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Impact of treatment strategies on outcomes in patients with stable coronary artery disease and type 2 diabetes mellitus according to presenting angina severity: A pooled analysis of three federally-funded randomized trials

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ABSTRACT

Background and aims: The impact of treatment strategies on outcomes in patients with stable coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) according to presenting angina has not been rigorously assessed.

Methods: We performed a patient-level pooled-analysis (n = 5027) of patients with stable CAD and T2DM randomized to optimal medical therapy [OMT], percutaneous coronary intervention [PCI] + OMT, or coronary artery bypass grafting [CABG] + OMT. Endpoints were death/myocardial infarction (MI)/stroke, post-randomization revascularization (both over 5 years), and angina control at 1 year.

Results: Increasing severity of baseline angina was associated with higher rates of death/MI/stroke ($p = 0.009$) and increased need for post-randomization revascularization ($p = 0.001$); after multivariable adjustment, only association with post-randomization revascularization remained significant. Baseline angina severity did not influence the superiority of CABG + OMT to reduce the rate of death/MI/stroke and post-randomization revascularization compared to other strategies. CABG + OMT was superior for angina control at 1 year compared to both PCI + OMT and OMT alone but only in patients with ≥ Class II severity at baseline. Comparisons between PCI + OMT and OMT were neutral except that PCI + OMT was superior to OMT for reducing the rate of post-randomization revascularization irrespective of presenting angina severity.

Conclusions: Presenting angina severity did not influence the superiority of CABG + OMT with respect to 5-year rates of death/MI/stroke and need for post-randomization revascularization. Presenting angina severity minimally influenced relative benefits for angina control at 1 year.

1. Introduction

Revascularization guidelines for the management of stable coronary artery disease (CAD) emphasize two treatment goals, namely, reduction of death or myocardial infarction (MI) and

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symptom relief [1–4]. In routine practice, CAD patients, particularly those with type 2 diabetes mellitus (T2DM) and severe angina, are more likely to have an expedited assessment of ischemic burden which, in turn, often leads to cardiac catheterization and revascularization with percutaneous coronary angioplasty (PCI) or coronary artery bypass grafting (CABG), often without a full assessment of the effects of optimal medical therapy (OMT) [5]. Conversely, patients with less severe or minimal angina understandably may be more accepting of an initial strategy of OMT, choosing to defer "upfront" revascularization, particularly CABG, unless symptom status dictates the need subsequently.

Prior observational studies assessing the long-term impact of baseline angina severity on the efficacy of therapeutic choices have yielded conflicting results, and interpretation of these findings is especially challenging in CAD patients with T2DM, many of whom display a higher frequency of absent or atypical angina, more diffuse and extensive atherosclerosis at the time of angiography, and a propensity for more rapid progression [6–15]. There has been only one assessment of the effect of baseline angina severity on clinical outcomes in stable CAD patients with T2DM suitable for revascularization who were enrolled in a randomized clinical trial [16]. The results unexpectedly suggested that patients be managed similarly, irrespective of presenting angina severity. However, this study had a limited number of subjects for subgroup analyses. Accordingly, we sought to determine in a larger, pooled-analysis of three federally-funded randomized trials of stable CAD patients with T2DM whether presenting angina severity impacts the clinical outcome of different initial therapeutic strategies with respect to: 1) the risk of death, MI or stroke, 2) symptom status at 1 year, and 3) the need for subsequent revascularization procedures during 5 years of follow-up.

