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ORIGINAL INVESTIGATIONS

Medical Treatment and Revascularization Options in Patients With Type 2 Diabetes and Coronary Disease

G.B. John Mancini, MD,[a] Michael E. Farkouh, MD, MSc,[b] Maria M. Brooks, PhD,[c] Bernard R. Chaitman, MD,[d] William E. Boden, MD,[e] Helen Vlachos, MSc,[c] Pamela M. Hartigan, PhD,[f] Flora S. Siami, MPH,[g] Mandeep S. Sidhu, MD,[e] Vera Bittner, MD, MSPH,[h] Robert Frye, MD,[i] Valentin Fuster, MD, PhD[j]

ABSTRACT

BACKGROUND There are scant outcomes data in patients with type 2 diabetes and stable coronary artery disease (CAD) stratified by detailed angiographic burden of CAD or left ventricular ejection fraction (LVEF).

OBJECTIVES This study determined the effect of optimal medical therapy (OMT), with or without percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), on long-term outcomes with respect to LVEF and number of diseased vessels, including proximal left anterior descending artery involvement.

METHODS A patient-level pooled analysis was undertaken in 3 federally-funded trials. The primary endpoint was the composite of death, myocardial infarction (MI), or stroke, adjusted for trial and randomization strategy.

RESULTS Among 5,034 subjects, 15% had LVEF <50%, 77% had multivessel CAD, and 28% had proximal left anterior descending artery involvement. During a median 4.5-year follow-up, CABG + OMT was superior to PCI + OMT for the primary endpoint (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.59 to 0.85; p = 0.0002), death (HR: 0.76; 95% CI: 0.60 to 0.96; p = 0.024), and MI (HR: 0.50; 95% CI: 0.38 to 0.67; p = 0.0001), but not stroke (HR: 1.54; 95% CI: 0.96 to 2.48; p = 0.074). CABG + OMT was also superior to OMT alone for prevention of the primary endpoint (HR: 0.79; 95% CI: 0.64 to 0.97; p = 0.022) and MI (HR: 0.55; 95% CI: 0.41 to 0.74; p = 0.0001), and was superior to PCI + OMT for the primary endpoint in patients with 3-vessel CAD (HR: 0.72; 95% CI: 0.58 to 0.89; p = 0.002) and normal LVEF (HR: 0.71; 95% CI: 0.58 to 0.87; p = 0.0012). There were no significant differences in OMT versus PCI + OMT.

CONCLUSIONS CABG + OMT reduced the primary endpoint during long-term follow-up in patients with type 2 diabetes and stable CAD, supporting this as the preferred management strategy. (J Am Coll Cardiol 2016;68:985-95)

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From the [a]Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [b]Department of Medicine, Peter Munk Cardiac Centre and the Heart and Stroke Richard Lewar Centre of Excellence, University of Toronto, Toronto, Ontario, Canada; [c]Department of Epidemiology, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, Pennsylvania; [d]St. Louis University School of Medicine, St. Louis, Missouri; [e]Department of Medicine, Albany Medical College, Albany, New York; [f]West Haven Veterans Administration Coordinating Center, West Haven, Connecticut; [g]New England Research Institutes, Incorporated, Watertown, Massachusetts; [h]University of Alabama at Birmingham, Birmingham, Alabama; [i]Mayo Clinic, Rochester, Minnesota; and the [j]Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Mancini has received honoraria from Regeneron, Merck Canada, Amgen, Sanofi, Boehringer Ingelheim, and AstraZeneca; and has served on the advisory board for Amgen and Sanofi. Dr. Brooks has received a research grant from Gilead Sciences. Dr. Chaitman has served on the speakers bureau for Gilead Sciences; has served on the advisory boards of Merck, Sanofi, Novo Nordisk, and Lilly; has served on clinical events committees for Merck, Novo Nordisk, and Lilly; and has served on the Data Safety and Monitoring Board of Sanofi. Dr. Boden has received research grants from Abbvie and Amgen; has served on the speakers bureau for Janssen, Merck, Sanofi, and Gilead Sciences; and has served on the advisory boards of Arisaph, CardioDx, Merck, and Sanofi. Ms. Siami has received a research grant from Cordis.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CI = confidence interval

