

Recent Landmark Trials in Cardiology

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Aspirin for Prevention of Recurrent Venous Thromboembolism

Becattini C, Agnelli G, Schenone A, et al. for the WARFASA Investigators. *N Engl J Med.* 2012; 366:1959–67.

Trial summary

Oral anticoagulants are a standard of care in patients with thromboembolic events, yet about 20% of patients with unprovoked venous thromboembolism have a recurrence of such events within 2 years after the withdrawal of oral anticoagulant therapy. Extending anticoagulation prevents recurrences but is associated with an increased risk of bleeding. The benefit of aspirin beyond the recommended duration of oral anticoagulation for the prevention of recurrent venous thromboembolism is unknown. This study was undertaken keeping this rationale in mind.

In this multicenter, investigator-initiated, double-blind study, patients with first-ever unprovoked venous thromboembolism who had completed 6–18 months of oral anticoagulant treatment were randomly assigned to aspirin, 100 mg daily, or placebo for 2 years, with the option of extending the study treatment. The primary efficacy outcome was recurrence of venous thromboembolism, and major bleeding was the primary safety outcome.

Venous thromboembolism recurred in 28 of the 205 patients who received aspirin and in 43 of the 197 patients who received placebo (6.6% vs. 11.2% per year; hazard ratio 0.58; 95% confidence interval [CI], 0.36–0.93) (median study period, 24.6 months). During

a median treatment period of 23.9 months, 23 patients taking aspirin and 39 taking placebo had a recurrence (5.9% vs. 11.0% per year; hazard ratio, 0.55; 95% CI, 0.33–0.92). One patient in each treatment group had a major bleeding episode. Adverse events were similar in the two groups.

Perspective

Beyond the periods of standard recommendations of oral anticoagulation, recurrent venous thromboembolism is a major problem. Long-term anticoagulation is associated with bleeding issues and compliance-related problems, related more so to routine INR estimations. This study clearly shows the benefits of aspirin in reducing the risk of recurrence when given to patients with unprovoked venous thromboembolism who had discontinued anticoagulant treatment, with no apparent increase in the risk of major bleeding. This study is bound to have important implications on our daily practice and positively translate into clinical benefit in such patient subsets.

Warfarin and Aspirin in Patients with Heart Failure and Sinus Rhythm

Homma S, Thompson JLP, Pullicino PM, et al. for the WARCEF Investigators. *Engl J Med.* 2012; 366:1859–69.

Trial Summary

Patients with heart failure have a considerable risk of ischemic events. It is unclear whether warfarin or aspirin therapy is superior for patients with heart failure with reduced left ventricular ejection fraction (LVEF) who are in sinus rhythm. Keeping this in mind the present trial was undertaken. The study population was randomized to receive either warfarin (with a target international normalized ratio of 2.0–3.5) or aspirin (at a dose of 325 mg/d); 2305 patients were followed for up to 6 years (mean [\pm SD], 3.5 \pm 1.8). The primary outcome

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was the time to the first event in a composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause. The rates of the primary outcome were 7.47 events per 100 patient-years in the warfarin group and 7.93 in the aspirin group (hazard ratio with warfarin, 0.93; 95% CI, 0.79–1.10; $P=0.40$). Thus, there was no significant overall difference between the two treatments. In a time-varying analysis, the hazard ratio changed over time, slightly favoring warfarin over aspirin by the fourth year of follow-up, but this finding was only marginally significant ($P=0.046$). Warfarin, as compared with aspirin, was associated with a significant reduction in the rate of ischemic stroke throughout the follow-up period (0.72 events per 100 patient-years vs. 1.36 per 100 patient-years; hazard ratio, 0.52; 95% CI, 0.33–0.82; $P=0.005$). The rate of major hemorrhage was 1.78 events per 100 patient-years in the warfarin group as compared with 0.87 in the aspirin group ($P<0.001$). The rates of intracerebral and intracranial hemorrhage did not differ significantly between the two treatment groups (0.27 events per 100 patient-years with warfarin and 0.22 with aspirin, $P=0.82$).

Perspective

Cardiac failure is associated with both stroke of presumed cardioembolic origin and a high mortality rate. The risk of stroke increases with decreasing EF and the risk of mortality increases with the clinical severity of cardiac failure. Data from heart failure treatment studies suggest that warfarin may reduce stroke and mortality in patients with reduced EF, but definitive answers are lacking. Moreover warfarin use is fraught with issues of bleeding and drug compliance. Thus it was postulated that an alternate and relatively safer strategy to use antiplatelet agents such as aspirin must be evaluated. Two studies to address this issue were devised namely Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) and Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF), comparing warfarin and antiplatelet agents in patients with low EF. In the present trial, among patients with reduced LVEF who were in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. The authors concluded that the choice between warfarin and aspirin should be individualized.

Impact of QRS Duration and Morphology on the Risk of Sudden Cardiac Death in Asymptomatic Patients With Aortic Stenosis. The SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) Study

Greve AM, Gerds E, Boman K, et al. *J Am Coll Cardiol.* 2012; 59:1142–49.

