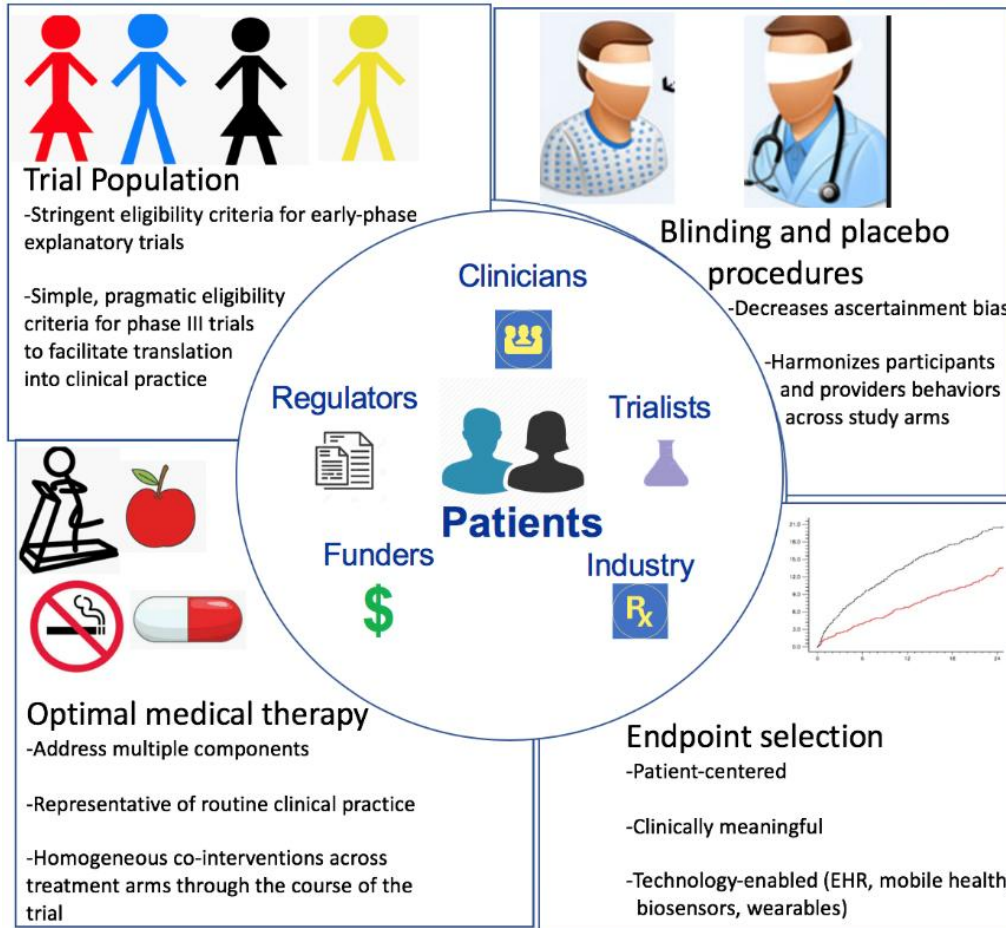


Figure 2. Expected and observed a) absolute, and b) relative effect size of PCI vs. medical therapy for the primary endpoint of major randomized controlled trials of PCI in stable CAD. In most randomized controlled trials evaluating the role of PCI for the treatment of CAD, the absolute and relative magnitudes of the treatment effect were lower than expected at the time of sample size calculation. This may partly result from over-representation of low-risk participants in the trials, or of evolving optimal medical therapy.

PCI = percutaneous coronary intervention.

Central illustration



Central Illustration. Optimizing the design of percutaneous coronary intervention randomized controlled trials in stable coronary artery disease. Methodological considerations encompassing proper participant selection, optimal background medical therapy, utilization of blinding and of placebo procedure controls, and selection of clinically meaningful and patient-oriented endpoints, need to be carefully crafted according to the specific goals of the study.

EHR = electronic health record.