HR = hazard ratio

LVEF = ejection fraction

MI = myocardial infarction

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

pLAD = proximal left anterior descending

T2DM = type 2 diabetes mellitus

Cardiovascular disease is highly prevalent in patients with type 2 diabetes mellitus (T2DM), accounts for over one-half of all deaths in this population, generates approximately one-quarter of all referrals for coronary revascularization, and commonly creates management challenges because of the increasing frequency of T2DM (1–4). Although optimal medical therapy (OMT) is the foundation of treatment, and although the evidence base strongly favors the use of coronary artery bypass grafting (CABG) over percutaneous coronary intervention (PCI), particularly for multivessel disease, the decision to proceed initially with any of these options remains complex for several reasons, including highly variable patient characteristics, anatomic variations in CAD location, technical issues affecting PCI and CABG procedures, higher rates of suboptimal PCI results in patients with diabetes, increased need for repeat revascularization after PCI, concerns about perioperative stroke and mortality early after CABG, and diverse patient and physician preferences (5–7).

SEE PAGE 996

Existing meta-analyses of outcomes in patients with T2DM address only multivessel CAD (8–21); of these, only 1 provides patient-level meta-analysis (19), whereas none evaluate the critical role of OMT as the foundation of any treatment strategy. This pooling project was undertaken to assess randomly-assigned treatment (OMT, PCI + OMT, and CABG + OMT), as represented by 3 landmark trials (22–24), with an initial emphasis on the possible effects on outcomes of underlying left ventricular ejection fraction (EF) and the full spectrum of angiographic CAD patterns, including the presence or absence of proximal left anterior descending (pLAD) disease.

METHODS

Patient-level data from 3 prospective, randomized, federally-funded clinical trials (BARI 2D [Bypass Angioplasty Revascularization Investigation 2 Diabetes], COURAGE [Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation], and FREEDOM [Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease]) that enrolled patients with stable CAD with T2DM between 1999 and 2010 were pooled. Key variables, common definitions, and coding for each covariate and outcome were established jointly. The coordinating center investigators extracted deidentified patient-level data from the respective databases, and the University of Pittsburgh Data Management and Biostatistics Core Laboratory merged these into a single, pooled, patient-level dataset.

The BARI 2D and FREEDOM trials included only patients with CAD and T2DM, whereas COURAGE enrolled a broader group of patients with CAD, of whom only those with baseline T2DM were included in this analysis. Patients in the COURAGE trial were randomly assigned to OMT or PCI + OMT; patients in the FREEDOM trial were randomly assigned to PCI + OMT or CABG + OMT. In the BARI 2D trial, patients were first selected for PCI or CABG eligibility on the basis of physician judgment and coronary anatomy, and were then randomly assigned in the PCI stratum to OMT or PCI + OMT, and in the CABG stratum to OMT or CABG + OMT. As a result, the 2 strata in BARI 2D were considered separate clinical trials.

The primary outcome was the composite of death, myocardial infarction (MI), or stroke. The outcome definitions were those established for each trial. MI was centrally adjudicated in each trial (Online Appendix), as was stroke in the BARI 2D and FREEDOM trials, whereas site-reported stroke events were not centrally adjudicated in COURAGE. All trials had core laboratories that assessed baseline angiographic CAD. When core angiographic data were missing (n = 18), site angiographic data were used when available (n = 15). When the core laboratory determined that there was no lesion exceeding the 50% stenosis threshold (n = 169), the vessel with the greatest stenosis by core laboratory assessment was designated as the single vessel with disease.

Baseline variables were compared across the trials and were assigned treatment groups using Kruskal-Wallis statistics for continuous variables and chi-square statistics for categorical variables. All outcome comparisons were conducted according to the intention-to-treat principle, and time-to-event

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