Antithrombotic Therapy After Percutaneous Coronary Intervention in Atrial Fibrillation

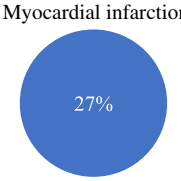
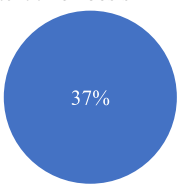
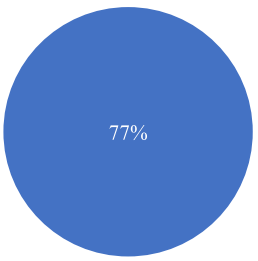
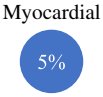
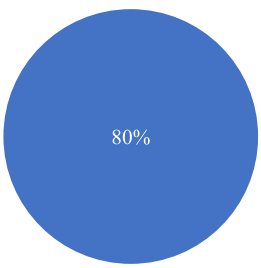
What is the optimal antithrombotic therapy in patients with atrial fibrillation (AF) who underwent percutaneous coronary intervention (PCI) remains one of the most doubtful and demanding topics in cardiology.

As of today, double antithrombotic therapy with single antiplatelet agent (a P2Y12 inhibitor) plus a direct oral anticoagulant is the regimen recommended by American guidelines, in AF patients after elective PCI with stent implantation (class IIa, level of evidence B-R).[1] In contrast, European recommendations point toward prolongation of triple antithrombotic therapy (dual antiplatelet therapy plus an oral anticoagulant) for up to 1 month with the possibility to prolong triple therapy for up to 6 months in patients at high thrombotic risk, whereas the use of double therapy immediately after PCI should be reserved for patients at very high bleeding risk (class IIa, level of evidence A).[2]

Four randomized clinical trials, evaluating different antithrombotic regimens in patients with AF undergoing PCI or with acute coronary syndrome have been published: the AUGUSTUS,[3] the PIONEER-AF PCI,[4] the RE-DUAL PCI,[5] and the ENTRUST-AF PCI trial.[6] In aggregate, the data of these trials on comparisons of double versus triple antithrombotic therapy seem to indicate that double therapy significantly reduces the risk of bleeding while maintaining the same level of efficacy. The positive results of the trials of double antithrombotic therapy has permeated the medical community because, before the release of these trials, the safety issues and the high rates of bleeding with triple therapy were an important unmet need in the field of PCI in AF patients.

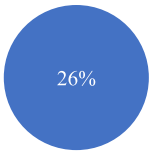
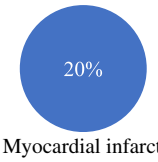
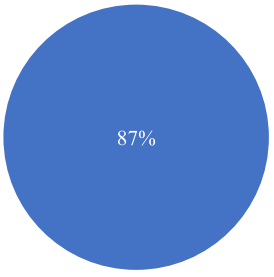
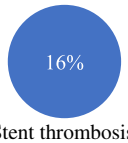
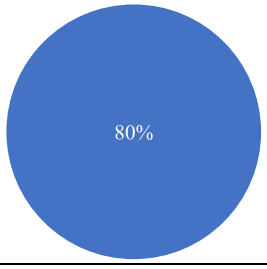
However, enthusiasm should be mitigated and not come at the cost of confusing clinical judgment when deciding between different treatment strategies. As a matter of fact, none of these trials was designed to prove the efficacy of double versus triple antithrombotic therapy in terms of ischemic coronary events prevention, mainly related to stent thrombosis and myocardial infarction. As shown in Table 1, while the reported power for primary end point (major or clinically relevant nonmajor bleeding) was higher than 75% for all the studies, the post hoc power for ischemic events was always lower than 40%. This finding is partly explained by the low rates of stent thrombosis observed in the 4 trials (<1%), in line with those reported in literature. Moreover, lesion and procedural characteristics (namely type and number of lesions treated, stent type, complete revascularization, and procedural success) were not specified, even if they correlate with worse ischemic outcomes. Moreover, most of patients included in the 4 trial and treated by PCI were not affected by acute coronary syndromes which predisposes to higher thrombotic risk over time. Finally, since these trials were designed to test bleeding end points, they enrolled a population where the hemorrhagic risk was higher than the thrombotic one.

Table 1
Summary of the 4 randomized controlled clinical trial (AUGUSTUS, PIONEER, RE-DUAL, and ENTRUST) and of their key results (population and trial design, ischemic event rates, and power for end points).

