

Research Highlights

Highlights from the latest articles in interventional cardiology



The ARISTOTLE trial: apixaban versus warfarin in patients with atrial fibrillation

Evaluation of: Granger CB, Alexander JH, McMurray J *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 365, 981–992 (2011).

Warfarin is the standard of care for stroke prevention in patients with atrial fibrillation (AF). However, it has several drawbacks: it carries a significant risk of bleeding, requires international normalized ratio monitoring for dose adjustment, has drug and food interactions and is associated with an inconsistent response. Because of these issues, approximately half of all patients that would benefit from the drug actually take it. A potential alternative is apixaban, an oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population when compared with aspirin.

The ARISTOTLE trial is a multicenter, randomized, double-blind trial that compared apixaban (5 mg twice-daily, orally) with warfarin (target international normalized ratio 2–3) in 18,201 patients with AF and at least one other risk factor for stroke, over a median duration of follow-up of 1.8 years. When compared with warfarin, it was found that apixaban significantly reduced the risk of stroke or systemic embolism by 21%, while significantly reducing the risk of major bleeding and all-cause mortality by 31 and 11%, respectively.

These results suggest that apixaban is superior to warfarin in several respects. Not only is it more effective than warfarin

in preventing stroke, but it does so with considerably less risk of bleeding, death and the added convenience of not requiring anticoagulation monitoring.

There are currently two other oral anti-coagulants that may be considered apixaban's legitimate competitors: dabigatran (a thrombin inhibitor) and rivaroxaban (a factor Xa inhibitor). Both have shown promise in their respective trials – RE-LY (dabigatran) [1] and ROCKET-AF (rivaroxaban) [2] – which concluded that both dabigatran and rivaroxaban were at least as good as warfarin in stroke reduction. However, both anti-coagulants did not show definite advantages over warfarin in terms of bleeding, whereas apixaban did.

Although indirect inferences can be made about the superiority of one drug over the other, direct comparisons of apixaban, dabigatran and rivaroxaban in randomized, controlled studies will be necessary. For now, it appears that physicians have new and improved options for management of AF with respect to stroke prevention in AF.

References

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- 2 Caixeta A, Leon MB, Lansky AJ *et al.* 5-year clinical outcomes after sirolimus-eluting stent implantation: insights from a patient-level pooled analysis of four randomized trials comparing sirolimus-eluting stents with bare-metal stents. *Am. Coll. Cardiol.* 54, 894–902 (2009).

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Cardiac conduction disturbances after percutaneous balloon aortic valvuloplasty

Evaluation of: Laynez A, Ben-Dor I, Hauville C *et al.* Frequency of cardiac conduction disturbance's after balloon aortic valvuloplasty. *J. Am. Coll. Cardiol.* 57, e2008 (2011).

Percutaneous balloon aortic valvuloplasty (BAV) is used as a bridge to definitive aortic valve replacement or transcatheter aortic valve implantation for patients with severe aortic stenosis and intractable hemodynamic symptoms. Early reports have described the development of new cardiac conduction abnormalities and BAV. Laynez *et al.* described an observational study comparing the pre- and post-procedural electrocardiograms of a total of 271 consecutive patients from one center, who underwent BAV with symptomatic, severe aortic stenosis. BAV was performed in 205 (75.6%) patients for palliation of heart failure symptoms, 19 (7%) for the treatment of cardiogenic shock and as a bridge to transcatheter aortic valve replacement or surgical aortic valve replacement in 36 (13.3%) and 11 (4.1%) patients, respectively. After BAV, there were no changes in the PR interval or heart rate.

Development of permanent atrial fibrillation occurred in eight (2.9%) patients. In addition, new atrioventricular (AV) block appeared in 23 (8.5%) patients. The breakdown of new conduction defects consists of nine (2.6%) patients with left bundle branch block, seven (2.6%) patients with left anterior hemiblock, two (0.7%) patients with right bundle branch block and one (0.4%) patient with left posterior hemiblock. Of patients with new conduction defects, four (1.5%) patients required permanent pacemaker implantation for advance AV block. An association of large balloon size to left ventricular outflow tract ratio was found with the development of new conduction disturbances (1.15 vs 1.21; $p < 0.03$).

Although these data regarding percutaneous BAV reveal a significant incidence of new cardiac conduction defects, only a small fraction of patients required permanent pacing. Given the close anatomic relation of the aortic valve and branching of the common AV bundle, as observed with other devices involving aortic annular manipulation, appropriate sizing using low balloon size to left ventricular outflow tract ratio may be helpful to prevent the development of cardiac conduction defects after BAV.

Everolimus-eluting stent versus paclitaxel-eluting stent in patients with and without diabetes mellitus

Evaluation of: Stone GW, Kedhi E, Kereiakes DJ *et al.* Differential clinical responses to everolimus-eluting and paclitaxel-eluting coronary stents in patients with and without diabetes mellitus. *Circulation* 123, 893–900 (2011).

Diabetes mellitus (DM) represents a major risk factor for coronary heart disease. Outcome after all types of revascularization procedures are worse in patients with DM than in patients without DM. DM is an independent risk factor for in-stent restenosis after bare- and drug-eluting stents (DES). Since the introduction of



the first DES, there has been great interest in comparing the long-term efficacy and safety of paclitaxel-eluting stent (PES) with the newer everolimus-eluting stent (EES) in the setting of DM patients.

