Interventional cardiology: in search of the balance between ischaemia and bleeding

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The introduction of any foreign body into the circulation, be it a catheter, a balloon, and/or a stent, as is common practice in interventional cardiology, is associated with a risk of thrombus formation. Therefore, from the very beginning, anticoagulants, and later platelet inhibitors, have been used prior to, during, and after such procedures. Any such measure, whether anticoagulants or platelet inhibitors, is associated with an increased risk of bleeding at the entry site and/or in other organs such as the skin, gastrointestinal and urinary tract, and/or the brain. Of note, bleeding has been associated in multiple studies with long-term outcome, including mortality. The degree and duration of inhibition of the coagulation cascade or of circulating platelets is of crucial clinical importance. For patients with stable coronary artery disease (CAD) or those with an acute coronary syndrome (ACS) receiving a modern drug-eluting stent (DES), the current European Society of Cardiology (ESC) Guidelines recommend 3–6 and 12 months, respectively. However, the issue remains unresolved following the results of several recent trials, which have come up with diverging conclusions. This is outlined in the Editor’s Page entitled ‘Duration of dual antiplatelet therapy after coronary artery stenting: where is the sweet spot between ischaemia and bleeding?’. Although cardiogenic shock remains an often fatal complication of myocardial infarction, the introduction of primary percutaneous coronary intervention (PCI) and mechanical support devices has markedly improved prognosis. In a timely Clinical Review article entitled ‘Management of cardiogenic shock’, by Holger Thiele from Lübeck in Germany, the progress achieved is discussed comprehensively. Mortality in patients presenting with cardiogenic shock could be reduced from ~80% to 40–50%, in large part due to the introduction of PCI or coronary artery bypass grafting (CABG), catecholamines, fluid management, and assist devices. However, there is only limited evidence for any of the above treatments, except for early revascularization. The author focuses on evidence-based revascularization, intensive care including ventilation, transfusion, adjunctive medication, and mechanical support devices.

The first clinical research paper, a FAST TRACK paper entitled ‘Long-term forecasting and comparison of mortality in the Evaluation of the Xience Everolimus Eluting Stent vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial: prospective validation of the SYNTAX Score II’ by Patrick W. Serruys in collaboration with the International Centre for Cardiovascular Health in London, UK, aimed to forecast and compare 4-year mortality in the PCI and CABG arms of the randomized EXCEL Trial. This manuscript is accompanied by an instructive Editorial by Robert A. Byrne from the Deutsches Herzzentrum München in Germany. EXCEL is a prospective, randomized multicentre trial designed to establish the efficacy and safety of the everolimus-DES compared with CABG in unprotected left main CAD and low to intermediate anatomical SYNTAX scores. After completion of patient recruitment in EXCEL, the SYNTAX Score II was prospectively applied to predict 4-year mortality in the CABG and PCI arms. The 95% prediction intervals for mortality were computer simulated. For the entire study cohort, the 4-year predicted mortalities were 8.5% and 10.5% in the PCI and CABG arms, respectively, resulting in an odds ratio of 0.79. In subjects with low (≤22) anatomical SYNTAX scores, the predicted odds ratio was 0.69, and in intermediate scores (23–32) it was 0.93. Based on 4-year mortality predictions in EXCEL, clinical characteristics shifted long-term mortality predictions in favour of either PCI (older age, male gender, chronic obstructive pulmonary disease) or CABG (younger age, lower creatinine clearance, female gender, impaired left ventricular ejection fraction). The authors conclude that the SYNTAX Score II indicates at least an equipoise for long-term mortality between CABG and PCI in subjects with unprotected left main disease up to an intermediate anatomical complexity and that clinical characteristics had a clear impact on long-term mortality predictions.

