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Update on Antithrombotic Therapy 2009

Clopidogrel is a pro-drug which has several disadvantages such as a slow and a variable transformation to the active metabolite resulting in modest and variable platelet inhibition. Moreover, there has been an ongoing debate on the optimal dosing in this syndrome: larger doses show a better effectiveness in patients undergoing PCI, but at the cost of more bleeding than the standard dose clopidogrel.

At the 2009 ESC congress in Barcelona the definitive answer has been given in the huge CURRENT-OASIS-7 trial of NSTEMI patients [1], in which 2 clopidogrel strategies were tested double-blindly: the classical 300 mg loading dose followed by a 75 mg daily dosing vs a 600 mg loading dose followed by a twice daily dosing of 75 mg for 7 days. On top of this, patients were randomized for a 30 days strategy of open label high dose (300–325 mg/d) or low dose (75–100 mg/d) aspirin after a loading dose 300 mg. All patients were planned for an early < 24 h) invasive management with intended percutaneous coronary intervention (PCI): 99 % of the patients underwent angiography and in 70 % followed by PCI. Patients who did not undergo PCI had no significant coronary artery disease, discontinued therapy because they were scheduled for CABG, or were treated conservatively. The major primary efficacy outcome was a composite of cardiovascular death, myocardial infarction or stroke at day 30. A key secondary outcome was stent thrombosis at day 30. The safety outcome was bleeding using a variety of definitions including the TIMI major definition and CURRENT major and severe bleeding definitions. A particular subgroup of interest was the group of patients undergoing a PCI.

In the clopidogrel arm there were no significant differences observed in the primary outcome or its components. The primary endpoint occurred in 4.4 % of the patients in the standard dose clopidogrel group versus 4.2 % of the patients in the double dose clopidogrel group (HR 0.95; 95 %-CI: 0.84–1.07). Major bleeding according to the CURRENT definition was seen in 2.0 % of the patients in the standard dose clopidogrel group vs 2.5 % of the patients in the double dose clopidogrel group (HR 1.25; 95 %-CI: 1.05–1.47). Severe bleeding according to the CURRENT definition occurred in 1.5 % of the patients in the standard dose clopidogrel group versus 1.9 % of the patients in the double dose clopidogrel group (HR 1.23; 95 %-CI: 1.02–1.49). There were no significant differences according to the TIMI definition of bleeding.

In the aspirin arm there were no significant difference observed in the primary outcome or its components. The composite of cardiovascular death, myocardial infarction and stroke occurred in 4.4 % of the patients in the low dose aspirin group versus 4.2 % of the patients in the high dose aspirin group (HR 0.96; 95 %-CI: 0.85–1.08). Major bleeding according to the CURRENT definition occurred in 2.3 % of the patients in the low dose aspirin group versus 2.3 % of the patients in the high dose aspirin group (HR 0.99; 95 %-CI: 0.84–1.17). Severe bleeding according to the CURRENT definition occurred in 1.7 % of the patients in the low dose aspirin group versus 1.7 % of the patients in the high dose aspirin group (HR 1.00; 95 %-CI: 0.83–1.21).

Subgroup analysis of the 17.232 patients who underwent PCI demonstrated a significant reduction in cardiovascular death, myocardial infarction and stroke: 4.5 % of the patients in the standard dose c1opidogrel group vs 3.9 % of the patients in the double dose clopidogrel group (HR 0.85; 95 %-CI: 0.74–0.99). This reduction was driven by a significant reduction in myocardial infarction: 2.6 % in the standard dose clopidogrel group vs 2.0 % in the double dose clopidogrel group (HR 0.78; 95 %-CI: 0.64–0.95). Stent thrombosis occurred significantly more often in the standard dose clopidogrel group: 1.2 vs 0.7 % in the double clopidogrel group (HR 0.58; 95 %-CI: 0.42–0.79). In terms of safety, significantly more CURRENT major bleeding occurred in the double c1opidogrel compared to the standard dose group (1.6 % in the double dose group vs 1.1 % in the standard dose group: HR 1.44; 95 %-CI: 1.11–1.86). There was also an increase in red blood cell transfusion. There were no differences in fatal bleeding, intracranial hemorrhage and CABG related bleeding between the two clopidogrel groups.

Thus, high dose clopidogrel did not show any benefit compared to standard dose clopidogrel in the overall population, but at the cost of more bleeding. Interestingly, no significant difference was observed in the overall cohort of patients who received the higher dose of aspirin. Patients with acute coronary syndromes undergoing a PCI within 24 hours, who were treated with double loading and maintenance dose clopidogrel for 7 days, suffered less from myocardial infarction and stent thrombosis, after 30 days of follow-up. But also this subgroup had a larger risk on non-fatal major bleeding. Different aspirin dosing did not influence the outcome in the PCI cohort either. This implies that both the current clopidogrel and aspirin strategies as advised in the European NSTE-ACS guidelines are still valid and do not need an update.

