Expanding revascularization trials to women and underserved minorities and shifting to patient-centered outcomes: RECHARGE trials program

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Purpose of review
We review the limited available evidence informing coronary revascularization decisions in women and minorities, and introduce the RECHARGE trial program, which consists of two separate but integrated parallel multicenter, randomized trials comparing coronary artery bypass grafting (CABG) to percutaneous coronary intervention (PCI), one exclusively enrolling women (RECHARGE:Women) and one exclusively enrolling Black or Hispanic patients (RECHARGE:Minorities).

Recent findings
The extensive evidence base supporting coronary revascularization suffers from under-representation of women, minorities and minoritized populations, and the use of heterogeneous primary composite outcomes whose components have varying strengths of association with prognosis and quality-of-life (QOL). In RECHARGE, participants will be followed for up to 10 years, with QOL assessments at baseline, 30 days, 3 months, every 6 months for 3 years, and annually thereafter. The primary endpoint is the hierarchical composite of time to all-cause mortality, time-averaged change from baseline in the physical component of the SF-12v2 physical summary score, and time-averaged change from baseline in the mental component of the SF12v2 summary score, evaluated using a win ratio. Independently adjudicated major adverse cardiovascular and noncardiovascular events and disease-specific QoL will be secondary endpoints.

Summary
The RECHARGE trials are the first revascularization trials to enroll exclusively women and minority patients and to use patient-centered outcomes as their primary outcome.

Keywords
coronary artery bypass grafting, minorities, percutaneous coronary intervention, quality of life, women

INTRODUCTION

For more than three decades randomized controlled trials (RCTs) have compared coronary arterial bypass grafting (CABG) to percutaneous coronary intervention (PCI) for coronary revascularization. These trials have predominantly enrolled White men, and most have shown that survival is similar after CABG and PCI, but have demonstrated lower procedural risks and faster recovery after PCI with lower risks of late myocardial infarction (MI), coronary reinterventions and slightly better disease-specific quality of life (QoL) after CABG [1–3]. Current clinical practice guidelines acknowledge the tradeoff between short- and long-term risks of adverse events after CABG versus PCI and highlight that the choice of revascularization method should be based on shared decision making to align treatment with patients' goals [4,5]. However, the prior studies that informed the guidelines are limited in that the data is predominantly from White men, and the extent to which nonlethal cardiovascular events, such as the need for a repeat coronary revascularization,

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KEY POINTS

- Women and especially minority patients have been underrepresented in prior coronary revascularization trials comparing coronary artery bypass grafting to percutaneous coronary intervention.
- Previous revascularization trials have focused on the time to the first occurrence of a composite outcome combining death and nonlethal adverse events, the latter having uncertain relevance to patient prognosis and quality of life (QoL).
- The two integrated RECHARGE trials (RECHARGE: Women and RECHARGE:Minorities) are the first revascularization trials to use a patient-centered endpoint as their primary outcome, and the first to enroll exclusively women and Black or Hispanic patients.
- Patients will be followed-up with QoL assessments at baseline, 1, 3, 6, 12, 18, 24, 30, and 36 months, and thereafter yearly for up to 10 years.
- The primary endpoint of both trials is the hierarchical composite outcome time to death, time-averaged changes from baseline in the physical and mental components of the SF-12 at 5 years, assessed when the last patient reaches 3 years postrandomization, evaluated using the win ratio method.

were included and drove the primary composite outcomes may not reflect patients' concerns in terms of the impact of the treatment on their QoL and other patient-centered outcomes.

To generate contemporary data to better inform patients' choice between revascularization modalities, the REvascularization CHoices Among under-Represented Groups Evaluation (RECHARGE) trials were designed to build on prior studies by studying exclusively women and minority patients for which data are scarce; and focusing on survival and QoL, the outcomes that matter most to patients, rather than the risk of nonlethal adverse events that may or may not affect prognosis and QoL.

