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EDITORIAL COMMENT

Ischemia and Bleeding on the Horns of a Dilemma

Do Only Hard Endpoints Count?*

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Acute coronary syndrome (ACS) is the main reason for hospital admissions and the leading cause of mortality in the developed nations. Economic burden of ACS on the society is enormous (1,2). Improvement of ACS-related outcomes and prevention of future cardiovascular events are major health care tasks. During the last few decades, a significant reduction of mortality and ischemic complications has been achieved in the early stages of ACS. Reduction became possible mainly due to wide and timely implementation of best reperfusion strategies in patients with ST-segment elevation myocardial infarction (STEMI), early invasive approaches in the management of moderate- and high-risk patients with non-STEMI ACS, and optimization of pharmacotherapy (3-6). Nonetheless, at later follow-up post ACS, cardiovascular events continue to occur in up to 20% of these patients, necessitating a search for new effective preventive therapies (7-9).

A deep understanding of mechanisms of thrombosis and hemostasis resulted in the development of pharmacological agents targeting specific paths in the chain of either platelet aggregation or thrombin formation. Introduction of new potent agents allowed improvement in survival and/or reduction of ischemic events in patients with ACS (5,10-14). However, improvement came at the price of increased bleeding complications, which may range from minor to life-threatening or fatal (15). Thus, dealing with ACS patients, physicians frequently find themselves on the horns of a dilemma: how to choose the most effective and the least harmful antiplatelet and/or antithrombotic strategy? To support decision making, a careful and thoughtful interpretation of the existing evidence is essential, with an explicit focus on the risk-versus-benefit assessment. Such assessment should embrace the following specific questions: 1) What is the most reliable way to measure risk versus benefit? 2) How much risk is acceptable? 3) How to mitigate the risks? 4) Is a new therapy, based on average outcome risks in the trial, applicable to everyone in a real-life setting? 5) How does a new treatment compare to other contemporary drug choices? 6) Are there time-dependent risks and benefits of the treatment?

Several methodological initiatives have emerged recently in an attempt to identify reliable tools to improve the quality and consistency of the risks versus benefits assessment and to simplify practical decision making in patients with ACS. A standardized approach has been applied to define universally most meaningful clinical outcomes, including MI, stent thrombosis, stroke, and bleeding (16,17). Based on data from the pivotal ACS trials, prognostic modeling of ischemic and bleeding events has been generated, allowing patient stratification depending upon the individual risk of events (18-20). Older age, female sex, impaired renal function, baseline anemia, and previous bleeding have been identified with remarkable consistency as risk factors for hemorrhagic events and have been incorporated into most risk models. Given the overlap between clinical predictors

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TABLE 1 Long-Term All-Cause Death, Cardiovascular Death, Major and Fatal Bleeding in Randomized Controlled Trials of Cardiovascular Diseases

Trial (Ref. #)	n	All-Cause Mortality, %	p Value	Cardiovascular Mortality, %	p Value	Major Bleeding, %	p Value	Fatal Bleeding, %	p Value
CHARISMA-MI (7)	9,478	5.0 vs. 5.4	0.32	3.0 vs. 3.4	0.08	1.7 vs. 1.5	0.51	0.3 vs. 0.2	0.32
DAPT (8)	9,961	2.0 vs. 1.5	0.05	1.0 vs. 1.1	0.98	2.5 vs. 1.6	0.001	0.2 vs. 0.1	0.38
PEGASUS (29)*	14,112	4.5 vs. 5.2	0.14	2.9 vs. 3.4	0.07	2.3 vs. 1.1	<0.0001	0.3 vs. 0.3	1.00
COMPASS-CAD (14)†	24,824	3.2 vs. 4.1	0.001	1.7 vs. 2.2	0.01	3.2 vs. 1.9	<0.0001	0.2 vs. 0.1	0.30
ATLAS ACS 2-TIMI 51 (25)†	10,227	2.7 vs. 4.5	0.001	2.5 vs. 4.2	<0.001	2.0 vs. 0.7	<0.001	0.1 vs. 0.2	0.45

*Data for ticagrelor, 60 mg twice daily. †Data for rivaroxaban, 2.5 mg twice daily.

ATLAS ACS 2-TIMI 51 = Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction; CHARISMA-MI = Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; COMPASS-CAD = Cardiovascular Outcomes for People Using Anticoagulation Strategies; DAPT = Dual Antiplatelet Therapy trial; PEGASUS = Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54 trial.

of bleeding and of recurrent ischemia, time-dependent impact of each of these complications on mortality has been studied to define optimal timing and duration of therapies post ACS (21,22). Complementing clinical information with laboratory variables and angiographic data on the degree of coronary disease as well as with data on cardiac function further improved the ability to predict prognosis in patients with ACS (23). However, several questions related to the risk-benefit analysis of contemporary antiplatelet or antithrombotic regimens in the scenario of ACS are unresolved, preventing unanimous recommendations on optimal therapies.

