EDITORIAL

Net Adverse Clinical Events With Antiplatelet Therapy in Acute Coronary Syndromes

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Clopidogrel, prasugrel, and ticagrelor are oral platelet P2Y12 receptor inhibitors that decrease the risk of platelet-mediated coronary artery thrombosis. Clinical guidelines have recommended ticagrelor or prasugrel over clopidogrel in combination with aspirin as dual antiplatelet therapy (DAPT) for 1 year after acute coronary syndrome (ACS), whether or not percutaneous coronary intervention (PCI) is performed.[1] The ticagrelor recommendation was based on the Study of Platelet Inhibition and Patient Outcomes (PLATO) trial, which enrolled 18 624 patients with ACS and randomized them to receive DAPT with either clopidogrel and aspirin or ticagrelor and aspirin.[2] The 1-year primary composite efficacy end point of death from vascular causes, myocardial infarction (MI), or stroke favored ticagrelor and aspirn vs clopidogrel and aspirin (9.8% vs 11.7%; hazard ratio, 0.84 [95% CI, 0.77-0.92]; $P < .001$), but major bleeding not related to coronary artery bypass graft surgery was increased with ticagrelor and aspirin vs clopidogrel and aspirin (4.5% vs 3.8%; $P = .03$).

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This trial illustrated the clinical challenge with DAPT in balancing ischemic benefit with bleeding risk. Importantly, how to define ischemic benefit and bleeding risk is an ongoing debate in the clinical research community, especially with antiplatelet therapy, because individual end point definitions can completely change how a trial is ultimately interpreted.

A 1-year composite end point of death, MI, and stroke is often used to evaluate efficacy in ACS trials. However, death can be defined as all-cause death, cardiovascular death, or death from vascular causes (cardiovascular plus cerebrovascular deaths). Although ticagrelor was associated with a reduction in death in the PLATO trial,[2] no subsequent trial with ticagrelor and no trials with clopidogrel or prasugrel have shown a mortality benefit with DAPT compared with antiplatelet monotherapy, so it is not clear that death is a relevant end point in DAPT trials. Similarly, MI can variably be defined by international, professional society, or clinical trial definitions. The most recent debate concerns whether periprocedural MI detected by high-sensitivity troponin values is equivalent to spontaneous MI as a prognostic end point. Since there is no difference among antiplatelet agents in preventing ischemic stroke,[3] and since hemorrhagic stroke risk is higher with ticagrelor and prasugrel compared with clopidogrel, stroke might better be a safety end point than an efficacy end point in DAPT trials. Therefore, the only consistent favorable efficacy outcome in DAPT trials has been reduction in MI rates across the different definitions of MI.

The definition of safety in DAPT trials is usually limited to bleeding risk. However, major bleeding has also been defined differently in trials, with at least 10 definitions used, making it more difficult to compare studies. For instance, in PLATO, there was no difference in major bleeding when coronary artery bypass graft surgery–related bleeding was included, but there was a difference when coronary artery bypass graft surgery–related bleeding was excluded.[2] Another trial reported benefit for a genotype-guided strategy for choosing oral $P2Y_{12}$ receptor inhibitors in primary PCI when major and minor bleeding were combined as the primary end point, but there were no differences in the more traditional end point of major bleeding using 3 different definitions or in transfusion rates.[4] Minor bleeding is often defined as any bleeding requiring medical intervention but not meeting the chosen definition for major bleeding, and it is usually not emphasized in reports of randomized clinical trials. Nuisance bleeding is defined as minor bleeding not requiring medical intervention.

The adverse net clinical event rate in DAPT trials represents the numerical difference between ischemic events avoided and excess bleeding events. Some clinical trialists oriented toward demonstrating efficacy have argued against this composite variable based on the challenges in how to define events, the differential severity of events, and the high probability of a null value when combining efficacy and safety end points in antithrombotic therapy trials.[5] Conversely, this equation is important to patients and clinicians in shared decision making, as are minor bleeding events and the copayment price for a drug prescription.