Table 1. Summary of major randomized trials evaluating the role of percutaneous coronary intervention versus medical therapy in stable coronary artery disease.

| Trials | Year | Sample size | Patients | Study groups | Primary endpoint | Key secondary endpoints |
|---------------|-------------|--------------------|--|---|---|---|
| ISCHEMIA(5) | 2019 | 5179 | Stable ischemic heart disease; moderate/severe ischemia on clinically indicated stress imaging or severe ischemia on non-imaging ETT | Cardiac catheterization and optimal revascularization + medical therapy (invasive strategy) vs. medical therapy alone (conservative strategy) | <u>CV death, MI, hospitalization for unstable angina, heart failure or resuscitated cardiac arrest</u> Adjusted HR= 0.93 (95% CI: 0.80, 1.08; p=0.34) | <u>CV death or MI</u> Difference in restricted mean time free from endpoint: 9.4 days longer in the invasive strategy group (95% CI: -16.5, 35.2) |
| ORBITA (14) | 2018 | 200 | Angina or equivalent symptom and ≥ 1 lesion appropriate for PCI | PCI vs. placebo procedure | <u>Exercise time improvement at 6 weeks</u> PCI minus sham procedure: 16.6 s (95% CI: -8.9 to 42.0 s; | <u>SAQ angina frequency at 6 weeks</u> PCI minus sham procedure: 3.5 points (95% CI: -2.6 to 9.6 points; |

| | | | | | | |
|--------------|------|------|---|---|---|--|
| | | | | | p=0.200) | p=0.260) |
| FAME-2 (12) | 2012 | 1220 | Stable CAD and ≥ 1 lesion with FFR ≤ 0.80 | FFR-guided PCI vs. medical therapy | <u>Composite of death, MI, or urgent revascularization</u> PCI: 4.3% Medical therapy: 12.7% (HR: 0.32; 95% CI: 0.19 to 0.53; p<0.001) | <u>Urgent revascularization</u> PCI: 1.6% Medical therapy: 11.1% (HR: 0.13; 95% CI: 0.06 to 0.30; p<0.001) |
| BARI 2D (98) | 2009 | 2368 | Type 2 diabetes and CAD | Revascularization (randomization stratified by PCI vs. CABG) or medical therapy | <u>Death from any cause</u> PCI: 10.8% at 5 years Medical therapy: 10.2% at 5 years p=0.48 | <u>Composite of death, MI, or stroke</u> PCI: 21.1% at 5 years Medical therapy: 23% at 5 years p=0.15 |
| JSAP (99) | 2008 | 384 | Low-risk stable CAD | PCI vs. medical therapy | <u>All-cause death</u> PCI: 2.9% Medical therapy: | <u>ACS</u> PCI: 5.0% Medical therapy: |

| | | | | | | |
|---------------|------|------|------------|-------------------------|--|---|
| | | | | | <p>3.9% (HR: 0.865; 95% CI: 0.278 to 2.604; p=0.794)</p> | <p>11.7% (HR: 0.384; 95% CI: 0.168 to 0.802; p=0.012)</p> <p><u>Emergency hospitalization</u></p> <p>PCI: 20.6% Medical therapy: 31.6% (HR: 0.658; 95% CI: 0.435–0.983; p=0.042)</p> |
| COURAGE (100) | 2007 | 2287 | Stable CAD | PCI vs. medical therapy | <p><u>Death from any cause of nonfatal MI</u></p> <p>PCI: 19.0% at 4.6 years Medical therapy: 18.5% at 4.6 years (HR: 1.05; 95% CI: 0.87 to 1.27;</p> | <p><u>Revascularization at 4.6 years</u></p> <p>PCI: 21.1% Medical therapy: 32.6% (HR: 0.60; 95% CI: 0.51–0.71; p<0.001)</p> |

| | | | | | | |
|--------------------------|------|-----|--|---|--|---|
| | | | | | P=0.62) | |
| MASS-II (101) | 2004 | 611 | Proximal multivessel CAD and documented ischemia | Revascularization vs. medical therapy | <u>Cardiac mortality, MI, or refractory angina requiring revascularization at one year</u> PCI: 50 events CABG: 13 events Medical therapy: 29 events P<0.001 | <u>Revascularization</u> PCI: 13.3% CABG: 0.5% Medical therapy: 8.3% P=0.000015 <u>Freedom from angina at one year</u> PCI: 52% CABG: 59% Medical therapy: 36% P=0.001 for PCI vs. medical therapy |
| Hambrecht et al. (17) | 2004 | 101 | Stable CAD and 1 <i>de novo</i> coronary stenosis | PCI vs. exercise training | <u>Ischemic event at one year:</u> PCI: 30% Exercise training: | <u>Physical work capacity at one year</u> PCI: from 130±5 |

