Differences between ACC/AHA and ESC Guidelines on antiplatelet therapy in patients with acute coronary syndromes

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Writing of guidelines underlies a complicated and time-consuming process, in which usually highly accepted experts in the respective fields are involved. These experts are relatively rare and due to their knowledge and expertise occasionally also involved in prospective randomised trials, or are co-authors of meta-analyses, both being prerequisites for high recommendations in guidelines in both continents. Accordingly, it is not always possible to exclude experts who have contributed to international trials or meta-analyses from writing committees, neither in the USA nor in Europe, but it should be made clear at this point that, based on the multidisciplinary structure and composition of guideline committees, as well as on the great efforts of numerous reviewers of guideline drafts, the opinion of single or few members of guideline committees will not necessarily prove decisive for the guideline content.

With regard to recent guidelines on antiplatelet therapy in patients with acute coronary syndromes (ACS), the same papers that were analysed and were the basis for the recommendations of antiplatelet agents in patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) (1, 2) or ST-elevation myocardial infarction (STEMI) (3, 4) led to somewhat different results in the ACC/AHA and ESC guidelines. This is the subject of a VIEW-POINT article in this issue of Thrombosis and Haemostasis written by Serebruany and DiNicolantonio (5).

Antiplatelet therapy in NSTE-ACS guidelines

ACC/AHA as well as ESC guidelines recommend the use of acetyl-salicylic acid (ASA) as early as possible (IA) (1, 2). After a decision for either conservative strategy or coronary intervention ASA is recommended as life-long therapy in both guidelines, although the recommended dosages differ (ACC/AHA: 162-325 mg/d or 75-162 mg/d in patients with increased bleeding tendency; ESC: 75-100 mg/d) (Class IA recommendation).

Both, ACC/AHA and ESC guidelines recommend the addition of a P2Y₁₂-receptor inhibitor as soon as possible (IA).

ACC/AHA guidelines recommend before PCI clopidogrel, initiated with a loading dose (LD, 600 mg) and followed by daily maintenance dose (MD, 75 mg) (IB) or also ticagrelor (LD 180 mg, MD 2x90 mg) (IB).

At time of PCI, prasugrel (LD 60 mg, MD 10 mg – 5 mg in the elderly, >75 years, and/or low weight patients, <60 kg) and ticagrelor have a IB recommendation (2).

Vice versa, the ESC guidelines gave both prasugrel (only after known anatomy and planned PCI) and ticagrelor a IB recommendation, thus accepting their advantage over clopidogrel as shown in the TRITON TIMI-38 (6) and PLATO trials (7), whilst clopidogrel should only be used in case prasugrel or ticagrelor are not available (IC) (1).

Both guidelines recommend albeit with slightly different strength of recommendation for the use of a higher MD of clopidogrel (ACC/AHA: IIbB; ESC: when prasugrel or ticagrelor were not available, IIaB): 150 mg for about one week, then reduction to 75 mg/day again.

In patients with a primarily conservative treatment strategy the ACC/AHA guidelines recommend clopidogrel or ticagrelor (LD plus daily MD) (IB), while ESC guidelines prefer ticagrelor (IB) to clopidogrel (IC) in this indication.

For both guidelines duration of dual antiplatelet therapy (DAPT) is recommended for 12 months (IB).

According to ACC/AHA guidelines, glycoprotein IIb/IIIa-inhibitors (GPIs), preferably eptifibatide or tirofiban (IB), can be used before PCI (IB) when patients are not pretreated with a P2Y12-receptor inhibitor (IA), which is a recommendation that is considered to have lower evidence in the ESC guidelines (IIaC). Eptifibatide or tirofiban should be used before diagnostic angiography, when patients with NSTE-ACS under ASA, clopidogrel or ticagrelor and an anticoagulant, are referred for coronary angiography±PCI and the bleeding risk is low (ACC/AHA: IIaC; ESC: IIbC). According to ACC/AHA guidelines upstream use of GPIs is not recommended in patients with low risk for ischemic events or at high bleeding risk (IIIB), while ESC guidelines do not recommend routine upstream use at all (IIIA).
**Antiplatelet therapy in STEMI guidelines**

As in NSTE-ACS, the early use of ASA is recommended in both guidelines (IB) with different doses (ACC/AHA: 162-325 mg; ESC: 150-300 mg oral or 80-150 mg IV) followed by life-long therapy with either 162-325 mg daily (ACC/AHA) or 75-100 mg daily (ESC) (IA). It should be mentioned at this point that dosing of ASA in the given ranges leads to a similar and fast platelet inhibition and should not make any difference with respect to clinical outcome (8). However, a recent publication has discussed a potential influence of higher doses of ASA on the action of ticagrelor (9), which might explain the missing beneficial effect of ticagrelor over clopidogrel in countries with a higher MD of ASA in secondary prevention, and which might have triggered the relatively cautious recommendation of ticagrelor in the ACC/AHA guidelines. Accordingly, the ACC/AHA guidelines ask for a dose reduction of ASA to 81 mg/day when ticagrelor was the chosen P2Y12-receptor inhibitor (3) and, for the first time, the guidelines find it reasonable to use a low MD of ASA (81 mg/day) in secondary prevention after STEMI in preference to higher MDs (IIaB).

Both guidelines ask for an additional loading dose of a P2Y12-receptor inhibitor (IA) but differ again with the recommendation of the available agents: ACC/AHA guidelines recommend clopidogrel, prasugrel and ticagrelor with the same classification (IB) (3), while ESC-guidelines again prefer prasugrel (in clopidogrel-naive patients younger than 75 years) or ticagrelor (both IB) over clopidogrel (IC, only when prasugrel or ticagrelor are not available) (4). As in NSTE-ACS, DAPT should be given for 12 months (IB for both ACC/AHA and ESC guidelines).

The routine use of GPIs during PCI is controversial (10-14). Differences in the interpretation of study results might be explained by the fact that European authors of NSTE-ACS and STEMI guidelines analyse primarily the data of international trials and meta-analyses that have been published in (often high-rated) journals, while North American experts occasionally also take additional information into account, which comes up, for example, during the approval process for new agents with the Food and Drug Administration (FDA). While European experts avoid giving subgroup analyses of original papers too much attention, this seems occasionally to happen with US-guidelines.

Moreover, European guidelines have recently started to be written in a short and easily understandable style and give clear advice of experts, regarding which agent should be preferred over the other. In contrast, ACC/AHA-guidelines are frequently very detailed and extensive, thus frequently leaving their readers without clear recommendations, a fact that has frequently been criticised also by North American colleagues.

It is obvious that the quality and outcome of international trials mainly contributes to the recommendation of treatment strategies in guidelines. Besides slightly differing classification systems, there is also room for different interpretation of study results, and knowledge about underlying mechanisms of action might influence weighing the importance of one antiplatelet agent up the other, all of which finally might explain the described differences. Debate and discussion would also allow healthy academic exchange of ideas where different points of view are evident, or where some issues remain controversial (10-14).

What's the bottom line? We all agree that it might be a great step forward in avoiding obvious differences in international guidelines, especially if future guidelines committees could be composed of experts from Europe and North America in order to exchange expertise and points of view, also in order to discuss and harmonise interpretation of results.

**Conflicts of interest**

K. Huber has received speaker fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, and Sanofi-Aventis. G. Y. H. Lip has received speaker fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Sanofi-Aventis; and consultant fees from Astellas, AstraZeneca, Bayer, Biotronik, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Merck, Sanofi-Aventis, Portola, and Pfizer.

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