

EuroThrombosis: annual meeting of the European Society of Cardiology Working Group on Thrombosis

Expert Rev. Hematol. 5(1), 39–42 (2012)

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EuroThrombosis Summit

Oporto, Portugal, 7–8 October 2011

EuroThrombosis is the annual meeting of the European Society of Cardiology Working Group on Thrombosis. It gathers clinicians and scientists interested in clinical/experimental thrombosis. The 2011 congress was held in Oporto, Portugal, and presented an appealing program with state-of-the-art sessions on new antiplatelet/anticoagulant agents, diabetes, cellular mechanisms of thrombosis and miRNAs.

KEYWORDS: acute coronary syndromes • antiplatelet/anticoagulant agents • atrial fibrillation • coronary stent • diabetes • microRNAs • thrombosis

This year's EuroThrombosis was held on 7–8 October 2011 in Oporto, Portugal, and was hosted by João Morais (Santo André's Hospital, Leiria, Portugal). The meeting is the official annual congress of the European Society of Cardiology (ESC) Working Group on Thrombosis, mainly devoted to clinical topics (EuroThrombosis Summit, as in 2011) or basic research (EuroThrombosis Science). The aim of these conferences is to advance knowledge in thrombosis-related disorders applied to cardiovascular diseases.

New antiplatelet agents

Robert Storey (University of Sheffield, UK) presented the pharmacology of the new antiplatelet agent, ticagrelor. Compared with clopidogrel (a prodrug binding irreversibly to platelet P2Y₁₂ receptors), ticagrelor differs in binding reversibly to P2Y₁₂, in not requiring metabolic activation and in having a more rapid onset/offset of action; adverse effects are mainly dyspnea and sinoatrial pauses, which are probably related to interaction with adenosine metabolism. Kurt Huber (Wilhelminen Hospital, Vienna, Austria) discussed the variability of platelet inhibition by clopidogrel, in particular, genetic

factors that affect bioavailability, and interaction with other drugs, such as omeprazole. Reduced *ex vivo* platelet inhibition in patients taking clopidogrel together with omeprazole has been attributed to inhibition by omeprazole of CYP2C19, one of the main enzymes, together with CYP3A4, involved in clopidogrel bioactivation; other drugs that may influence clopidogrel's antiplatelet effect are esomeprazole, cimetidine, etravirine (by inhibiting CYP2C19), fluconazole, ketoconazole, voriconazole, clarithromycin, fluoxetine, fluvoxamine (by inhibiting CYP3A4) and felbamate (by inducing CYP3A4 and inhibiting CYP2C19). On the other hand, ranitidine, famotidine, nizatidine and antacids were presented as not interfering with clopidogrel's antiplatelet activity. Miguel Uva (Hospital da Cruz Vermelha Portuguesa, Lisbon, Portugal) discussed the PLATO trial, which compared ticagrelor (180-mg loading dose, 90 mg twice daily [b.i.d.]) to clopidogrel (300–600-mg loading dose, 75 mg daily thereafter) in 18,624 acute coronary syndrome patients followed for 1 year [1]. The primary end point (cardiovascular death, myocardial infarction or stroke) was significantly reduced by ticagrelor (hazard ratio: 0.84; 95% CI: 0.77–0.92; $p < 0.001$). Ticagrelor

is an attractive 'bridge' toward surgery, given the reversibility of its antiplatelet effects. In the subgroup of 1261 patients undergoing coronary artery bypass grafting within 7 days after the last drug intake, ticagrelor versus clopidogrel was associated with a reduction in total mortality, from 9.7 to 4.7% (hazard ratio: 0.49; 95% CI: 0.32–0.77; $p < 0.01$), without excess risk of coronary artery bypass grafting-related major bleeding [1]. European and North American regulatory agencies have approved ticagrelor use in acute coronary syndrome patients.

Coronary stent thrombosis

José Baptista (Santa Cruz Hospital, Lisbon, Portugal) and Jean-Philippe Collet (Hopital la Pitié-Salpêtrière, Paris, France) discussed the incidence, prevention and possible pathophysiological differences among early (within 30 days), late (within 1 year) and very late (beyond 1 year) coronary stent thrombosis (ST). The annual frequency of ST is estimated to be approximately 0.6–2%. Predictors include nonadherence to antiplatelet therapy, angiographic features (small arteries, bifurcations, long, thrombotic or ulcerated lesions, or low Thrombolysis In Myocardial Infarction [TIMI] flow), reduced left ventricular ejection fraction, stenting for acute myocardial infarction, small stent diameter, drug eluting stent restenosis, stent underexpansion, presence of thrombus and neointimal hyperplasia. Malapposition, stent fracture and eosinophilic reaction were discussed as associated with very late ST. New-generation bioresorbable stents hold promise in terms of safety and reduced ST rates.