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In this issue of the *Journal*, Gibson et al. (24) propose an alternative approach to interpreting risk-versus-benefit data by limiting analyzed outcomes exclusively to fatal or irreversible events, from the ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction) trial comparing 2 different dosages of rivaroxaban versus placebo (25). Such a restricted approach to endpoint analysis aims to focus only on the clinically meaningful outcomes to assist in deciding whether to add rivaroxaban to antiplatelet therapy. The analyzed fatal and irreversible ischemic endpoints included cardiovascular death not related to bleeding, MI, and ischemic stroke, whereas bleeding resulting in death and intracranial bleeding were classified as fatal or irreversibly harmful events. Only 9,435 of 15,526 patients (61%) from the main trial were part of this analysis, including patients who, by discretion of the enrolling physician, were treated with dual antiplatelet therapy (aspirin plus clopidogrel or ticlopidine). Also, given in the main trial, there were survival benefit and less prominent increase in major bleeding, compared to patients receiving placebo, with the lower dosage (2.5 mg twice daily) than with the higher dosage (5 mg twice daily) of rivaroxaban (25), only patients who were randomized to the lower dosage were included in the analysis. Assessment of net clinical outcome (death from cardiovascular causes, MI, ischemic stroke, or noncoronary artery bypass graft Thrombolysis In Myocardial Infarction [TIMI] major bleeding) revealed no significant differences between rivaroxaban and placebo therapy (10.3% vs. 10.7%, respectively; hazard ratio [HR]: 0.95; 95% confidence interval [CI]: 0.82 to 1.10; $p = 0.47$), whereas there was a highly significant decrease in all-cause mortality (2.7% vs. 4.5%, respectively; HR: 0.64; 95% CI: 0.49 to 0.83; $p = 0.0001$) as well as in cardiovascular mortality (2.5% vs. 4.2%, respectively; HR: 0.62; 95% CI: 0.47 to 0.82; $p < 0.001$) and a significant increase in major bleeding (2.0% vs. 0.7%, respectively; HR: 2.90; 95% CI: 1.81 to 4.67; $p < 0.001$). Analysis restricted to hard clinical endpoints showed that the use of rivaroxaban compared with placebo was associated with 115 fewer fatal or irreversible ischemic events at the price of 10 fatal or irreversibly harmful bleeding events per 10,000 patient-years of exposure. Exclusion of periprocedural MIs and then all MIs from the analysis was associated with prevention of 115 and 90 fatal or irreversible events, respectively. Once the analysis was limited to nonbleeding cardiovascular death, 95 events would be prevented. Importantly, time-to-event sensitivity data showed favorable dynamics over time with no increase in fatal or irreversible harmful bleeding events and continued reduction in fatal or irreversible ischemic events at 2 years in the group taking 2.5 mg twice daily.

Randomized controlled trials represent the gold standard in a treatment effect. The methodology most frequently applied to assess the magnitude of

this effect includes absolute risk reduction, relative risk reduction, HR, and number needed to treat or to harm. Combined analysis of fatal or irreversible events (either ischemic or hemorrhagic) in the study by Gibson et al. (24) is an interesting supplementary approach the authors used to show the magnitude of the treatment effect and its change over time. Such a way of reporting provides readers with an extra piece of information to assist in deciding whether a treatment should be used.

However, the method used to analyze hard clinical outcomes is not free of limitations, including bias in patient selection, wide confidence interval for the prevention of fatal or irreversible events (low and upper limits of 6 and 204, respectively), unaccounted information for the actual duration of treatment with the study drug as well as for the rates of adherence to therapy, and consideration of only events that occurred first. Not including other than fatal/irreversible bleeding in the analysis is also troublesome, given that the patients who have not met the study criteria for bleeding severity still may have unfavorable prognosis due to high rates of discontinuation of antiplatelet/antithrombotic agents and adverse effect of blood product transfusion (15,26). The same is true for ignoring data for ischemia-driven revascularization. Although commonly successful, repeat revascularizations are not free from complications, which may include occurrence of large infarctions, stroke, and serious bleeding. Furthermore, distinction between all-cause and cardiac mortality is not always possible. Although pre-specified in the main ATLAS ACS 2-TIMI 51 study, the endpoint of cardiovascular death has its own limitations, mainly due to ambiguity in adjudication and potential endorsement of a positive outcome (16).

Notwithstanding the limitations, the study by Gibson et al. (24) provides, in addition to conventional analysis, demonstration of the quantifiable risk-benefit assessment, enhancing consideration of the use of low-dose rivaroxaban therapy in addition to antiplatelet agents early after ACS. Highly significant reduction of all-cause and cardiac mortality (both $p = 0.002$) at a mean follow-up of 13.3 months in the main ATLAS ACS 2-TIMI 51 trial of patients treated with either mono- or dual-antiplatelet agent(s) (25), as well as in the present subanalysis of patients treated with dual-antiplatelet therapy ($p \leq 0.001$) is remarkable. Later data from the recent large-scale COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial in 27,395 patients, of whom approximately two-thirds had ACS previously, was also associated with significantly lower all-cause and cardiovascular mortality in the group receiving low-dose rivaroxaban combined with aspirin ($p = 0.02$ and $p = 0.01$, respectively) (27). Remarkably, in both trials, Kaplan-Meier curves of mortality continued to diverge at 2 years, strongly favoring the use of the factor Xa inhibitor rivaroxaban for long-term protection in patients with cardiovascular disease (25,27,28). These results contrast with those from 2 other ACS trials in which dual-antiplatelet therapy was extended for more than 1 year (**Table 1**). Those studies found there was a significant decrease in the composite endpoint of death, MI, or stroke but no decline in all-cause or cardiovascular mortality at follow-up (8,29).

Reduction of recurrent ischemic events without increase in bleeding complications continues to be the main target in the contemporary ACS trials of novel antiplatelet or antithrombotic regimens. Although we are getting closer to therapy optimization, the final word regarding the use of low-dose rivaroxaban and other agents for secondary prevention of cardiovascular diseases has not yet been said. This is primarily due to substantial variation in the magnitude of the risks and benefits across a population. Comprehensive individualized profiling of the patients with respect to their ischemic and bleeding risks is crucial to further improve ACS-related outcomes. Preventive pharmacological strategies to mitigate risks of bleeding associated with contemporary antiplatelet or antithrombotic regimens may contribute to improvement of prognosis after ACS (30,31).

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