Editorial

Cardiovascular events after discontinuation of low-dose aspirin

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Fueled by the massive ~50% relative risk reduction of death or myocardial infarction demonstrated in early randomized, controlled trials of patients with acute coronary syndromes, aspirin has played a pivotal role in treatment and prevention of cardiovascular disease for more than 30 years (1,2). Aspirin irreversibly inhibits the cyclooxygenase-1 enzyme and reduces the biosynthesis of thromboxane A_2, ultimately leading to decreased platelet activation and aggregation (3). While platelet inhibition inevitably comes at the expense of an increased risk of bleeding, several studies have found low-dose aspirin to be safer than, and at least as effective as, high-dose aspirin (4-7). Therefore, low-dose aspirin is generally preferred for long-term prevention of cardiovascular events in patients with acute and stable cardiovascular disease (8-10), whereas the use of low-dose aspirin for primary prevention is debatable (3,8-12). Unfortunately, discontinuation rates as high as 30% have been reported and may impact clinical outcomes (13).

A recent nationwide, registry-based cohort study by Sundström *et al.* in *Circulation* examined the risk of cardiovascular events, defined as myocardial infarction, stroke, or cardiovascular death, associated with discontinuation of long-term aspirin at a daily dose of 75–160 mg (14). The authors included a total of 601,527 aspirin users who were more than 40 years of age, free from cancer, and had an estimated adherence rate of 80% or more during the first year of treatment. Patients who experienced a cardiovascular event or died during this first year were excluded, and the first 3 months after a major bleeding or surgical procedure were excluded from the time at risk. The cumulative proportion of aspirin discontinuation among long-term users was 15% at 3 years. The risk of cardiovascular events was significantly increased in patients who discontinued aspirin [adjusted hazard ratio (HR), 1.37, 95% confidence interval (CI), 1.34–1.41] and was greater among patients who received aspirin for secondary prevention (adjusted HR, 1.46, 95% CI, 1.41–1.51) than in those who received it for primary prevention (adjusted HR, 1.28, 95% CI, 1.22–1.34). The numbers needed to harm were 74, 36, and 146 per year, respectively. Finally, the authors used a subgroup of 38,736 patients to demonstrate an early appearance of the adverse risk after discontinuation.

The analysis was thorough and based on a very large sample size. As the authors appropriately note, a major problem with conducting registry-based analyses of low-dose aspirin is its over-the-counter availability in most countries, which would tend to dilute its effect. However, since this drug mandates prescription in Sweden, the study setting was appropriate. Furthermore, the investigators focused on aspirin discontinuation not related to surgery or bleeding events. The observed risk estimates displayed similar patterns, but were slightly more pronounced than those found in the meta-analysis of individual participant data from randomized trials by the Antithrombotic Trialists' (ATT) Collaboration, in which the risk ratio of serious vascular events, i.e., myocardial infarction, stroke, or vascular death, with the use of long-term aspirin was 0.88 (95% CI, 0.82–0.94; P<0.001) in 6 primary prevention trials

(95,000 patients) and 0.81 (95% CI, 0.75–0.87; P<0.001) in 16 secondary prevention trials (17,000 patients) (11). A possible explanation for the higher estimates might be some degree of residual confounding despite multivariable adjustments for age, sex, and certain comorbidities and drugs. In this sense, it is important to keep in mind the potential for intentional or non-intentional non-adherence to medications (15,16). Factors associated with the more complex, intentional non-adherence include individual patient preference, physician decision, patient demographics, and contraindications (whether real or perceived), and most of these variables could not be accounted for. Similarly, it was not possible to adjust for smoking and other lifestyle-related and traditional risk factors despite a prior systematic review reporting that cigarette smoking was a common predictor of both poor compliance and treatment discontinuation (13). Indeed, many of these risk factors may themselves associate with an increased risk of cardiovascular events, either directly or through suboptimal adherence with aspirin and other preventive medications.

While there is consensus that aspirin should be given to patients with known cardiovascular disease, controversies still exist regarding its use in the primary preventive setting, due to the less clear balance between ischemic benefits and bleeding disadvantages (8,10). For example, the European Society of Cardiology guidelines do not endorse aspirin for patients without cardiovascular disease (12). Conversely, the U.S. Preventive Services Task Force (USPSTF) recommends the use of low-dose aspirin for primary prevention of both cardiovascular disease and colorectal cancer in adults aged 50–59 years who have a 10-year risk of cardiovascular disease of 10% or more (using the pooled cohort equations from the American College of Cardiology/American Heart Association), are not at an increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take daily aspirin for 10 years or more (9). The decision may be individualized in persons who are 60–69 years old, while the USPSTF recognizes that there is insufficient evidence to provide recommendations in persons outside this age range. The study by Sundström *et al.* supports the prevailing concept of lifelong aspirin for patients with a previous cardiovascular event, yet the authors defined secondary prevention as prior hospitalization for myocardial infarction or stroke only, i.e., conditions like stable angina and peripheral artery disease may have driven some of the hazard associated with discontinuation in the primary prevention subgroup (14).