The second paper ‘Impact of clinical presentation on ischaemic and bleeding outcomes in patients receiving 6- or 24-month duration of dual antiplatelet therapy after stent implantation: a pre-specified analysis from the PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) trial’ by Marco Valgimigli from the Erasmus University Rotterdam in The Netherlands again refers to the issue of the duration of dual antiplatelet therapy in
patients undergoing coronary stenting when presenting as an ACS or as stable CAD.16 The paper is accompanied by a thought-provoking Editorial by Laura Mauri from the Brigham and Women’s Hospital in Boston, USA.17 In the Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia (PRODIGY) trial, three-quarters of patients presented with ACS, whereas a quarter had stable CAD. They were randomized to either 6 or 24 months of dual antiplatelet therapy. At 2 years, the composite of death, myocardial infarction, or cerebrovascular accident did not differ between the long- vs. the short-term dual antiplatelet therapy in both ACS and stable CAD. However, long-term dual antiplatelet therapy was associated with a 75% increase of BARC (Bleeding Academic Research Consortium) class 2, 3, or 5 bleeding in ACS and a 5-fold increase in stable CAD, with a borderline interaction. As a result, overall cardiovascular events (death, infarction, cerebrovascular accident plus bleeding) more than doubled in stable CAD patients receiving 24 months dual antiplatelet therapy, but not in those with ACS. The authors conclude that the clinical presentation could be used for decision-making with respect to dual antiplatelet therapy duration after stenting in stable CAD, but not ACS patients since the former exposed to a significant increase in bleeding and net adverse clinical events when treated long term rather than short term.

The third manuscript, ‘ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting’, by Stefanie Schulz-Schüppke et al. from the Deutsches Herzzentrum in Munich, Germany further expands on this issue. In their multicentre, randomized, double-blind, placebo-controlled trial the authors compared, in patients undergoing implantation of a DES, 6 or 12 months of clopidogrel on top of aspirin. Unfortunately, due to slow recruitment and low event rates, the trial had to be stopped prematurely after 4000 patients had been recruited. The primary endpoint of death, myocardial infarction, stent thrombosis, stroke, and major bleeding occurred in 1.5% assigned to 6 months and in 1.6% assigned to 12 months of clopidogrel, whereas stent thrombosis was observed in 0.3% and 0.2%, respectively. TIMI (Thrombolysis in Myocardial Infarction) major bleeding was noted in 0.2% and 0.3%, respectively. The authors conclude that after implantation of a DES, 6 months clopidogrel therapy is non-inferior to 12 months. Obviously, as also pointed out in the accompanying Editorial by Marco Valgimiglì from Erasmus University Rotterdam18,19 and the Editor’s Page,20 the results of the trial must be interpreted with caution in view of its premature termination and lower than expected event rates.

The fourth paper, ‘Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial’ by Claes Held et al. from the Uppsala University in Sweden, addresses the issue of bleeding in patients with atrial fibrillation enrolled in the ARISTOTLE trial comparing apixaban with warfarin.21 Major International Society of Thrombosis and Hemostasis (ISTH) bleeding was defined as overt bleeding with a decrease in haemoglobin of ≥2 g/dL or transfusion of ≥2 units occurring at a critical site or resulting in death. Time of death, ischaemic stroke, or myocardial infarction was evaluated. The excess risk associated with bleeding was evaluated by separate time-dependent indicators for intracranial and non-intracranial haemorrhage. Major bleeding occurred in 4.7%, of whom 14.9% died. Of the patients with an intracranial haemorrhage 43.2% died, while of those with major non-intracranial haemorrhage 9.2% died. The risk of death, ischaemic stroke, or infarction was increased 12-fold after major non-intracranial haemorrhage bleeding. The risk of death after intracranial haemorrhage was increased 122-fold, and that of stroke or infarction 22-fold. Among patients with major bleeds, 21% received vitamin K and/or fresh frozen plasma, coagulation factors, or factor VIIIa to stop bleeding, and 37% received blood transfusion. The authors concluded that in patients with atrial fibrillation receiving either apixaban or warfarin, major bleeding was similarly associated with an increased risk of death, ischaemic stroke, or myocardial infarction. Future research should focus on the prevention of bleeding in anticoagulated patients.

The editors hope that this issue of the European Heart Journal will attract the interest of its readers.

References