| | | | | | | |
|-------------|------|-----|---|--|--|--|
| | | | | | 12% (OR: 0.33; 95% CI: 0.12 to 0.90; p=0.023) | to 130±5 W Exercise training: from 133±5 to 159±5 W P<0.001 |
| DEFER (15) | 2001 | 325 | Referred for PTCA of <i>de novo</i> lesion with FFR >0.75 | PTCA vs. deferral | <u>Composite of all- cause mortality, MI, CABG, coronary angioplasty, procedure complication at 24 months</u> PTCA: 17% Deferral: 11% (95% CI of absolute difference: - 15.7% to 4.6%; p=0.27) | <u>Freedom from angina at 24 months</u> PTCA: 51% Deferral: 70% P=0.02 |
| AVERT (102) | 1999 | 341 | Stable CAD with asymptomatic | PCI vs. atorvastatin 80 mg daily alone | <u>Ischemic events at 18 months</u> PCI: 37% | <u>Worsening angina with objective</u> |

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| | | | or mild-to-moderate angina and LDL \geq 115mg/dL | | Atorvastatin: 13% P=0.048 | <u>evidence of myocardial ischemia resulting in hospitalization</u> PCI: 14.1% Atorvastatin: 6.7% P-value N/A |
|--|--|--|--|--|------------------------------|---|

CABG = coronary artery bypass graft; CAD = coronary artery disease; CI = confidence interval; ETT = exercise tolerance test; FFR = fractional flow reserve; HR = hazards ratio; LDL = low density lipoprotein; MI: myocardial infarction; OR = odds ratio; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; SAQ = Seattle Angina Questionnaire.

Table 2. Patient selection in major trials of percutaneous coronary intervention for stable coronary artery disease.

| Trials | Number of inclusion criteria | Number of exclusion criteria | Key cardiovascular high-risk exclusion criteria | Presence of angina and/or degree of objective ischemia |
|---------------------|-------------------------------------|-------------------------------------|---|--|
| ISCHEMIA (22,25) | 3 | 28 | <ul style="list-style-type: none"> -Left main stenosis $\geq 50\%$ -Coronary anatomy unsuitable for revascularization -LVEF $< 35\%$ -NYHA class III-IV at entry, or hospitalization for chronic HF within 6 months -Previous CABG* | <p>No angina in the past month: 20.1%</p> <p>Never had angina: 10.3%</p> <p>No ischemia on stress imaging: 5.8%</p> <p>Mild ischemia: 8.1%</p> <p>Moderate ischemia: 41.0%</p> <p>Severe ischemia: 44.8%</p> |
| ORBITA (14) | 2 | 14 | <ul style="list-style-type: none"> -Angiographic stenosis $\geq 50\%$ in non-target vessel -Left main disease -heavily calcified or tortuous vessel -CTO in target vessel -Known severe LV systolic | <p>No angina:</p> <p>5/200 (3%) at enrolment</p> <p>22/200 (11%) pre-randomization following run-in period</p> |

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| | | | impairment -Severe valvular disease -Previous CABG | |
| FUTURE (103) | 5 | 4 | -Previous CABG | N/A |
| FAME-2 (12) | 4 | 15 | -Left main disease requiring revascularization -Extremely tortuous or calcified coronary arteries -LVEF <30% -Previous CABG | No angina: 99/887 (11%) Silent ischemia: 16% |
| BARI 2D (98) | 3 | 17 | -Left main stenosis $\geq 50\%$ -Planned revascularization of a graft -NYHA class III or IV -Previous CABG within 12 months | Not reported. Presence of symptoms was not required to qualify for study. |
| JSAP (99) | 3 | 9 | -3-vessel disease -Left main or ostial LAD disease -CTO -Culprit lesion in a graft -LVEF <50% | No angina: 45/384 (11.7%) |

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| COURAGE (100) | 4 (including 16 sub- criteria) | 11 | -Left main stenosis $\geq 50\%$ and no prior CABG -Coronary anatomy unsuitable for PCI -In-stent restenosis -LVEF $< 30\%$ ($< 35\%$ if 3- vessel disease including $> 70\%$ proximal LAD stenosis) -CABG within 6 months | No angina: 283/2287 (12%) No reversible defects on nuclear imaging: 13% in the PCI group; 9% in the medical therapy group (among those who underwent testing) |
| MASS II (101) | 3 | 12 | -Left main stenosis $\geq 50\%$ -Congenital or valvular heart disease -LVEF $< 40\%$ -Previous CABG | Not available |
| Hambrecht et al. (17) | 4 | 9 | -Left main stenosis $> 25\%$ or high-grade proximal LAD stenosis -LVEF $< 40\%$ -Significant valvular disease -Previous CABG within 12 months | All patients were symptomatic. |

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| DEFER (15) | 2 | 4 | -Total occlusion of the target artery | All patients were symptomatic. |
| AVERT (102) | 7 | 11 | -Left main disease -3-vessel disease -LVEF <40% -NYHA class III or IV -Previous CABG | Asymptomatic: 16.4% |

PCI = percutaneous coronary intervention

* Unless CABG was performed more than 12 months ago and coronary anatomy has been demonstrated to be suitable for PCI or CABG to accomplish complete revascularization of ischemic areas.

