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CONTENTS

Introduction of FATE-MAIN Trial: A Randomized Comparison of FFR-Guided Versus Angiography-Guided PCI in Patients with Significant Left Main Coronary Artery Disease

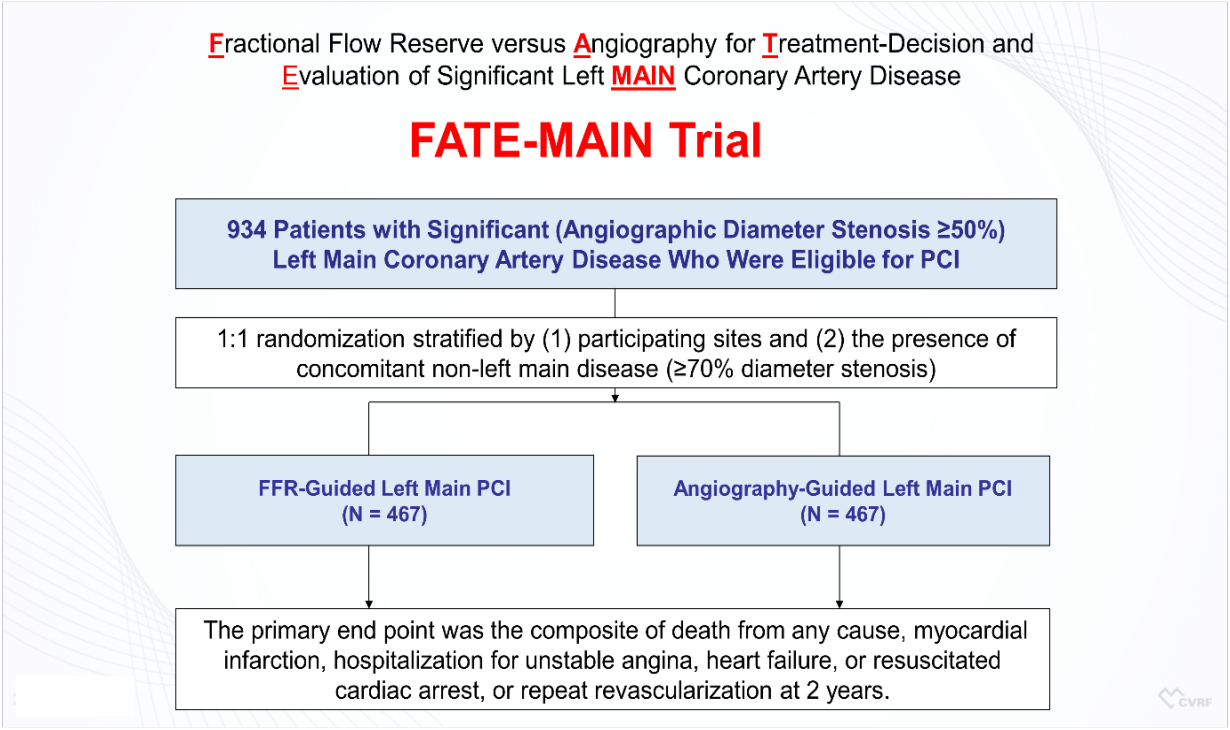
Introduction

The left main coronary artery (LMCA) is important, supplying over 70% of the left ventricular myocardium. Due to its large myocardial territory, LMCA disease represents the highest-risk subset of coronary artery disease (CAD), with significant implications for morbidity and mortality. Historically, LMCA stenosis ≥50% on angiography has been considered significant, based on older studies showing catastrophic outcomes with medical therapy alone. Consequently, guidelines have recommended routine revascularization—either PCI or CABG—for LMCA stenosis ≥50%. However, this threshold of 50% on angiographic assessment lacks concrete contemporary validation. Recent landmark trial, the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, have questioned the survival benefit of revascularization over optimal medical therapy (OMT) in stable CAD, though LMCA disease was excluded from the ISCHEMIA trial. In patients with intermediate LMCA stenosis (50–70%), recent data suggest that routine revascularization may not improve outcomes, especially in the absence of ischemia. These findings highlight the need to re-evaluate current practice. Angiographic assessment of LMCA is often limited by technical challenges such as vessel angulation, eccentricity, and foreshortening, resulting in high inter-observer variability. In contrast, functional assessment tools like fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) provide more accurate evaluation of lesion significance. Studies have shown that deferring PCI in LMCA lesions with FFR >0.80 is safe and may avoid unnecessary interventions. However, guidelines have yet to fully adopt physiology-based decision-making for LMCA. Given these gaps, we propose the FATE-MAIN (Fractional Flow Reserve versus Angiography for Treatment-Decision and Evaluation of Significant Left MAIN Coronary Artery Disease) trial. This study will compare outcomes between FFR-guided and angiography-guided PCI in patients with LMCA disease. We hypothesize that FFR-guided PCI will lead to better patient selection, avoid unnecessary procedures, and improve clinical outcomes by targeting only ischemia-producing lesions. This trial aims to provide the evidence needed to optimize revascularization strategies in LMCA disease.