Trial name, population and design	Ischemic coronary event rates (DATT VS TATT)	Post hoc power for ischemic coronary event rates	Reported power for primary end point(major or clinically relevant nonmajor bleeding)
AUGUSTUS[3] 4614 patients with AF and recent ACS or PCI. -Apixaban 5 mg bid + DAPT (aspirin + P2Y12 inhibitor) vs -Apixaban 5 mg bid + P2Y12 inhibitor vs -VKA + DAPT (aspirin + P2Y12 inhibitor) vs -VKA + P2Y12 inhibitor	Myocardial infarction 3.6% vs 2.9% Stent thrombosis 0.9% vs 0.5%	Myocardial infarction  Stent thrombosis 	-Sample size: 4,600 patients -CI: 1-sided 97.5% 
PIONEER AF-PCI[4] 2124 patients with AF and recent PCI. -Rivaroxaban 15 mg + P2Y12 for 12 months vs - Rivaroxaban 2.5 mg bid + DAPT for 1, 6 or 12 months (rivaroxaban 15 mg + aspirin for the remainder of the 12-month treatment period) vs - VKA + DAPT for 1, 6 or 12 months (VKA + aspirin for the remainder of the 12-month treatment period)	Myocardial infarction 2.7% vs 3% Stent thrombosis 0.7% vs 0.6%	Myocardial infarction  Stent thrombosis 	-Sample size: 1,500 patients -CI: 2-sided 95.0% 

(*continued*)

Table 1 (***Continued***)

Trial name, population and design	Ischemic coronary event rates (DATT VS TATT)	Post hoc power for ischemic coronary event rates	Reported power for primary end point(major or clinically relevant nonmajor bleeding)
RE-DUAL PCI[5] 2725 patients with AF and recent PCI. -Dabigatran etexilate 110/150 mg bid + P2Y12 inhibitor vs -VKA + DAPT for 1 or 3 months (VKA + P2Y12 for the remainder of the 12-month treatment period)	Myocardial infarction 4.0% vs 3.0% Stent thrombosis 1.3% vs 0.8%	Myocardial infarction  Stent thrombosis 	-Sample size: 2,500 patients -CI: 1-sided 97.5% 
ENTRUST AF-PCI[6] 1506 patients with AF and recent PCI. -Edoxaban 60/30 mg + P2Y12 inhibitor for 12 months vs -VKA + DAPT for 1 to 12 months (aspirin and a P2Y12 inhibitor)	Myocardial infarction 3.9% vs 3.0% Stent thrombosis 1.1% vs 0.8%	Myocardial infarction  Stent thrombosis 	-Sample size: 1,500 patients -CI: 1-sided 97.5% 

Note. Bleeding events were evaluated according to International Society of Thrombosis and Haemostasis (ISTH) definition, except for PIONEER AF-PCI that used Thrombosis in Myocardial Infarction (TIMI) definitions. Stent thrombosis definitions were not overlapping, and rates refer to definite or probable stent thrombosis for AUGUSTUS, likely definite stent thrombosis also for PIONEER-AF PCI (not clearly reported, but low numbers suggest this), and definite stent thrombosis for the RE-DUAL PCI and ENTRUST AF-PCI trials.

AF = atrial fibrillation; ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; DATT = dual antithrombotic therapy; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist; TATT = triple antithrombotic therapy.

The lack of robustness of the available meta-analyses and network meta-analyses is reflected by apparently conflicting results, because the understanding of the risk of ischemic events with triple therapy versus double pathway is complex and highly dependent on the methods used to pool the data.[7,8]

Therefore, further evidence with individual patient-level data analyses, whether trial-specific or pooled, and ad hoc designed trials are required to draw definitive conclusions on which is the best antithrombotic strategy (double vs triple antithrombotic therapy) for patients with AF after PCI. Until then, we recommend a personalized strategy, with a careful individual assessment of the patient ischemic and bleeding risk.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declines in Acute Cardiovascular Emergencies During the COVID-19 Pandemic

The coronavirus disease 2019 (COVID-19) pandemic (December 2019 − present) is a global public health crisis with no modern-day equivalent. Several lines of evidence suggest that it is reasonable to forecast a significant increase in cardiovascular (CV) related events and deaths immediately following, and for some time after, the current pandemic.[1−3] We examined cardiac catheterization laboratory activations at Harford Hospital in Hartford, Connecticut, United States (US) for ST-segment elevation myocardial infarctions (STEMI) and non-ST elevation acute coronary syndromes (NSTE-ACS) by month for December-April 2020, compared to the monthly average for the previous 4 years (2015−2019). These months were selected to quantify monthly changes in acute cardiac events since first knowledge of COVID-19 (late December 2019). The first case of suspected local transmission in the United States was reported on February 26, 2020 and the first case in Connecticut was confirmed on March 8, 2020. Local schools were closed March 17, 2020, and executive stay at home orders were put into effect on March 17, 2020.

