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CLINICAL INVESTIGATION

NEWS

from the European Society of Cardiology Congress 2011

Atrial fibrillation (AF) is a common abnormal heart rhythm, affecting over 2.6 million Americans alone, which has the potential to form blood clots, leading to an increased risk of stroke. Warfarin is a vitamin K antagonist, well documented for its ability to prevent blood clots. However, studies have shown that only about half of patients who could benefit from warfarin actually do, leading doctors and patients to await alternative therapies.

Christopher Granger from Duke University, USA, lead ARISTOTLE investigator explained that "there is an enormous unmet need in terms of treatment of patients at risk for stroke associated with AF." He continued, "only about half of patients who should be treated are being treated. The disparity exists because warfarin treatment has several limitations."

ARISTOTLE, a double-blind clinical trial, randomized apixaban (5mg twice daily) or warfarin for an average of 1.8 years in 18,201 patients, in 1034 clinical sites across 39 countries. The results of the trial, presented at the European Society of Cardiology Congress 2011 (Paris, France) and simultaneously published in the *New England Journal of Medicine* have demonstrated that apixaban is superior to warfarin in preventing stroke and systolic embolism (the primary end point), and was also associated with less bleeding and lower mortality.

Results demonstrated that, compared with wafarin, apixaban exhibited:

- 21% relative reduction in stroke and systemic embolism;
- 31% relative reduction in major bleeding;
- 11% relative reduction in overall mortality;
- ~50% relative reduction in hemorrhagic stroke.

Granger commented on the significance of the trial, noting the statistics below:

- Better prevention of stroke: $p = 0.011$;
- Lower rate of major bleeding: $p < 0.001$;
- Lower mortality: $p = 0.047$.

Absolute risk reduction, as indicated by the number of events prevented per 1000 patients, demonstrated that apixaban prevented six patients from suffering a stroke (four from suffering hemorrhagic stroke and two patients from suffering an ischemic or uncertain type of stroke), 15 patients from suffering major bleeding and eight patients from dying.

Co-presenter of the ARISTOTLE data, Lars Wallentin from Uppsala Clinical Research Center (Uppsala, Sweden), noted that apixaban showed many practical advantages over warfarin, as apixaban does not require monitoring and demonstrated few interactions with other medications or food. In addition, Apixaban was shown to be better tolerated than warfarin, with fewer discontinuations.

Wallentin celebrated the positive results in the European Society of Cardiology press release, stating that the study "indicates treatment with apixaban is more effective than warfarin in preventing stroke without the need for anticoagulation monitoring." Wallentin also commented on the safety of apixaban compared with warfarin, "our findings show a single dose of apixaban accomplishes the same stroke prevention goal as adjusted-dose warfarin with a substantially lower risk of all types of bleeding across different ages, and with lower rates of discontinuation."

Granger publicly commented on the results, telling Heartwire that the research team were "delighted" with the studies results, "it is very exciting to see large significant reductions in both stroke and bleeding simultaneously. We seem to have hit the sweet spot on the dose of apixaban, which produced both great efficacy and safety."

Sources: ARISTOTLE: a major win for apixaban in AF: www.theheart.org/article/1268723.do; European Society of Cardiology press release: www.escardio.org/about/press/press-releases/esc11-paris/Pages/HL1-ARISTOTLE.aspx; Granger CB, Alexander JH, McMurray JV *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* DOI: 10.1056/NEJMoa1107039 (2011) (Epub ahead of print).

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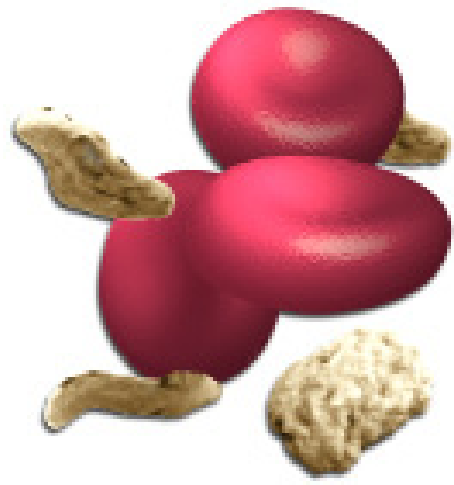
PRODIGY: prolonging therapy with dual antiplatelet treatment following coronary stenting is questioned

The PRODIGY study has shown that 24 months of dual antiplatelet therapy following coronary stenting was no more effective in preventing adverse cardiac events than 6 months of treatment, with prolonged therapy almost doubling the rate of major bleeding.

