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Dual platelet inhibition in ACS—The Styrian consensus

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ABSTRACT

Dual antiplatelet therapy facilitated treatment of acute coronary syndromes and enabled the wide use of stents after clopidogrel emerged on the market about twenty years ago. Although this was a milestone in cardiology, clopidogrel inherits several disadvantages which are likely to reduce clinical benefit of its use and a new generation of drugs including prasugrel and ticagrelor is now available. One megatrial was done for each substance and various publications regarding subgroups have been published. Since these broad data is difficult to overview, especially for clinicians not focused on cardiology patients, the invasive centers of Styria aimed to design an easy-to use algorithm for dual antiplatelet therapy in ACS. The algorithm divides patients with acute coronary syndromes into STEMI patients with preferred use of prasugrel and NSTEMI patients being preferentially treated with ticagrelor. Only two subgroups were included to facilitate the use of the algorithm. Recommended treatment in diabetic patients is the use of prasugrel and ticagrelor is recommended in small and old patients.

Contents

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1. Introduction

Dual antiplatelet therapy facilitated treatment of acute coronary syndromes and enabled the wide use of stents after clopidogrel emerged on the market about twenty years ago. Although this was a milestone in cardiology, clopidogrel inherits several disadvantages which are likely to reduce clinical benefit of its use.

First, there is a significant interindividual variability of platelet inhibition due to genetic polymorphisms in CYP2C19 [1] resulting in less effective platelet inhibition after clopidogrel administration and which are especially frequent in Caucasians. The GRAVITAS trial revealed that even dose adaption after platelet function testing did not improve cardiovascular outcome [2].

Second, clopidogrel has to be metabolized before inhibiting platelet function. This step needs time and might be further prolonged in clinical states of hemodynamic instability. Increasing loading doses of 300 mg and 600 mg are recommended to shorten the period to significant platelet inhibition, however, the metabolic steps towards the active metabolite still consume time which can take longer than the invasive therapy including stenting, resulting in implanted stents without active dual platelet inhibition until clopidogrel is converted into active metabolites to a significant extent.

Therefore, pharmacological companies put a lot of effort in developing new drugs overcoming these drawbacks and two of these drugs delivered positive data in recent megatrials. Both, prasugrel and ticagrelor significantly improved outcome in ACS patients compared to clopidogrel. This led to new recommendations in the latest guidelines which suggest the preferred use of the new drugs in ACS [3,4]. However, a comparative trial of both substances is neither ongoing nor planned and register data is still weak. One therefore has to decide between the two new substances based on the two megatrials PLATO and TRITON-TIMI 38 and their substudies as well as on experimental and pathophysiological data which drug to use in which patient. Since these broad data is difficult to overview, especially for clinicians not focused on cardiology patients, the invasive centers of Styria aimed to design an easy-to use algorithm for dual antiplatelet therapy in ACS (Fig. 1). It has to be mentioned that the underlying trials recruited different cohorts and used different pre-specified subgroups and thus are not perfectly comparable, leaving all suggestions drawn from this data in a subjective environment.

A basic idea underlying this algorithm was that an early onset of antiplatelet therapy is beneficial in ACS. Therefore, use of the new and faster acting substances is recommended in these patients and administration of these substances in the preclinical setting is encouraged, if diagnosis of myocardial infarction is safe or very likely. This approach follows the ESC guideline recommendation for NSTE-ACS to "add a $P2Y_{12}$ inhibitor as soon as possible" although the same table of the same guideline only recommends prasugrel use after knowing coronary anatomy because this was part of the study protocol in TRITON-TIMI 38. Typical ST-elevation will lead to the diagnosis of STEMI in the vast majority of cases and the drug can be administered early on a regular basis. In suspected NSTE-ACS, however, far more differential diagnoses need to be considered and early administration is only recommended if the physician dealing with the first medical contact is confident of the diagnosis NSTE-ACS.

