BRIEF COMMUNICATION

Pooled Analysis of Bleeding, Major Adverse Cardiovascular Events, and All-Cause Mortality in Clinical Trials of Time-Constrained Dual-Antiplatelet Therapy After Percutaneous Coronary Intervention

John D. McClure, PhD; Jennifer C. Ramsay, MBChB; Colin Berry, MD, PhD

BACKGROUND: The net clinical benefit of dual antiplatelet therapy (DAPT) reflects the paradoxical effects of an increased risk of bleeding and a reduced risk of major adverse cardiovascular events. A time-constrained approach to DAPT has been recently investigated in 5 multicenter trials including GLOBAL LEADERS, STOPDAPT2 (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2), SMART-CHOICE, TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention), and TICO (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus Stent for Acute Coronary Syndrome).

METHODS AND RESULTS: We undertook a pooled analysis of these trials to assess the overall associations between time-constrained P2Y12 inhibitor monotherapy (aspirin-free regimen) for bleeding events, major adverse cardiovascular events, and all-cause mortality as compared to standard care with DAPT for at least 12 months post-percutaneous coronary intervention. We implemented a DerSimonian and Laird random effects meta-analysis using the metafor package in R. 32,361 randomized trial participants, including 16,898 (52.2%) who had a history of acute coronary syndrome, underwent percutaneous coronary intervention, and had outcome data available. P2Y12 inhibitor monotherapy from 1 to 3 months was associated with a reduced risk for bleeding (hazard ratio [HR] 0.60; 95% CI, 0.45-0.81), including in the acute coronary syndrome group in which the magnitude of risk reduction was greatest (HR 0.50; 95% CI, 0.41-0.61). The estimates of the effect of P2Y12 inhibitor monotherapy on the HR were also favorable for major adverse cardiovascular events (0.88; 95% CI, 0.77-1.02) and all-cause mortality (0.85; 95% CI, 0.71-1.03).

CONCLUSIONS: Compared with DAPT for 12 months post-percutaneous coronary intervention, P2Y12 inhibitor monotherapy from 1 to 3 months substantially reduces the risk of major and fatal bleeding and, in addition, confers potentially protective effects, for major adverse cardiovascular events and all-cause mortality. Considering patient safety, the results support a strategy of DAPT for 1 to 3 months followed by aspirin-free P2Y12 inhibitor monotherapy.

Key Words: acute coronary syndrome ■ antiplatelet agent ■ dual antiplatelet therapy ■ meta-analysis ■ percutaneous coronary intervention

Aspirin is established as the first-choice antiplatelet medication for secondary prevention of atherothrombotic events in patients with coronary artery disease.1–3 Because aspirin leads to incomplete antiplatelet inhibition, additional, dual antiplatelet therapy (DAPT) with an inhibitor of the platelet P2Y12 receptor is now evidence based.2,3 In patients with stable coronary artery disease or an acute coronary syndrome (ACS) who are undergoing percutaneous coronary intervention (PCI), DAPT for 12 months is...
Aspirin or Alone in High-Risk Patients After Coronary

The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial showed that in 19,855 patients with atherosclerotic disease, including 11,630 with myocardial infarction as the qualifying event, compared with aspirin monotherapy (325 mg per day), clopidogrel monotherapy (75 mg per day) for 1.91 years reduced the incidence of ischemic stroke, myocardial infarction, or vascular death by 8.7% (95% CI, 0.3–16.5; \( P = 0.043 \)). There was a treatment interaction by disease subgroup suggesting that the true benefit of clopidogrel was less certain in patients with myocardial infarction (7.4% [−5.2 to 18.6]). On the other hand, severe bleeding was more common with aspirin, notably severe gastrointestinal bleeding (2.66% versus 1.99%; \( P < 0.05 \)). A meta-analysis of 9 randomized trials of P2Y12 inhibitor monotherapy or aspirin for secondary prevention involving 42,108 patients found a borderline risk reduction conferred by P2Y12 inhibitor for myocardial infarction (odds ratio, 0.81; 95% CI, 0.66–0.99) but no evidence of a between-group difference in the risks of bleeding or all-cause mortality. The on-going ADAPTABLE trial aims to clarify the optimal dose of aspirin, particularly for patients with ACS. The results of the GLOBAL LEADERS trial for post-PCI participants (though not for ACS subgroup) are presented as relative risk ratios whereas hazard ratios (HRs) are reported in the other trials. The definitions for major bleeds, for example, Bleeding Academic Research Consortium grades 3 or 5, were broadly similar across the trials.