Marco Valgimigli, investigator on the PRODIGY study, from the University Hospital of Ferrara (Ferrara, Italy), said that the results "question the validity of current guideline recommendations – which were based on registry data – that at least 12 months dual antiplatelet therapy should be pursued after implantation of a drug-eluting stent."

The PRODIGY study, a 4-by-2, randomized, three-center open-label clinical trial, including >2000 patients scheduled for elective, urgent or emergency coronary angioplasty (74% with acute coronary syndromes and 26% with stable angina), evaluated the efficacy and safety of prolonged antiplatelet therapy in patients with coronary disease following stenting. Patients were randomly assigned in a 1:1:1:1 fashion to one of four stent types, and at 30 days patients in each stent group were further randomized to either 6 or 24 months of dual antiplatelet treatment (clopidogrel plus aspirin).

The study's primary end point was to assess whether 2 years of dual antiplatelet treatment could result in a lower cumulative incidence of all-cause mortality, nonfatal myocardial infarction or cerebrovascular accident (the primary outcome), compared with 6-month dual therapy. Results showed that the overall risk of the primary end point was almost identical between the two groups, with cumulative risk of the primary outcome at 24 and 6 months being 10.1% and 10.0%, respectively.



Results also demonstrated that there was a roughly twofold greater risk of type 5, 3 or 2 bleeding events among the patients receiving long-term dual antiplatelet therapy, according to the Bleeding Academic Research Consortium classification. The 24-month group also showed an increase in the risks of thrombolysis in myocardial infarction-defined major bleeding and red blood cell transfusion.

It was noted that results were similar to two other trials presented at the European Society of Cardiology: REAL-LATE and EXCELLENT. "Our study clearly shows that the benefit:risk ratio of prolonged therapy has been overemphasized", Valgimigli said. He continued, "the results of this study have important implications for heathcare expenditure – for this study shows that prolonging therapy with clopidogrel beyond 6 months is not only associated with no clinical benefit but also with a significant increase in actionable bleeding events requiring re-hospitalisations and multiple diagnostic and therapeutic resources."

ESC press release: www.escardio.org/about/press/press-releases/esc11-paris/Pages/HL3-PRODIGY.aspx

EMPHASIS-HF: further analysis shows benefits for high-risk subgroups taking eplerenone

Last year, main results from the EMPHASIS-HF trial showed that eplerenone prescribed to patients with systolic heart failure and mild symptoms performed significantly better than a placebo in reducing the risk of death and hospitalization. Now, a new analysis of the EMPHASIS-HF trial reinforces such findings, and demonstrates the additional benefit in five predefined high-risk patient sub-groups with chronic heart failure.

After the EMPHASIS-HF trial was prematurely stopped, for efficacy there was a possibility that the observed effect seen in the trial might have been exaggerated. However, in some countries, where eplerenone was not commercially available, the blinded study continued, allowing researchers to further assess the results for the primary end point for an additional 10 months, and complete a sub-analysis to further demonstrate the beneficial effect of eplerenone remained significant across the wider study population over an additional follow-up period.

By evaluating the efficacy and safety of eplerenone 25–50 mg/day in five prespecified high-risk subgroups, the researchers noted large reductions in the primary end point of cardiovascular mortality or hospitalization for heart failure:

- Patients >75 years old: 78 (23.6%) of 330 patients on eplerenone and 107 (32.7%) of 327 on placebo reached a primary end point;