SEX DISPARITY AND LACK OF DIVERSITY IN CORONARY ARTERIAL BYPASS GRAFTING VERSUS PERCUTANEOUS CORONARY INTERVENTION TRIALS

Women have represented fewer than 25% of patients enrolled in prior trials comparing CABG versus PCI for coronary artery revascularization (Table 1). This sex disparity is potentially important since there are known sex differences in the outcomes after both CABG and PCI. Outcomes after CABG are reportedly worse in women than men. A meta-analysis from 84 observational CABG studies including 903 346 patients (24.8% women) reported that women were at significantly higher risk of both peri-operative and late mortality, MI, stroke and major adverse cardiac or cerebrovascular events (MACCE) than men [6]. An individual patient data meta-analysis (IPDMA) of the 4 largest CABG RCTs including 13 193 patients (20.6% women) confirmed that women had higher risks of MACCE, MI and repeat revascularization at 5 years [7]. A meta-analysis of QoL after CABG of 14 randomized trials and 13 595 participants (22% women) from 15 countries found that women had significantly less QoL improvement at 1 year than men [8▪]. Multiple studies have also reported sex differences in outcomes after PCI.[9–11] The most extensive, patient-level comparison of clinical outcomes by sex after PCI with drug-eluting stents pooled data from 21 RCTs and 32 877 patients (27.8% women). Women had higher 5-year rates of the composite outcome of cardiac death, MI, or ischemia-driven target lesion revascularization (TLR), including higher rates of all-cause death compared with men [9]. Arguably, a case is made for equipoise regarding preferred revascularization strategies for women.

Table 1. Proportion of patients enrolled in prior trials who were women or minorities

Trial name	Women	
	PCI	CABG
FREEDOM [10]	26.8%	30.5%
PRECOMBAT [11]	24%	23%
SYNTAX [12]	23.6%	21.1%
BEST [13]	30.6%	26.5%
EXCEL [14]	23.8%	22.5%
ERACI II [15]	22.7%	18.6%
VA CARDS [16]	1%	1%
NOBLE [17]	20%	24%
FAME-3 [18]	18.6%	16.7%

BEST, The Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease; CABG, coronary artery bypass grafting; ERACI, Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease; EXCEL, Evaluation of XIENCE Everolimus Eluting Stent versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FAME, Fractional Flow Reserve versus Angiography for Multivessel Evaluation; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; NOBLE, Coronary Artery Bypass Grafting versus Drug Eluting Stent Percutaneous Coronary Angioplasty in the Treatment of Unprotected Left Main Stenosis; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease; SYNTAX, Synergy between PCI with Taxus and Cardiac Surgery; VA CARDS, Percutaneous Coronary Intervention Versus Coronary Bypass Surgery in United States Veterans With Diabetes.

The representation of non-White patients in past revascularization trials is even lower than that of women. None of the trials listed in Table 1 reported on the proportion of Black and Hispanic patients in their primary publication [10–18]. In a pooled analysis of the EXCEL, NOBLE, SYNTAX, and PRECOMBAT trials, in which data on race and ethnicity was available for 3206/4396 (72.9%), disappointingly only 2.3% of the participants were Black and 1.4% Hispanic [2]. While 34.5% of FREEDOM trial participants were Hispanic, only 2.7% were non-Hispanic Blacks [19].

Outcomes after CABG have been reported to be worse in Black and Hispanic patients compared with White patients. A meta-analysis of 28 studies and 4 million patients found a higher risk of operative mortality after CABG in Black (5.4% of treated patients) compared with White patients [20]. Another study of over 1 million patients from the Society of Thoracic Surgery (STS) database found that Black patients (7.8% of those treated) undergoing CABG had a higher risk of mortality, sepsis, and postoperative stroke than White patients [21]. Although data on race-specific outcomes after PCI are limited, a large IPDMA of 22 638 patients enrolled in 10 PCI RCTs has been done, in which 20 585 (90.9%) patients were White, 918 (4.1%) were Black, and 473 (2.1%) were Hispanic. Black and Hispanic patients had worse PCI results despite having less extensive CAD. After multivariable adjustment, Black race was independently associated with worse outcomes after PCI [22]. Once again, the case is made for equipoise regarding best revascularization strategies for minorities with coronary artery disease.

The worse prognosis in women and minorities compared with men likely extends beyond differences in anatomical and clinical characteristics to also include healthcare access and the impact of adverse Social Determinants of Health (SDOH). Consequently, the relative benefits of CABG and PCI derived from even landmark predicate studies with nonrepresentative cohorts cannot necessarily be translated to women and under-represented minority patients with coronary artery disease.

