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ORIGINAL INVESTIGATIONS

Dual Antiplatelet Therapy Versus Aspirin Monotherapy in Diabetics With Multivessel Disease Undergoing CABG

FREEDOM Insights

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ABSTRACT

BACKGROUND Clinical practice guidelines recommend post-operative dual antiplatelet therapy (DAPT) in patients who undergo coronary artery bypass grafting (CABG) following acute coronary syndromes (ACS).

OBJECTIVES The authors have evaluated DAPT utilization rates and associated outcomes among post-CABG patients with diabetes.

METHODS In a post hoc, nonrandomized analysis from the FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) trial, we compared patients receiving DAPT (aspirin plus thienopyridine) and aspirin monotherapy at 30 days post-operatively. The primary outcome was the risk adjusted 5-year FREEDOM composite of all-cause mortality, nonfatal myocardial infarction, or stroke. Safety outcomes included major bleeding, blood transfusion, and hospitalization for bleeding.

RESULTS At 30 days post-CABG, 544 (68.4%) patients received DAPT and 251 (31.6%) patients received aspirin alone. The median (25th, 75th percentile) duration of clopidogrel therapy was 0.98 (0.23 to 1.91) years. There was no significant difference in the 5-year primary composite outcome between DAPT- and aspirin-treated patients (12.6% vs. 16.0%; adjusted hazard ratio [HR]: 0.83; 95% confidence interval [CI]: 0.54 to 1.27; p = 0.39). The 5-year primary composite outcomes were similar for patients receiving DAPT versus aspirin monotherapy respectively, in subgroups with pre-CABG ACSs (15.2% vs. 16.5%; HR: 1.06; 95% CI: 0.53 to 2.10; p = 0.88) and those with stable angina (11.6% vs. 15.8%; HR: 0.82; 95% CI: 0.50 to 1.343; p = 0.42). The composite outcomes of both treatment groups were also similar by SYNTAX score, duration of DAPT therapy, completeness of revascularization, and in off-pump CABG. No treatment-related differences in major bleeding (5.6% vs. 5.7%; HR: 1.00; 95% CI: 0.50 to 1.99; p = 0.99), blood transfusions (4.8% vs. 4.5%; HR: 1.09; 95% CI: 0.51 to 2.34; p = 0.82), or hospitalization for bleeding (2.6% vs. 3.3%; HR: 0.85; 95% CI: 0.34 to 2.17; p = 0.74) were observed between aspirin- and DAPT-treated patients, respectively.

CONCLUSIONS The use of DAPT in patients with diabetes post-CABG in our cohort was high. Compared with aspirin monotherapy, no associated differences were observed in cardiovascular or bleeding outcomes, suggesting that routine use of DAPT may not be clinically warranted. (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease [FREEDOM]; NCT00086450) (J Am Coll Cardiol 2017;69:119–27)

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass surgery

CI = confidence interval

DAPT = dual antiplatelet therapy

HR = hazard ratio

MI = myocardial infarction

NSAID = nonsteroidal anti-inflammatory drug

PPI = proton pump inhibitor

Coronary artery bypass surgery (CABG) reduces long-term morbidity and mortality in patients with multivessel disease with or without diabetes (1–3). Aspirin alone has been reported to improve vein graft patency and mortality (4,5). Dual antiplatelet therapy (DAPT) with aspirin and a thienopyridine is a theoretically attractive secondary prevention therapy, given that bypass graft thrombosis and systemic hypercoagulability are potential causes of saphenous vein graft failure (6). In addition, native coronary artery atherothrombotic risk for plaque rupture, ulceration, or erosion remains post-CABG (7,8). Clinical practice guidelines currently recommend DAPT in patients who undergo CABG for an acute coronary syndrome; however, the efficacy of DAPT reported in observational studies, subgroup analyses, and small randomized trials that underpin these recommendations is uncertain, and DAPT may be associated with a higher risk of bleeding (9–16).

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Diabetes is independently associated with increased perioperative and long-term mortality in CABG patients, and may be a clinical risk factor for vein graft failure (17–20). Hence, diabetics may be a unique high-risk subgroup that may benefit from DAPT secondary prevention therapy, but little evidence is available to support this hypothesis. The purpose of this analysis is to compare the long-term clinical and bleeding outcomes associated with DAPT versus aspirin monotherapy in post-bypass diabetics with multivessel coronary artery disease from the FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) trial (1).

METHODS

DATA SOURCE. The methods and results of the FREEDOM trial have been published (1,21). Briefly, this international multicenter study enrolled patients ≥ 18 years of age with diabetes mellitus (DM) and with ≥70% stenosis of 2 or more major epicardial vessels. Patients were randomized to either CABG or percutaneous coronary intervention with drug-eluting stents. All study participants provided written consent.

STUDY POPULATION AND DEFINITIONS. This analysis included all patients who underwent primary revascularization with CABG (per-protocol analysis) and were taking aspirin 30 days post-operatively. Patients undergoing DAPT were defined as all patients who were receiving aspirin and a thienopyridine (clopidogrel or ticlopidine) at 30 days post-operatively. The aspirin cohort was defined as those receiving aspirin monotherapy at 30 days. Patients receiving warfarin at 30 days were excluded. The primary analysis compared 5-year outcomes in patients treated with DAPT versus aspirin alone at 30-days post-CABG. The secondary analysis examined 1-year outcomes.

OUTCOMES. The primary outcome was the FREEDOM trial primary endpoint of 5-year all-cause mortality, nonfatal myocardial infarction (MI), or stroke. Secondary outcomes included the individual components of the composite outcomes: vascular death, MI, and cardiovascular hospitalization (defined as unstable angina, MI, heart failure, chest pain, arrhythmia, peripheral vascular disease, or stroke or transient ischemic attack). Safety outcomes were major bleeding, blood transfusions, and bleeding hospitalization. All events were adjudicated by a clinical events committee.

In a priori analysis, we also explored the primary outcome and major bleeding in the following subgroups: 1) patients revascularized following an acute coronary syndrome event versus stable angina; 2) SYNTAX score (<22, 22 to 32, ≥32); 3) complete versus incomplete revascularization; 4) patients with an endarterectomy or vein graft patching; 5) on- and off-pump CABG; 6) patients who maintained DAPT for a minimum of 1 year; and 7) post-operative glomerular filtration rate.

STATISTICAL METHODS. Categorical baseline characteristics were summarized as number of subjects and percentages. The difference between the 2 treatment groups was tested using Fisher exact test. Continuous baseline characteristics were summarized as median and quartiles. The differences between the 2 treatment groups were tested using Kruskal-Wallis test statistics. The times to primary, secondary, and safety outcomes were analyzed using Cox proportional

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