Opportunities for enhancing the care of older patients with ST-elevation myocardial infarction presenting for primary percutaneous coronary intervention: Rationale and design of the SAFE-STEMI for Seniors trial

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Abstract Advanced age is directly related to worse outcomes following ST-elevation myocardial infarction (STEMI) and higher complication rates from antithrombotic therapies and primary percutaneous coronary intervention (PCI). Often excluded from clinical trials, seniors presenting with STEMI remain an understudied population despite contributing to 140,000 hospital admissions annually. The SAFE-STEMI for Seniors study is a prospective, multicenter, unblinded, randomized clinical trial designed to examine the efficacy and safety of instantaneous wave-free ratio–guided complete revascularization in multivessel disease, while also investigating other components of STEMI care for patients ≥60 years including the efficacy and safety of zotarolimus-eluting stents for primary PCI and transradial PCI with the Glidesheath Slender and TR band. The SAFE-STEMI trial represents North America's first and only prospective randomized investigational device exemption study to use a Coordinated Registry Network infrastructure with collaborative partnering across industry manufacturers, promoting both efficiency and reduced cost of evidence development for regulatory decisions related to both diagnostic and therapeutic technologies in a single study design. The study has been powered to evaluate 2 independent co-primary end points in a population of older patients with STEMI: (1) third-generation drug-eluting stents for primary PCI and (2) instantaneous wave-free ratio–guided complete revascularization versus infarct-related artery–only revascularization. (Am Heart J 2019;218:84-91.)

Ischemic heart disease remains one of the leading causes of mortality in the United States, with ST-elevation myocardial infarction (STEMI) accounting for roughly 115,000 deaths annually.[1] Advances in STEMI diagnosis and treatment include improved antithrombotic therapy and accelerated access to primary percutaneous coronary intervention (PCI). More than 60% of STEMI presentations occur in patients at least 65 years of age, and over a quarter of STEMI cases occur in patients 75 years or older.[2-3] In older patients,[4] multivessel disease, comorbidities, and adverse outcomes are common, including higher complication rates after primary PCI and concomitant antithrombotic therapies.[5-6] Despite these increased risks, older patients are underrepresented in STEMI clinical trials. The SAFE-STEMI for Seniors trial is a prospective, multicenter, unblinded, randomized clinical trial designed to simultaneously examine 3 components of STEMI care for patients ≥60 years. Operationally, this trial represents North America's first and only prospective randomized investigational device exemption (IDE) study to use a Coordinated Registry Network infrastructure as a demonstration program for the National Evaluation System for health Technologies (NEST).[7]

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New-generation drug-eluting stents in STEMI

Amid stent thrombosis concerns which initially limited use of drug-eluting stents (DESs) for primary PCI, the HORIZONS-AMI study showed superior effectiveness of paclitaxel-eluting stents compared to bare metal platforms with acceptable safety,[8] supporting an FDA approval for Taxus DES for STEMI. Subsequent-generation DESs, including durable biocompatible polymer zotarolimus-eluting stents (ZESs), are safer than paclitaxel-eluting stents in the STEMI population,[9] yet there is no current-generation DES approved for STEMI in the United States. The SAFE-STEMI for Seniors trial will evaluate the Medtronic Resolute ZES family of DESs, including the currently used Onyx, in a population of older patients with STEMI.

Multivessel intervention during primary PCI

Initial observational data examining the outcomes of patients with STEMI who undergo treatment of the infarct-related artery (IRA)–only versus multivessel PCI suggested that patients who underwent multivessel PCI during the index procedure had significantly higher in-hospital mortality.[10] This limited evidence established the foundation for clinical practice guidelines. The randomized Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial, however, demonstrated that complete revascularization at the time of primary PCI was significantly reduced ischemic outcomes at 23 months compared with IRA-alone PCI.[11] In an independent randomized cohort, the CvLPRIT study showed a 65% reduction in the 1-year end point of all-cause death, recurrent myocardial infarction (MI), heart failure, and ischemia-driven revascularization among STEMI patients who underwent complete revascularization.[12] Subsequent meta-regression evidence suggests that staged PCI and complete revascularization provide a mortality advantage over PCI of the IRA alone, particularly in the setting of 3-vessel disease.[13] The recently published results of the COMPLETE trial demonstrated that complete revascularization was superior to culprit-only revascularization in patients with STEMI and multivessel disease in terms of reducing the risk of cardiovascular death or MI.[14] Evaluations of immediate versus staged revascularization after STEMI have had heterogeneous outcomes, with systematic overviews reaching contradictory conclusions.[13,15] Because angiography at the time of STEMI diagnosis may overestimate nonculprit lesion severity,[16] intraprocedural physiologic measurements may help identify important non–infarct-related targets for complete revascularization.[17]