LIMITATIONS OF CONVENTIONAL OUTCOMES AND METHODS OF ANALYSES IN CORONARY ARTERIAL BYPASS GRAFTING VERSUS PERCUTANEOUS CORONARY INTERVENTION TRIALS

Primary endpoints of coronary revascularization trials have conventionally been composite endpoints (e.g., MACCE) composed of death and nonlethal cardiovascular adverse events such as MI, stroke and repeat revascularization, evaluated using time-to-first event analyses [23]. While both CABG and PCI aim to reduce the risk of MI and the need for repeat revascularization, a MI event is generally more severe than a revascularization, and the pathophysiological mechanisms and clinical context in which these events occur vary considerably between CABG and PCI [24▪▪]. Moreover, not all events within a single category have a similar effect on prognosis. For example, a stent thrombosis or acute graft occlusion causing a large ST-elevation myocardial infarction is very different from a MI caused by a subtotal occlusion of a small branch, or a type-2 MI from oxygen supply-demand mismatch causing modest biomarker elevations. Procedural MIs, which have proven difficult to define after both CABG and PCI, are common events of uncertain clinical significance when defined using current criteria [24▪▪]. Less clinically impactful events such as repeat revascularizations and small MIs, which may not result in significant impairment in patients' QoL, tend to be more frequent than death and large MIs, thus dominating conventional composite endpoints with the least clinically important events [25]. The principal conclusions drawn from a trial greatly depend on which endpoints are included in the primary composite outcome [14,17].

Conventional MACCE endpoints also ignore noncardiovascular events that may be affected by the intervention, such as postprocedural renal failure, procedural bleeding complications and later bleeding events related to concomitant therapies and arrhythmias, as well as depression, impaired ability to engage in social activities or return to work, fatigue, etc. [26].

All major trials comparing CABG to PCI to date have used time-to-first-event analyses to assess their primary composite endpoint [10–17]. Although earlier events may be more likely to be causally linked to the revascularization procedure itself rather than concomitant disease processes, conventional time to first event analyses consider all events in a composite equal, and prioritize nonlethal events that occur earlier during follow up over deaths that occur later [23]. The burden of late events may well be under-recognized in extant databases addressing revascularization for coronary artery disease.

THE RECHARGE TRIAL DESIGN

The RECHARGE trial program consists of two separate but integrated parallel trials, one exclusively enrolling women (RECHARGE:Women, NCT06399692) and one exclusively enrolling Black or Hispanic patients (RECHARGE:Minorities,

NCT06399705). Women who are also Black or Hispanic will be included in both trials to maximize efficiency. The two trials are each multicenter, 1 : 1 randomized, open-label superiority trials. The key eligibility criterion is left main or multivessel disease for which the local Heart Team has equipoise for revascularization with either CABG or PCI. There are no exclusion criteria based on extent of coronary disease, diabetes or ventricular function. Participants will be followed for up to 10 years. Telephone follow-up will be conducted by the follow-up coordinating center at frequent intervals for the entire duration of the study (Fig. 1). The primary outcome in both RECHARGE:Women and RECHARGE: minorities will be a hierarchical composite endpoint combining all-cause death and time-averaged QoL through 5 years, measured when the last enrolled patient reaches 3-year follow-up.

NEW HIERARCHICAL PATIENT-CENTERED PRIMARY OUTCOME

The hierarchical patient-centered primary outcome introduced in RECHARGE addresses major concerns as voiced by patients: how long and how well they live. Because mortality rates are relatively low after contemporary coronary revascularization, it is not possible to adequately power a clinical trial exclusively for all-cause mortality [10–17]. Fortunately, with increasing recognition of the importance of QoL to patients, robust generic and disease-specific QoL questionnaires have been developed and validated [27].

Traditionally, QoL as a continuous metric has been difficult to incorporate alongside mortality in a conventional composite endpoint. The win ratio (WR) analytical method overcomes this challenge and allows for QoL to be hierarchically incorporated with mortality (and other outcomes if desired) within a single composite endpoint [23,28]. In RECHARGE, the primary endpoint is the hierarchical composite of time to all-cause mortality, time-averaged change from baseline in the physical SF-12v2 physical component score (PCS), and time-averaged change from baseline in the mental SF12v2 component score (MCS); evaluated using the WR (Table 2). The change from baseline will be time-averaged to accurately reflect the impact on patient well being (with the QoL assessment weighted according to the length of the time-interval between its preceding and succeeding assessments). Thus, by combining mortality and QoL, the RECHARGE trial primary endpoint will reflect both the quantity, as well as the quality, of life after revascularization – the outcomes most important to patients.

