JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 21, 2018

PUBLISHED BY ELSEVIER

THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Antithrombotic Therapy for Peripheral Artery Disease

Recent Advances

Mohamad A. Hussain, MD, PHD,[a,b,c] Mohammed Al-Omran, MD, MSC,[b,c,d] Mark A. Creager, MD,[e] Sonia S. Anand, MD, PHD,[f] Subodh Verma, MD, PHD,[b,g] Deepak L. Bhatt, MD, MPH[a,h]

ABSTRACT

Peripheral artery disease (PAD) affects over 200 million people globally and is a cause of significant morbidity, mortality, and disability due to limb loss. Although secondary prevention with antithrombotic therapy is a mainstay of treatment to prevent adverse cardiovascular events, PAD patients are often undertreated with antithrombotic agents. Furthermore, there is a paucity of high-quality data from randomized controlled trials of PAD patients, leading to wide variations in clinical practice and guideline recommendations. Recently, there have been important advances that have further increased the number of antiplatelet and anticoagulant choices potentially available for patients with PAD. In this context, this paper aims to summarize the current available evidence for the safety and efficacy of various antithrombotic agents in PAD, and discuss how to integrate this emerging evidence into actual clinical practice. An evidenced-based approach to PAD patients is essential to achieve optimal outcomes, weighing cardiovascular and limb benefits against bleeding risks. (J Am Coll Cardiol 2018;71:2450–67) © 2018 by the American College of Cardiology Foundation.

From the [a]Brigham and Women's Hospital Heart & Vascular Center, Boston, Massachusetts; [b]Department of Surgery, University of Toronto, Toronto, Ontario, Canada; [c]Division of Vascular Surgery, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada; [d]Department of Surgery, King Saud University, Riyadh, Kingdom of Saudi Arabia; [e]Dartmouth-Hitchcock Medical Center, Geisel School of Medicine at Dartmouth, Lebanon, New Hampshire; [f]Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada; [g]Division of Cardiac Surgery, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada; and the [h]Harvard Medical School, Boston, Massachusetts. Dr. Anand has received speaker honoraria from Bayer and Novartis. Dr. Verma has received speaker honoraria from Boehringer Ingelheim, Bayer, Pfizer, Sanofi, Eli Lilly, Amgen, AstraZeneca, Mylan, Merck, Janssen, Novo Nordisk, and Abbott; and research support from Amgen, AstraZeneca, Boehringer Ingelheim, and Eli Lilly. Dr. Bhatt has served on the advisory board for Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; has served on the board of directors of the Boston VA Research Institute and Society of Cardiovascular Patient Care; has served as the chair of American Heart Association Quality Oversight Committee; has served on the data monitoring committees of the Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; has received honoraria from the American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor; associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (CME steering committees); has served as the deputy editor for *Clinical Cardiology*; has served as the chair of the NCDR-ACTION Registry Steering Committee and VA CART Research and Publications Committee; has received research funding from Abbott, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi, and The Medicines Company; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald Heart Disease*); has served as a site co-investigator for Biotronik, Boston Scientific, and St. Jude Medical (now Abbott); has served as a trustee of American College of Cardiology; and has performed unfunded research for FlowCo, PLx Pharma, and Takeda. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 26, 2017; revised manuscript received March 16, 2018, accepted March 21, 2018.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.03.483

Peripheral artery disease (PAD) is the third most common manifestation of atherosclerosis after coronary artery disease and cerebrovascular disease. Globally, 202 million people were estimated to be living with PAD in 2010—this number has increased by nearly a quarter since 2000 (1). Furthermore, in contrast to the declining rate of age-adjusted mortality due to cardiovascular causes (2,3), mortality due to PAD has increased over the last 2 decades (3,4). Coincidently, and unfortunately, the most feared complication of PAD, namely amputation, has also remained relatively unchanged (5).