Compared to historical averages ("expected"), there was a 38% increase in STEMI activations in February 2020, followed by 16% and 21% reductions in March and April, respectively (Figure 1). Compared with expected, there were 21%, 37%, and 80% reductions in NSTE-ACS activations for February, March, and April, respectively (Figure 2). Only 3 of 140 patients died February-April 2020; one delayed seeking medical attention for ~24 hours for fear of COVID-19 infection and died from cardiogenic shock. Patients with documented time to presentation (n = 24) admitting March-April reported an average duration of 75 ± 196 hours from symptom onset to seeking medical attention. Patients had an average (±SD) age of 63 ± 14 years; 85% were white and 64% were men. Most were overweight (body mass index; mean ± SD: 30 ± 5, range: 21 to 42 kg/m^2), current/former smokers (73%), and had chronic conditions (hypercholesterolemia, 63%; hypertension, 56%; diabetes mellitus, 22%). Most (85%) had no previous history of myocardial infarction.

These data, to our knowledge, are the first to confirm similar findings in the United States[4] reporting a 38% (95% confidence interval 26 to 49) reduction in STEMI activations from March 1 to March 31, 2020 compared with the preceding 14 months. These findings are consistent with data from Spain (40% reduction in STEMI in March)[5]; Austria (39% reduction in STEMI/NSTE-ACS in March)[6]; and poll results from US cardiologists (50% in STEMI/NSTE-ACS in February-March).[7] Our addition of data after March and including April highlights the magnitude and direction of the reduction in acute cardiac event presentation and can likely be extrapolated to a national level.

We observed a 38% *increase* in STEMI activations for February, which has not been described. Recent reports documenting reductions in post-COVID STEMI activations have evaluated January-February or February-March and have not evaluated February activations separately, and thus reductions in March activations may be greatly underestimated. This increase immediately prior to the epidemic needs verification, but may indicate an increase in events due to psychological stress since a 22% to 35% increase in STEMI/NSTE-ACS usually occurs immediately following the onset of a community crisis.[1−3] It is unclear why there was not a similar increase in NSTE-ACS with COVID-19. Future

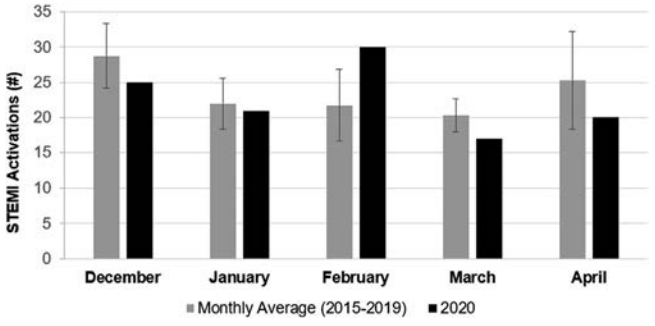

Figure 1. STEMI activations per month before and after COVID-19 compared to historical averages.

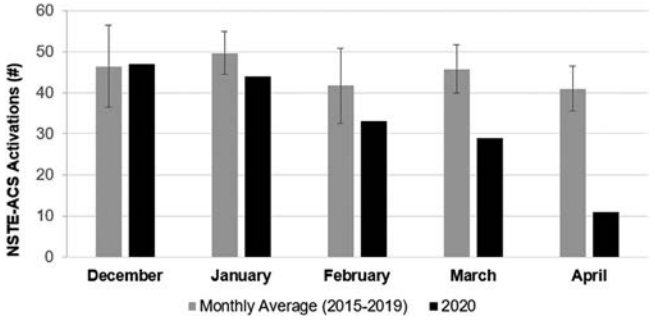

Figure 2. NSTE-ACS activations per month before and after COVID-19 compared to historical averages.