2. Patients and methods

2.1. Population

Patient-level data were pooled as previously described [17–20] 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 Multi-vessel Disease]) that enrolled stable CAD patients with T2DM and cardiac ischemic symptoms or documented myocardial ischemia who were suitable for revascularization. Written informed consent was obtained from each patient included in the studies, the study protocols conform to the ethical guidelines of the 1975 Declaration of Helsinki and the study protocols had been approved by the Institution's ethics committee on research on humans (NCT 0007657 [COURAGE]; 00006305 [BARI 2D]; 00086450 [FREEDOM]). Patients were enrolled between 1999 and 2010. Treatment strategy was randomly allocated within each of 4 trial cohorts (COURAGE diabetic subset [OMT vs PCI + OMT], FREEDOM [PCI + OMT vs CABG + OMT], BARI 2D PCI stratum [OMT vs PCI + OMT], and BARI 2D CABG stratum [OMT vs CABG + OMT]). We have previously reported that of the 2051 (97%) patients who underwent the assigned PCI, 94% received stents and 58% received a drug-eluting stent. Of the 1232 (93%) patients who underwent the assigned CABG, 94% had an internal mammary artery graft [17]. Angina status was assessed by the site investigators and study coordinators at baseline and at regular intervals during long-term follow-up using Canadian Cardiovascular Society (CCS) class. To allow for more detailed analysis, we also considered asymptomatic patients and modified CCS Class I to include patients with known CAD but with atypical symptoms (Class I or Atypical: angina that occurred only with strenuous or rapid or prolonged exertion, or atypical symptoms that occurred with physical activities). The remaining were defined as usual (Class II: angina causing slight limitation during normal physical activity; Class III/IV: angina causing marked limitation of normal activity or episodes of angina at rest). Within this pooled cohort, a subset of patients recently stabilized after acute coronary syndrome (ACS) from the FREEDOM trial were included in the Class III/IV category for the overall analysis in order to represent the full spectrum of patients studied, but were then excluded and data re-analyzed to provide a sensitivity analysis.

2.2. Outcomes

The previously assessed composite outcomes of death, MI, or stroke over 5 years were ascertained based on the adjudicated events according to the definitions established for each trial [17]. Additionally, we examined: 1) angina status $\geq$ Class II (i.e. Class II, III or IV versus Class I or asymptomatic status) at 1 year after randomization; and 2) the need for the first revascularization procedure received for patients assigned initially to OMT alone and the need for the first subsequent procedure received after the index procedure for patients assigned initially to PCI or CABG during up to 5 years of follow-up (i.e. post-randomization, unplanned or subsequent revascularization). This analysis included all patients without missing baseline angina status and, for assessment of angina at 1 year, all patients with both baseline and 1 year angina status available for review.

2.3. Statistical methods

Baseline variables were compared across the four angina severity groups using Kruskal-Wallis statistics for continuous variables and chi-square statistics for categorical variables. We evaluated the impact of baseline angina severity on the clinical outcomes of death/MI/stroke, and subsequent revascularizations using Kaplan-Meier curves with log rank statistics and multivariable Cox regression models that were created to adjust for features of the study design, known risk factors for cardiovascular events, and clinical features that were distributed differentially among the angina groups (trial, age, sex, country, body mass index, smoking status, hypertension, prior MI, prior revascularization, heart failure, abnormal left ventricular ejection fraction $< 50\%$, number of diseased vessels and use of insulin). All time-to event outcomes were censored at 5 years. Treatment comparisons were conducted according to the intention-to-treat principle. For the time-to-event outcomes, the unadjusted event rates by assigned treatment strategy were derived from Kaplan-Meier estimates. Trial-adjusted estimates of treatment effects were obtained using Cox proportional hazards regression models. Proportions and trial-adjusted logistic regression models were used to compare the 1-year angina outcome by assigned treatment strategy. Since treatment strategy was randomly allocated within each of the 4 trial groups (COURAGE diabetic subset, FREEDOM, BARI 2D PCI stratum, BARI 2D CABG stratum), adjusting for trial group allowed us to obtain a valid risk estimate for the 3 treatment strategies accounting for the different patient profiles and risk-levels in the 4 trial groups [17–20]. Importantly, this process ensured that each treatment comparison included patients with anatomical burden of angiographically-significant CAD deemed suitable for either of the treatment options being compared as reflected by randomization within the original trials. Thus, the trial-adjusted multivariable model hazard ratios (HRs) and odds ratios (ORs) are unbiased estimates of the risk of an event for a given pair of treatments.

Outcomes were compared by initial treatment strategy in the

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