With the WR method, every patient in the PCI arm will be compared with every patient in the CABG arm. For every pairwise comparison, one will compare the two patients for the longest common follow-up duration. First, one assesses which of the two patients died first, where the longer survivor 'wins'. If neither patient died (a 'tie'), then one assesses whether the pair differs in their change over time from baseline in SF-12v2 PCS by $\geq$5 points (a one-half standard deviation of the cross-sectional distribution). If they do, then the patient with the

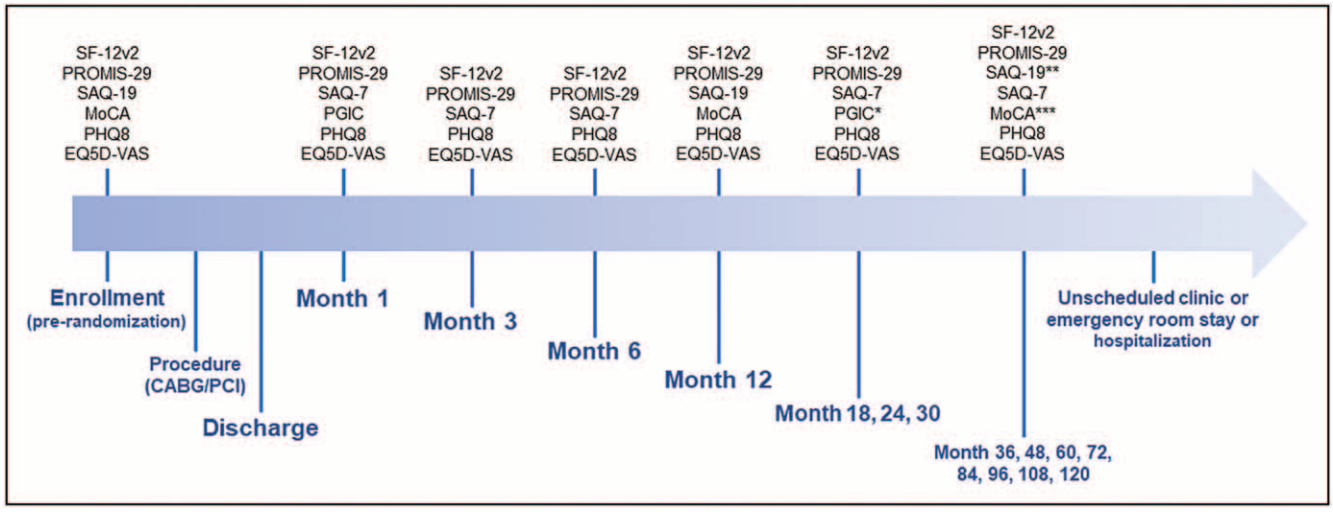

FIGURE 1. QoL follow-up in RECHARGE. At each follow-up visit, QoL will be assessed using several different generic and disease-specific QoL questionnaires. All follow-up assessments are performed by a blinded, independent follow-up unit not participating in trial enrollment. EQ5D-VAS, EuroQol 5 Dimension - Visual Analogue Scale; MoCA, Montreal Cognitive Assessment; PGIC, Patient's Global Impression of Change; PHQ8, Patient Health Questionnaire 8 items; PROMIS-29, Patient-Reported Outcomes Measurement Information System 29 items; SAQ-7, Seattle Angina Questionnaire 7 items; SAQ-19, Seattle Angina Questionnaire 19 items; SF-12v2, Short form 12 item health survey version 2.