The SAFE-STEMI for Seniors trial will evaluate the safety and efficacy of complete revascularization versus IRA-only PCI with modern antithrombotic therapy in the more vulnerable population of older patients. The use of instantaneous wave-free ratio (iFR) is intended to promote an objective, generalizable, nonprovocative methodology to identify lesions appropriate for PCI in the STEMI setting.

Transradial primary PCI in older patients

Several non–North American clinical trials have demonstrated a clinical benefit for transradial access over transfemoral access in the subset of patients with STEMI. In the RadIal Vs femorAL access for coronary intervention (RIVAL) trial, there was clinical benefit demonstrated for transradial access in the prespecified group of STEMI patients.[18] A subanalysis of RIVAL showed a significant association of transradial access with lower rates of major access site complications in patients ≥75 years.[19] Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS), a multicenter randomized control trial at 4 Italian centers, demonstrated a mortality benefit in the group of STEMI patients treated via transradial access.[20] Finally, the MATRIX study was a European randomized control trial which reported a reduction in net adverse cardiovascular events in STEMI patients with radial primary PCI but did not demonstrate a mortality benefit.[21] Whether the results of these trials generalize to older patients remains uncertain. The SAFE-STEMI for Seniors trial will primarily evaluate the safety of transradial access in older, North American STEMI patients by examining the rates of failed access and acute and 30-day radial artery occlusion (RAO).

Sheath size is an important indicator of access-site related complications after transradial procedures. In a randomized trial of 171 patients undergoing transradial PCI with a 5F versus a 6F guiding catheter, procedural success was obtained in 95.4% of 5F versus 92.9% of 6F patients.[22] Additionally, 1.1% of 5F versus 5.9% of 6F patients ($P = .05$) experienced radial artery occlusion postprocedurally. Achieving patent hemostasis after transradial catheterization is also one of key factors affecting RAO. SAFE-STEMI for Seniors will evaluate both the Terumo Glidesheath Slender and TR Band in this population of older patients.

Coordinated registry network–based randomized trials supporting regulatory decisions: device study designs in the 21st century

In 2014, Rao et al reported the prospective, randomized registry-based SAFE PCI for Women study.[23] Funded in part by the NIH National Cardiovascular Research Infrastructure, the objective was a pragmatic design to preserve scientific quality while significantly reducing workload at the site level and trial costs by around 30%. SAFE PCI for Women partnered the Duke Clinical Research Institute with the National Cardiovascular