Recently, the novel platelet ADP-receptor antagonist prasugrel has been introduced: it is also a pro-drug like clopidogrel, but it is much faster metabolized to the active metabolite by blood esterases and the liver than clopidogrel. Therefore, it has a faster onset of action and a higher occupancy of the platelet ADP-receptor. In the 13,608 patients TRITON-TIMI 38 trial this drug significantly showed to be superior to c1opidogrel in patients presenting acute coronary syndromes with and without ST-segment elevation all treated with PCI with regard to death (3.0 vs 3.2 %), MI (7.3 vs 9.5 %; $p < 0.001$) and stroke (1.0 vs 1.0 %) during the 15 months follow-up [2]. However, the drug was associated with a significant 32 % increase in major non-surgical bleeding (1.8 vs 2.4 %; $p < 0.03$) including fatal bleeding. The latter resulted in no benefit on mortality. Stent thrombosis was halved by prasugrel over clopidogrel. The major difference between the earlier CURE and the TRITON trial is that in CURE only non ST-segment elevation acute coronary syndromes were included and a mere 20 % of the patients underwent PCI, whereas in TRITON also STEMI

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patients were randomized and all patients went for PCI. In TRITON patients often double antiplatelet therapy was combined with the use of intravenous glycoprotein IIB/IIIA blockers which may also have contributed to major bleeding. Anyway, the outcome of the TRITON trial suggests that faster and more intense blockade of the platelet ADP-receptor is associated with less ischemic events but also at the cost of more bleeding. The slow offset of both c1opidogrel and prasugrel may also have been responsible for the excess bleeding compared to aspirin alone. Therefore, alternative platelet ADP-receptor antagonists had to be developed.

Cangrelor is an intravenous platelet ADP-receptor antagonist with very fast onset and offset of action, and ticagrelor is an oral reversible platelet ADP-receptor antagonist with fast onset and offset of action. Both drugs are not a pro-drug which explains the fast onset of action. There have been 2 large trials with cangrelor in patients undergoing PCI, but the outcome is not available yet.

The second major trial presented at ESC 2009 in Barcelona was the huge multinational clopidogrel-controlled PLATO trial, in which ticagrelor on top of aspirin was compared to clopidogrel on top of aspirin in patients presenting with acute coronary syndromes with and without ST-segment elevation irrespective of whether they would go for PCL [3]. The study was done in 18,624 patients in 43 countries and 862 hospitals. Nearly 38 % of the patients presented with ST-segment elevation myocardial infarction, 43 % with non ST-elevation myocardial infarction, 17 % with unstable angina and 3 % eventually without a cardiac diagnosis. Vascular death, MI and stroke was the primary endpoint which was reduced by 16 % from 11.7 % with clopidogrel to 9.8 % with ticagrelor ($p < 0.001$) during the median of 9 months follow up. During hospitalisation an invasive strategy was planned in72 % of the patients, and PCI was performed in 61 % and coronary surgery in 4 %. During follow-up, these figures increased to 64 % PCI and 10 % coronary surgery. The secondary endpoints showed a significant reduction of MI from 6.9 % with clopidogrel to 5.8 % with ticagrelor (RR 0.84; $p = 0.005$) and cardiovascular death from 5.1 % with clopidogrel to 4.0 % with ticagrelor ($p = 0.001$). Most striking was the reduction in overall mortality from 5.9 % with clopidogrel to 4.5 % with ticagrelor: 22 % relative reduction with a p-value of < 0.001. Total stent thrombosis was reduced from 3.8 % with clopidogrel to 2.8 % with ticagrelor ($p = 0.01$). The overall safety of ticagrelor was strikingly similar to clopidogrel: TIMI major bleeding was 7.7 % with clopidogrel and 7.9 % with ticagrelor ($p = 0.57$). TIMI major bleeding related to coronary surgery was 5.8 % with clopidogrel and 5.3 % with ticagrelor ($p = 0.32$), but non coronary surgery related TIMI major bleeding was 2.2 % with clopidogrel and 2.8 % with ticagrelor ($p = 0.03$) and rare fatal intracranial bleeding was 0.01 % with clopidogrel and 0.1 % with ticagrelor ($p = 0.02$). Safety issues regarded both dyspnoea – which was nearly doubled from 7.8 % to 13.8 % by ticagrelor – and bradycardia, which was rare and not associated with an increase in heart block or the insertion of a pacemaker. Yet, Holter monitoring in a subset of patients showed significantly more ventricular pauses over 3 seconds in patients on ticagrelor (5.8 % compared to clopidogrel 3.6 %; $p = 0.01$).