Methods

This study is an investigator-initiated, multicenter, open-label, randomized superiority trial designed to evaluate whether FFR-guided PCI is superior to angiography-guided PCI in patients with significant LMCA disease. Eligible patients are those with ≥50% LMCA diameter stenosis on diagnostic angiography. Participants are randomized to either an FFR-guided or angiography-guided PCI strategy. In the FFR-guided arm, FFR is measured, and PCI is performed only if FFR ≤0.80; otherwise, revascularization is deferred and the patient is treated medically. In the angiography-guided arm, PCI is performed based solely on angiographic findings without physiological assessment. In both arms, post-stent intracoronary imaging is strongly encouraged for stent optimization. Decisions regarding stent type and bifurcation technique (provisional one-stent vs. upfront two-stent) are at the operator's discretion. Background medical therapy, including antiplatelet agents, lipid management, and diabetes control, is provided

according to current guidelines. The primary endpoint is a composite of death from any cause, myocardial infarction (MI), hospitalization for unstable angina, heart failure, resuscitated cardiac arrest, or repeat revascularization at 2 years. Key secondary endpoints include individual components of the primary outcome, all-cause mortality, and composite hard clinical outcomes such as death or MI. Inclusion criteria include adults ≥20 years with angina or evidence of MI and de novo LMCA stenosis ≥50%, feasible for PCI. Key exclusion criteria include LAD or LCX chronic total occlusion (CTO), severe vessel calcification or tortuosity precluding FFR, recent STEMI (<7 days), cardiogenic shock, severe LV dysfunction (EF <30%), and contraindications to dual antiplatelet therapy. Sample size calculation was based on prior trials with an assumed 2-year primary event rate of 20% in the angiography-guided group. Expecting a 30% relative risk reduction in the FFR-guided group, and accounting for a 5% attrition rate and a 5-year study duration (3-year enrollment), a total of 934 patients will be enrolled to achieve 80% power at a 0.05 two-sided significance level using a log-rank test.



Discussion

Despite the critical importance of LMCA disease, there remains a notable paucity of adequately powered randomized trials evaluating the clinical utility of physiology-guided PCI in this high-risk population. Current guideline recommendations for revascularization of LMCA stenosis ≥50% continue to rely primarily on angiographic assessment, despite this threshold being established from historical data that predates both modern medical therapy and contemporary physiologic assessment tools. This evidence gap underscores the particular significance of the present trial in clarifying the role of FFR-guided PCI in patients with intermediate LMCA disease. We anticipate that a substantial proportion of patients presenting with angiographically intermediate LMCA stenosis (50–70%) will demonstrate non-ischemic FFR values (>0.80), indicating the potential for safe management with optimal medical therapy alone. By avoiding unnecessary PCI in functionally insignificant lesions, we expect to achieve improved clinical outcomes through reduction of procedure-related complications, healthcare costs, and long-term adverse

events. The rationale for this physiologic approach is strengthened by consistent evidence demonstrating considerable discordance between angiographic and physiologic assessments in LMCA disease. Hamilos et al. and Park et al. reported discordance rates between visual angiographic estimation and FFR ranging from 29% to 37% in patients with intermediate LMCA lesions. This substantial mismatch highlights the inherent limitations of relying solely on angiographic interpretation, particularly given the complex three-dimensional anatomy and frequent bifurcation involvement characteristic of LMCA disease. The anatomical complexity of distal LMCA bifurcation lesions presents additional challenges that extend beyond diagnostic accuracy to procedural considerations. These lesions require sophisticated stent selection and technique, are associated with higher risks of procedural complications, and demonstrate increased rates of restenosis compared to non-bifurcation lesions. This complexity underscores the critical importance of patient selection—ensuring that revascularization is reserved for those who will derive genuine clinical benefit. The integration of FFR-guided decision-making offers a more individualized and evidence-based approach to LMCA management, enabling clinicians to focus revascularization efforts precisely on hemodynamically significant lesions while safely deferring intervention in functionally insignificant stenoses. Through the FATE-MAIN trial, we aim to provide high-level evidence supporting the integration of physiologic assessment into routine LMCA disease management. We believe this strategy will enhance clinical outcomes by reducing overtreatment and targeting PCI more precisely to lesions that truly contribute to myocardial ischemia.

Limitations

Several limitations warrant consideration in the interpretation of this study. First, the open-label design inherently introduces potential bias in outcome reporting and clinical decision-making. To mitigate this limitation, all endpoints were rigorously predefined and independently adjudicated by a Clinical Event Committee using standardized criteria, thereby minimizing subjective interpretation of clinical events. Second, the trial's sample size was calculated based on composite endpoints rather than being specifically powered to detect differences in individual hard clinical endpoints such as cardiovascular death or myocardial infarction. Moreover, contemporary advances in medical therapy and the widespread adoption of imaging-guided percutaneous coronary intervention for stent optimization may result in lower actual event rates than initially projected. This phenomenon could potentially diminish the statistical power necessary to detect clinically meaningful treatment differences, representing a valid methodological concern inherent to cardiovascular outcome trials in the modern era. Third, protocol deviations may occur in the angiography-guided arm when operators defer revascularization following intracoronary imaging that reveals an LMCA luminal area >6.0 mm^2, despite meeting initial angiographic inclusion criteria. While these instances will be classified as protocol violations, they reflect real-world clinical practice patterns. To address potential bias introduced by these deviations, comprehensive sensitivity analyses including per-protocol and as-treated analyses will be performed alongside the primary intention-to-treat analysis. This multi-faceted analytical approach will provide a more nuanced understanding of treatment effects and enhance the robustness of our findings. Fourth, procedural heterogeneity may be introduced in distal LMCA bifurcation lesions, where clinical outcomes can vary depending on the stenting technique employed (provisional one-stent versus upfront two-stent technique). While this variability reflects contemporary clinical practice, it may confound the interpretation of treatment effects attributable specifically to the decision-making strategy (FFR-guided versus angiography-guided). Finally, the utilization of different intracoronary imaging modalities (intravascular ultrasound versus optical coherence tomography) could theoretically influence procedural outcomes. However, evidence from the OCTIVUS trial, which specifically included LMCA lesions, demonstrated no significant difference in clinical outcomes between these imaging modalities in this anatomical subset. Therefore, this methodological variability is unlikely to introduce meaningful bias into the overall study

results. Despite these limitations, the study design incorporates appropriate safeguards and analytical strategies to ensure robust and clinically relevant findings that will contribute meaningfully to the evidence base for LMCA disease management.