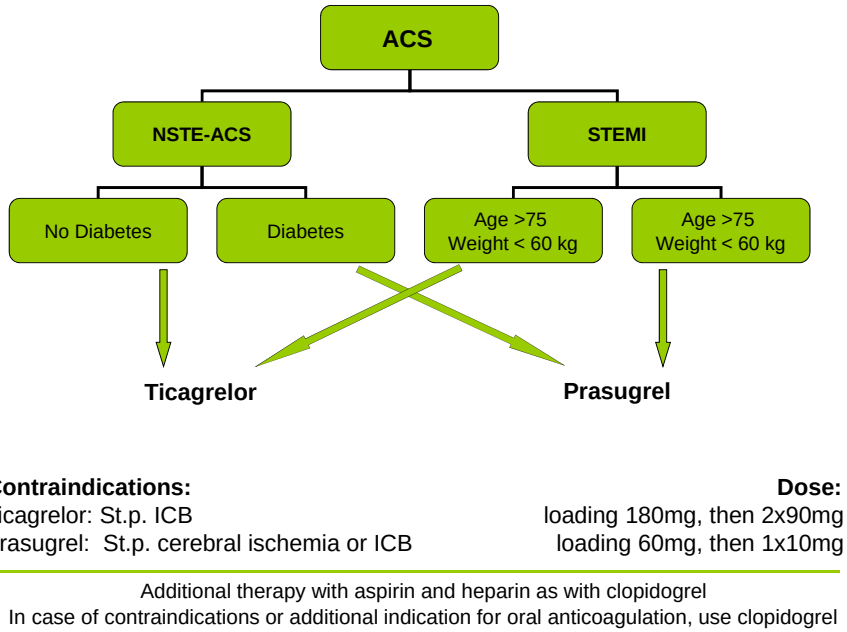

Fig. 1 – Flow chart of the styrian ACS consensus. Upon diagnose of ACS patients are seperated in STEMI and NSTE-ACS patients. Patients with NSTE-ACS and comorbidity of diabetes shift to the prasugrel branch whereas old and small STEMI patients shift to the ticagrelor branch. Immediate initiation of therapy is recommended in STEMI patients whereas NSTE-ACS patients should only be treated with dual platelet therapy in presence of a positive troponin or a clinically very likely diagnose of NSTEMI since only in patients with positive troponin ticagrelor has shown beneficial effects in the PLATO trial.

2. STEMI vs. NSTE-ACS

The decision to prefer prasugrel in STEMI patients is based on STEMI substudies of both megatrials [5,6]. Hazard ratio compared to clopidogrel are 0.79 (0.65–0.97) and 0.87 (0.75–1.01) for prasugrel and ticagrelor, respectively. Moreover, prasugrel administration resulted in a more pronounced reduction of HR in STEMI compared to NSTE-ACS patients (0.79 vs. 0.83) whereas ticagrelor was more potent in NSTE-ACS patients compared to STEMI patients (0.83 for NSTE-ACS and 0.87 for STEMI). The main beneficial effects of the two drugs seem to occur at different time points. Whereas prasugrel reduced HR within the first 3 days beneficial effects of ticagrelor get more pronounced over the following moths. These data support that the main effects of ticagrelor may not relate to rapidity of acute reperfusion but rather prevention of recurrent vascular events known to modulate long term outcome (Armstrong et al., Circulation 125 (2012) 514–521). Moreover, in STEMI patients the number needed to treat (NNT) was 42 for prasugrel but 71 for ticagrelor [7]. Although this appears to be solid data it has to be acknowledged that in TRITON-TIMI 38 an untypical large number of STEMI were subacute. Especially these patients exerted the strongest benefit from prasugrel treatment. Therefore, positive effects might be overestimated compared to a real life setting.

The opposite argumentation was basis of the recommendation of ticagrelor in NSTE-ACS patients. Since these patients had a larger profit than STEMI patients with ticagrelor but less effect with prasugrel, ticagrelor seems to have advantages comparing both new drugs in NSTE-ACS. We believe that this still holds true even though HR is 0.83 and NNT is 46 for NSTE-ACS both in PLATO and in TRITON-TIMI 38 [7]. The argumentation in favor of ticagrelor in NSTE-ACS is based on different patient's population and the fact that positive effects on mortality were only seen in PLATO although STEMI patients had less benefit compared to prasugrel treated patients in TRITON-TIMI 38.

2.1. *Diabetes*

Although many subgroups were evaluated in both megatrials only diabetes represents a subgroup large enough and with relevant differences between the two new drugs. Whereas HR is even more reduced in diabetic patients with prasugrel (HR 0.70 vs. 0.86), diabetic and non-diabetic patients do not show different results using ticagrelor (0.88 with medical history of diabetes vs. 0.83 without diabetes). HR further declines with prasugrel if diabetes is treated with drugs (0.74) or even more so if it is insulin-dependent diabetes mellitus (0.63). This underlines the idea of a pathophysiological mechanism being treated with prasugrel, however, *p*-value for interaction did not reach significance due to small numbers of diabetic patients. Nevertheless, these effects were the basis for the decision to recommend prasugrel for all diabetic patients including patients with NSTE-ACS.

2.2. *Old and small patients*

The algorithm is complicated by warnings in the product information for prasugrel made by the company. This is due to a predefined subgroup of patients older than 75 years, smaller than 60 kg and with history of TIA or stroke in TRITON-TIMI38. These patients did show a worse outcome with prasugrel compared to clopidogrel. Although these negative effects result almost completely from TIA/stroke patients the predefined subgroup results in the actual warning and was adopted in the Styrian algorithm to prevent potential legal problems. In addition, despite the product information of prasugrel suggests using 5 mg/d maintenance dose in small and old patients this is not recommended in the algorithm since this suggestion only bases on pharmacokinetic data and no clinical study has evaluated this approach so far. It has to be noted that ticagrelor must not be used, too, in patients with history of intracerebral bleeding whereas patients with history of TIA did not show impaired outcome with ticagrelor.