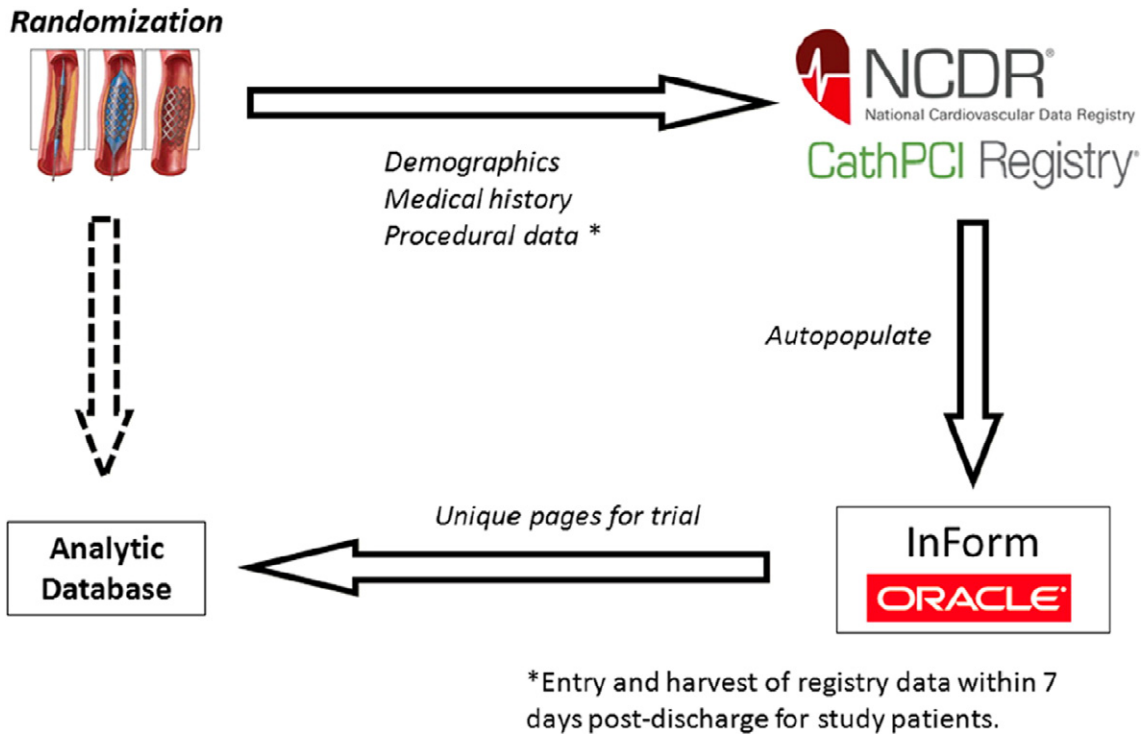
Data Registry (NCDR)'s CathPCI Registry to leverage existing registry work flow to autopopulate the randomized study case report forms (Fig. 1). The CathPCI Registry is the largest registry of PCI records in the world and includes >1,500 US sites and >5 million patient records.[24] In the SAFE PCI study, this registry-based approach reduced the site coordinator workload by nearly 60% per patient and encouraged a brisk rate of enrollment.

From the use of this model for public health studies like SAFE PCI, interest has recently been extended to models of more efficient prospective regulatory science for device evaluation. Linking complementary real-world electronic data systems as coordinated registry networks is the operational core of this NEST.[7] The SAFE STEMI for Seniors study design is a NEST Coordinating Center program intended to demonstrate the use of NCDR CathPCI Registry data for the index procedure/hospitalization, linked to long-term follow-up event ascertainment of death, MI, stroke, rehospitalization, and repeat revascularization, identified through national claims billing data. Central to this approach will be the validation of parallel event ascertainment through billing data as compared to long-term events captured through more traditional clinical trial methodologies in the same patients. The data element definitions used in this trial are designed to be compatible with the NCDR CathPCI Registry and therefore maximize the interoperability between the case report form and quality registry data structures.

Study objectives

The SAFE-STEMI for Seniors study is a prospective, multicenter, unblinded, randomized clinical trial to simultaneously address 3 aspects of STEMI care and 2 regulatory device evaluations in patients at least 60 years old. Primary clinical objectives with primary PCI in older patients include failed access and radial artery occlusion rates, clinical outcomes with third-generation ZESs, and outcomes of iFR-guided complete revascularization versus IRA only. Vascular outcomes will be correlated with the use of thinner Glidesheath Slender and TR band devices (Terumo). Two co-primary end points of Resolute DES outcomes (Medtronic) and iFR diagnostic guidewire use (Volcano/Philips) have been developed through IDE dialogue with the US FDA to support labeling extensions for STEMI. The primary end point for evaluating ZESs for radial PCI in STEMI is 1-year infarct-related artery *major adverse cardiovascular events*, which are defined in HORIZON as cardiac death, index infarct-vessel MI, or ischemia-driven index infarct-related vessel

Figure 1



The coordinated registry network model used in the SAFE-PCI for Women trial.

revascularization. The primary end point for examining iFR-guided complete revascularization versus infarct-only revascularization is 1-year modified *CvLPRIT MACE,*[12] defined as all-cause mortality, recurrent MI, heart failure (requiring hospitalization or a 12-hour emergency room visit), or ischemia-driven revascularization.