Table 3. Optimal medical therapy recommended in major PCI trials for stable coronary artery disease

| | Anti-ischemic therapy | Concomitant CV risk factors | Lifestyle interventions | Antiplatelets |
|---------------|---|--|--|-------------------------|
| ISCHEMIA (22) | Algorithm incorporating beta-blockers, long-acting nitrates, calcium channel blockers, ivabradine, nicorandil, trimetazidine, and a risk factor management team provided to investigators | Highest-tolerated dose of high-intensity statin; evolocumab or ezetimibe if LDL treatment goals not met with statin; algorithm for treatment of hypertension incorporating ACEi/ARB, beta-blockers, calcium channel blockers, and diuretics; aim for systolic BP <130 mmHg; aim for HbA1c <8%, and specific weight | Smoking cessation, >30 minutes of moderate intensity exercise >5 times/week, and <7% of total calories from saturated fats | Aspirin 75-162 mg daily |

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| | | loss goals | | |
| ORBITA (14) | ≥2 anti-anginal drugs up-titrated during a 6-week run-in phase (1-3 telephone consultations per week; equipment provided for measurements of pulse and blood pressure) | Atorvastatin ≥40 mg daily | None | Aspirin 75 mg and clopidogrel 75 mg daily |
| FAME-2 (12) | Metoprolol 50 to 200 mg daily (or other β-1-selective blocker), alone or in combination with a calcium-channel blocker or a long-acting nitrate) | Lisinopril ≥5 mg daily, or another ACEi/ARB if not tolerated; atorvastatin 20 to 80 mg daily (or another statin with or without ezetimibe) targeting LDL <70 mg/dL | Smoking cessation counseling, reference to a specialist in diabetes for participants with diabetes. | Aspirin 81 to 325 mg daily and clopidogrel 75 mg daily |
| BARI 2D | β-blocker with target | Therapy to reach | Counseling for smoking | Aspirin 325 mg |

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| (98,104,105) | heart rate <60 beats per minute | blood pressure target of \leq 130/80 mmHg; lipid management and hypertension according to standardized treatment algorithms; glycated hemoglobin <7.0%; ACEi if tolerated | cessation, weight management, and regular exercise; feedback on risk factor control by clinical management centers; distribution of the BARI 2D Lifestyle Handbook | daily |
| JSAP (99) | Evidence-based antianginals recommended to the treating physician | Evidence-based drugs recommended to the treating physician | None | N/A |
| COURAGE (13) | Long-acting metoprolol, amlodipine, and/or isosorbide mononitrate | Lisinopril or losartan; aggressive therapy to reach target levels of LDL, | None | Aspirin 81 to 325 mg daily |

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| | | HDL, and triglycerides | | |
| MASS II (101) | “Stepped-care approach” for nitrates, β -blockers, calcium channel blockers | ACEi, Statins | Low-fat diet on an individual basis | Aspirin (dose unspecified) |
| Hambrecht et al. (17) | Current clinical guidelines therapy. | Current clinical guidelines therapy. | None | Current clinical guidelines therapy. |

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CV = cardiovascular; HDL = high density lipoprotein; LDL = low density lipoprotein.

Table 4. Proposed strategies to enhance the design of future randomized controlled trials evaluating percutaneous coronary interventions for stable coronary artery disease.

| Strategies | Strength | Challenges | Future perspectives on implementation |
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| Endpoint selection | | | |
| Favor patient-oriented primary endpoints and analytical methods | <p>-Ensures endpoints are aligned with patients' treatment expectations;</p> <p>-Alternative statistical methods to traditional time-to-first event analysis, such as time to treatment failure or total number of events, may be more reflective of patients' experience.</p> | <p>-Patients' perspectives are heterogeneous, and no single endpoint can fully capture their preference.</p> | <p>-Surveying patients regarding their endpoint preferences encompassing a broad representativeness of the disease spectrum and of demographic characteristics.</p> <p>-Actively involving patient-partners in protocol development and in leadership committees within the trial.</p> |
| Develop novel endpoints leveraging technologies (mobile devices, wearables, etc.) | <p>-Collecting endpoint data continuously in participants daily lives is immune the recall bias.</p> <p>-Creates efficiencies by allowing participants to</p> | <p>-Standardization, acceptability, and validity of novel endpoints generated from devices need to be established to produce real world evidence.</p> | <p>-Pilot studies are required to evaluate feasibility, validity, and relevancy of technology-enabled novel patient-centered endpoints.</p> |