Conclusions

The FATE-MAIN trial will provide critical insight into the comparative effectiveness of FFR-guided versus angiography-guided PCI in patients with significant LMCA disease.

Comment

The FATE-MAIN trial is a multicenter, randomized, open-label study designed to evaluate whether fractional flow reserve (FFR)-guided PCI is superior to angiography-guided PCI in patients with significant left main coronary artery (LMCA) disease. LMCA supplies a large portion of the left ventricular myocardium, and disease in this vessel carries high morbidity and mortality. Although a ≥50% angiographic stenosis is traditionally considered significant, this threshold lacks robust modern validation, especially in the absence of ischemia. Particularly, left main (LM) disease frequently involves bifurcation lesions affecting the left anterior descending artery (LAD) or left circumflex artery (LCX), making PCI technically challenging in these cases.

Furthermore, the recent large-scale EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial investigating LM disease did not perform revascularization in all patients with angiographically significant stenosis ≥50%. For intermediate LM disease (50-70% stenosis), revascularization was performed only when ischemic evidence was confirmed through invasive or non-invasive testing. This approach was based on previous studies that reported substantial mismatch between angiographic and functional assessments.

Accordingly, the practice of determining significant LM disease based solely on visual assessment of 50% stenosis using old data and proceeding with revascularization remains questionable among many physicians. The FATE-MAIN study is designed to address this specific issue and aims to provide evidence for optimal decision-making regarding revascularization in significant LM disease.

The primary endpoint is a composite of death, MI, unstable angina, heart failure, resuscitated cardiac arrest, or repeat revascularization at 2 years. The trial aims to enroll 934 patients to detect a 30% relative risk reduction with 80% power. Through this investigation, we anticipate establishing a more robust foundation for clinical decision-making in the management of significant left main coronary artery disease. FATE-MAIN seeks to provide high-level evidence to refine LMCA revascularization strategies.

Source

Park, Seung-Jung. "Fractional Flow Reserve Versus Angiography for Treatment-Decision and Evaluation of Significant Left MAIN Coronary Artery Disease (FATE-MAIN)." *ClinicalTrials.gov*, 25 Apr. 2024, clinicaltrials.gov/study/NCT05829889. Accessed 11 June 2025.

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Revascularization Strategy for Multivessel Coronary Artery Disease Patients with Diabetes Mellitus PCI Versus CABG

Introduction

Percutaneous coronary intervention (PCI) has been considered revascularization strategy for coronary arterial disease (CAD) patients. Recently with the current generation drug-eluting stent and state-of-the-art PCI, which use the intracoronary imaging guidance- and invasive physiology guidance-PCI, PCI has been comparable with coronary artery bypass graft (CABG). However, current guideline for coronary revascularization recommended CABG as class IA in multivessel CAD patients with diabetes. PCI is recommended as class IIa in patients with high surgical risk or unsuitable for CABG.

In subgroup analysis for SYNTAX trial, CABG reduced the composite of death, myocardial infarction (MI), stroke or repeat revascularization compared with PCI for DM patients. The BEST trial, which compared PCI and CABG in multivessel CAD patients, showed similar outcomes of composite of death MI or target vessel revascularization. However, CABG group showed significantly reduced primary outcomes in DM subgroup. However, Main differences in both trials were observed in only repeat revascularization. The freedom trial, which landmark trial for multivessel CAD patient with DM, showed significant reduction of composite of death, MI or stroke. In BARDI-2D trial, MACE, defined as composite of death, MI, or stroke, were significantly reduced in revascularization with CABG compared with optimal medical treatment.

However, these prior studies had several limitations. Subgroup analyses of SYNTAX trial and BEST trial were not focused on patients with diabetes and just subgroup analysis with study underpower. These studies did not use current generation DES and did not frequently use intracoronary imaging or physiologic guidance PCI. Current anti-diabetic medication, such as sodium-glucose transporter 2 inhibitor or glucagon-like peptide-1 receptor agonist, which demonstrated cardiovascular benefits, were not used. So, these studies and current guidelines may not reflect the current real-world practice.

The **D**iabetes-centered **E**valuation of revascularization strategy of **F**unctional and **I**maging-combi**NE**d state-of-the-art percutaneous coronary intervention or coronary-artery bypass grafting in patients with **D**iabetes **M**ellitus and multivessel coronary artery disease (DEFINE-DM) trial aimed to evaluate the treatment effect of revascularization strategy in multivessel CAD with diabetes.