Our objective was to assess the overall associations in these trials between time-constrained P2Y12 inhibitor monotherapy (aspirin-free regimen) for bleeding events, MACE, and all-cause mortality as compared to standard care with DAPT for up to at least 12 months post-PCI.

We will make the data and methods used in the analysis available to any researcher for the purposes of reproducing the results and procedures.

We undertook a pooled analysis of the data from these trials using DerSimonian and Laird random effects meta-analysis in the metafor package in R. The results of the GLOBAL LEADERS trial for post-PCI participants (though not for ACS subgroup) are presented as relative risk ratios whereas hazard ratios (HRs) are reported in the other trials. The outcomes were primary bleeding outcomes (major and fatal bleeds), MACE, and all-cause mortality at 12 months. Sensitivity analyses without the GLOBAL LEADERS trial and without the TWILIGHT trial also varied between the trials. STOPDAPT-2 involved ticagrelor and ticagrelor monotherapy, SMART-CHOICE involved any P2Y12 inhibitor, and GLOBAL LEADERS, TWILIGHT, and TICO involved ticagrelor monotherapy.

The TWILIGHT and TICO trials had similar designs although there were some important differences. TWILIGHT enrolled 7119 patients (n=4614 [65%] with an ACS) in 187 sites across 11 countries. TICO enrolled 3056 patients with an ACS in 38 centers in Korea. TWILIGHT involved a double-blind, placebo-controlled design whereas TICO involved an open-label design without a placebo. The definitions for major bleeds, for example, Bleeding Academic Research Consortium grades 3 or 5, were broadly similar across the trials.

Our objective was to assess the overall associations in these trials between time-constrained P2Y12 inhibitor monotherapy (aspirin-free regimen) for bleeding events, MACE, and all-cause mortality as compared to standard care with DAPT for up to at least 12 months post-PCI.

**METHODS**

We will make the data and methods used in the analysis available to any researcher for the purposes of reproducing the results and procedures.

We undertook a pooled analysis of the data from these trials using DerSimonian and Laird random effects meta-analysis in the metafor package in R. The results of the GLOBAL LEADERS trial for post-PCI participants (though not for ACS subgroup) are presented as relative risk ratios whereas hazard ratios (HRs) are reported in the other trials. The outcomes were primary bleeding outcomes (major and fatal bleeds), MACE, and all-cause mortality at 12 months. Sensitivity analyses without the GLOBAL LEADERS
RESULTS
In total, 32,361 patients treated with PCI had outcome data available from 5 randomized, controlled trials of time-constrained DAPT for 1 to 3 months post-PCI followed by P2Y12 inhibitor monotherapy versus DAPT for 12 months or longer. The trials (subjects) were GLOBAL-LEADERS (n=15,968), SMART-CHOICE (n=2,993), STOPDAPT-2 (n=3,045), TWILIGHT (n=7,199), and TICO (n=3,056). The majority of these patients had undergone PCI following an ACS (n=16,898 [52.2%]).

The main results are shown in Figure S2. The P2Y12 inhibitor monotherapy strategy was associated with a reduced risk for bleeding post-PCI (HR, 0.60; 95% CI, 0.45-0.81) (Figure—Panel A), including in the subgroup of patients presenting with an ACS in whom the magnitude of risk reduction was greatest (HR 0.50; 95% CI, 0.41-0.61) (Figure—Panel B). The effect was directionally consistent across the studies. P2Y12 inhibitor monotherapy was also associated with reductions in the overall estimates of the hazard of MACE (0.88; 95% CI, 0.71-1.03) (Figure—Panel C), including in the ACS subgroup (0.86; 0.72-1.03) (Figure—Panel D), and all-cause mortality (0.85; 0.71-1.03) (Figure—Panel E), although the upper limit of the CIs marginally exceeded unity.
reduces the risk of major bleeding. The effect is greatest in patients with ACS in whom the risk of bleeding is halved.

The purpose for prescribing DAPT is to reduce the risk of MACE. Therefore, antiplatelet monotherapy that is prescribed instead of DAPT within 12 months of receiving PCI might be expected to be associated with an increased risk of MACE, especially in post-ACS patients. In fact, reassuringly, we observed a directionally opposite effect. In our analysis, the effect estimates for MACE and all-cause mortality were less than unity consistent with a lowering of the risks with P2Y12 inhibitor monotherapy. Importantly, considering the worst-case scenario for the CI, the increase in the HRs was very small. By contrast, the magnitudes of the reductions in the HRs for MACE and all-cause mortality that were associated with P2Y12 inhibitor monotherapy are substantially greater and consistent with meaningful protective effects. These results are relevant to patient safety. Compared with DAPT for 12 months post-PCI, P2Y12 inhibitor monotherapy from 1 to 3 months post-PCI halves the risk of major bleeding and may reduce the risks of MACE and death.