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| | be followed remotely without costly and burdensome study visits. | -Inherently excludes participants with low technological literacy; -Requires technical team to address device technical failure or required software updates. | |
| Trial population | | | |
| Favor broad eligibility criteria | -RCT findings readily applicable to routine clinical practice | -Heterogeneity of treatment effect not accounted for -Lower internal consistency | -Engaging patients and clinicians can help informing the development of eligibility criteria truly embracing clinical needs. |
| Harness national registries and/or EHR systems to identify participants | -Permits to identify a large number of potentially eligible participants in a short time frame -Allows to characterize a population representing the whole spectrum of the disease. | -Large national outpatient registries suitable for outpatients with stable CAD trials are lacking. -Standardized definitions of medical vocabulary and inter-operability of EHR systems across institutions are required to permit data aggregation. | -Standardization of data element definitions across EHR systems allowing to apply computable phenotypes queries to characterize trial patient populations is currently done within the US PCORnet.(27,71) This initiative could be expanded and/or emulated. |
| Implement | -Maximizes | -The demographic spectrum | -Capping randomization at a pre |

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| <p>mechanisms to include women and minorities</p> | <p>generalizability of study findings to real-life populations;</p> <p>-Potential to identify heterogeneous treatment effects across subgroups.</p> | <p>of the disease is variable across sites, regions, and countries.</p> | <p>specified proportions of males and Caucasian/white individuals aligning with demographics of the country in which the study is conducted should be considered.</p> |
| <p>Background medical therapy</p> | | | |
| <p>Prescribe DAPT for the same amount of time in all treatment arms</p> | <p>-Allows to disentangle the treatment effect of PCI vs. DAPT by isolating the effect of PCI.</p> | <p>-Exposes participants to excess bleeding risk if DAPT is not clinically indicated.</p> | <p>-Ensuring participants are informed of the potential additional risk of DAPT.</p> |
| <p>Minimize changes in pharmacological co-interventions across study arms during the course of the trial</p> | <p>-Mitigates the performance bias resulting from unequal, unplanned modifications of secondary prevention drugs (statins, anti-diabetic drugs, etc.) across study arms after randomization.</p> | <p>-Unethical to forbid clinically indicated modifications of secondary prevention drugs.</p> | <p>-Collecting data on co-interventions throughout follow-up to understand the extent of performance bias.</p> <p>-Pre-specifying sensitivity analyses with statistical adjustments for co-interventions if differences across study arms exceed an <i>a priori</i> determined threshold.</p> |

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| <p>Ensure participants are treated as similarly as possible to routine clinical practice with concomitant pharmacological and lifestyle interventions</p> | <p>-Maximizes applicability of study findings to real-life patients; -Avoids logistically demanding efforts to maximize adherence to concomitant medical therapy, over what is done in routine clinical practice.</p> | <p>-Heterogeneous adherence to maximally tolerated anti-anginal drugs and to concomitant cardiovascular risk management strategies may decrease internal consistency.</p> | <p>-Establishing a multi-stakeholder consensus (investigators, clinicians, patients, IRBs, regulators, funding agencies) on a standardized approach to background medical therapy in PCI trials for stable CAD.</p> |
|--|---|---|---|

Placebo procedures and blinding

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| <p>Use blinded placebo procedures</p> | <p>-Eliminates the placebo effect component of PCIs from the evaluation of treatment effect; -Eliminates biased interpretation of symptoms.</p> | <p>-Invasive placebo procedures might expose participants to additional risks deemed unacceptable; -Logistically demanding; -More costly than unblinded trials.</p> | <p>-Placebo procedures to be considered in all PCI trials for stable CAD, as long as ethical standards are respected, participant safety remains at the center of the investigator's concerns, and expectations are not overstated to participants.</p> |
|--|---|---|---|

CAD = coronary artery disease; DAPT = dual antiplatelet therapy; EHR = electronic health record; PCI = percutaneous coronary intervention; RCT = randomized controlled trial.