Association of dual-antiplatelet therapy with reduced major adverse cardiovascular events in patients with symptomatic peripheral arterial disease

Ehrin J. Armstrong, MD, MS,[a] David R. Anderson, MD,[b] Khung-Keong Yeo, MBBS,[b] Gagan D. Singh, MD,[b] Heejung Bang, PhD,[c] Ezra A. Amsterdam, MD,[b] Julie A. Freischlag, MD,[d] and **John R. Laird, MD,[b]** *Denver, Colo; and Sacramento, Calif*

Objective: **This study was conducted to determine whether there is additive benefit of dual-antiplatelet therapy (DAPT) with aspirin (acetylsalicylic acid [ASA]) and clopidogrel compared with ASA monotherapy among patients with symptomatic peripheral arterial disease.**

Methods: **This was an observational cohort analysis that included 629 patients with claudication or critical limb ischemia. The prevalence of patients taking ASA monotherapy vs DAPT was assessed monthly for up to 3 years. A propensity model was constructed to adjust for baseline demographic characteristics and to assess the effect of DAPT on major adverse cardiovascular events (MACEs) and major adverse limb events.**

Results: **At baseline, 348 patients were taking DAPT and 281 were taking ASA monotherapy. During 3 years of follow-up, 50 events (20%) occurred in the DAPT group vs 59 (29%) in the ASA monotherapy group. After propensity weighting, DAPT use was associated with a decreased risk of MACEs (adjusted hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.44-0.96) and overall mortality (adjusted HR, 0.55; 95% CI, 0.35-0.89). No association was found between DAPT use and the risk of major amputation (adjusted HR, 0.69; 95% CI, 0.37-1.29). In a subgroup of 94 patients who underwent point-of-care platelet function testing, 21% had decreased response to ASA and 55% had a decreased response to clopidogrel. No association was found between a reduced response to ASA or clopidogrel and adverse events at 1 year.**

Conclusions: **DAPT may be associated with reduced rates of MACEs and death among patients with symptomatic peripheral arterial disease. (J Vasc Surg 2015;62:157-65.)**

Patients with peripheral arterial disease (PAD) are at increased risk of major adverse cardiovascular events (MACEs) and overall mortality.[1-3] A number of medical therapies have been shown to reduce cardiovascular mortality among patients with PAD, including statins, angiotensin-converting enzyme (ACE) inhibitors, and abstention from smoking.[4-10] Antiplatelet agents also reduce MACEs in patients with symptomatic PAD, with a small additional benefit of clopidogrel relative to aspirin (acetylsalicylic acid [ASA]) monotherapy.[11-13] There are little data, however, regarding the possible additive benefit of dual-antiplatelet therapy (DAPT) in this patient population. A subgroup analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial suggested that DAPT use may be associated with a reduction in myocardial infarction (MI) and hospitalization for ischemic events in patients with PAD.[14,15] However, DAPT vs ASA monotherapy has not been systematically studied among a group of patients with more advanced PAD, including severe lifestyle-limiting claudication or critical limb ischemia (CLI). These patients represent a high-risk cohort of patients with PAD who may be most likely to benefit from more intensive antiplatelet therapy.

In this study, we assessed the relationship between DAPT and subsequent mortality, MACEs, and limb-related outcomes among a cohort of patients with moderate to severe claudication or CLI treated at a multidisciplinary vascular center. We also studied the association between antiplatelet resistance and outcomes among a subgroup of these patients.

METHODS

The University of California (UC), Davis Medical Center Institutional Review Board approved the study protocol with a waiver of informed consent.

Study design and data sources. We conducted a cohort study using data from the UC Davis PAD Registry. This registry comprises all patients with a clinical diagnosis of PAD who underwent diagnostic angiography or

From the Division of Cardiology, University of Colorado, and Veterans Affairs Eastern Colorado Health Care System, Denver[a]; and the Vascular Center and Division of Cardiovascular Medicine, Department of Internal Medicine,[b] Division of Biostatistics, Department of Public Health Sciences,[c] and Department of Surgery,[d] University of California, Davis, Sacramento.

E.J.A. is supported by American Heart Association grant 11CRP7260031.

Author conflict of interest: J.R.L. is a consultant for Boston Scientific, Covidien, Abbott, Bard, and Medtronic. E.J.A. is a consultant for Abbott, Medtronic, and Spectranetics.

Additional material for this article may be found online at www.jvascsurg.org.

Reprint requests: John R. Laird, MD, UC Davis Medical Center, 4860 Y St, Ste 3400, Sacramento, CA 95817 (e-mail: john.laird@ucdmc.ucdavis.edu).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

Published by Elsevier Inc. on behalf of the Society for Vascular Surgery.

http://dx.doi.org/10.1016/j.jvs.2015.01.051

therapeutic endovascular intervention, or both, at the UC Davis Medical Center between June 2006 and May 2013, as previously described.[16] At the time of data extraction, the registry included 1201 patients who underwent 1897 procedures. A total of 753 patients presented with claudication or CLI and were included in this study; the other patients in the registry included those presenting with acute limb ischemia, carotid artery stenosis, subclavian artery stenosis, or renal artery stenosis. The median length of patient follow-up was 3.2 years.

