EDITORIAL COMMENT

Parenteral antiplatelet therapy in acute myocardial infarction complicated by cardiogenic shock – A field still worthy of future randomized trials?

Terapêutica antiplaquetar parentérica no enfarte agudo do miocárdio complicado por choque cardiogénico - são necessários mais ensaios clínicos?

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Cardiogenic shock occurs in up to 10% of patients presenting with acute myocardial infarction (AMI) and despite notable improvements in logistics of care and the increased availability of mechanical circulatory support (MCS), short-term mortality has stagnated at around 30–40%.1 Paired with timely reperfusion through percutaneous coronary intervention (PCI), potent antithrombotic therapy is one of the cornerstones of adjunctive treatment of acute coronary syndromes.2 By contrast, in the setting of acute myocardial infarction complicated by cardiogenic shock (AMICS), the evidence supporting pharmacotherapeutic preferences is limited, most of it being imported from the non-shocked patient population.1

The study by Saleiro et al. in this issue of the Journal1 aims to increase our understanding of the use and clinical impact of glycoprotein IIB/IIIa inhibitors (GPIs) in the context of AMICS. Based on data from the Portuguese Registry of Acute Coronary Syndromes (ProACS), the authors analyzed the use of GPIs in AMICS during a recent nine-year span and investigated possible associations with clinical outcomes.

Several important findings of this study deserve emphasis and should be put into perspective. Although the use of GPIs shows a modest trend toward decrease (we can arguably assume 2018 to be an outlier), about one in four patients would still currently receive one of these drugs during PCI for AMICS, 80% of which as non-bailout therapy.3 Overseas, the US National Cardiovascular Data Registry shows an even higher proportion, as almost 50% of patients in cardiogenic shock received a GPI.4 Hence, real-world data seem to be at odds with current recommendations, in which the option for GPI therapy has been narrowed to selected cases of suboptimal angiographic flow and/or large intracoronary thrombus burden.4 Although the case-to-case reasoning behind the decision to administer GPIs is not fully discernible from ProACS and despite the small sample size limiting our interpretation, these numbers still merit thoughtful reflection. What are the arguments favoring a parenteral antiplatelet agent during PCI for AMICS? Data from IABP SHOCK-2 and large registries show that from 40% to over 80% of patients admitted to the cardiac intensive care unit with AMICS will need invasive mechanical ventilation (and thus will likely have received opioids and be unable to take drugs orally) and just under 50% will have suffered cardiac arrest.5,6 This is further compounded by shock-related splanchnic...

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hypoperfusion and liver dysfunction, making the enteral route problematic due to limitations in rapid administration, absorption and transformation of parent drugs into metabolically active molecules by hepatic cytochromes. In order to ensure a prompt antiplatelet effect in a context in which time delays are critical, an intravenous platelet inhibitor would seem to be an appropriate choice. In the realm of intravenous agents, GPs are ascribed effects that go beyond their antiplatelet properties, such as an anti-inflammatory effect and earlier restoration of the microcirculation, which could theoretically translate into clinical benefit.

Hitherto, however, retrospective observational studies have yielded conflicting results on the impact of GPs in the setting of AMICS. In this regard, one of the best sources of information is a meta-analysis also by Saleiro et al. In seven studies involving 1216 patients, the use of GPs (66% abciximab, 22% epifibatide, 12% not reported) was associated with a reduction in short- and long-term mortality, improved thrombolysis in myocardial infarction flow post-PCI and no increase in bleeding rates. Still, only one of the included studies had a randomized design and in that trial (PRAGUE-7) no clinical benefit was found, nor was angiographic flow post-PCI better. Furthermore, the majority of observational studies driving the favorable effect of GPs were carried out before the introduction of prasugrel and ticagrelor, had an elevated risk of bias, and in two of them the oral antiplatelet therapy was not specified. More recently, a large nationwide registry-based study analyzing 10,193 patients with AMICS, of whom 3934 received GPs, pointed to reduced 12-month mortality without increased in-hospital event rates. Of note, the use of ticagrelor in this cohort was quite low and was significantly higher in GP-treated patients (4.9% vs. 3.8%, p=0.001). There are further contradictions concerning increased bleeding risk, since in randomized trials assessing GPI use in AMI without cardiogenic shock, bleeding complications were consistently higher in the active treatment arm. In PRAGUE-7, major bleeding was also more frequent (17.5% vs. 7.5%, p=0.310), although this did not reach statistical significance due to the small sample size (n=80).

The present work by Saleiro et al. brings valuable insights concerning contemporary antithrombotic strategies during PCI in AMICS. By including a significant proportion of patients treated with ticagrelor (26.6% overall), it is probably more reflective of current practice than previous studies and questions the potential benefit of GPs once high rates of potent double antiplatelet therapy are guaranteed. After multivariate adjustment that accounted for illness severity, the authors found that GPs had no impact on in-hospital mortality, or on secondary endpoints such as successful PCI, reinfarction or bleeding rates.

How can one reconcile these differences? In the absence of definitive evidence, it may be tempting to explain them by varying levels of antiplatelet inhibition, whether related to dose, timing of administration, transition from a parenteral to an oral route, drug metabolism, or co-administration of different antiplatelet and antiocoagulant drugs. A way to simplify matters would be to assess in-vitro platelet reactivity as a means to guide antithrombotic pharmacotherapy during the peri-procedural period. In AMICS, the evidence for this strategy is once again scarce, but promising data have been published and in time may prove useful if corroborated by larger studies, preferably including not only all three GPs but also cangrelor. Indeed, the few available studies comparing cangrelor with GPs for AMICS showed lower risk-adjusted bleeding, which could be due to cangrelor’s rapid therapeutic onset and short half-life.

What is the road ahead for parenteral antiplatelet therapy in AMICS? For the time being, there is only one ongoing randomized clinical trial, DAPT-SHOCK-AMI (NCT03551964), which will compare cangrelor and ticagrelor in this setting. Current recommendations from a recent position paper on antithrombotic therapy in cardiogenic shock and out-of-hospital cardiac arrest consider the use of GPs in AMICS, recognizing a balance between benefit and risk, while also considering the option of cangrelor. Thus, more evidence on antithrombotic strategies is definitely needed, particularly when MCS is envisioned or after resuscitated cardiac arrest, scenarios in which bleeding complications are particularly feared. Until more data from well-designed trials can provide answers to the questions raised, real-world registry analyses like the one by Saleiro et al. should continue to add informative snapshots to current knowledge in this important field.

**Conflicts of interest**

The author has no conflicts of interest to declare.

**References**