Patients with PAD have systemic atherosclerosis, and their natural history is worse than those of patients with coronary or cerebrovascular disease (6–9). In the multinational REACH (Reduction of Atherothrombosis for Continued Health) registry, 40% of PAD patients experienced myocardial infarction, stroke, vascular death, or hospitalization over 3 years—this was considerably higher in those with coronary (30%) or cerebrovascular disease (28%) (8). Likewise, in contemporary clinical trials involving patients with diabetes, cardiovascular event rates are higher in patients with PAD compared with those without PAD (10). In the REACH registry, as well as contemporary cardiovascular outcome trials in diabetes, vascular event rates were even higher among patients with polyvascular disease (established vascular disease in 2 or 3 arterial beds) (7,9,11). The majority (62%) of PAD patients enrolled in the REACH registry had polyvascular disease (6). In addition, symptomatic PAD patients are at increased risk for adverse limb events, which include progression to debilitating claudication, critical limb ischemia (rest pain, ulcers, or gangrene), and ultimately amputation (12). A total of 24% of symptomatic PAD patients experienced a limb event after 4 years in the REACH registry (13).

Atherosclerotic narrowing of the infrarenal aorta and arteries of the legs is the most common cause of PAD (14). Platelet activation plays a central role in the development of these atherosclerotic lesions, and also contributes to acute arterial thrombosis in conjunction with the coagulation cascade (15,16); therefore, medical management of PAD includes antithrombotic therapy to reduce adverse cardiovascular and limb events (17,18). However, several studies have shown that PAD patients, who are at highest for atherothrombotic events, are also the most likely to be undertreated with antithrombotic agents (19–22). Part of this care gap may be explained by a lack of consensus around the optimal antithrombotic strategy in PAD patients. A paucity of high-quality data has led to variations in prescribing patterns among clinicians and some discrepancies in guideline recommendations (23–25). In addition to a paucity of original literature on antithrombotic therapy in PAD patients, there is also a paucity of high-quality review articles in this area (26). In this context, we sought to summarize the current available evidence for the safety and efficacy of various antithrombotic agents in PAD patients, and propose a clinical decision-making algorithm that may aid clinicians in selecting the most appropriate antithrombotic treatment strategy in patients with PAD (**Central Illustration**).

ABBREVIATIONS AND ACRONYMS

ABI = ankle-brachial index

HR = hazard ratio

MACCE = major adverse cardiovascular or cerebrovascular events

MALE = major adverse limb events

NNT = number needed to treat

OR = odds ratio

PAD = peripheral artery disease

RR = risk ratio

SVS = Society for Vascular Surgery

ANTITHROMBOTIC THERAPY IN STABLE PAD

Data on antithrombotic therapy for stable PAD are largely derived from subanalyses of randomized trials that enrolled patients with various manifestations of atherosclerosis, including coronary disease, cerebrovascular disease, and PAD. Importantly, the definition of PAD employed in various clinical trials varies. In general, these trials defined stable PAD as an ankle-brachial index (ABI) of <0.90 with or without symptoms of claudication, >50% peripheral artery stenosis on duplex ultrasound or angiography, or previous intervention for PAD (peripheral angioplasty, surgical bypass, or lower extremity amputation). The primary efficacy outcome in these trials was generally a composite of major adverse cardiovascular or cerebrovascular events (MACCE), with some trials also reporting major adverse limb events (MALE). In addition, the majority of these trials have focused on patients with symptomatic PAD; few have examined the influence of antithrombotic therapy in asymptomatic PAD. **Table 1** provides details and results of studies of various antithrombotic agents in patients with stable asymptomatic and symptomatic PAD.

ASYMPTOMATIC PAD. Aspirin. Two randomized, placebo-controlled trials studied the effect of aspirin on cardiovascular outcomes in patients with asymptomatic PAD: the POPADAD (Prevention of Progression of Arterial Disease and Diabetes) trial (27) and the AAA (Aspirin for Asymptomatic Atherosclerosis) trial (28). The POPADAD trial, which enrolled 1,276 patients with an ABI of ≤0.99 and diabetes, found no significant difference in the composite risk of MACCE or amputation between aspirin and placebo (18.2% vs. 18.3%, respectively; hazard ratio [HR]: 0.98 [95% confidence interval (CI): 0.76 to 1.26). The AAA trial randomized 3,350 patients with an ABI of ≤0.95 to aspirin or placebo. After a mean follow-up of 8.2 years, there was no significant