Trial Summary

The duration and morphology of the QRS complex has been closely studied in different cardiac disorders and used as a marker to predict the risk of sudden cardiac death (SCD). The aim of the study was to examine the predictive value of QRS duration and morphology during watchful waiting in asymptomatic patients with aortic stenosis (AS). Data were obtained in asymptomatic AS patients randomized to simvastatin/ezetimibe combination versus placebo in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study. The impact of QRS duration, evaluated as a categorical variable of <85 ms versus 85–99 and 100 ms (excluding bundle branch block [BBB]) and QRS morphology in those with BBB, on cardiovascular morbidity and mortality was assessed by adjusting for clinical and echocardiographic covariates. QRS data were available in 1542 patients who were followed for a mean of 4.3 ± 0.8 years (6631 patient-years of follow-up). There were 68 cardiovascular deaths (4.6%), including 27 SCDs (1.8%). QRS duration was <85 ms in 900 patients (58.4%), 85–99 ms in 396 (25.7%), 100 ms in those without BBB in 144 (9.3%), and 102 (6.6%) in those with BBB. In multivariable analyses, those with QRS duration 100 ms had, compared with those with QRS duration <85 ms, a fivefold higher risk of SCD (95% CI: 1.8–13.7, $p=0.002$) and a 2.5-fold higher risk of cardiovascular death (95% CI: 1.2–5.1, $p=0.01$).

Perspective

This study has brought forward certain interesting facts which could help us to identify patients at high risk of SCD, who otherwise are not candidates for aortic valve replacement as per standard recommendations. These are as follows:

- A longer QRS duration is associated with risk of SCD and overall cardiovascular death independent of clinical and echocardiographic findings. Patients

with QRS <85 ms have the best prognosis

- Among patients with QRS duration ≥ 120 ms, only those with LBBB or combined RBBB and LAFB the risk is high for adverse cardiac events

These parameters which are easily obtainable and reproducible could help in risk stratifying patients at high risk of SCD in the future in this particular subset and possibly guide treatment protocols in the near future.

FAME II Trial (Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment versus Optimal Medical Treatment Alone in Patients with Stable Coronary Artery Disease): Preliminary Results

Presented by, Bernard De Bryune on behalf of the FAME II study group (16 May 2012 at the EURO PCR 2012).

Rationale for the Study

In patients with clinically stable coronary disease, PCI has not been shown to affect clinical outcomes such as death, non-fatal myocardial infarction, and the need for urgent revascularization. In previous trials on revascularization, the latter has been guided by the angiographic appearance of the lesions and hence it is likely that in previous trials dealing with patients with non-acute CAD, a sizable proportion of patients without ischemia may have been included. This study was undertaken in such a subset of patients and treatment was driven based on the results of Fractional flow reserve (FFR) measurements.

Trial Summary

This randomized, prospective study was conducted among a cohort of over 1200 patients across 28 centers in Europe and the US. Patients with stable CAD scheduled for one-, two-, three-vessel stenting with DES were included. FFR was done in all target lesions. Patients with at least one stenosis with $FFR < 0.80$ were included in the trial and then randomized in a 1:1 fashion into the PCI plus OMT (optimal medical treatment) or OMT alone. PCI was conducted using the very latest second generation drug-eluting stent systems (DES). In patients without ischemia ($FFR > 0.80$) received treatment with OMT alone and were a part of the registry. Follow-up was planned after 1, 6 months, 1, 2, 3, 4, and 5 years.

The primary end point recorded was a composite of all cause death, myocardial infarction (MI), and unplanned hospitalization leading to urgent revascularization. Patients were only considered as urgent revascularization cases if they entered the hospital through the emergency ward and their revascularization procedure was performed during the same hospitalization episode, or if they presented at the clinic with increased angina symptoms requiring urgent revascularization. The independent Data and Safety Monitoring Board recommended halting patient recruitment due to a significantly increased patient risk of major adverse cardiac events among patients randomized to OMT alone compared to patients randomized to OMT plus FFR-guided PCI. In the RCT arm, the cumulative incidence of urgent revascularization in the OMT versus PCI+OMT arm was 6.0% versus 0.6%, HR (95% CI): 11.2 (2.62–47.9); logrank $p < 0.0001$. The rates of nonurgent revascularization in the OMT versus PCI+OMT were 6.2% versus 1.1%, respectively, HR (95% CI): 5.54 (1.90–16.1); logrank $p = 0.002$ while the cumulative rates of any revascularization were 12.1% versus 1.7% in the OMT and PCI+OMT groups, HR (95% CI): 7.63 (3.24–18.0); logrank $p < 0.0001$. The investigators concluded that

- in patients with stable CAD and at least one hemodynamically significant stenosis ($FFR \leq 0.80$) in at least one major epicardial artery, OMT alone was associated with a significantly larger number of urgent revascularizations than FFR-guided PCI plus OMT and
- in patients with stable CAD without invasively documented ischemia-inducing lesions ($FFR > 0.80$) OMT alone was associated with a very favorable clinical outcome.

Perspective

In the quest for the practice of evidence-based medicine, this is a landmark trial of sorts as these results will go a long way in clinical decision making in patients with stable CAD. Targeting PCI to the right patients and the right lesions using second-generation DES systems is bound to have a major impact on the success rate for these interventions. Patients who deserve medical management could be identified and this approach is bound to have major economic impact on structured modern healthcare delivery systems, where they exist.