In this issue of *JAMA*, You and colleagues[6] evaluated the net adverse clinical events associated with ticagrelor or clopidogrel among patients with ACS undergoing PCI in routine clinical practice. The authors performed a retrospective, propensity-matched, cohort analysis of 62 580 patients enrolled in 2 US electronic health-record databases and 1 nationwide South Korean administrative claims database. Net adverse clinical events were defined as a composite outcome of ischemic events (recurrent MI, revascularization, or ischemic stroke) and hemorrhagic events (hemorrhagic stroke or gastrointestinal bleeding). At 12 months, there was no difference in the primary outcome of net adverse clinical event rates between treatment groups (ticagrelor patients, 15.1% [3484/23 116 person-years] vs clopidogrel patients, 14.6% [3290/22 587 person-years]; summary hazard ratio, 1.05 [95% CI, 1.00-1.10]; $P = .06$). In secondary analyses, there were no significant differences between treatment groups in the risk of all-cause mortality (2.0% in ticagrelor patients vs 2.1% in clopidogrel patients) or composite

ischemic events (13.5% in ticagrelor patients vs 13.4% in clopidogrel patients), but ticagrelor was associated with significantly more hemorrhagic events (2.1% in ticagrelor patients vs 1.6% in clopidogrel patients), and more drug-related dyspnea (27.3% in ticagrelor patients vs 22.6% in clopidogrel patients).

The findings for the primary outcome are not surprising based on the expected regression toward a null effect when combining competing efficacy and safety end points. The ischemic end points did not include death or periprocedural MI. The safety end point did not include bleeding events included in other reports (ie, procedural, ocular, pericardial, defined hemoglobin decrease, transfusion). In addition, as in other observational studies of evaluations of drug comparative effectiveness, this study has several limitations.[7] In this study, You et al[6] performed many sophisticated statistical analyses in an attempt to decrease the influence of confounding variables in such an analysis. Moreover, complete and accurate ascertainment of events and miscoding are uncorrectable limitations in such studies. Their conclusion of no added benefit associated with ticagrelor is consistent with prior studies from Canada, Korea, Japan, China, and the Netherlands that used different study designs to reach the same conclusion without attracting much clinical attention.[6]

These results challenge the conventional wisdom promoted in clinical guidelines and communicated by thought leaders and in the media that ticagrelor is more effective than clopidogrel in DAPT. The interpretation of 2 randomized clinical trials that tested DAPT with ticagrelor against aspirin monotherapy for secondary prevention helps illustrate the clinical conundrum. Both of these trials reported 3-year outcomes instead of 1-year outcomes.[8,9] One study enrolled 21 162 patients 1 to 3 years after MI with high-risk charactistics and concluded that DAPT compared with aspirin monotherapy was efficacious—a message amplified in multiple subsequent substudy reports.[8] However, the annualized efficacy benefit with ticagrelor, 90 mg, was 4.0 ischemic events prevented per 1000 patients treated or 4.2 ischemic events prevented per 1000 patients treated with ticagrelor, 60 mg. The annualized safety risk with ticagrelor, 90 mg, was 4.1 excess major bleeding events per 1000 patients treated or 3.1 excess major bleeding events per 1000 patients treated with ticagrelor, 60 mg. Minor bleeding and transfusion rates were 3- to 4-fold higher with ticagrelor (eg, transfusion occurred in 2.43% of patients who received 90 mg 2.09% with 60 mg vs 0.72% who received aspirin).

Another trial enrolled 19 220 patients with type 2 diabetes and high-risk characteristics and concluded that there was no significant difference in net adverse clinical events between DAPT with ticagrelor vs aspirin alone.[9] The annualized efficacy benefit with ticagrelor compared with aspirin was 2.14 ischemic events prevented per 1000 patients treated, and the annualized safety risk was 2.73 major bleeding events per 1000 patients treated. The minor bleeding rate was increased with ticagrelor compared with aspirin (0.83% vs 0.30%), and there was an excess of intracerebral hemorrhage events (0.7% vs 0.5%; hazard ratio, 1.71; 95% CI, [1.18-2.48]; P = .005) . However, a prespecified substudy analysis that included 58% of the patients who underwent prior PCI was published the same year and widely promoted as proving the benefit of DAPT despite being a substudy report of a neutral trial.[10] The US Food and Drug Administration has approved long-term DAPT with ticagrelor for secondary prevention in high-risk patients based on these trial results.