Methods

Study population

There will be a total study cohort of 875 patients older than 60 years presenting with STEMI or left bundle-branch block on an electrocardiogram (ECG) with chest pain ≤12 hours who undergo primary PCI. Patients will be enrolled at approximately 70 centers in the United States and Canada. STEMI and left bundle-branch block have been defined by previously established criteria.[25]

Eligibility criteria

Eligibility criteria are listed in Table I. Patients age 60 years or older with significant STEMI or LBBB on ECG and chest pain <12 hours with an accessible right or left radial artery conduit for PCI are eligible to provide informed consent to participate in the study. Key exclusion criteria included patients with known conditions that would prevent the recommended medical treatment after a DES (including dual antiplatelet therapy), stroke, or transient ischemic attack within the prior 6 months or conditions that would prevent radial artery access. Patients providing informed consent are actually enrolled in the trial at the time that angiography defines coronary anatomy amenable to primary PCI.

Patients who meet the above eligibility criteria and have angiographic multivessel CAD are eligible for randomization to iFR-guided revascularization versus IRA-only unless they (1) have developed shock requiring pressors or mechanical circulatory assist support, (2) have unprotected left main coronary artery disease, or (3) had 1 or more epicardial territories with chronic total occlusion.

Site selection

Sites will be selected primarily from the SAFE site network, which includes sites with experienced radial operators who have demonstrated the ability to randomize subjects for clinical investigations, such as in the SAFE-PCI for Women trials. This network includes approximately 60 US sites and selected Canadian sites.

Enrollment and randomization

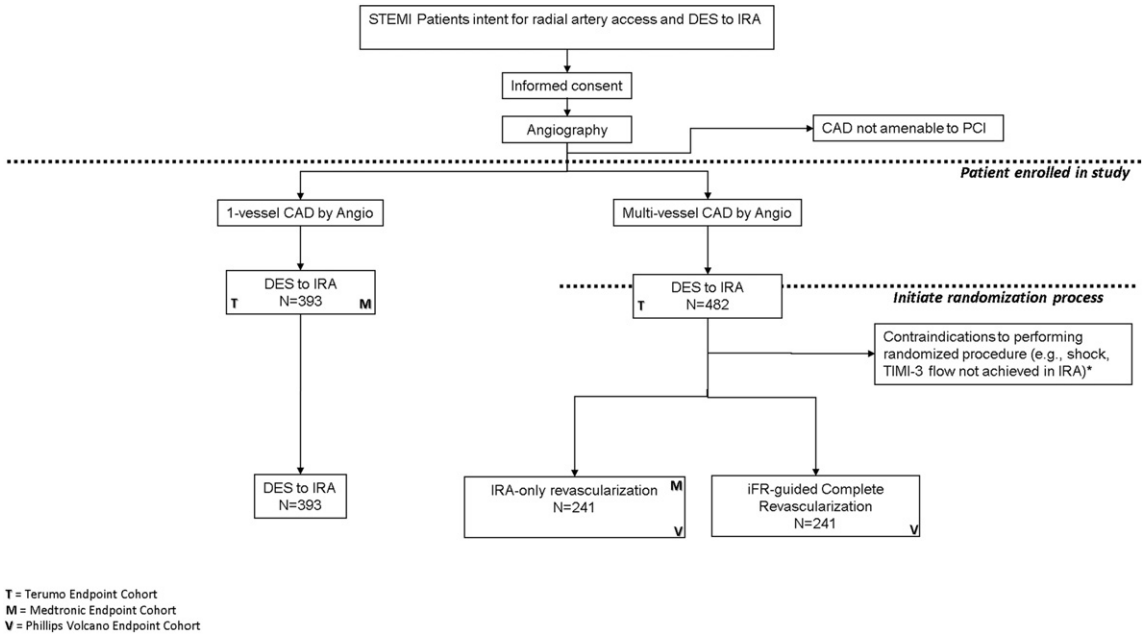
If a patient meets all of the general inclusion and exclusion criteria (Table I), he/she will be enrolled into the study. Figure 2 depicts the study design and treatment schema. If the patient is DES-eligible and has 1-vessel disease by angiography, the patient will receive a ZES in the IRA. If a patient has an angiographic stenosis of >50% in a noninfarct artery, the patient will be randomized at the time of the primary PCI procedure so long as the inclusion and exclusion criteria for randomization to the complete revascularization versus IRA-only inclusion criteria are met (Table I). These patients will be randomized by site in a 1:1 ratio to an iFR-guided complete revascularization versus IRA-only strategy. The site investigator may choose to treat iFR-guided patients in a staged approach as long as the additional procedure(s) is performed during the index hospitalization. Per protocol, all index interventions will be performed with ZESs.