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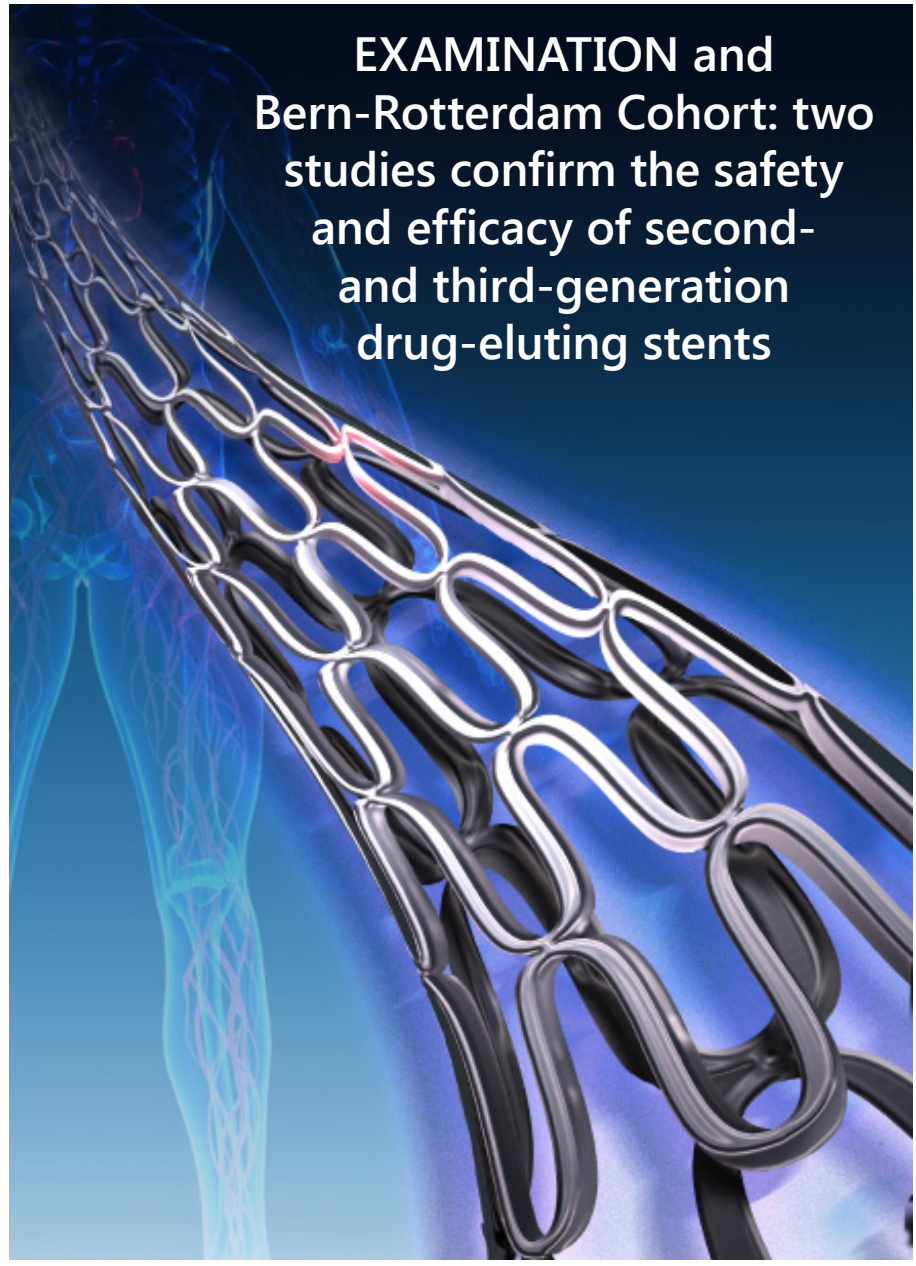
Continued from previous page...

- Patients with a history of diabetes: 99 (21.6%) of 459 on eplerenone and 141 (35.2%) of 400 on placebo reached a primary end point;
- Patients with an estimated glomerular filtration rate <60 ml/min/1.73 m^2: 107 (24.4%) of 439 on eplerenone and 163 (34.5%) of 473 on placebo reached a primary end point;
- Patients with a left ventricular ejection fraction <30%: 180 (19.3%) of 934 patients on eplerenone and 267 (27.3%) of 978 on placebo reached a primary end point ;
- Patients with systolic blood pressure median <123 mmHg: 138 (20.6%) of 669 patients on eplerenone and 201 (29.4 %) of 683 on placebo reached a primary end point.

"...new analysis of the EMPHASIS-HF trial ... demonstrates the additional benefit in five predefined high-risk patient sub-groups with chronic heart failure."

Bertram Pitt, investigator on the EMPHASIS-HF study and professor at the University of Michigan School of Medicine (MI, USA), said that, "the consistency of the efficacy and safety of eplerenone in addition to standard therapy on prespecified 'high-risk subgroups' presents compelling evidence for the use of eplerenone in patients with systolic chronic heart failure New York Heart Association class II and mild symptoms."

Source: ESC press release: www.escardio.org/about/press/press-releases/esc11-paris/Pages/HL2-EMPHASIS.aspx



EXAMINATION and Bern-Rotterdam Cohort: two studies confirm the safety and efficacy of second- and third-generation drug-eluting stents

The EXAMINATION trial and Bern-Rotterdam Cohort study have looked into second- and third-generation drug-eluting stents, particularly in the setting of ST-elevation myocardial infarction (STEMI).

EXAMINATION, a multicenter, multinational, prospective, two-arm, single-blind controlled trial, randomized 1498 patients to either Xience V® (everolimus-eluting) stent or a cobalt chromium bare-metal stent, and evaluated all comers with very few exclusions, with a high follow-up of 98%. The all-comers design of the EXAMINATION trial applied wide inclusion and few exclusion criteria, with the aim of gaining a more representative sample of the target population.