The reversible oral platelet ADP-receptor antagonist ticagrelor is a new promising antiplatelet agent in the management of patients with acute coronary syndromes whether they are treated with intervention or not. The agent is not a pro-drug, and has a fast onset and offset of anti platelet activity. It proved to be superior to clopidogrel in the prevention of vascular death, MI and stroke, and in particular total mortality, without a significant excess in overall major bleeding. The striking equivalence in safety with clopidogrel is probably due to the fast offset of action when the drug is discontinued in case of surgery or bleeding. This advantage may have contributed to the reduction in total mortality.

Considerable mortality benefits with antiplatelet therapy have rarely been seen after the 2 major aspirin trials Veteran Administration Cooperative Study [4] and ISIS-2 [5]. The PLATO trial shows that the number of patients to treat with ticagrelor to save one life is only 71. The downside of ticagrelor may be the increased bleeding seen in the large subset of patients, who did not undergo coronary artery bypass surgery. Yet, the increased risk in non surgery related bleeding is modest compared to that with prasugrel. And unlike TRITON, PLATO did not show overall excess in fatal bleeding. Other concerns may be new occurrence of dyspnoea which proved to be mild, but was nearly doubled by ticagrelor and it was reason for drug discontinuation in 0.9 % of patients on ticagrelor and 0.1 % in those on clopidogrel. Although not clinically apparent, bradycardia was more frequently observed with ticagrelor and serum uric acid rose 15 % after a year ticagrelor vs 7 % with clopidogrel, whereas serum creatinine rose 11 % by one year with ticagrelor and 9 % with clopidogrel. It is likely that this minor side defects will not hamper the introduction of the ticagrelor which can be expected in about a year.

Thus, an oral reversible and faster acting platelet ADP-receptor antagonist may be a more effective and safe alternative to clopidogrel in patients, who present with acute coronary syndrome whether intervened or not. This may be a further leap forward in the management of this large group of patients. Given the mortality benefit with ticagrelor and the relative low number of patients to treat to save one life, cost effectiveness may be large, but this will become apparent shortly. Especially, the absence of excess fatal bleeding as was seen with prasugrel will make ticagrelor plus aspirin the preferred antiplatelet strategy in acute coronary syndromes.

The most remarkable study presented at ESC 2009 in Barcelona is the RE-LY study, in which the novel direct oral thrombin antagonist dabigatran was compared to warfarin for stroke prevention in warfarin-eligible patients with atrial fibrillation [6]. After the promising oral thrombin antagonist ximelagatran, which showed liver toxicity, the concept of oral thrombin blockade for this purpose in atrial fibrillation remained an actual one. The RE-LY study randomized 18,113 patients in 44 countries and 951 hospitals to dabigatran 150 mg or 110 mg twice daily in a double-blind fashion, or to open label warfarin (INR 2–3). Stroke and systemic embolism was the primary endpoint which was reduced by 33 % from 1.7 %/yr with warfarin to 1.1 %/yr with high dose dabigatran ($p < 0.001$) and to 1.5 %/yr with low dose dabigatran ($p = 0.34$) during the median of 2 years follow up. The secondary endpoint myocar-

dial infarction showed a significant increase from 0.5 %/yr with warfarin to 0.7%/yr with high dose dabigatran (p = 0.05) and to 0.7 %/yr with low dose dabigatran (p = 0.07). Death was not different between groups. Most striking was the reduction in bleeding by dabigatran. Intracranial bleeding was reduced by 60 % from 0.7 %/yr with warfarin to 0.3 %/yr with high dose dabigatran (p < 0.001) and by 69 % to 0.2 %/yr with low dose dabigatran (p < 0.001). However, gastrointestinal bleeding was increased from 1.0 %/yr with warfarin to 1.5 %/yr with high dose dabigatran (p < 0.001) and to 1.1 %/yr with low dose dabigatran (p = 0.43). Yet, the net clinical benefit (absence of the primary outcome, death, myocardial infarction, pulmonary embolism and major bleeding) was still in favour of dabigatran.

Although RE-LY had the major flaw of its open design against warfarin, the concept of simple oral direct thrombin inhibition has been solidly confirmed by RE-LY in that dabigatran is at least as good as warfarin for stroke prevention in atrial fibrillation with a safety profile that is probably better. The only concern may be the increase in myocardial infarction, or lack of protection against it, with dabigatran. Other studies with warfarin, especially those in ischemic heart disease, have shown a reduction in myocardial infarction when compared to antiplatelet drugs. Standard addition of aspirin to dabigatran may prevent the untoward effect on myocardial infarction, but this may dilute the beneficial effect of dabigatran against bleeding and may further increase the so far unexplained excess gastrointestinal bleeding seen with dabigatran.

In conclusion, the 2009 ESC congress has brought important leaps forward in the management of acute coronary syndromes with antiplatelet agents and in anticoagulant therapy for stroke prevention in atrial fibrillation.

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F. W. A. Verheugt, MD
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