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Since the last newsflash from ACC 2010 some interesting studies on antiplatelet and anticoagulant therapy have been presented and/or published.

**INNOVATE-PCI** (Sunil Rao, Chapel Hill) presented at ESC 2010, was a randomized, double-blind, phase II study on elinogrel (an oral and intravenous reversible P2Y12 receptor antagonist with a half-life of 12 hours) versus clopidogrel in 652 patients undergoing non-urgent PCI. Like ticagrelor, elinogrel is not a prodrug neither requires metabolic activation. It has no CYP metabolism resulting in low potential drug-drug interactions. Patients were randomized to clopidogrel (300/600 mg, followed 75 mg qd) or elinogrel (80 mg i.v., followed by oral 50, 100 or 150 mg bid) pre-PCI. Initially, follow-up was 60 days, but the protocol was amended with an extended follow-up of 120 days. Enrolment in the 50 mg oral dose arm was discontinued after 117 patients were enrolled. The intravenous dose was increased to 120 mg after 170 patients were enrolled (recommendations of the DSMC) (Fig. 1).

This level of inhibition was sustained during the transition to an oral dose and persisted at day 30. In the different elinogrel arms there was no excess of TIMI major or minor bleeding after 24 h and 120 d (Fig. 2, 3).

Asymptomatic elevation (5 times ULN) of transaminases occurred within the first 60 days of treatment (clopidogrel 0.5%, elinogrel 100 mg 2.0% and elinogrel 150 mg 3.4%). This resolved in all patients, even when treatment was continued. Results look promising and phase III trials in PCI and secondary prevention will follow.

**ATOLL** presented at ESC 2010 by Gilles Montalescot from Paris compared head-to-head i. v. enoxaparin and UFH in 910 patients undergoing primary PCI for STEMI. Patients were randomized prior to coronary angiography to enoxaparin 0.5 mg/kg intravenously (STEEPLE dose) with or without a glycoprotein inhibitor (GPI) versus UFH 50–70 U/kg intravenously with GPI or UFH 70–100 U/kg without. Subcutaneous enoxaparin was recommended to be given until discharge. PCI was performed via radial access in 69%, stents were implanted in 96% and a GPI was used in 71% of patients. Median time from symptom onset until randomization was 2.5 hrs. The primary outcome (composite of all-cause mortality, complications of myocardial infarction, procedural failure, and non-CABG major bleeding during hospitalization and up to 30d) occurred in 28% with enoxaparin versus 34% with UFH group (p = 0.07). All-cause mortality at 30 d was seen 3.8% with enoxaparin versus 6.3% for UFH (p = 0.08).
Only the secondary endpoint of death, recurrent ischemia/reinfarction or urgent revascularisation was significantly better with enoxaparin than with UFH: 6.7% and 11.3% respectively, p = 0.01 (Fig. 4)

Unexpectedly, the main safety endpoint (non-CABG related major bleeding) was quite similar (4.5% for enoxaparin and 4.9% for UFH). This may due to the high rates of radial access and use of GPI. Thus, ATOLL did not show major improvements in primary clinical outcomes for enoxaparin over UFH in patients undergoing primary PCI for STEMI. On the other hand, intravenous enoxaparin in STEMI is an acceptable and safe alternative to UFH for primary PCI.

Stuart Connolly from Hamilton, Canada, presented at ESC 2010 AVERROES (Apixaban VERsus Acetylsalicylic acid to pRevent strOkES) study. This double blind trial randomized 5,600 patients with AF and a mean CHADS2 score of 2.1 (± 1.1), who were deemed intolerant (40%) or unsuited for vitamin K antagonist (VKA) therapy (60%), to the novel oral direct factor Xa blocker apixaban 5 mg bid or aspirin (81–324 mg/d, mean 162/d). Unsuitability was determined at the discretion of the treating physician. Patients had a mean age of 70 y and 30% had a high risk for stroke (CHADS2 ≥ 3). The study was prematurely stopped at 1-year follow-up by the DSMB because of a significant benefit with apixaban (Fig. 5).

As expected, apixaban led to a decrease in the number of strokes or systemic embolic events (SEE) annually from 3.6%/y to 1.6%/y (p < 0.001). This result was mainly driven by a reduction in ischemic strokes (2.9%/y versus 1.1%/y). There was no difference in vascular or all cause mortality, or in the occurrence of myocardial infarctions (MI). Surprisingly, these results occurred without the expected increase in the risk of bleeding. A slight increase in minor bleeding was observed (5.2%/y versus 4.1%/y, p = 0.04), but intracranial
haemorrhage was similar: 13 for apixaban and 12 for aspirin (p = 0.83). Apixaban was well tolerated without significant effects on transaminases. Thus, apixaban significantly reduces strokes and SEE compared to aspirin in patients with AF unsuitable or intolerant for VKA with a favourable risk-benefit profile. Results in comparison to warfarin (ARISTOTLE study) are eagerly awaited and will be available in the summer of 2011.