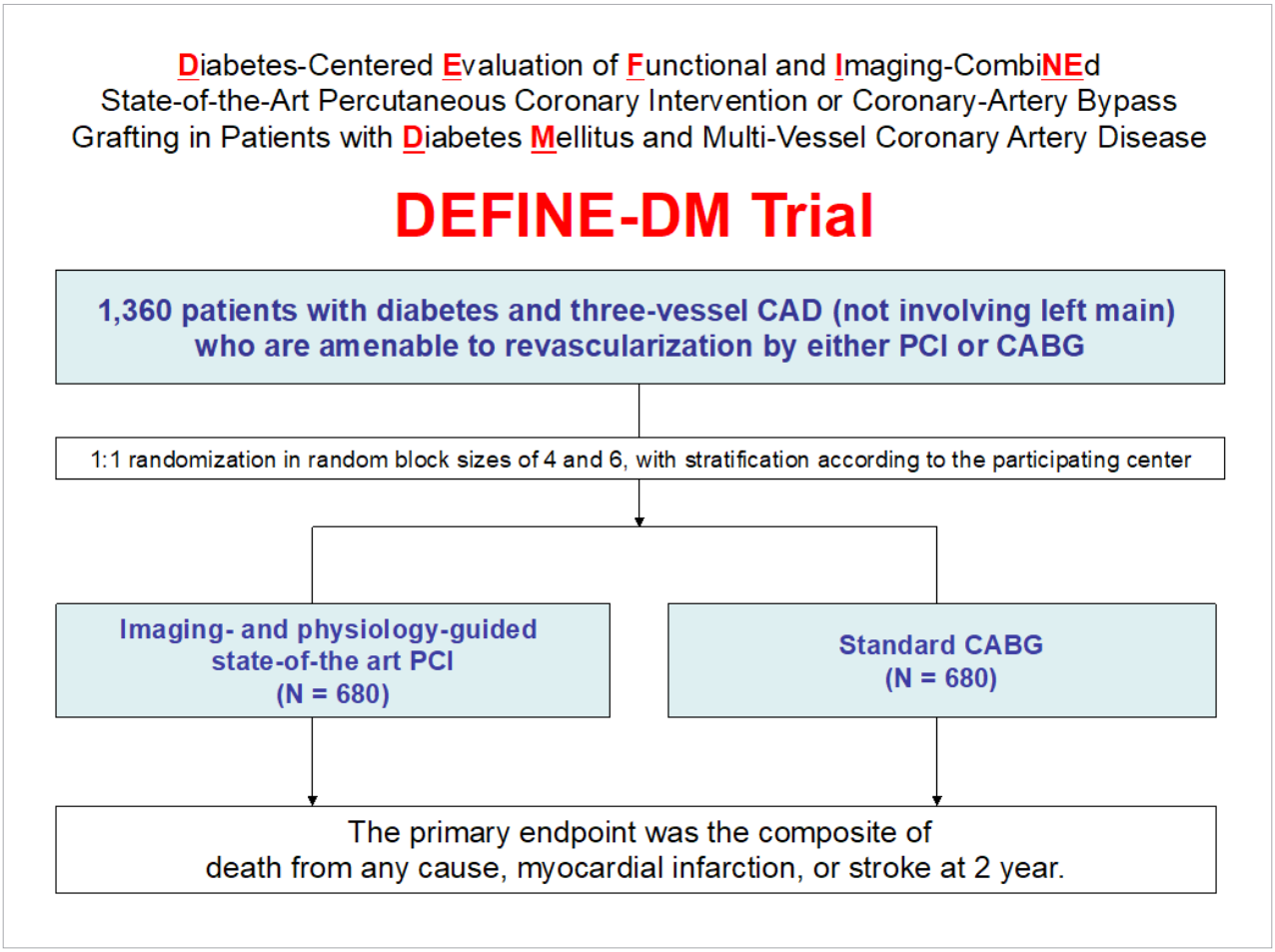
Method

The DEFINE-DM trial is a multicenter, international, randomized, controlled non-inferiority trial. Approximately 1369 patients who have diabetes and angiographically confirmed three-vessel coronary arterial disease (defined as at least 50% diameter stenosis as assessed by visual estimation in each of the three major epicardial vessels or major side branches but no involving the left main artery) will be randomized in a 1:1 fashion to either imaging-and physiology-guided state-of-the-art PCI or standard CABG. Primary endpoint is a composite of death from any causes, MI, or stroke at 2 years. Secondary endpoints included individual components of primary composite outcome, periprocedural

major adverse events, functional class or angi-related quality of life index.

Conclusion

This DEFINE-DM study will provide new evidence of revascularization strategy for multivessel CAD patients with diabetes.



Comment

The current guideline-recommended revascularization strategy for multivessel CAD patients with diabetes is based on outdated evidence and does not fully reflect real-world clinical practice, resulting in a significant gap. The DEFINE-DM trial is expected to provide new evidence on the optimal revascularization strategy in this patient population, as it incorporates state-of-the-art PCI using current-generation DES and GDMT that includes new-generation antidiabetic drugs with proven cardiovascular benefits.

Source

Park, Duk-Woo. "Diabetes-Centered Evaluation of Revascularization Strategy of Functional and Imaging-CombiNEd State-of-the-Art Percutaneous Coronary Intervention or Coronary-Artery Bypass Grafting in Patients With Diabetes Mellitus and Multivessel Coronary Artery Disease (DEFINE-DM)." *ClinicalTrials.gov*, 14 June 2024, clinicaltrials.gov/study/NCT05831085. Accessed 2 June 2025.

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Potassium-Competitive Acid Blocker Versus Proton-Pump Inhibitor in Patients Receiving Antithrombotic Therapy Who Are at High Risk for Gastrointestinal Bleeding: Rationale and Design of PROTECT-HBR Trial

Introduction

Long-term antithrombotic therapy, including antiplatelet agents and oral anticoagulants (OACs), is associated with an increased risk of gastrointestinal (GI) complications, particularly upper GI bleeding. This risk is heightened in patients who are elderly, have a history of ulcers or GI bleeding, or are concomitantly using NSAIDs or steroids. Proton pump inhibitors (PPIs) are recommended for gastroprotection in such high-risk patients, but concerns exist regarding the safety and pharmacological limitations of chronic PPI use—such as delayed onset, incomplete acid suppression, adverse effects, and potential drug interactions, especially with clopidogrel. Potassium-competitive acid blockers (P-CABs), such as tegoprazan, offer several advantages over PPIs, including rapid onset, sustained acid suppression, CYP2C19-independent metabolism, and food-independent dosing. The PROTECT-HBR trial was designed to compare the efficacy and safety of tegoprazan versus rabeprazole in patients with cardiovascular disease receiving antithrombotic therapy who are at high risk of GI bleeding.