A potential caveat of aspirin is the variable platelet inhibition, particularly at the end of the dosing interval (17-19). In addition, advances in thrombocardiology, including the development of more potent platelet inhibitors as well as the recent introduction of combination therapy with very low-dose anticoagulation on top of platelet inhibitors have questioned its role in cardiovascular prevention (20-23). Supporting this notion, the authors did not find an adverse effect of aspirin discontinuation among patients who were concomitantly treated with another antiplatelet agent or an oral anticoagulant (14). The latter is particularly interesting, given the increased activation of the coagulation system among patients with atherosclerotic cardiovascular disease (24). Indeed, the GEMINI-ACS-1 trial (Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome) demonstrated the safety of rivaroxaban 2.5 mg twice daily compared with aspirin 100 mg daily, in patients receiving a $P2Y_{12}$-receptor antagonist after an acute coronary syndrome (22). Nevertheless, the recently published COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) of 27,395 individuals with stable coronary or peripheral artery disease showed consistent benefits favoring combination therapy with rivaroxaban 2.5 mg twice daily plus aspirin 100 mg (23). In other words, the primary composite endpoint of cardiovascular death, stroke, or myocardial infarction was significantly reduced with rivaroxaban plus aspirin versus aspirin 100 mg daily (HR, 0.76, 95% CI, 0.66–0.86; P<0.001), but not with rivaroxaban 5 mg twice daily versus aspirin (HR, 0.90, 95% CI, 0.79–1.03; P=0.12). Major bleeding was significantly increased with both rivaroxaban plus aspirin and with rivaroxaban. The combination regimen did not significantly increase fatal or intracranial hemorrhage and provided significant net clinical benefit, although with a delicate balance between numbers needed to treat and harm.

Finally, as follow-up in the study by Sundström *et al.* ended in 2009, the impact of more potent $P2Y_{12}$-receptor antagonists could not be studied (14), but we eagerly await results from several trials. For instance, in patients who have undergone percutaneous coronary intervention, the TWILIGHT trial (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention; NCT02270242) is examining the safety and efficacy of ticagrelor, with or without aspirin, in patients who have completed 3 months of dual antiplatelet therapy, while the GLOBAL LEADERS trial (Clinical Study Comparing Two

Forms of Anti-platelet Therapy After Stent Implantation; NCT01813435) is comparing dual antiplatelet therapy for 12 months, followed by aspirin, with short-term dual antiplatelet therapy for 1 month, followed by ticagrelor. In addition, at least four studies of aspirin for primary prevention are ongoing (12). Still, the specific question of whether long-term monotherapy with aspirin can be safely discontinued is unlikely to be answered in a randomized setting, and the Swedish study perfectly illustrates the value of large-scale registries (25). Discontinuing long-term aspirin outside the setting of major surgery or bleeding appears unsafe, and efforts should be made to improve adherence (15).

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Footnote

Conflicts of Interest: Dr. Pareek has served on the advisory board for, and received speaker honoraria from AstraZeneca; Dr. Kristensen has received speaker honoraria from Aspen, AstraZeneca, Bayer, and Bristol-Myers Squibb/Pfizer; Dr. Grove has received speaker honoraria from AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, and Pfizer and has previously participated in advisory board meetings for AstraZeneca, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb.

References

1. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. N Engl J Med 1983;309:396-403.
2. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988;2:349-60.
3. Patrono C, Garcia Rodriguez LA, Landolfi R, et al. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005;353:2373-83.
4. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation 2003;108:1682-7.
5. Steinhubl SR, Bhatt DL, Brennan DM, et al. Aspirin to prevent cardiovascular disease: the association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann Intern Med 2009;150:379-86.
6. Yu J, Mehran R, Dangas GD, et al. Safety and efficacy of high- versus low-dose aspirin after primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. JACC Cardiovasc Interv 2012;5:1231-8.
7. Hall HM, de Lemos JA, Enriquez JR, et al. Contemporary patterns of discharge aspirin dosing after acute myocardial infarction in the United States: results from the National Cardiovascular Data Registry (NCDR). Circ Cardiovasc Qual Outcomes 2014;7:701-7.
8. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139-228.
9. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2016;164:836-45.
10. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
11. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849-60.
12. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on

Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315-81.
13. Herlitz J, Toth PP, Naesdal J. Low-dose aspirin therapy for cardiovascular prevention: quantification and consequences of poor compliance or discontinuation. Am J Cardiovasc Drugs 2010;10:125-41.
14. Sundström J, Hedberg J, Thuresson M, et al. Low-Dose Aspirin Discontinuation and Risk of Cardiovascular Events: A Swedish Nationwide, Population-Based Cohort Study. Circulation 2017;136:1183-92.
15. Kolandaivelu K, Leiden BB, O'Gara PT, et al. Non-adherence to cardiovascular medications. Eur Heart J 2014;35:3267-76.
16. Arts DL, Voncken AG, Medlock S, et al. Reasons for intentional guideline non-adherence: A systematic review. Int J Med Inform 2016;89:55-62.
17. Würtz M, Grove EL. Interindividual variability in the efficacy of oral antiplatelet drugs: definitions, mechanisms and clinical importance. Curr Pharm Des 2012;18:5344-61.
18. Würtz M, Hvas AM, Jensen LO, et al. 24-Hour Antiplatelet Effect of Aspirin in Patients with Previous Definite Stent Thrombosis. Int J Cardiol 2014;175:274-9.
19. Christensen KH, Grove EL, Wurtz M, et al. Reduced antiplatelet effect of aspirin during 24 hours in patients with coronary artery disease and type 2 diabetes. Platelets 2015;26:230-5.
20. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
21. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
22. Ohman EM, Roe MT, Steg PG, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. Lancet 2017;389:1799-808.
23. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. N Engl J Med 2017;377:1319-30.
24. Bhatt DL, Hulot JS, Moliterno DJ, et al. Antiplatelet and anticoagulation therapy for acute coronary syndromes. Circ Res 2014;114:1929-43.
25. Bhatt DL, Drozda JP Jr, Shahian DM, et al. ACC/AHA/STS Statement on the Future of Registries and the Performance Measurement Enterprise: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and The Society of Thoracic Surgeons. J Am Coll Cardiol 2015;66:2230-45.

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