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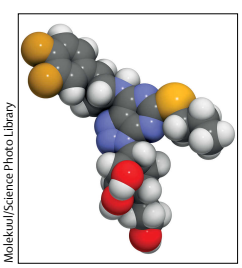
Aspirin—still the GLOBAL LEADER in antiplatelet therapy



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Dual antiplatelet therapy for at least a year is the standard of care after an acute coronary syndrome. Attempts to shorten the duration of therapy have resulted in an increase in myocardial infarction.[1,2] Lengthening of the duration of dual antiplatelet therapy beyond a year in high-risk patients with acute coronary syndromes further reduces the risk of myocardial infarction and even ischaemic stroke.[3] In patients undergoing elective percutaneous coronary intervention with current-generation drug-eluting stents, treatment guidelines recommend 6 months of dual antiplatelet therapy (or potentially longer if complex stenting is necessary).[4] The downside to prolonged dual antiplatelet therapy is an inevitable increased risk of major bleeding.[5] Concurrently, stent design has also evolved, with a significant reduction in the frequency of stent thrombosis with contemporary drug-eluting stents compared with earlier-generation drug-eluting stents and possibly even bare-metal stents.[6,7] Therefore, strategies to de-escalate the duration or intensity of dual antiplatelet therapy are of interest.[8]

In *The Lancet*, Pascal Vranckx and colleagues have examined one such approach.[9] In the GLOBAL LEADERS trial, 15 991 patients who underwent percutaneous coronary intervention were randomly assigned to 1 month of aspirin plus ticagrelor followed by 23 months of ticagrelor monotherapy or to a control regimen of 1 year of standard dual antiplatelet therapy (aspirin plus either clopidogrel or ticagrelor) followed by 1 year of aspirin monotherapy. The primary endpoint of mortality or new Q-wave myocardial infarction at 2 years occurred in 304 (3·81%) participants in the experimental group and 349 (4·37%) in the control group (rate ratio 0·87 [95% CI 0·75–1·01]; p=0·073). Consistent with the findings for the primary endpoint, the individual frequencies of death or new Q-wave myocardial infarction did not differ significantly between groups, and the addition of stroke to the composite endpoint did not significantly affect results (rate ratio 0·87 [95% CI 0·76–1·00]; p=0·056). Definite stent thrombosis (rate ratio 1·00 [95% CI 0·71–1·42]; p=0·98) and major bleeding (0·97 [0·78–1·20]; p=0·77) occurred at similar frequencies in both groups. There was no heterogeneity with respect to efficacy endpoints among the key subgroups of patients with acute coronary syndrome or stable coronary artery disease. Thus, compared with standard treatment, the experimental regimen had no clear benefits and no clear harms either. However, in view of the higher rates of discontinuation, the increased frequency of dyspnoea, and the higher cost associated with the experimental regimen than with the control group, as well as the necessity of twice daily dosing with ticagrelor, aspirin should remain the preferred antiplatelet therapy for secondary prevention.

As a pragmatic trial, GLOBAL LEADERS had a complex design, inasmuch as patients in the control group could receive aspirin in combination with either ticagrelor (if they had acute coronary syndrome) or clopidogrel (if they had stable coronary artery disease). Thus, a limitation of the trial is that different antiplatelet regimens and different durations of dual antiplatelet therapy were concomitantly assessed, making formal assessments of non-inferiority challenging, especially because the trial was open label. The short follow-up of 2 years limited the ability to establish whether the

numerical trends in the trial would become significant. Even though the number of patients was large, the number of events was not, further restricting the ability to assess subgroups, such as patients with acute coronary syndromes.

The safest interpretation of GLOBAL LEADERS is that an innovative strategy of antiplatelet therapy was tested but was not superior to standard dual antiplatelet therapy. Thus, practice should not be changed on the basis of the trial's results. The current standards of care for antiplatelet therapy should continue for the time being. That does not mean that aspirin monotherapy cannot be improved upon. The addition of low-dose anticoagulation to aspirin has been shown to lower ischaemic events compared with aspirin alone in patients with high-risk coronary artery disease or peripheral artery disease—although low-dose anticoagulation alone was not better than aspirin.[10–12] Several trials are underway to establish whether the duration of dual antiplatelet therapy after elective stenting can be shortened. The best way to optimise the balance between reduction of the risk of ischaemic events and avoidance of bleeding risk could be to use biological assays or simple risk scores to establish the ideal intensity and duration of antithrombotic therapy in individual patients.[8,13,14] Thus, the field of tailoring therapy remains ripe for investigation.

Deepak L Bhatt
Brigham and Women's Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA 02115, USA
dlbhattmd@post.harvard.edu

I have served on advisory boards for Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences, the board of directors for Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft, as chair of the American Heart Association Quality Oversight Committee, and on data monitoring committees for the Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St Jude Medical, now Abbott), Cleveland Clinic, Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), and Population Health Research Institute. I have received honoraria from the American College of Cardiology (for work as a Senior Associate Editor, Clinical Trials and News and as the vice-chair of the Accreditation Committee), Baim Institute for Clinical Research (for work on the RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (for work as the Editor in Chief of *Harvard Heart Letter*), the Duke Clinical Research Institute (for serving on clinical trial steering committees), HMP Global (for work as the Editor in Chief, *Journal of Invasive Cardiology*), the *Journal of the American College of Cardiology* (for work as a guest or associate editor), the Population Health Research Institute (for work on the COMPASS operations committee, publications committee, and steering committee, and as USA national co-leader, funded by Bayer), Slack Publications (for work as the chief medical editor of *Cardiology Today's Intervention*), the Society of Cardiovascular Patient Care (for serving as secretary and treasurer), and WebMD (for work on continuing medical education steering committees). I have been the deputy editor of *Clinical Cardiology* and chaired the NCDR-ACTION Registry Steering Committee and VA CART Research and Publications Committee (unpaid). I have received research funding from Abbott, Amarin, Amgen, AstraZeneca (including for my role as co-chair of the THEMIS study of ticagrelor in patients with diabetes), Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi Aventis, Synaptic, and The Medicines Company. I have received royalties from Elsevier for my work as editor of *Cardiovascular Intervention: a Companion to Braunwald's Heart Disease*. I have been a site co-investigator for Biotronik, Boston Scientific, and St Jude Medical (now Abbott), and Svelte, and a trustee of the American College of Cardiology. I have done unfunded research in collaboration with FlowCo, Merck, PLx Pharma, and Takeda. With regard to dual antiplatelet therapy, for my role in the CHARISMA trial, the Cleveland Clinic received research funding. In the PEGASUS and THEMIS trials, Brigham and Women's Hospital received research funding.

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