Methods

The PROTECT-HBR trial is a multicenter, randomized, double-blind, double-dummy, active comparator–controlled, phase 4 clinical study designed to evaluate whether tegoprazan (50 mg once daily), a potassium-competitive acid blocker (P-CAB), is non-inferior to rabeprazole (20 mg once daily), a proton pump inhibitor (PPI), in preventing upper gastrointestinal (GI) events in patients at high risk of GI bleeding. Eligible participants are adults aged 18 years or older with documented cardiac or vascular disease requiring chronic antithrombotic therapy—including antiplatelet agents, oral anticoagulants (OACs), or their combinations—and at least one GI bleeding risk factor such as age ≥65 years, concurrent use of OAC and antiplatelet agents, long-term NSAID or steroid use, a history of GI bleeding or peptic ulcer disease, or Helicobacter pylori infection. After obtaining written informed consent, patients are randomized in a 1:1 ratio to receive either tegoprazan or rabeprazole for 12 months using a double-dummy design to ensure blinding. The primary endpoint is the time to first occurrence of a composite of upper GI clinical events, including overt or occult GI bleeding, symptomatic gastroduodenal ulcers, obstruction, or perforation, assessed over 12 months of follow-up. Secondary endpoints include each individual GI event, gastroesophageal reflux disease, cardiovascular outcomes (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke), all-cause mortality, and any adverse effects related to the study drugs.

The study aims to enroll 3,100 patients to provide 80% power to demonstrate non-inferiority, assuming a 4% event rate in the PPI group and using a one-sided alpha of 0.025 with a non-inferiority margin set at a hazard ratio of 1.40. All efficacy analyses will follow the intention-to-treat principle, with supplementary analyses performed in both as-treated and per-protocol populations. Time-to-event outcomes will be analyzed using Kaplan–Meier survival

estimates and compared via log-rank tests, while Cox proportional hazards models will be used to derive hazard ratios and 95% confidence intervals. The proportional hazards assumption will be assessed through Schoenfeld residuals and log(-log) plots. Prespecified subgroup analyses will be conducted to evaluate the consistency of the treatment effect across clinically relevant categories such as age, sex, body mass index, diabetes status, renal function, Helicobacter pylori status, underlying cardiovascular disease, and type of antithrombotic therapy.

Discussion

PROTECT-HBR is the first large-scale randomized trial designed to directly compare a novel P-CAB (tegoprazan) with a standard PPI (rabeprazole) in patients at high risk for GI bleeding receiving antithrombotic therapy. While PPIs are the standard gastroprotective therapy, their limitations—especially potential drug-drug interactions and adverse effects—warrant investigation into alternative strategies. Existing evidence on PPI efficacy from trials like COGENT and COMPASS is limited by their inclusion of lower-risk populations. P-CABs provide pharmacological benefits such as more consistent and potent acid suppression, faster onset, and fewer interactions, making them promising candidates for high-risk populations. This trial aims to address the unmet need for more effective and safer GI prophylaxis in patients receiving antithrombotic agents.

Conclusion

The PROTECT-HBR trial is a pivotal randomized clinical trial evaluating the efficacy and safety of tegoprazan compared with rabeprazole in high-GI-bleeding-risk patients with cardiovascular disease on antithrombotic therapy. Its findings will provide critical evidence regarding the potential role of P-CABs as an alternative to PPIs in this high-risk population and may influence future clinical guidelines and regulatory decisions for GI protection strategies.

Comment

The PROTECT-HBR trial is a multicenter, randomized, double-blind, phase 4 clinical study designed to evaluate the efficacy and safety of tegoprazan, a novel potassium-competitive acid blocker (P-CAB), compared with rabeprazole, a standard proton pump inhibitor (PPI), in patients with cardiovascular disease who are at high risk of gastrointestinal (GI) bleeding due to long-term antithrombotic therapy. Unlike previous studies such as COGENT or COMPASS that included lower-risk populations, PROTECT-HBR specifically targets patients with high GI bleeding risk, including those who are elderly, use dual antithrombotic therapy, or have a history of ulcers. Tegoprazan offers pharmacologic advantages over PPIs, including rapid onset, sustained acid suppression, and fewer drug interactions, particularly with clopidogrel. This study is the first to directly compare a P-CAB and a PPI in this context and is expected to provide critical evidence for optimal GI protection in high-risk cardiovascular patients. If tegoprazan proves to be non-inferior or superior to rabeprazole, it could offer a safer and more effective alternative to traditional PPIs, potentially influencing future clinical guidelines and daily practice in antithrombotic management.

Source

Park, Duk-Woo. "Potassium-Competitive Acid Blocker Versus pROton-Pump Inhibitor for GastroproTECTion Strategies In Patients at High Gastro-Intestinal Bleeding Risk Receiving Antithrombotic Therapy (PROTECT-HBR)." *ClinicalTrials.gov*, 12 May 2021, clinicaltrials.gov/study/NCT04416581. Accessed 9 June 2025.

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ENAVO-TAVR Trial: SGLT2 Inhibitor Therapy for HFpEF in Post-TAVR Patients

Introduction

Transcatheter aortic valve replacement (TAVR) was initially indicated for high-risk or inoperable patients with severe aortic stenosis (AS), and its indications have gradually broadened to include intermediate- and low-risk populations.