All patients in the registry with symptomatic PAD defined by claudication or CLI were included in the study cohort. All patients underwent diagnostic or interventional lower extremity angiography at the UC Davis Medical Center. Data collection was based on detailed electronic medical records and angiographic review. Baseline demographic, clinical, laboratory, and procedural data were obtained through preprocedure clinical notes, admission history, and in-patient documentation. Prescriptions for ASA, clopidogrel, ticlopidine, and prasugrel were verified by pharmacy prescriptions during the month before the procedure and at 1-month intervals during 36 months of follow-up. All records were reviewed by trained chart abstractors and verified by a board-certified cardiologist.

During the study period, 753 patients with claudication or CLI underwent lower extremity angiography; of these, 96 patients were prescribed warfarin before the procedure, and 28 were not taking any antiplatelet therapy, leaving 629 patients in the analysis cohort. Patients were categorized as taking ASA monotherapy if they were prescribed ASA without concomitant clopidogrel, ticlopidine, or prasugrel. Patients were categorized as taking DAPT if they were prescribed ASA and clopidogrel (n = 342), ticlopidine (n = 1), or prasugrel (n = 5). Continued antiplatelet therapy use was assessed every month after lower extremity angiography for up to 3 years. Use of ASA and other antiplatelet agents was determined by the electronic medical record, prescribing records, and clinic visit notes.

Data definitions. MACEs were defined as MI, stroke, or death. MI was defined as symptoms of chest pressure and elevation of troponin with evidence of infarct by myocardial perfusion imaging or cardiac catheterization. Stroke was defined as focal neurologic deficit with computed tomography or magnetic resonance imaging evidence of cerebral ischemic or hemorrhagic infarct. All deaths were confirmed via direct record documentation or the Social Security Death Index, with most cases determined via the Social Security Death Index.[17] Because a combination of data sources was used for mortality determination, only all-cause mortality is reported.

Major adverse limb events (MALEs) were defined as major lower extremity limb amputation above the level of the ankle joint, thrombolysis, or surgical bypass.[18] Claudication was classified as Rutherford category 1 to 3 disease (mild, moderate, or severe claudication, respectively), and CLI was classified as Rutherford category 4 to 6 disease (ischemic rest pain, minor tissue loss, or major tissue loss, respectively).[19]

Measurement of antiplatelet resistance. Testing for antiplatelet resistance was performed in a subset of 94 patients as part of an Institutional Review Board-approved study that included provision of informed consent by participants. This was a separately funded study conducted during 2011 to 2012. All patients underwent lower extremity intervention for claudication or CLI. If patients were taking clopidogrel preprocedure, blood was drawn at the start of the procedure. For patients who started taking ASA or clopidogrel during the procedure, blood was drawn at least 5 hours after the initial dosing. Blood was then tested ≤2 hours using the VerifyNow assay (Accumetrics, San Diego, Calif) for ASA or thienopyridine resistance. ASA resistance was defined as aspirin reaction units ≥550 based on prior studies,[20] and thienopyridine resistance was defined as $P2Y_{12}$ reaction units (PRU) ≥235.[21]

Outcomes. The primary outcome of the study was the occurrence of MACEs during the 3-year follow-up period. Loss to follow-up during the 3 years consisted of 68 of 348 patients (19.5%) in the DAPT group and 56 of 281 (20%) in the ASA monotherapy group, suggesting that there was not any differential censoring. Prespecified secondary outcomes included the occurrence of MALEs, the individual components of MACEs and MALEs, and the combined incidence of death or major amputation during the 3-year follow-up period. For the subgroup of patients with testing performed for antiplatelet resistance, a combined end point of death, MI, stroke, major amputation, surgical bypass, or repeat revascularization was used.

Statistical analysis. Means with standard deviations are used to describe continuous variables and frequencies and percentages are used for categoric variables. Continuous variables were compared using the Wilcoxon rank sum test and categoric values using χ^2 or Fisher exact tests.

Propensity scores were developed to adjust for covariates that may influence the decision to prescribe ASA monotherapy vs DAPT.[22] A comprehensive set of baseline covariates was included in the propensity model: age, sex, patient-reported race/ethnicity (Caucasian, Hispanic, African American, Asian), body mass index, glomerular filtration rate, history of diabetes, congestive heart failure, coronary artery disease, prior MI, smoking status (active, former, or never), hypertension, stroke, carotid artery disease, chronic obstructive pulmonary disease, malignancy, abdominal aortic aneurysm, prior gastrointestinal bleeding, prior above-ankle amputation, left ventricular ejection fraction (in 5% increments from ≤10% to ≥65%), Rutherford score (1-6), and prescription of concomitant medications, including statin medications, β-blockers, and ACE inhibitors.

Diagnostic tests to demonstrate balance of the covariates after inverse probability of treatment weighting (IPTW) included calculation of the standardized difference before and after weighting and visual inspection of a kernel density plot to verify propensity score overlap between groups (Supplementary Table I, online only). Visual inspection of propensity scores by treatment group before