High-risk percutaneous coronary intervention is associated with reverse left ventricular remodeling and improved outcomes in patients with coronary artery disease and reduced ejection fraction

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Background Therapies that reverse pathologic left ventricular (LV) remodeling are often associated with improved outcomes. The incidence and impact of reverse LV remodeling after high-risk percutaneous coronary intervention (PCI) are unknown.

Methods The PROTECT II study was a multicenter trial in patients with complex, multivessel coronary artery disease and reduced ejection fraction (EF) that revealed an increase in visual EF after high-risk PCI. Among patients with quantitative echocardiography (LV volumes and biplane EF), we assessed the extent and predictors of reverse LV remodeling, defined as improved systolic function with an absolute increase in EF ≥5% and correlated these findings with clinical events.

Results Quantitative echocardiography was performed in 184 patients at baseline and longest follow-up. Mean EF at baseline was 27.1%. Ninety-three patients (51%) demonstrated reverse LV remodeling with an absolute increase in EF of 13.2% ($P < .001$). End-systolic volume decreased from 137.7 to 106.6 mL ($P = .002$). No significant change in EF or end-systolic volume was seen among non-remodelers. Reverse LV remodeling occurred more frequently in patients with more extensive revascularization (odds ratio, 7.52; 95% CI [1.31-43.25]) and was associated with significantly fewer major adverse events (composite of death/myocardial infarction/stroke/transient ischemic attack): 9.7% versus 24.2% ($P = .009$). There was also a greater reduction in New York Heart Association class III/IV heart failure among reverse LV remodelers (66.7% to 24.0%) than non-remodelers (56.3% to 34.4%), $P = .045$.

Conclusions Reverse LV remodeling can occur after high-risk PCI in patients with complex coronary artery disease and reduced EF and is associated with improved clinical outcomes. (Am Heart J 2015;170:550-8.)

Pathologic left ventricular (LV) remodeling, characterized by an increase in LV volume and a decrease in systolic function, can occur in response to ischemia and myocardial infarction (MI) and is associated with poor clinical outcomes.[1,2] Echocardiographic imaging in patients with coronary artery disease (CAD) has demonstrated that a decrease in ejection fraction (EF) over time is an independent predictor of death and heart failure hospitalization.[3-6] Conversely, reversal of pathologic LV remodeling, as demonstrated by an increase in EF, has been associated with improved clinical outcomes including lower mortality.[7-9]

Although coronary artery bypass grafting (CABG) remains the standard of care for 3-vessel or unprotected left main CAD, certain patients are at prohibitively high risk for surgical revascularization due to poor distal targets and multiple comorbidities.[10] In these high-risk patients with severe obstructive CAD, percutaneous coronary intervention (PCI) with hemodynamic support may be considered as an alternative treatment strategy. The PROTECT II study was a multicenter trial of high-risk patients with complex CAD and reduced EF requiring nonemergent, percutaneous revascularization.[11] The PROTECT II study reported an increase in visually estimated EF after high-risk PCI but did not examine the extent and predictors of improved LV systolic function or correlate these findings with clinical events. To investigate this, we conducted an analysis of patients with quantitative echocardiographic data to evaluate for reverse LV remodeling after high-risk PCI.

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Methods

Study design and patient population

The methods for the PROTECT II study have been previously published.[11] Briefly, PROTECT II was a prospective, multicenter, randomized trial conducted in 112 sites in the United States, Canada, and Europe. The study population was composed of complex multivessel CAD patients with LV dysfunction and a clinical indication for nonemergent, high-risk PCI for either (1) unprotected left main stenosis or last patent coronary vessel and an EF ≤35%; or (2) 3-vessel CAD and EF ≤30%. Patients were randomized to hemodynamic support during PCI with either the Impella 2.5 device or intra-aortic balloon pump (IABP). Inclusion and exclusion criteria have been detailed previously.[11] The PROTECT II study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed and approved by the ethics review committee of each participating center, and all patients provided written informed consent before enrollment.

Baseline (before high-risk PCI) and postprocedural follow-up echocardiograms at 30 and 90 days were required as part of the PROTECT II trial. Those patients with adequate image quality who had quantitative biplane analysis performed on both the baseline and longest follow-up echocardiograms were included in the current substudy population. Patients were excluded due to poor image quality on either the baseline or follow-up echocardiogram or because they did not have a baseline or follow-up echocardiogram performed.

Echocardiographic data management

Transthoracic echocardiography was performed at baseline and 30 and/or 90 days after high-risk PCI. Two-dimensional, spectral Doppler, and color Doppler were obtained from standard parasternal and apical views. All echocardiographic interpretations and measurements were performed at an independent echocardiographic core laboratory (Duke Clinical Research Institute, Durham, NC) in accordance with current guidelines.[12,13] Interpreting cardiologists were level III certified in echocardiography and blinded to the study intervention.

The echocardiographic parameters analyzed were EF, end-diastolic volume (EDV), end-systolic volume (ESV), and mitral regurgitation (MR). Ejection fraction, EDV, and ESV were calculated using the biplane method of disks (modified Simpson rule). Mitral regurgitation severity was based on a combination of quantitative methods and expert visual interpretation and graded on a scale ranging from none to severe. Using these data, a composite MR severity score was calculated. The number of patients in each MR grade was multiplied by the following severity values: no MR, 0; mild MR, 1; moderate MR, 2; and severe MR, 3. The sum total for all grades was then divided by the total number of patients using the following equation:

$$\frac{[(\text{No. With No MR} \times 0) + (\text{No. With Mild MR} \times 1) + (\text{No. With Moderate MR} \times 2) + (\text{No. With Severe MR} \times 3)]}{(\text{Total No. of Patients})}$$

Reproducibility

All sonographers and interpreting cardiologists adhered to established best practice standards for echocardiography core laboratories, which included reproducibility testing for biplane EF and MR.[14] Interreader reproducibility for the echocardiographic parameters was excellent with intraclass correlation coefficient of 0.81 (95% CI [0.44-0.95]) for biplane EF and κ of 1.00 for MR.

Study end points

In the PROTECT II trial, the primary clinical end point was a composite rate of major adverse events at 30 days after high-risk PCI.[11] In addition, an analysis of the primary end point was also conducted at 90 days. These study results were previously reported and showed no statistical difference in outcomes between patients randomized to Impella 2.5 and IABP at 30 days ($P = .092$), but improved outcomes for per protocol patients supported with Impella 2.5 were observed at 90 days ($P = .023$).[11] All events were independently adjudicated by Harvard Clinical Research Institute, Boston, MA.

In the current analysis, the primary end point included the presence and extent of reverse LV remodeling as assessed by transthoracic echocardiography. Reverse LV remodeling was defined as improved systolic function with an absolute increase in EF of ≥5% from baseline to longest follow-up. This degree of quantitative EF change has been shown to correlate with reduced mortality in similar patients with heart failure and reduced EF.[15] Secondary end point analyses for this study involved the following composite rate of major adverse events: death, MI, stroke, and transient ischemic attack (TIA). The adverse events analyzed in this study were the same adjudicated events used in the PROTECT II trial.[11] Cardiac biomarkers were captured every 8 hours for the first 48 hours after PCI and daily thereafter for the duration of hospitalization. Periprocedural MIs were defined as creatine kinase-MB (CK-MB) isoenzyme ≥3 times the upper limit of normal within 72 hours of the PCI procedure. Spontaneous MIs were defined as new symptoms suggestive of MI with either positive biomarkers (CK-MB ≥2 times upper limit of reference range) or electrocardiographic changes occurring