Diabetes

Carlo Patrono (Catholic University Medical School, Rome, Italy) discussed the issue of primary prevention with aspirin in patients with diabetes mellitus. The current uncertainty concerning its efficacy and safety in this setting does not seem to justify general guidelines advocating the routine use of aspirin in all asymptomatic individuals above a moderate level of coronary risk, unless additional long-term benefits of antiplatelet therapy become established [2]. José Gonzalez-Juanatey (University Hospital, Santiago de Compostela, Spain) discussed the cardiovascular implications of oral antidiabetic drugs. Hypoglycemia with such drugs may increase the probability of ischemia, arrhythmias, heart failure and neurological impairment. Metformin, new dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonists are safe and induce reduced glycated hemoglobin, no bodyweight gain, and favorable blood pressure and lipid changes. By contrast, insulin, glitazones and sulfonylureas are associated with increased bodyweight.

Nonvalvular atrial fibrillation

Lars-Hvilsted Rasmussen (Aarhus University Hospital, Denmark) discussed the practical implementation of the 2010 ESC atrial fibrillation (AF) guidelines 1 year after publication [3]; in particular, refinement of stroke risk by the CHA2DS2-VASc (congestive heart failure, hypertension, age >75 years, diabetes mellitus, stroke/transient ischemic attack/thromboembolism, vascular disease and female sex) compared with the established CHADS2 score. The guidelines distinguish between patients with CHA2DS2-VASc

score <1 – not requiring anticoagulation – versus those ≥ 1 , benefiting from anticoagulation [3]. The HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history/predisposition, labile international normalized ratio, elderly >65 years of age, drugs affecting hemostasis/alcohol) is a tool for bleeding risk assessment during anticoagulation. Close follow-up is recommended for patients with HAS-BLED scores >3 [3].

Jean-Philippe Collet, Carlos Aguiar (Santa Cruz Hospital, Lisbon, Portugal) and Gregory Lip (University of Birmingham, UK) discussed which AF patients should be treated with vitamin K antagonists (VKA), such as warfarin. Many AF patients with moderate-to-high thromboembolic risk (CHADS2 ≥ 2) are prescribed low-dose aspirin. However, a meta-analysis of 14 randomized trials in AF shows that warfarin versus placebo reduces the relative risk of stroke by 64%, while aspirin versus placebo reduces it by 22% [4]. Aspirin plus clopidogrel is superior to aspirin alone (relative stroke risk reduced by 28% at the price of more severe bleeding) [5], but inferior to warfarin (relative stroke risk increased by 44% with similar rates of major bleeds) [6]. Population-based studies show that less than half of AF patients receive appropriate anticoagulant therapy. Contraindications or barriers to current anticoagulation include: gastrointestinal/genitourinary hemorrhages, alcohol abuse, renal insufficiency, other high bleeding risk, lack of understanding of the risks and benefits of therapy, difficult international normalized ratio monitoring (inpatient variable plasma warfarin concentration and/or nonadherence to therapy) and patient refusal. Limitations of VKA also include unpredictable effect, slow onset/offset, food/drug/alcohol interactions, need for routine laboratory monitoring, and narrow therapeutic window. Only half of treated patients remain in the therapeutic range more than 67% of the time [7]. Vittorio Pengo (University of Padova, Italy) discussed adjustment of warfarin's loading dose in relation to age, body surface and individual genetic polymorphisms as a potential way of reducing complications.

The 2010 ESC AF guidelines recommend aspirin plus clopidogrel for patients who refuse VKA or have a clear contraindication to anticoagulation. For patients ineligible for VKA, an emerging alternative may be the new oral anticoagulants, in particular, direct inhibitors of factor Xa, such as apixaban. The AVERROES trial followed 5599 patients for 1 year: apixaban 5 mg b.i.d. compared with aspirin 81–324 mg/day, reduced the relative risk of stroke by 55% without increasing the risk of major bleeding (including intracranial bleeds) [8]. Gregory Lip and Hans-Christoph Diener (Essen University Hospital, Germany) discussed the cardiologist's and neurologist's perspective on the use of aspirin in AF patients. As stated, the benefit of aspirin 75–325 mg daily is inferior to warfarin for stroke prevention, while major bleeding rates are not significantly different [9]. Aspirin may be recommended only in patients at low risk of stroke (CHA2DS2-VASc = 0–1). Interestingly, Chinese guidelines for stroke prevention in AF do not report aspirin as a prophylactic drug.