Table 2. General principle behind the win ratio

Comparison of each potential patient pair (e.g., 1 from CABG group and 1 from PCI group) over the course of their common follow-up time	Assessment
Step 1.	
If one or both patients die:	
Patient in PCI group dies first	CABG wins
Patient in CABG group dies first	PCI wins
Both patients die on the same date	Go to step 2
If neither of the patients die	Go to step 2
Step 2. If no ranking yet available:	
The mean time-averaged change in the physical component of SF-12v2 is at least 5 points greater for the patient in the CABG versus PCI group	CABG wins
The mean time-averaged change in the physical component of SF-12v2 is at least 5 points greater for the patient in the PCI versus CABG group	PCI wins
The mean time-averaged change in the physical component of SF-12v2 for the patients in the PCI and CABG groups is less than 5 points	Go to step 3
Step 3. If no ranking yet available:	
The mean time-averaged change in the mental component of SF-12v2 is at least 5 points greater for the patient in the CABG versus PCI group	CABG wins
The mean time-averaged change in the mental component of SF-12v2 is at least 5 points greater for the patient in the PCI versus CABG group	PCI wins
The mean time-averaged change in the mental component of SF-12v2 for the patients in the PCI and CABG groups is less than 5 points	Tie

CABG, coronary arterial bypass grafting; PCI, percutaneous coronary intervention; SF-12, Short form 12 items.

greater improvement 'wins'. If the difference between the patients in the change from baseline in SF-12v2 PCS is <5 points, then one assesses whether the pair differs in their change over time from baseline in SF-12v2 MCS by ≥5 points. If the difference between the patients in the change from baseline in SF-12v2 MCS is also <5 points, then the patients tie and no winner is assigned for that pairwise comparison. When all possible patient pairs have been assessed, the sum of the wins in the CABG group divided by the sum of the wins in the PCI group is the WR.

The interpretation of the WR, as it pertains to the primary endpoint in RECHARGE, is as follows: if any two patients are compared, one from the CABG group and one from the PCI group, and they are not a tie, then the WR represents the odds that the patient in the CABG group has a more favorable outcome. The probability that the patient from the CABG group has a more favorable outcome is WR/(WR+1). The win difference, which accounts also for tied comparisons, is the % of all decisions that are 'wins' for CABG minus the % of all decisions that are 'wins' for PCI, representing an absolute measure of benefit. For example, if in a trial 45% of the pairwise comparisons favor CABG and 36% favor PCI (with 26% ties), then the win ratio is 1.25 and the win difference is 8%, in favor of CABG (Fig. 2). Conversely, if 12.5% of the pairwise comparisons favor CABG and 10% favor PCI, then the win ratio is also 1.25, but the win difference is smaller at 2.5%.

TARGETING INFORMED INDIVIDUALIZED DECISIONS BASED ON EXPECTED DIFFERENCES IN QUALITY OF LIFE AND PROGNOSIS OVER TIME

The frequent QoL assessments over the course of 5 years for the primary endpoint and 10 years for the longest duration of follow-up in the RECHARGE trials should allow the investigators to determine with considerable detail the expected effects of CABG versus PCI on early, intermediate and late QoL. This information could help patients make informed personalized decisions about their care, depending on their life expectancy and personal circumstances. In addition, ~20 discrete adverse cardiovascular and noncardiovascular events will be collected and adjudicated, some traditional (e.g. MACCE and its components) and others that are less often reported (e.g. arrhythmias, heart failure, renal failure, hospitalizations for any cause, etc.). In addition, disease-specific QoL will be measured throughout the study using the Seattle Angina