In patients randomized to iFR-guided complete revascularization, any stenosis with a >50% diameter reduction by angiographic estimation and reference vessel diameter ≥2.25 mm in the noninfarct artery will be evaluated using iFR. iFR of <0.90 will be considered a physiologic indication appropriate for PCI. If the iFR measurement cannot be evaluated because of rhythm or pressure artifacts, revascularization should be performed if the angiographic estimation of the stenosis is ≥70% reduction in diameter. Otherwise, medical management will be pursued. Figure 3 demonstrates the procedure flow for iFR-guided complete revascularization.

Table I. Eligibility criteria

Inclusion criteria
Age ≥65 y at the time of signing informed consent and/or randomization
Presentation with STEMI or LBBB on ECG with chest pain ≤12 h
Right or left radial artery accessible for PCI
Capacity to understand and sign informed consent OR have a legally authorized representative that can understand and sign consent
Physician Intent to perform transradial PCI
Willing to be contacted at 1 y by the study staff
Complete revascularization vs IRA-only inclusion criteria (must meet all of the above inclusion criteria)
Eligible for DES implantation
Angiographic multivessel CAD determined by local visual estimation
Exclusion
Known medical conditions that would prevent or interrupt the recommended postprocedure DES treatment regimen
Known medical condition that would prevent cardiac catheterization through the radial artery
Known medical condition that would increase the patient's risk if iFR used
Cerebrovascular accident or transient ischemic attack within the past 6 m
Known history of substance abuse which may result in noncompliance with the protocol
Condition with associated life expectancy <1 y
Participation in another clinical study using an investigational agent or device within the last 3 m
Complete revascularization vs IRA-only exclusion criteria (in addition to exclusion criteria listed above)
Shock requiring vasopressors or mechanical circulatory assist support
Significant chronic renal disease (eGFR <30) and/or dialysis
Single-vessel CAD
Unprotected left main CAD
One or more major coronary distributions with CTO or indeterminate IRA
Previous CABG and territory with dual supply (eg, supply from both a native vessel and a patent vein graft)
Clinical circumstances which prevent randomization

Figure 2



Study design and treatment schema.

Medical therapy before, during, and after PCI

All patients will be preloaded with 81-325 mg aspirin as well as with an approved adenosine diphosphate receptor antagonist or a glycoprotein IIb/IIIa receptor antagonist prior to PCI. Drug and dose selection, including for anticoagulation, is left to the discretion of the site investigator and determined prior to randomization in patients with multivessel disease. Per protocol, dual antiplatelet therapy will be maintained for 1 year if tolerated. The use of additional guideline-directed medical therapy before and after PCI, including β-blockers, statins, and angiotensin-converting enzyme inhibitors, is highly recommended.

Study end points

Co-primary end points. Two statistically independent co-primary end points will be evaluated. To assess iFR-guided complete revascularization in STEMI, the end point is 1-year modified *CvLPRIT MACE,*[12] defined as all-cause mortality, recurrent MI, heart failure (requiring hospitalization or a 12-hour ED visit), or ischemia-driven revascularization. For evaluation of ZESs for radial PCI in STEMI, the end point will be the 1-year *infarct-related artery MACE* which was defined in HORIZON as cardiac death, index infarct (P1-MI), or ischemia-driven index infarct-related vessel revascularization (IIVR). The TR band for transradial access in the elderly will be assessed using acute and 30-day rates of RAO. However, the study is powered statistically for the iFR and ZES end points above (Table II).