Steen Husted (Aarhus University Hospital, Denmark) discussed the pharmacology of the oral direct thrombin inhibitor, dabigatran etexilate, a synthetic small peptidomimetic that binds reversibly to thrombin's catalytic site. It is a prodrug rapidly converted into active

form by esterase hydrolysis, with a half-life of 12–14 h, eliminated mainly by the kidneys. Raffaele De Caterina ('G. d'Annunzio' University, Chieti, Italy) discussed the recent Phase III AF trials RE-LY [10], ROCKET-AF [11] and ARISTOTLE [12], where dabigatran (110 or 150 mg b.i.d.), rivaroxaban (20 mg once daily) and apixaban (5 mg b.i.d.), respectively, were compared with warfarin for prevention of stroke and systemic embolism. These new anticoagulants are either equally or more effective than warfarin, have a good safety profile, and are easier to use in daily practice [13]. Edoxaban (DU-176b) is under evaluation in the Phase III ENGAGE AF TIMI-48 trial (30 or 60 mg once daily) [14]. The direct thrombin inhibitor AZD0837 and factor Xa inhibitors brixaban and YM-150 are in Phase II clinical development.

Gianluca Botto (Sant'Anna Hospital, Como, Italy) discussed vernakalant hydrochloride as a promising new drug approved in Europe but not in the USA for rapid conversion of postoperative and recent nonsurgical AF to sinus rhythm. It is atrial selective in blocking potassium currents and prolonging the action potential plateau, without significantly affecting QT interval or ventricular refractory period [15]. In Phase III trials, intravenous vernakalant was more effective versus placebo or amiodarone [15]. For patients with AF lasting <72 h, the median time to conversion was between 8 and 14 min, with 79% of those who converted remaining in sinus rhythm at 24 h [15].

Advances in basic science

The mechanisms of thrombogenesis in AF were reviewed by Gregory Lip. Although von Willebrand factor and D-dimer are recognized markers of thromboembolism, limited data are available in AF patients. Among 829 anticoagulated AF patients followed for 2 years, multivariate analysis showed that age >75 years, previous stroke, heart failure and von Willebrand factor levels ≥ 221 IU/dl, but not D-dimer levels, were significantly associated with adverse cardiovascular events (including mortality, stroke and major bleeding) [16]. Lina Badimon (Cardiovascular Research Center, Barcelona, Spain) discussed proteomic analysis identifying crucial platelet proteins involved in motility, coagulation and transcription/transduction signals. The oral administration of a new exogenous nitric oxide donor (LA419) in pigs significantly inhibited platelet deposition on damaged vascular walls [17]. Treatment prevented thrombin-induced translocation of cytoskeleton proteins, 14-3-3 ζ , PI3K- γ and growth factor receptor-bound protein 2 [17]. LA419 thus inhibited thrombosis by interfering with platelet shape-change mechanisms [17]. Ongoing studies are examining functional

proteins within the thrombus. Jan Fiedler (Institute of Molecular and Translational Therapeutic Strategies, Hannover, Germany) discussed miRNAs in cardiovascular disease. miRNAs are endogenous small noncoding ribonucleotides that regulate mRNA translation. miR-24 is upregulated after cardiac ischemia [18]. It induces endothelial cell apoptosis and abolishes endothelial capillary network formation and endothelial cell sprouting. Blocking endothelial miR-24 limits myocardial infarct size in mice via enhanced vascularity [18]. Agneta Siegbahn (Uppsala University Hospital, Sweden) discussed tissue factor/FVIIa signaling in blood coagulation and tumor development. Platelets, monocytes and macrophages express tissue factor mRNA in specific conditions. The tissue factor/FVIIa complex induces the inflammatory cytokines IL-1 β , -6, -8 and TNF- α and, in cancer cells, governs apoptosis by reducing the levels of death-associated-with-protein-kinase-1, independently of protease-activated receptor-1 and -2. Robin Choudhury (University of Oxford, UK) discussed molecular imaging of atherosclerosis, thrombosis and vascular inflammation: in particular, optical coherence tomography, a high-resolution technique used to assess superficial atherosclerotic plaque morphology; its utility can be enhanced by contrast agents targeting molecular mediators of inflammation, such as microparticles of iron oxide.

Conclusion

EuroThrombosis is an opportunity for expert clinicians and scientists to interact, discuss clinical guidelines and understand basic mechanisms of cardiovascular disease. EuroThrombosis 2012 will take place on October 11–13 in Vienna, Austria. To become members of the working group, free of charge, visit www.escardio.org/communities/Working-Groups/thrombosis.

Acknowledgements

The authors thank Carlo Patrono and Bianca Rocca for their constructive criticisms.

Financial & competing interests disclosure

All authors are active members of the ESC working group on Thrombosis. F Andreotti served as Chair in 2010–2012. F Andreotti has received consultant or speaker fees from Astra Zeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, Pfizer and Servier. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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