Efficacy results can be magnified by increasing trial sample sizes, extending the timeframe of the primary end point determination, reporting relative risk reductions (rather than absolute risk differences), and emphasizing the P value result (rather than point estimates and CIs). Efficacy results can be minimized by reporting 1-year absolute risk reductions and calculating the number needed to treat to prevent 1 event. Similarly, bleeding risk can be magnified by including more events in the bleeding definition or by including minor and nuisance bleeding. Bleeding risk can be minimized by limiting the types of bleeding events in the definition or by only counting major bleeding as significant. Whereas some have suggested that different events should be weighted differently in interpreting net adverse clinical event rates (ie, net clinical benefit), others have suggested that MI and major bleeding, the important efficacy and safety end points in DAPT randomized clinical trials, have equivalent prognostic value.[11]

Ticagrelor has a more favorable pharmacodynamic profile than clopidogrel.[12] However, compared with clopidogrel and prasugrel, ticagrelor may not demonstrate greater clinical benefit because of adverse effects (dyspnea), inconvenience (twice-daily dosing), or higher cost (clopidogrel and prasugrel are generics), which may decrease medication adherence.[13] The pragmatic clinical recommendation, yet to be proven in randomized trials, may be to prescribe ticagrelor (or prasugrel because it was more effective than ticagrelor in one randomized trial[14]) for patients with ACS, if the patient tolerates and can afford this medication, and to consider de-escalating to clopidogrel at 1 month after the greatest ischemic risk period has passed to decrease subsequent bleeding risk and cost.[15] At 12 months, DAPT can be transitioned to low-risk aspirin monotherapy for secondary prevention.[1]

ARTICLE INFORMATION

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The Opioid Epidemic During the COVID-19 Pandemic

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Drug overdose deaths in the US increased in 2019, despite a slight decrease from 2017 to 2018; this increase was largely driven by illicitly manufactured fentanyl.[1] The opioid epidemic has also been complicated by increasing use of methamphetamine in combination with opioids.[1] It is likely that the emergence of coronavirus disease 2019 (COVID-19) and subsequent disruptions in health care and social safety nets combined with social and economic stressors will fuel the opioid epidemic. Reports from national, state, and local media suggest that opioid-related overdoses are increasing,[2] but the absence of real-time national reporting of overdose-related mortality limits the ability to confirm these reports.

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In this issue of *JAMA*, 2 studies report on indicators that reflect the opioid epidemic before and after the widespread emergence of COVID-19 in the US in March 2020: urine drug test results[3] and emergency department visits for nonfatal opioid overdose.[4]

Wainwright et al[3] reported an increase in the detection of 4 tested substances in random samples (150 000 total) of urine drug tests ordered by health professionals nationwide 4 months before (November 14, 2019, to March 12, 2020) and after (March 13, 2020, to July 10, 2020) the national emergency declaration. The most noteworthy increases in prevalence were for fentanyl (3.80% to 7.32%; adjusted odds ratio, 1.67 [95% CI, 1.55-1.81]) and methamphetamine (5.89% to 8.16%; adjusted odds ratio, 1.23 [95% CI, 1.14-1.32]); increases in cocaine and heroin were also noted. Although the large sample size is a strength, there likely was bias in clinician selection of patients for urine drug testing[5] and the sample was not nationally representative. For example, only 2% of all COVID-19 era samples were from New England, a region with high rates of opioid-related death. COVID-19 era samples, compared with pre–COVID-19 samples, were more likely to be from men, individuals aged 24 to 44 years, and drug treatment programs and were less likely to be from behavioral health and pain treatment clinics. These characteristics were adjusted for in the models but unmeasured confounding is possible and may suggest that the increase in substance detection reflected a shift in who received in-person health care and urine testing in the COVID-19 era (ie, patients at highest risk for substance use) rather than changes in substance use in the general population.

The study by Ochalek et al[4] found that the number of cases of nonfatal opioid-related overdose in 1 emergency department in Virginia increased from 102 cases in March-June 2019 to 227 cases in March-June 2020, whereas the total number of emergency department visits and diagnoses of myocardial infarction decreased during this same period. Patients diagnosed with opioid-related overdose in 2020, compared with 2019, were more likely to be Black (63% vs 80%). While the use of records from March to June across 2 years serves as a control for underlying seasonal variation in overdose, the generalizability of these findings is limited by the small sample size and reporting of a single emergency department. Patients with overdose may have gone to different emergency departments due to closures or ambulance diversion during the pandemic. The number of fatal overdoses was not yet available; therefore, it is possible that the proportion of overdoses that were nonfatal increased while the total (fatal and nonfatal) remained the same. This scenario is perhaps unlikely but could manifest in several ways: (1) increased availability and administration of naloxone;