Despite procedural success, many patients experience persistent or new-onset heart failure symptoms, largely driven by maladaptive cardiac remodeling that may continue after valve replacement. Therefore, implementing an effective postprocedural cardiac protection strategy is crucial. Heart failure with preserved ejection fraction (HFpEF), which is commonly observed in patients with AS, contributes significantly to morbidity after TAVR. However, evidence regarding the efficacy and safety of SGLT2 inhibitors in patients with severe AS and HFpEF remains limited. The ENAVO-TAVR trial aims to evaluate the efficacy and safety of enavogliflozin, a novel sodium–glucose cotransporter 2 (SGLT2) inhibitor, in improving clinical outcomes among post-TAVR patients with HFpEF. This trial addresses a critical unmet need in a growing cohort with few evidence-based medical therapies.

Methods

ENAVO-TAVR is a multicenter, double-blind, randomized controlled trial enrolling 1,040 patients with symptomatic severe AS and HFpEF (LVEF ≥40%) following successful TAVR. Participants were randomized within two weeks post-procedure in a 1:1 fashion to receive either enavogliflozin (0.3 mg/day) or a matching placebo. Stratification was performed by participating centers, baseline diabetes status, and eGFR (<60 or ≥60 mL/min/1.73 m^2). The primary endpoint is the composite of all-cause mortality, myocardial infarction, stroke, or hospitalization for heart failure at 12 months. The secondary endpoints include individual components of the primary endpoint, rehospitalization rates for any reasons, echocardiographic parameters (LVEDVI, LVESVI, LAVI, E/e′), NYHA functional class, quality of life (KCCQ), and renal outcomes. Safety monitoring includes predefined adverse events of special interest, such as hypoglycemia, renal dysfunction, and genitourinary infections.

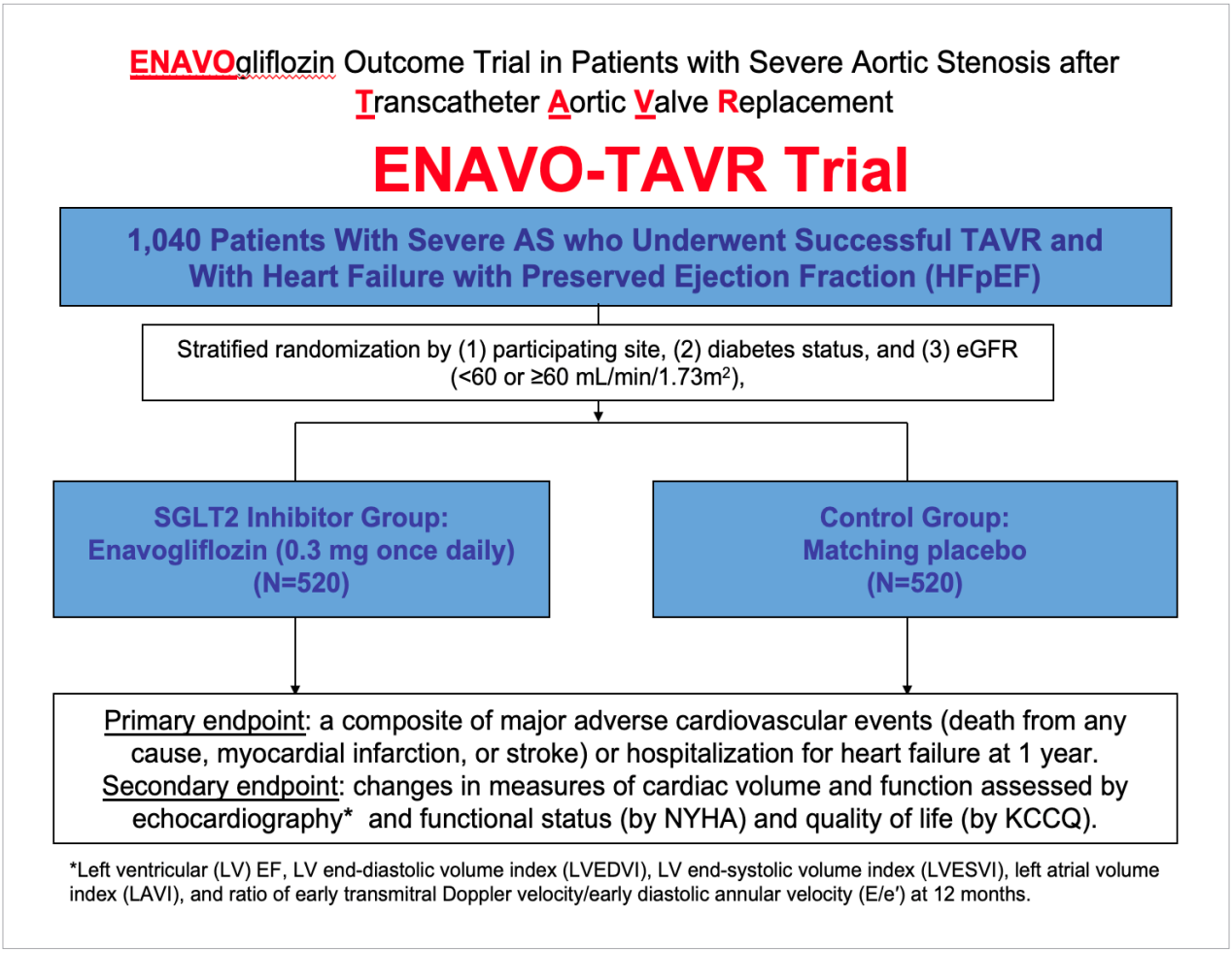
Discussion & Conclusion

The rationale for ENAVO-TAVR is grounded in recent evidence from SGLT2 inhibitor trials, such as EMPEROR-Preserved and DELIVER, which demonstrated significant benefit in reducing heart failure events in HFpEF populations. However, prior studies did not include patients with severe AS undergoing TAVR, a group with unique pathophysiology characterized by myocardial fibrosis, hypertrophy and persistent neurohormonal activation even after valve replacement. ENAVO-TAVR trial aims to determine whether SGLT2 inhibitor can mitigate these mechanisms and improve outcomes in this high-risk group.