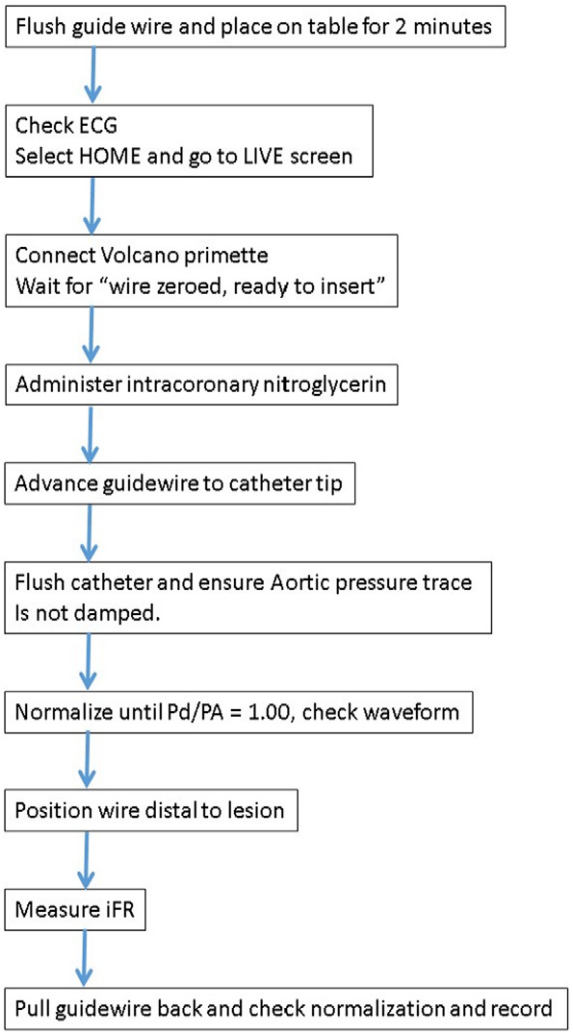
Secondary end points

The complete list of secondary end points by study objective is shown in Appendix Table I.

Statistical methods

The SAFE-STEMI for Seniors trial is statistically powered to evaluate 2 independent co-primary end points, namely, (1) the ZESs for radial PCI in STEMI; the study uses a performance goal derived from historical controls. Event rates from the Bern-Rotterdam registry, COMPARE-AMI, Diaz de La Lera, EXAMINATION, HAAMU-STENT, HORIZONS-AMI, KOMER, MISSION, PASEO, PASSION, PROSIT, Resolute AC, SESAMI, STRATEGY, TYPHOON, and ZEST-AMI were pooled to derive MACE estimates for DES. Taking an upper bound for pooled DES of 9.39%, based on HORIZONS-AMI study [13], we estimated a relative risk of 1.25 for MACE in patients at least 60 years old (assuming the age distribution in previous DES trials is similar to HORIZONS). The RR of 1.25 was estimated from HORIZONS-AMI study, which among subjects older than 65 years had a 1-year adjudicated MACE rate of 10% (112/1114). The study had an overall 8% MACE rate at 1 year; thus, 1.25 was estimated at 0.10/0.08. We further assume a multiplier of 1.50 (ie, an increase of 20% relative margin) to establish a

Figure 3



iFR-guided complete revascularization procedure flow.

performance goal for the intended population at 14%. Thus, for the hypothesis:

$$H_0 : P_1 \geq .14 \text{ vs } \quad H_a : \quad P_1 < .14$$

Where P_1 is the proportion of MACE in the Medtronic Resolute Family of Stents arm. The null hypothesis (H_0) will be rejected when the upper 2-sided 95% CI excludes 0.14.

If site operators designate 875 seniors enrolled into SAFE-PCI for STEMI as DES candidates, we expect about 45% (n = 393) to have single-vessel disease, and from the multivessel disease subjects (n = 482), 241 would be randomized to IRA-only revascularization. Thus, the available cohort for this indication could reach a total of 600 Medtronic Resolute Family of Stents DES exposures, all treated with IRA-only approach as used in the HORIZONS study.[13]

To evaluate the primary end point for iFR-guided multivessel PCI, which is 1-year modified CvLPRIT[12] MACE, we assumed a 1-year CvLPRIT MACE rate of 22% in the IRA-only arm and a 12% MACE rate in the complete revascularization arm. To achieve 80% power to detect a 45% relative reduction in 1-year modified CvLPRIT MACE and 10% lost to follow-up, we planned for 550 patients in the multivessel cohort. For iFR-guided multivessel PCI with 1-year modified CvLPRIT MACE end point,[12] the difference in the Kaplan-Meier estimate at 1 year will be used as the primary analytic tool for assessing outcome differences between the 2 randomized arms.[26] The difference in 1-year KM rates (and the 95% CI) will be calculated between the two randomized arms. Thus, the following 2-sided alternative hypothesis will be tested using the intent-to-treat cohort:

H0:(1YIRA only) −S(1Ycomplete revascularization) = 0 vs

HA (1YIRA only) −S(1Ycomplete revascuralization) ≠ 0.