In clinical practice, discontinuation of antiplatelet therapy in patients who are bleeding may lead to MACE, including spontaneous myocardial infarction and stent thrombosis. We have found that prolongation of DAPT to 12 months substantially increases the risk of bleeding. Therefore, the clinical scenario that we describe may be less likely in patients receiving time-constrained, short-term DAPT for 1 to 3 months, which may be one explanation for the favorable safety signal for MACE as well as for bleeding. Bleeding and MACE are highly undesirable events. Considering the net clinical benefit of antiplatelet therapy, bleeding has a very strong association with persisting morbidity and mortality and elderly patients are particularly at risk. In this regard, practice guidelines recommend a focus on individualized risk (low versus high bleeding risk). Accordingly, prevention of bleeding should be a primary consideration when prescribing the duration of DAPT in PCI and ACS patients.

The results of our analysis lend support to a strategy of discontinuing aspirin from 3 months post-PCI and continuing P2Y12 inhibitor monotherapy. Aspirin has been a long-established, first-line treatment for secondary prevention of coronary atherosclerosis and a shift to prescribing P2Y12 monotherapy is a new concept for clinicians. Recommendations from practice guideline committees will be important if clinical practice is to evolve in line with the evidence from these trials. The results are also relevant to the safety of participants in ongoing clinical trials comparing DAPT regimens.

Clinicians should still implement individualized therapy decisions for their patients as would normally occur in daily practice. Currently, global prescribing practices for the type of P2Y12 inhibitor are influenced by several factors including access, absolute cost, clinical effectiveness, and practice guidelines.

**Limitations**

The risks and benefits of aspirin monotherapy versus P2Y12 inhibitor monotherapy from 1/3 to 12 months following an ACS and/or PCI are not well established. In the future, a large clinical trial will be needed to address this evidence gap.

**CONCLUSIONS**

P2Y12 inhibitor monotherapy from 1 to 3 months post-PCI substantially reduces the risk of bleeding without an increase in MACE; rather, reductions in the risks of MACE and all-cause mortality are evident. There is no evidence of benefit with prolonged DAPT and clear signals harm. Our findings are highly relevant to the safety of patients prescribed DAPT, especially after an ACS. The results support a strategy of discontinuing aspirin from 3 months post-PCI and continuing with “aspirin free” P2Y12 inhibitor monotherapy in the longer term.

**REFERENCES**

1. Antithrombotic Trialists’ (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Hennekens C, Kearney P, Meade T, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849–1860.
2. Ibanez I, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Cattoir ALP, Crea F, Goudevanos JA, Hlavorsen S, et al.; ESC Scientific Document Group, ESC Scientific Document Group. 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;39:119–177.
3. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Kelly RF, Kontos MC, et al.; ACC/AHA Task Force Members. 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. Circulation. 2014;130:e344–e426.

4. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, et al.; ESC Scientific Document Group. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019;40:87–165.

5. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet. 1996;348:1329–1339.

6. Chiarito M, Sanz-Sánchez J, Cannata F, Cao D, Sturla M, Panico C, Godino C, Regazzoli D, Reimers B, De Caterina R, et al. Monotherapy with a P2Y12 inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. Lancet. 2020;395:1487–1495.

7. Marquis-Gravel G, Roe MT, Robertson HR, Harrington RA, Pencina MJ, Berdan LG, Hammill BG, Faulkner M, Muñoz D, Fanoroc GC, et al. Rationale and design of the aspirin dosing-a patient-centric trial assessing benefits and long-term effectiveness (ADAPTABLE) Trial. JAMA Cardiol. 2020;5:598. [epub ahead of print].

8. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, et al.; GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet. 2018;392:940–949.

9. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohyama T, Suwa S, Takagi K, Nanasato M, et al.; STOPDAPT-2 Investigators. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. JAMA. 2019;321:2414–2427.

10. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, Im ES, Jeong JO, Cho BR, Oh SK, et al.; SMART-CHOICE Investigators. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. JAMA. 2019;321:2428–2437.

11. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med. 2019;381:2032–2042.

12. Kim BK, Hong SJ, Cho YH, Yun KH, Kim YH, Suh Y, Cho JY, Her AY, Cho S, Jeon DW, et al. Effect of ticagrelor monotherapy vs ticagrelor with aspirin on major bleeding and cardiovascular events in patients with acute coronary syndrome. JAMA. 2020;323:2407–2416.

13. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010;36:1–48.