The study also builds on insights from DAPA-TAVI, reinforcing a potential class benefit of SGLT2 inhibitors in post-TAVR patients.

ENAVO-TAVR is the first large-scale, randomized trial to assess SGLT2 inhibition in patients with HFpEF after

TAVR. With robust endpoint definitions and a well-powered sample size, the trial is expected to provide pivotal data to inform guideline-based therapy. If enavogliflozin demonstrates clinical benefit, the findings could redefine medical management strategies for a rapidly expanding population of post-TAGR patients.



Comment

As TAVR is increasingly performed in younger and lower-risk patients, there is an urgent need to optimize long-term outcomes beyond the index procedure. Addressing residual heart failure risk has emerged as the next frontier. ENAVO-TAVR is a timely and methodologically rigorous trial that targets a critical gap in post-procedural care. The study's emphasis on HFpEF and multidimensional endpoints, including imaging, biomarkers, and patient-reported outcomes, strengthens its potential to guide clinical practice. Future analyses focusing on frailty, diabetes, and renal function subgroups may further refine the therapeutic role of enavogliflozin in TAVR recipients.

Source

Park, Duk-Woo. "ENAVOgliflozin Outcome Trial in Patients With Severe Aortic Stenosis After Transcatheter Aortic Valve Replacement (ENAVO-TAVR)." *ClinicalTrials.gov*, 18 Dec. 2024, clinicaltrials.gov/study/NCT05672836. Accessed 30 May 2025.

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PREVENT Subgroup Analysis: Identifying Enhanced Benefit of Preventive PCI in Patients with Prior Non-Target Vessel Revascularization

Background

Acute coronary syndromes and sudden cardiac death are frequently caused by the rupture and thrombosis of non-obstructive, lipid-rich coronary plaques, often referred to as vulnerable plaques. Despite appearing angiographically mild and not inducing ischemia, these lesions carry significant risk. Advanced intracoronary imaging modalities such as intravascular ultrasound, optical coherence tomography, and near-infrared spectroscopy allow precise identification of high-risk plaque features, including thin-cap fibroatheromas, large plaque burden, and lipid core content, providing an opportunity for preventive intervention. The PREVENT trial previously demonstrated that preventive stenting of high-risk plaques, when added to optimal medical therapy, significantly reduced major adverse cardiovascular events compared to medical therapy alone. However, whether this benefit extends uniformly across different clinical scenarios, particularly in patients with prior revascularization of other flow-limiting lesions, remained unclear. This prespecified subgroup analysis evaluated whether the presence of prior non-target vessel intervention modified the efficacy of preventive percutaneous coronary intervention for non-flow-limiting vulnerable plaques.

Methods

The PREVENT trial was a multicenter, open-label, randomized controlled trial conducted across 15 hospitals in South Korea, Japan, Taiwan, and New Zealand. Patients with non-flow-limiting coronary lesions, defined by a fractional flow reserve greater than 0.80, underwent invasive imaging to identify high-risk plaques. Lesions were considered high-risk if they met at least two of the following criteria: minimum lumen area less than 4 mm^2, plaque burden greater than 70%, lipid-rich core with a maximum lipid core burden index over 315, or thin-cap fibroatheroma on imaging. Eligible patients were randomized to receive either preventive stenting plus optimal medical therapy or optimal medical therapy alone. In this subgroup analysis, patients were stratified based on whether they had undergone non-target vessel intervention prior to randomization: 576 patients had received prior non-target vessel intervention, while 1,030 had not. The primary endpoint was a composite of cardiac death, target-vessel myocardial infarction, ischemia-driven target-vessel revascularization, or hospitalization for unstable angina, assessed at both 2-year and 7-year follow-up.

Results

Patient Characteristics

Among the 1,606 patients enrolled, 35.9% had undergone non-target vessel intervention prior to randomization. These individuals presented with more complex clinical characteristics, including higher rates of multivessel coronary artery disease, diabetes, prior acute coronary syndromes, and lower left ventricular ejection fraction, suggestive of a higher overall cardiovascular risk profile.

Two-Year and Long-Term Outcomes

At 2 years, preventive PCI significantly reduced the incidence of the primary composite endpoint in patients with prior non-target vessel intervention (0% vs. 6.7%; hazard ratio 0.04; $p = 0.03$). In those without prior non-target vessel intervention, a smaller but still significant benefit was observed (0.6% vs. 2.8%; hazard ratio 0.21; $p = 0.01$; interaction $p = 0.99$). At the 7-year follow-up, the benefit remained robust in the prior intervention group (1.7% vs. 8.4%; hazard ratio 0.19; $p < 0.001$). In contrast, no long-term benefit was evident in patients without prior non-target vessel intervention (4.1% vs. 4.4%; hazard ratio 0.91; $p = 0.74$; interaction $p = 0.0074$). Preventive PCI also significantly reduced the rate of target-vessel revascularization in patients with prior non-target vessel intervention (hazard ratio 0.21; $p < 0.001$), with similar favorable trends noted for hospitalization and myocardial infarction.