3. Discussion

The situation that only STEMI but not NSTE-ACS can be diagnosed with high likelihood in preclinical settings and the algorithm favors prasugrel for STEMI patients it has been discussed if ticagrelor was needed on the ambulance vehicle at all. The decision to have both drugs in store was made due to two reasons. First, depending on the physician working on the ambulance vehicle it is likely that NSTE-ACS is proposed to be very likely due to typical clinical signs, ECG alterations and possibly qualitative troponin testing. In such a setting immediate start of ticagrelor therapy is supposed to be beneficial. Second, there is no data on switching the two new platelet-function inhibitors which would be necessary if prasugrel was given in a NSTE-ACS patient preclinically but later switched to ticagrelor due to better long term data in NSTE-ACS.

Another topic under discussion was the need to store clopidogrel on the ambulance vehicle anymore. If all potential ACS patients were either treated with only aspirin in case that ACS was not very likely and dual anti-platelet therapy was only given after definite diagnosis in the clinic or immediate dual platelet therapy including the two new substances, there would be no need to have clopidogrel anymore. However, three groups of patients have been identified in which clopidogrel is preferred; first, patients with atrial fibrillation, second, patients with mechanic valves and third, patients with thrombolysis. In the first two groups loading dose of one of the new drugs was considered to be of justifiable risk in STEMI or high risk NSTE-ACS patients if clopidogrel was used for chronic treatment as part of triple therapy (together with aspirin and oral anticoagulation, or considering the data of the WOEST study presented at the ESC 2012 clopidogrel and oral anticoagulation alone). On the other hand, in low risk patients single therapy with aspirin in the preclinical setting and consecutive administration of clopidogrel loading in the hospital was regarded to be reasonable. For the rather small but important group of patients treated with thrombolysis there is no data available using the two new drugs and clopidogrel is recommended in these patients to be used early. The Styrian algorithm therefore recommends having clopidogrel on board, too. To simplify drug use on the

ambulance vehicle and to limit the number of different drug packages one tablet of 300 mg clopidogrel (recommended dose if thrombolysis is given) can be sticked to each vial for thrombolysis and administered simultaneously.

The consensus did not differentiate therapy based on potential side effects or estimated compliance. Nevertheless, it has to be kept in mind that ticagrelor has additional side effects compared to former therapy using clopidogrel due to its modulation of adenosine receptors which can lead to dyspnea and bradycardia. Both have been observed in PLATO more often in the ticagrelor group, however, without affecting total outcome. Therefore, patients with known chronic obstructive pulmonary disease or known bradycardia should rather be treated with prasugrel. Furthermore, compliance might be more difficult in daily practice with ticagrelor as it has to be taken twice daily.

Comparing bleeding complications in PLATO and TRITON-TIMI 38 indicates higher bleeding complications with prasugrel, mainly due to fewer coronary artery bypass grafts (CABG) related bleedings in the ticagrelor group. In this context it has to be mentioned that bleeding definitions were different in the two groups and emergency CABG (at the day of myocardial infarction) was rare. In our hands both new drugs show significantly increased bleeding during emergency CABG compared to clopidogrel. However, emergency CABG remains a small group of patients and patients treated with PCI with beneficial effects outweigh this disadvantage of the new drugs.

4. Conclusion

The presented algorithm was designed on the basis of published trials as well as pathophysiological and pharmacological concepts. The recommendation of the ESC guidelines to administer dual platelet inhibition “as soon as possible” was weighted higher than the recommendation to use prasugrel only after knowing the coronary status (following the study design). The latter recommendations had to be made following the rules of evidence based medicine.

The algorithm is thought to be differentiated enough to maximize the benefit even for relevant subgroups but still easy enough to be feasible for non-cardiologists, too.

REFERENCES

[1] J.L. Mega, T. Simon, J.P. Collet, et al., Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis, JAMA: The Journal of the American Medical Association 304 (16) (2010) 1821–1830.

[2] M.J. Price, P.B. Berger, P.S. Teirstein, et al., Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial, JAMA: The Journal of the American Medical Association 305 (11) (2011) 1097–1105.

[3] C.W. Hamm, J.P. Bassand, S. Agewall, et al., ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC), European Heart Journal 32 (23) (2011) 2999–3054.

[4] Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC), The European Association for Cardio-Thoracic Surgery (EACTS), European Association for Percutaneous Cardiovascular Interventions (EAPCI), et al., Guidelines on myocardial revascularization, European Heart Journal 31 (20) (2010) 2501–2555.

[5] S.D. Wiviott, E. Braunwald, C.H. McCabe, et al., Prasugrel versus clopidogrel in patients with acute coronary syndromes, The New England Journal of Medicine 357 (20) (2007) 2001–2015.

[6] L. Wallentin, R.C. Becker, A. Budaj, et al., Ticagrelor versus clopidogrel in patients with acute coronary syndromes, The New England Journal of Medicine 361 (11) (2009) 1045–1057.

[7] H.F. Alber, K. Huber, O. Pachinger, M. Frick, Prasugrel vs. ticagrelor in acute coronary syndromes: which one to choose?, Wiener klinische Wochenschrift 123 (15–16) (2011) 468–476.