To determine the relationship of DM with EES and PES, Stone *et al.* performed a meta-analysis of 6780 patients after percutaneous coronary intervention, including the SPIRIT II, SPIRIT III, SPIRIT IV and COMPARE trials, of whom 1869 (27.6% of the population) had DM. The adverse event rate of mortality, myocardial infarction, stent thrombosis and target lesion revascularization (TLR) was collected. After a 2-year follow-up, patients without DM randomized to EES, rather than PES, had significantly lower adverse event rates across all end points: mortality (1.9 vs 3.1%; $p = 0.01$), myocardial infarction (2.5 vs 5.8%; $p < 0.0001$), stent thrombosis (0.3 vs 2.4%; $p < 0.0001$), and ischemia-driven TLR (3.6 vs 6.9%; $p < 0.0001$). There was no difference in outcomes of DM patients, regardless of stent type or insulin treatment

status. The rate of ischemia-driven TLR was reduced among non-insulin-treated DM patients assigned to EES compared with PES. Lastly, although stent type was not observed to have a significant association with adverse events in DM patients, Stone *et al.* demonstrated the greatest adverse event rate was found in DM patients on insulin treatment, followed by non-insulin-treated DM patients, and the lowest rates were observed in non-DM patients. The 2-year adverse event rate for PES was independent of DM status or insulin treatment. The authors concluded that treatment with EES in patients without DM offers a benefit compared with PES and routine deployment of EES in patients with DM might be justified.

As the largest analysis of randomized DES data to date in patients with DM, these data support the use of EES versus PES in non-DM patients. However, further study is needed to advocate for the optimal stent choice in DM patients in relation to their DM regimen.

Comparison of angioscopic findings and 3-year cardiac events between sirolimus-eluting and bare-metal stents in acute myocardial infarction

Evaluation of: Nishino N, Yoshimura T, Nakamura D *et al.* Comparison of angioscopic findings and three-year cardiac events between sirolimus-eluting stent and bare-metal stent in acute myocardial infarction. *Am. J. Cardiol.* 108(9), 1238–1243 (2011).

The safety of sirolimus-eluting stents (SES) in acute myocardial infarction (AMI) is unclear. Recent reports have shown that drug-eluting stents elicit a pathologic response by the vessel wall with delayed healing, potentially serving as precursors to thrombus formation and major adverse

cardiac events. By directly visualizing the vessel wall via angiography, Nishino *et al.* conducted a rather unique investigation comparing SES with bare-metal stents (BMS) in AMI.

The use of BMS versus SES was compared in 87 consecutive patients with AMI by direct angiographic visualization of neointimal coverage after stent implantation and correlating with 3-year clinical events. At 8 months post-AMI, coronary angiography with angiography was performed to evaluate neointimal coverage using an angiographic score (0–3) and a heterogeneity score, calculated as maximum minus minimum angiographic score. A score of 0 represented stents with exposed



struts, similar to findings just after implantation; score of 1 for stent struts with very thin intimal coverage and no metallic luster; score of 2 for struts that are embedded but visible and score of 3 for struts that are fully embedded and invisible. Other angioscopic parameters included serum parameters, thrombi and plaque color.

The restenosis rate of the SES group (n = 56) was lower than that of the BMS group (n = 31; 9 versus 31%; p = 0.015). The minimum angioscopic score of neointimal coverage in the BMS was significantly higher than in the SES group, while the

heterogeneity score and incidence of mural thrombus were significantly lower. Despite these findings by angiography, there was no difference in clinical events between the two groups, suggesting that the controversy surrounding SES safety in AMI is unfounded. However, the number of patients in the study is small and may be underpowered to assess clinical events. Further angioscopic investigations with long-term follow-up in larger study groups should be performed to analyze the correlation between neointimal coverage after SES or BMS implantation, and clinical outcomes.

Late cardiac events after sirolimus-eluting stenting: EVASTENT registry

Evaluation of: Barone-Rochette G, Foote A, Motreff P *et al.* Stent-related cardiac events beyond three years after implantation of the sirolimus-eluting stent (from the EVASTENT patients). *Am. J. Cardiol.* 108(10), 1401–1407 (2011).

(2.6 vs 0.9% per year, and 0.63 vs 0.18%, respectively). After 3 years, diabetic and nondiabetic patients had low target lesion revascularization rates and diabetics an increased overall but not stent-related mortality.

Wenaweser *et al.* and Caixeta *et al.* previously reported in *The Journal of the American College of Cardiology* a cumulative incidence of ST with sirolimus-eluting stents of 3.3 and 3.8%, 4–5 years after stent implantation, respectively [1,2]. These findings are consistent with the 4.1% ST rate reported in EVASTENT at 6 years. The minimal differences beyond 3 years between trials may be more related to population differences and continuing use of antiplatelet drugs than long-term drug-eluting stents or BMS effect.

Comparisons of up to 3 years of sirolimus-eluting stents and bare-metal stents (BMS) have shown differences in the rate of in-stent restenosis and target vessel revascularization. After 3 years, the rate of restenosis requiring target vessel revascularization and major adverse cardiac events are minimal (0.6%) with drug-eluting stents, but associated with a higher rate (0.4%) of stent thrombosis (ST) per year compared with BMS.

This study included 1731 patients (844 diabetic) from the EVASTENT registry with follow-up for 6 years. Analysis was performed by number of vessels involved and diabetic status.

The study did not show a difference between single and multiple vessel disease. However, morbidity and mortality was higher in diabetic patients. Before 3 years, ST was higher in diabetic patients, but after 3 years the difference was unremarkable. Target lesion revascularization and ST were higher during the first 3 years

References

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