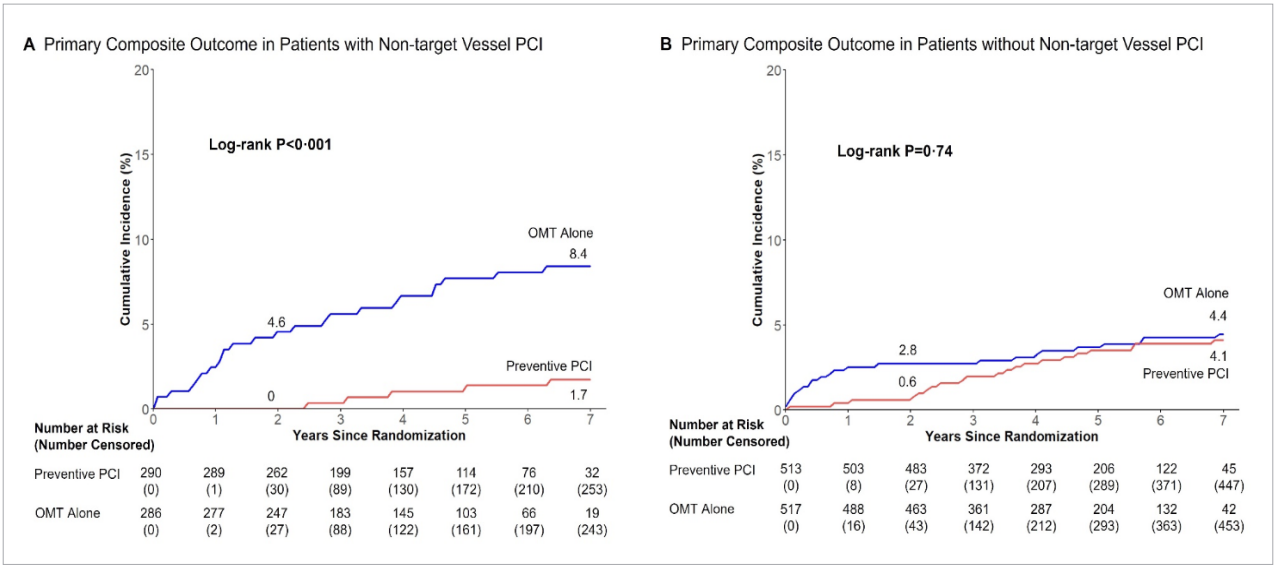

Figure 1. Kaplan–Meier curves showing the 7-year cumulative incidence of the primary composite outcome. **(A)** In patients with prior non-target vessel intervention, preventive percutaneous coronary intervention significantly reduced events compared to optimal medical therapy alone (1.7% vs. 8.4%; log-rank $p < 0.001$). **(B)** In patients without prior intervention, no significant difference was observed (4.1% vs. 4.4%; log-rank $p = 0.74$).

Discussion

This analysis indicates that the clinical efficacy of preventive stenting for non-flow-limiting vulnerable plaques is significantly influenced by whether the patient had prior non-target vessel intervention. The presence of such intervention may serve as a surrogate marker for more extensive or aggressive atherosclerotic disease. In these higher-risk patients, preventive plaque stabilization offers substantial and sustained benefit. Conversely, patients with isolated, single-vessel disease who did not undergo prior intervention derived a more modest absolute benefit, suggesting that optimal medical therapy may be sufficient for lower-risk individuals. These findings align with prior studies such as the COMPLETE and FAME II trials, which emphasized the importance of complete revascularization, and the ISCHEMIA trial, which questioned the incremental value of intervention in stable disease. Unlike those trials, this analysis expands the preventive paradigm to include plaques that are anatomically high-risk but not flow-limiting—particularly in patients with diffuse atherosclerosis.

Limitations

Although this was a prespecified subgroup analysis within a randomized trial, the decision to perform non-target vessel intervention was made before randomization, introducing the possibility of selection bias. Procedural and imaging approaches were left to operator discretion, potentially affecting consistency. Furthermore, the trial population was predominantly Korean and male, which may limit generalizability to other populations. The overall event rate was relatively low, which could impact the statistical power for some endpoints.

Conclusion

This subgroup analysis of the PREVENT trial demonstrated that preventive PCI of non-flow-limiting vulnerable plaques provides long-term clinical benefit in patients with prior non-target vessel intervention. These patients likely represent a population with more advanced coronary artery disease and are therefore more likely to benefit from a preventive strategy. Careful patient selection remains essential. Future research should aim to refine criteria for identifying those most likely to benefit, incorporating detailed plaque characteristics and overall disease burden.

Comment

This analysis provides important clinical insights into the tailored use of preventive percutaneous coronary intervention in the management of coronary artery disease. While the primary trial confirmed overall benefit, this subgroup analysis shows that not all patients benefit equally. The greatest advantage was observed in patients with prior revascularization, likely reflecting a more extensive atherosclerotic process.

The study supports a paradigm shift from reactive to preventive intervention, guided by advanced imaging. It underscores the value of integrating plaque morphology with systemic disease assessment in selecting candidates for preventive therapy. The use of imaging modalities to identify high-risk features combined with evidence-based medical therapy may offer a new standard for managing patients with high-risk coronary plaques.

Future research should validate these findings in more diverse populations, assess cost-effectiveness, and explore the role of emerging technologies, including artificial intelligence, in refining risk stratification. The PREVENT subgroup analysis paves the way for a more personalized and proactive approach to coronary intervention.

Keywords

Preventive PCI, vulnerable plaque, non-target vessel PCI, coronary artery disease, intravascular imaging, long-term outcomes

Source

Park, Seung-Jung, et al. **"Preventive percutaneous coronary intervention versus optimal medical therapy alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT): a multicentre, open-label, randomised controlled trial"** *The Lancet*, vol. 403, issue 10438, 2024, p. 1753, doi:10.1016/S0140-6736(24)00413-6

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