Acute Coronary Syndrome in Patients with Atrial Fibrillation: Which is the Benefit/Risk Profile of Triple Antithrombotic Therapy?

Running title: Maggioni; Role of the triple antithrombotic therapy

Aldo Pietro Maggioni, MD, FESC

ANMCO Research Center, Firenze, Italy

Address for Correspondence:
Aldo Pietro Maggioni, MD, FESC
ANMCO Research Center
Via La Marmora 34
Florence, Italy
Tel: +39-055-5101361
Fax: +39-055-5101310
E-mail: maggioni@anmco.it

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What we know

Dual antiplatelet therapy is the recommended treatment for all patients with an acute coronary syndrome treated or not with an invasive procedure\textsuperscript{1-4}. Several trials testing clopidogrel\textsuperscript{5-7} or new antiplatelet agents\textsuperscript{8,9} clearly showed that the addition of a thienopyridine to aspirin is associated with a significant improvement of patients’ outcomes. Further, even in the case of elective percutaneous coronary procedures, the use of dual antiplatelet therapy is recommended for a medium-long period of time after the procedure\textsuperscript{2,4,10}.

A similar level of good evidence is available for the prevention of ischemic stroke and peripheral thromboembolic events in patients with atrial fibrillation\textsuperscript{11,12}. In this clinical condition, appropriate use of vitamin K antagonists (VKAs) is associated with a significant reduction of thromboembolic events, in particular ischemic stroke\textsuperscript{13}. Specifically, in patients with nonvalvular atrial fibrillation, when the risk of stroke is relevantly high (CHA2DS2-VASc $\geq$2)\textsuperscript{14} and the risk of bleeding is acceptable (HAS-BLED <3)\textsuperscript{15}, a favorable risk/benefit profile of VKAs, at a dosage that maintains the INR between 2 and 3, has been clearly demonstrated.

What we do not know

The problem is when these clinical conditions coexist. When, for example, a patient with nonvalvular AF, treated appropriately with VKAs, needs to be percutaneously revascularized for an acute coronary syndrome or when a patient treated with dual antiplatelet therapy抱怨s episodes of atrial fibrillation with a high CHA2DS2-VASc score. This kind of patients is difficult to manage in clinical practice owing to the need to balance carefully the risk of bleeding against the risk of thromboembolism.

The benefit/risk profile of the combination of VKAs and dual antiplatelet therapy, both theoretically indicated for these coexisting clinical problems, is not well defined by convincing
clinical trials.

Guidelines, in these cases, suggest “common-sense based” decisions more than “evidence based” recommendations. Indeed, the evidence on which the recommendations for how to manage patients with an indication for the triple therapy (both VKAs and dual antiplatelet therapy) is based on limited and of relative poor quality evidence.\(^\text{16}\) In any case, these data represented the basis on which the first consensus document was built.\(^\text{17}\) According to this document, patients with atrial fibrillation (and probably also with other indications for VKAs), who present with an acute coronary syndrome and/or who are undergoing a percutaneous coronary revascularization, should receive the triple therapy. Owing to the inherent risk of major bleeding, the triple therapy should be prolonged for as short a time as possible, and, if possible, the implantation of drug-eluting stents should be avoided.

**Some news from a community setting**

The manuscript by Lamberts et al.\(^\text{18}\) provides more objective knowledge on the risk of bleeding and on the potential benefit of the triple antithrombotic therapy in a cohort of patients with atrial fibrillation with an indication to be treated with dual antiplatelet therapy for the occurrence of an acute coronary syndrome or following an elective percutaneous coronary revascularization.

Using nationwide administrative databases, these authors demonstrated that the triple antithrombotic therapy is associated with an early, higher risk of serious bleeding, determining hospitalization or death, in comparison with the use of antiplatelets or a VKA alone, or the combination of VKA and just one antiplatelet agent. The risk of serious bleeding is elevated immediately after the initiation of the triple therapy, being statistically significant after 30 days from treatment initiation and remaining higher over time in comparison with the other less aggressive antithrombotic treatment strategies. A trend toward a reduction of the combined end-
point of cardiovascular death, myocardial infarction and ischemic stroke was the
counterbalanced, favorable effect of the more aggressive antithrombotic strategy. Overall, these
findings suggest that the current recommendations of using triple therapy for short periods of
time\(^{17}\) can be hazardous and that a more careful evaluation of the risk of bleeding should be
considered before starting a triple antithrombotic therapy.

The link between discharge databases, survival databases, and prescription databases of
the entire country of Denmark provided important information on relevant patients’ outcomes
that could not be gleaned from any single institution or from observational or controlled studies,
performed in limited specialty settings; and this is a major strength of the paper\(^{18}\). The reported
findings include the full universe of the institutions of a whole country, including the small and
less visible clinical units committed to the care of a relevant proportion of real-life patients. The
other relevant strength is the public, independent nature of the data, that reinforces the
transparency of the results differentiating them from those generally provided by company-
sponsored observational or controlled studies. However, as in all administrative datasets, the type
and number of clinical variables are quite limited and not specifically collected, and this is the
major limitation of the paper.

What next

Further reliable information have been provided by the paper by Lambert et al\(^{18}\) but some
questions remain still unanswered. Patients who theoretically need to be treated with both a VKA
and dual antiplatelet agents should be evaluated very carefully in terms of bleeding risk because
serious hemorrhages can occur very early after the beginning of treatment and this kind of risk
persists over time. However, the trade-off between the risk of bleeding and the potential benefit
in the prevention of thromboembolic events cannot be clarified by this paper due to the brief
period of follow-up and the insufficient sample size of the study.

Therefore, a definite evidence of the benefit/risk profile of the triple therapy versus less intensive antithrombotic regimens is not yet available. Some specific trials are ongoing\textsuperscript{19,20}, which could, in the near future, add further knowledge to this relevant clinical issue, but an alternative/complementary way to provide evidence could be the systematic adoption of the methodology used by Lamberts et al\textsuperscript{18}.

The possibility to pool and link administrative data from US and several European countries should be strongly encouraged in order to create huge data warehouse of patients of real clinical practice. The methodologies to minimize the possible biases and the limitations in the analyses of this kind of datasets surely need to be further improved, but the possibility to deliver scientific information from the totality of the populations living in large areas of the world, at low cost, with more transparency and independency in comparison with the traditionally sponsored studies, is too attractive an opportunity to be disregarded.

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