Results showed that there was a non-significant trend towards an increased benefit with the Xience-V stent, due to a lower rate of new revascularisations during follow-up when compared with the bare metal stents. In terms of safety, results showed that the rates of definite and definite/probable stent thrombosis at

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1-year follow-up were significantly lower with the Xience V stent, accounting for 0.5% (definite) and 0.9% (definite/probable), when compared with the bare metal stent, accounting for 1.9% (definite) and 2.6% (definite/probable).

The Bern-Rotterdam Cohort study assessed 12,000 patients treated between 2002 and 2009. The study aimed to compare the incidence of stent thrombosis between newer generation drug-eluting stent Xience (everolimus-eluting) and early generation drug-eluting stents Cypher (sirolimus-eluting) and Taxus (paclitaxel-eluting), with particular focus on stent thrombosis occurring between one and 4 years.

Results showed that in up to four years the rate of stent thrombosis was lower among patients treated with everolimus-eluting stents (1.4%) than with sirolimus-eluting stents (2.9%) and paclitaxel-eluting stents (4.4%). The relative risk reduction in stent thrombosis for everolimus-eluting stents versus sirolimus-eluting stents and paclitaxel-eluting stents was 67% and 76%, respectively.

Both studies were highly celebrated by their researchers, with the EXAMINATION authors noting that results presented "the first 'real world' results we have from a randomized trial about the performance of the new generation drug-eluting stents in the high-risk context of STEMI," and the Bern-Rotterdam Cohort study investigators noting that "for the first time we now have robust evidence of the long-term therapeutic benefit of newer generation drug-eluting stents over the early generation DES", highlighting the positive results for the new generation of drug-eluting stents.

> "...we now have robust evidence of the long-term therapeutic benefit of newer generation drug-eluting stents over the early generation DES..."

Source: EXAMINATION press release: www.escardio.org/about/press/press-releases/esc11-paris/Pages/HL3; Bern-Rotterdam Cohort study press release: www.escardio.org/about/press/press-releases/esc11-paris/Pages/HL3-Everolimus-DES.aspx

RUBY-1: results establish that darexaban now requires a large Phase III trial

RUBY-1, a Phase II dose-finding study, has found that darexaban, a new oral Factor Xa inhibitor, when added to dual antiplatelet therapy, is associated with a two-to-four fold increase in bleeding in patients following an acute coronary syndrome (ACS).

Currently, the recurrence of ischaemic events after ACS remains high, with recorded rates of up to 9.1% at 6 months. Long-term antithrombotic therapy with vitamin K antagonists, such as warfarin, have proved beneficial in ACS patients, but with reported complications.

The potential of darexaban has already been indicated in venous thromboembolic disease and has been explored in the prevention of stroke in subjects with nonvalvular atrial fibrillation in RUBY-1.

RUBY-1, a multicenter, double-blind, randomized, parallel-group study of 1279 patients with recent high-risk non-ST-segment elevation and ST-segment elevation ACS, aimed to explore the safety, tolerability and optimal dosing regimen in the secondary prevention of ischaemic vascular events in subjects with recent ACS. After discontinuation of parenteral antithrombotic therapy, patients received one of six darexaban regimens: 5 mg twice daily, 10 mg once daily, 15 mg once daily, 30 mg once daily, 30 mg twice daily or 60 mg once daily, or placebo, in addition to dual antiplatelet treatment (aspirin and clopidogrel) for 24 weeks.

> "...darexaban, a new oral Factor Xa inhibitor, when added to dual antiplatelet therapy, is associated with a two-to-four fold increase in bleeding in patients following an acute coronary syndrome..."

Results showed that the primary outcome, major or clinically relevant nonmajor bleeding event, was numerically higher in all darexaban arms compared with the placebo group. Using the placebo as reference (with a bleeding rate of 3.1%), results showed a dose-response relationship for increased bleeding rates of 6.2%, 6.5% and 9.3% for increasing darexaban doses of 10, 30 and 60 mg daily, respectively.

The study was underpowered to evaluate efficacy; however, results demonstrated that with darexaban versus placebo there was no decrease in outcome rates of efficacy (a composite of death, stroke, myocardial infarction, systemic thromboembolic events and severe recurrent ischaemia). Also, darexaban was not associated with any other significant drug-related safety concerns.

Discussing the results, Gabriel Steg, presenter of the results and professor at the Hôpital Bichat (Paris, France) commented that "establishing the role of low-dose darexaban in preventing major cardiac events after ACS now requires a large Phase III trial."

ESC press release: www.escardio.org/about/press/press-releases/esc11-paris/Pages/HL3-RUBY-1.aspx