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Fibroblast Growth Factor-23, Cardiovascular Prognosis, and Benefit of Angiotensin-Converting Enzyme Inhibition in Stable Ischemic Heart Disease

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Objectives This study sought to test 2 hypotheses: 1) fibroblast growth factor (FGF)-23 identifies patients with stable ischemic heart disease (SIHD) at high risk of cardiovascular events independent of clinical factors, renal function, and established cardiovascular biomarkers; and 2) FGF-23 identifies patients who derive greater clinical benefit from angiotensin-converting enzyme inhibitor therapy.

Background FGF-23 is an endocrine regulator of mineral metabolism and markedly elevated levels are associated with cardiovascular events in patients with chronic kidney disease. Data in patients with SIHD are more sparse.

Methods FGF-23 levels were measured in 3,627 patients with SIHD randomly assigned to trandolapril or placebo within the PEACE (Prevention of Events With Angiotensin-Converting Enzyme) trial and followed up for a median of 5.1 years.

Results After adjustment for clinical risk predictors, left ventricular ejection fraction, markers of renal function, and established cardiovascular biomarkers, FGF-23 concentration was independently associated with an increased risk of cardiovascular death or heart failure among patients allocated to placebo (quartile 4 hazard ratio: 1.73; 95% confidence interval, 1.09 to 2.74; $p = 0.02$) and significantly improved metrics of discrimination. Furthermore, among patients in the top quartile of FGF-23 levels, trandolapril significantly reduced cardiovascular death or incident heart failure (hazard ratio: 0.45; 95% confidence interval: 0.28 to 0.72), whereas there was no clinical benefit in the remaining patients (hazard ratio: 1.07; 95% confidence interval: 0.75 to 1.52; p interaction = 0.0039). This interaction was independent of and additive to stratification based on renal function.

Conclusions Elevated levels of FGF-23 are associated with cardiovascular death and incident heart failure in patients with SIHD and identify patients who derive significant clinical benefit from angiotensin-converting enzyme inhibitor therapy regardless of renal function. (Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy [PEACE]: NCT00000558) (J Am Coll Cardiol 2014;63:2421–8) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ACR = albumin to creatinine ratio
CI = confidence interval
CKD = chronic kidney disease
eGFR = estimated glomerular filtration rate
FGF = fibroblast growth factor
HR = hazard ratio
hs-CRP = high-sensitivity C-reactive protein
hs-cTnT = high-sensitivity cardiac troponin T
MI = myocardial infarction
NT-proBNP = *N*-amino terminal fragment of the prohormone B-type natriuretic peptide
RU = reference units
SIHD = stable ischemic heart disease

Fibroblast growth factor (FGF)-23 is a phosphatonin, a circulating endocrine regulator of mineral metabolism that rises in the earliest stages of renal impairment (1–3). Markedly elevated levels of FGF-23, observed in patients with moderate-to-severe chronic kidney disease (CKD), are associated with an increased risk of mortality (4,5). Data also suggest that FGF-23 levels at the higher end of the range seen within the general population may be associated with an increased risk of cardiovascular events in patients at risk for or with stable ischemic heart disease (SIHD) (6–10). However, the extent to which FGF-23 is a significant predictor of cardiovascular events independent of clinical comorbidities, conventional markers of renal function, and established cardiovascular biomarkers is unknown. Furthermore, whereas biomarkers of reduced renal function identify patients with SIHD who derive greater benefit from angiotensin-converting enzyme (ACE) inhibitor therapy (11,12), whether levels of FGF-23 can do the same or better remains untested. Therefore, we tested the hypotheses that in patients with SIHD, higher levels of FGF-23 were associated with an increased risk of cardiovascular events and identified patients who derived greater clinical benefit from ACE inhibition.

Methods

Study design and participants. The PEACE (Prevention of Events with Angiotensin-Converting Enzyme) Trial was a randomized trial of trandolapril versus placebo in 8,290 participants age ≥50 years with SIHD, left ventricular ejection fraction >40%, and serum creatinine ≤2.0 mg/dl that enrolled patients from November 1996 through June 2000 (13,14). All participants from the United States and Canada were eligible for biospecimen sampling at the discretion of each clinical center, and approximately half agreed to participate. All participants provided written informed consent, and this study was approved by the relevant institutional review boards. The current analysis included all patients who had an enrollment blood sample available for measurement of FGF-23 (n = 3,627). There were no clinically relevant differences between patients included in the substudy and the overall trial population (Online Table 1).

Biomarkers. FGF-23 levels were measured with a well-established *C*-terminal human enzyme-linked immunoabsorbent assay (Immunotopics, San Clemente, California) (15) in the Thrombolysis in Myocardial Infarction (TIMI) Clinical Trials Laboratory (Boston, Massachusetts) as detailed in the supplemental Methods section in the Online Appendix. In adults with preserved renal function, normal values for this assay are 55 ± 50 reference units (RU)/ml (15). Baseline levels of the *N*-amino terminal fragment of the prohormone B-type natriuretic peptide (NT-proBNP), cardiac troponin T measured with the high-sensitivity assay (hs-cTnT), C-reactive protein measured with a highly sensitive assay (hs-CRP), midregional pro-atrial natriuretic peptide, midregional pro-adrenomedullin, *C*-terminal pro-endothelin-1, estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation (16), cystatin C, and urinary albumin to creatinine ratio (ACR) have been determined in this population previously (12,17–21). All biochemical testing was performed by study personnel who were unaware of the clinical outcome and treatment assignment.

Endpoints. On the basis of prior data regarding the predictive ability of FGF-23 (6,7), the primary outcome of this analysis was the composite of cardiovascular death or hospitalization for heart failure. Additionally, we explored other major adverse cardiovascular events that had been part of the primary endpoint for the parent PEACE trial, including myocardial infarction (MI), stroke, and coronary revascularization. All clinical events were documented and adjudicated before this biomarker was measured (13).

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