For the time-to-event (MACE) analysis above that will be performed according to the principle of "intention to treat," in subjects who did not experience an event, their efficacy measure will be censored on the last visit (or last contact date). For those with an event, their efficacy measure (in days) will be measured as the time from randomization to the first occurrence of any of the CvLPRIT MACE components.[12] We will examine the data for consistency and robustness of the findings across clinically important subgroups such as sex and geographical regions.

The 2 co-primary end points are considered statistically independent, and thus, each will be tested at .05 level of significance. All statistical analyses will be conducted using SAS version 9.4 or higher (SAS Institute, Inc, Cary, NC).

Safety monitoring

The DSMC is made up of 2 clinicians and a statistician and will review safety data at prespecified times which were established prior to the start of enrollment. The DSMC makes recommendations regarding any safety or compliance issues throughout the course of the trial.

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Conclusions

Most clinical events in existing trials of primary PCI for STEMI occur in elderly patients, yet assessments addressing the optimal contributors to the safety and efficacy of STEMI management in these patients remain uncertain.

The Safe STEMI for Seniors protocol represents a prospective randomized registry-based design to encourage innovation and robust evaluation of state-of-the-art technologies to support extensions to device regulatory labeling through IDE investigations. Collaborative models strategically partnering multiple manufacturers can mitigate costs related to studying and developing labeling extensions, while encouraging the expansion of state-of-the-art devices into new markets to address previously unmet needs.

Disclosures

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Appendix Table I

Secondary end points: ZESs for primary PCI in STEMI
Efficacy
Adjudicated death (all causes) at 30 d and 1 y
Adjudicated cardiac death at 30 d and 1 y
Adjudicated nonfatal (re-)P1-MI at 30 d and 1 y
Adjudicated index infarct-related-vessel (re-)P1-MI at 30 d and 1 y
Adjudicated index infarct related lesion revascularization (IILR) (ischemia driven) at 30 d and 1 y
Adjudicated IIVR (ischemia driven) at 30 d and 1 y
Safety
Adjudicated Academic Research Consortium (ARC) definite/probable stent thrombosis at postprocedure, 30 d, and 1 y
Adjudicated ARC definite stent thrombosis at postprocedure, 30 d, and 1 y
Adjudicated stroke at postprocedure, 30 d, and 1 y
Device performance end points
Site determination of *device success*, defined as attainment of <20% residual stenosis of the infarct-related lesion at the time of the index procedure (IILR) using only the study stent.
Site determination of *lesion success*, defined as attainment of <20% residual stenosis using any percutaneous method at the time of the index procedure.
Site determination of *procedure success*, defined as lesion success without the occurrence of in-hospital death, nonfatal MI, stroke, or emergency end points for evaluating iFR-guided complete revascularization in STEMI.
Secondary end points: iFR-guided complete revascularization in STEMI
Adjudicated all-cause death at postprocedure, 30 d, and 1 y
Adjudicated cardiac death at postprocedure, 30 d, and 1 y
Adjudicated (re-)P2-MI at postprocedure, 30 d, and 1 y
Heart failure (requiring hospitalization or 12-h ER visit) postprocedure, 30 d, and 1 y
Ischemia-driven revascularization for index infarct related (IIVR) or any treated index non–infarct-related vessels (INIVR).
Adjudicated stroke at postprocedure, 30 d, and 1 y
Device performance end points
Site-reported index hospitalization bleeding and vascular complication defined as bleeding or vascular complication requiring intervention
Total procedure time
Total contrast used
Occurrence of renal insufficiency (increase from baseline creatinine of at least 0.5 mg/dL or at least 25%) assessed at 48-72 h postprocedure and 30 d
Secondary end points: Slender Guidesheath and TR Band for radial access in the elderly
Time to hemostasis stratified by whether the Terumo TR Band was used
Incidence rate of crossover from the initial access point to another stratified by whether or not Terumo Slender GlideSheath was used
Incidence rate of *access success* defined as successfully deploying the stent through the right or left radial artery stratified by whether or not Terumo Slender GlideSheath was used
Incidence of RAO acute and at 30 d stratified by whether or not the Terumo TR Band was used in combination with Glidesheath Slender

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