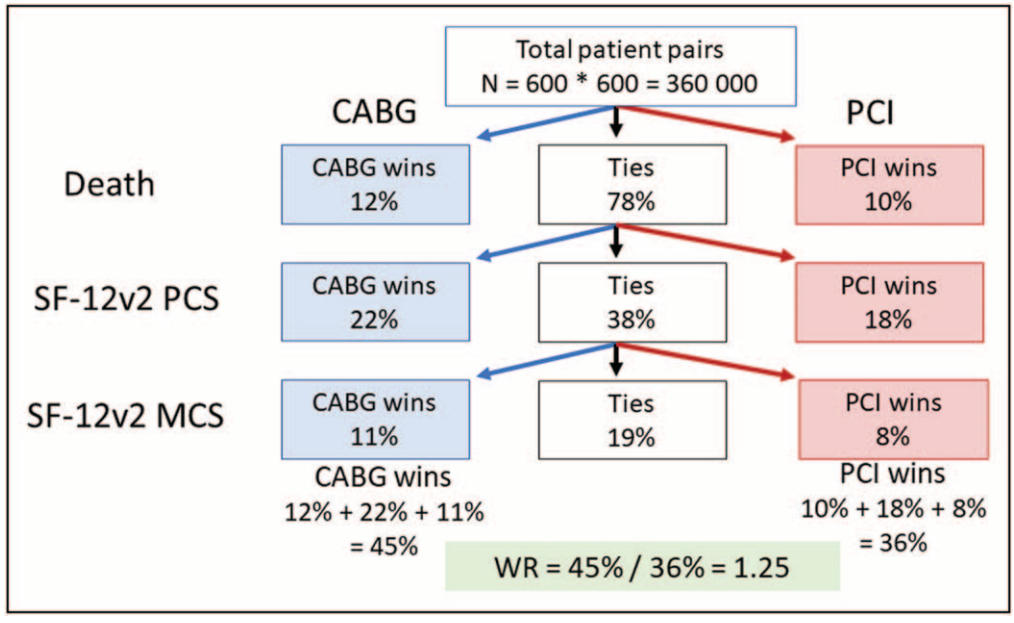

FIGURE 2. Example of the distribution of wins and losses in a hypothetical trial. All patients in the CABG group are compared to all patients in the PCI in a pairwise manner. If in a hypothetical trial a total of 45% of these comparisons results in a win for the CABG patient and 36% result in a win for the PCI patient, then the win ratio is 1.25. CABG, coronary artery bypass grafting; QoL, quality of life; PCI, percutaneous coronary intervention; SF-12v2 MCS, SF-12 Short form 12 items mental component summary; SF-12v2 PCS, SF-12 Short form 12 items physical component summary.

Questionnaire. An Advanced QoL Metrics and Methodology Development Task Force, assembled prior to study initiation to ensure collection of relevant data, will develop sophisticated models for determining both average and individual treatment effects, using state-of-the-art statistical and machine learning techniques, and the relationship between these outcome events and survival and improvement in QoL outcomes [29].

POTENTIAL LIMITATIONS OF THE RECHARGE TRIALS

The RECHARGE trial design has some potential limitations. First, since mortality is expected to be relatively low after contemporary CABG and PCI, the results of the primary endpoint analysis may be driven predominantly by changes in QoL. However, due to declining mortality rate in modern cardiovascular medicine, QoL is arguably the most important outcome. Because of the distinct nature of the two revascularization procedures, it is not possible to blind patients or treating physicians to their treatment assignment. However, since both randomized arms will undergo a revascularization procedure a placebo-like effect would be expected in both arms, and any placebo-like effects may diminish during the course of the relatively long follow-up. Importantly, a recent meta-analysis found no evidence for a difference in the estimated treatment effect of trials with and without blinded patients, or outcome assessors [30]. Nevertheless, as an added quality control, QoL in the RECHARGE trials will be ascertained by an independent QoL follow-up unit blinded to treatment assignment. The wisdom of excluding potentially life-threatening major adverse events such as MI may be questioned. However, as previously discussed, not all strokes or MIs affect prognosis or impact QoL similarly [31]. Thus, large procedural MIs that affect left ventricular function, functional capacity and thus QoL will be represented in the primary endpoint measure whereas small 'biochemical' infarcts with minimal or no clinical relevance (despite having been included in the MACCE outcomes of prior studies) will likely not affect the RECHARGE primary endpoint. The extensive collection of these traditional events, however, will still be done in RECHARGE to support additional insights and to compare with prior trials. Lastly, the choice of primary endpoint in RECHARGE may be criticized because a postoperative reduction in short-term QoL is known to occur after surgery that could disfavor CABG in the primary analysis. However, as QoL changes are time-averaged and the RECHARGE primary follow-up duration is for a minimum of 3 years, the contribution of a change in QoL limited to the first few months to the overall QoL estimate will be marginal.

CONCLUSION

The two integrated trials within the RECHARGE trial program are novel as they are the first to enroll exclusively women and previously under-represented minority patients and to have its primary outcome be so directly aligned with patients' priorities. With frequent QoL assessments over up to 10 years, these trials aim to inform physicians and especially patients who undergo coronary revascularization about their expected short-term, intermediate-term, and long-term QoL and prognosis after CABG versus PCI. The findings should lead to much more informative shared decision-making discussions.

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Conflicts of interest

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