Another study on novel oral anticoagulation in atrial fibrillation was presented at ACC 2010 and recently published: the RE-LY substudy on the INR quality for warfarin relative to the efficacy of the oral direct thrombin blocker dabigatran [1]. Time in therapeutic range (TTR) was available in 18,024 (99%) patients and ranged from 44% (Taiwan) to 77% (Sweden). TTR was split into quartiles (Fig. 6, 7).

Thus, relative to warfarin dabigatran was most efficacious when TTR was lowest, and the least when TTR was maximal. Safety with warfarin was lowest when TTR was lowest and comparable with dabigatran when TTR was maximal. This prespecified subgroup analysis suggests that the net clinical benefit of dabigatran is the largest in regions where TTR is suboptimal. This is especially true for the high dose of dabigatran (150 mg bid).

At ESC 2010 EINSTEIN-DVT (Harry Büller, Amsterdam) was presented. This randomized open label trial was designed to show non-inferiority of the oral direct factor Xa blocker rivaroxaban compared to conventional treatment (enoxaparin (1 mg/kg bid, ≥5 days) followed by warfarin with target INR 2–3) in 3449 patients with a confirmed deep venous thrombosis without signs of pulmonary embolism. Rivaroxaban was dosed 15 mg bid for the first three weeks and 20 mg daily thereafter. Treatment duration (3, 6 or 12 months) was at the discretion of the physician. Among patients using rivaroxaban, 2.1% experienced recurrent DVT vs 3.0% of the controls (p < 0.0001 for non-inferiority) and almost reached statistical superiority (p = 0.076). A combination of major and minor clinically-relevant non-major bleeding was similar (8.1%, p = 0.77). Rivaroxaban was not associated with liver toxicity. Thus, rivaroxaban seems to be an attractive and simple alternative for the initial and long-term treatment of deep vein thrombosis.

Two important studies on genotype analysis (CYP2C19 loss-of-function carrier status) of the clinical antiplatelet activity of clopidogrel have been published on line.

The first originated from the placebo-controlled CURE (non-ST elevation acute coronary syndromes) and ACTIVE-A
(stroke prevention in atrial fibrillation) trials [2]. No differences could be observed between the clinical efficacy of clopidogrel over placebo in carriers of the loss of function allele and those with the gain of function allele of CYP2C19. Also major bleeding was not influenced by the carrier status.

The second study addressed the genotype analysis of several CYP2C19 loss-of-function alleles and of the ABCB1 single nucleotide polymorphism 3435C → T (all heavily involved in clopidogrel metabolism) relative to the clinical antiplatelet activity of both clopidogrel and ticagrelor in the well known PLATO trial in patients with acute coronary syndromes [3]. Except for the first 30 days when thrombotic risk is highest, neither the CYP2C19 loss-of-function allele polymorphisms nor the ABCB1 single nucleotide polymorphism 3435C → T were associated with differences in long-term clinical outcomes or bleeding with clopidogrel. For ticagrelor similar results were found.

Although the above polymorphisms heavily interfere with ex vivo platelet reactivity, the observations from the 2 clinical analyses suggest that they are of little, if any, clinical relevance. Thus genotyping for clopidogrel metabolism as recommended by the FDA appears hardly important for clopidogrel and unnecessary for the novel ADP receptor blockers, since the clinical efficacy of Prasugrel [4] and ticagrelor has shown to be independent of the above polymorphisms.

One year after the presentation at ESC 2009, the final results of the CURRENT OASIS-7 comparing 2 dose regimens of clopidogrel and 2 doses of aspirin in 25,086 patients with non-ST elevation acute coronary syndromes eligible for an early invasive treatment were published. The outcome was split into 2 papers: one of the outcome in all patients [5] and one on the results of the subset of patients (69%) that underwent PCI [6]. Overall, the primary study outcome (CV death, MI and stroke) was neutral: clopidogrel 600 mg loading followed by 150 mg daily for a month was not better than 300 mg loading with 75 mg daily, but led to significant 24% increase in major bleeding. For the higher dose of aspirin (300–325 mg daily) for a month there was no benefit or excess bleeding risk over 75–100 mg daily (after 300 mg loading). In the PCI substudy in 17,263 patients the high dose clopidogrel regimen resulted in a 14% reduction of the primary endpoint (p = 0.04) and 46% reduction in stent thrombosis (p < 0.001), but also a significant 41% increase in major bleeding. For high dose aspirin there was no benefit or excess harm in this subgroup.

Given the neutral outcome of the main CURRENT OASIS-7 trial, it is likely that future guidelines on non-ST elevation acute coronary syndromes will not change with regard to the maintenance dose clopidogrel and aspirin. The 600 mg loading dose has been accepted for a long time, especially for patients undergoing PCI in that setting.

References:

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