A randomised trial of dabigatran, a oral direct thrombin inhibitor, compared to warfarin in 18 113 patients with atrial fibrillation at high risk of stroke

Stuart J. Connolly and John Camm

Background: Warfarin reduces stroke in atrial fibrillation, but increases hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

Methods: In a non-inferiority trial, 18 113 patients with atrial fibrillation at risk of stroke were randomised to blinded fixed doses of dabigatran 110 mg or 150 mg twice daily versus unblinded adjusted warfarin. Median follow-up was 2.0 years. The primary outcome was stroke or systemic embolism.

Results: Rates of the primary outcome were 1.69% per year on warfarin versus 1.53% per year on dabigatran 110 mg (relative risk 0.91, 95% confidence interval 0.74 to 1.11; p [non-inferiority]<0.001) and 1.11% per year on dabigatran 150 mg (relative risk 0.66, 95% confidence interval 0.53 to 0.82; p [superiority]<0.001. Rates of major hemorrhage were 3.36% per year on warfarin versus 2.71% per year on dabigatran 110 mg (p=0.003) and 3.36% per year on dabigatran 150 mg (p=0.31). Rates of hemorrhagic stroke were 0.38% per year on warfarin versus 0.12% per year on dabigatran 110 mg (p<0.001) and 0.10% per year on dabigatran 150 mg (p<0.001). Mortality rates were 4.13% per year on warfarin versus 3.74% per year on dabigatran 110 mg (p=0.13) and 3.64% per year on dabigatran 150 mg (p=0.05).

Conclusions: In patients with atrial fibrillation, dabigatran 110 mg was associated with similar rates of stroke and systemic embolism to warfarin, and lower rates of major hemorrhage. Dabigatran 150 mg was associated with lower rates of stroke and systemic embolism than warfarin, and similar rates of major hemorrhage.

B-CONVINCED. Beta-blocker CONtinuation Versus INterruption in patients with Congestive heart failure hospitalisED for a decompensation episode

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Whether or not beta-blocker therapy should be stopped during acutely decompensated heart failure (ADHF) is unsure.

In a randomised, controlled, open label, non-inferiority trial, we compared beta-blockade continuation versus discontinuation during ADHF in patients with LVEF below 40% previously receiving stable beta-blocker therapy. 169 patients were included, among which 147 were evaluable. Mean age was 72±12 years, 65% were males.

After 3 days, 92.8% of patients pursuing beta-blockade improved for both dyspnea and general well being according to a physician blinded for therapy vs. 92.3% of patients stopping beta-blocker. This was the main end point and the upper limit for unilateral 95% CI for the difference (6.6%) is lower that the predefined upper limit (12.5%), indicating non-inferiority. Similar findings were obtained at 8 days and when evaluation was made by the patient. Plasma BNP at day 3, length of hospital stay, re-hospitalisation rate and death rate after 3 months were also similar. Beta-blocker therapy at 3 months was given to 90% of patients vs. 76% (p<0.05).

During ADHF, continuation of beta-blocker therapy is not associated with delayed or lesser improvement, but with a higher rate of chronic prescription of beta-blocker therapy after 3 months, the benefit of which is well established.

Comparison of ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: results of the PLATelet inhibition and patient Outcomes (PLATO) trial

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Ticagrelor versus clopidogrel in patients with acute coronary syndromes: the PLATelet inhibition and patient Outcomes (PLATO) trial.
Current clinical practice guidelines for patients with acute coronary syndrome recommend dual antiplatelet treatment with aspirin and clopidogrel. The efficacy of clopidogrel is hampered by slow and variable transformation of the prodrug to the active metabolite, modest and variable platelet inhibition, increased risk of bleeding and increased risk of stent thrombosis and myocardial infarction in poor responders. Ticagrelor is an oral reversible direct acting P2Y12-inhibitor providing faster and greater platelet inhibition than clopidogrel.
The PLATO trial was a multicenter double-blind randomised trial, comparing treatment with ticagrelor (180 mg loading dose followed by 90 mg twice daily) to treatment with clopidogrel (300 to 600 mg loading dose followed by 75 mg daily) for prevention of cardiovascular events. We included 18,624 patients admitted either with ST-elevation ACS intended for primary PCI (38%) or with non-ST-elevation ACS intended for an invasive or medical approach (62%). Prior to randomisation 94% were treated with aspirin; 46% with clopidogrel. The patients were treated for an average of 278 days (minimum 6 and maximum 12 months). The follow-up was complete in 99.97% with only 5 patients lost to follow-up.
The primary composite of death from vascular causes (CV) death, myocardial infarction (MI) and stroke was reduced from 11.7% to 9.8% (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001). In the predefined hierarchical testing of secondary endpoints there were reductions of the composites of total death, MI and stroke from 12.3% to 10.2% (P=0.0001), CV-death, MI, stroke, severe recurrent, recurrent ischaemia, transient ischaemic attack (TIA) and other arterial thrombotic events from 16.7% to 14.6% (P<0.001), MI alone from 6.9% to 5.8% (P=0.005) and CV-death from 5.1% to 4.0% (P=0.001). Total mortality was reduced from 5.9% to 4.5%, (P<0.001). There was no difference in total major bleeding, 11.6% vs. 11.2% (P=0.434), but higher occurrence of non-CABG related major bleeding 4.5% vs. 3.8% (p=0.026). Episodes of dyspnoea were more common with ticagrelor, 14.2%, than clopidogrel, 9.2%, which led to discontinuation of treatment in respectively 1.0% and 0.3%. There was no difference in other important side effects.
Treatment with ticagrelor instead of clopidogrel in a broad spectrum of patients with acute coronary syndrome provides a clinically important reduction in mortality and myocardial infarction without an increase in total major bleeding, but with a rise in non-procedure related bleeding.

Commentary on the PLATO trial

Steen Dalby Kristensen

Ticagrelor compared with clopidogrel in patients with acute coronary syndromes – the PLATO trial presented by Lars Wallentin, ESC Congress Barcelona 2009.
The new reversible oral P2Y12 receptor antagonist, ticagrelor, was compared to the 'classic' irreversible P2Y12 blocker clopidogrel in 18 264 patients with acute coronary syndromes (ACS) comprising a broad population with non-ST- or ST-elevation myocardial infarction (MI). Ticagrelor

was superior to clopidogrel in terms of preventing the combination of cardiovascular death/MI/stroke without causing a significant increase in major bleedings. Also, cardiovascular mortality, total mortality and the incidence of stent thrombosis were significantly reduced. There was an increased risk of non-procedure-related bleedings in the ticagrelor group. Ticagrelor has the potential to improve prognosis in patients with ACS.

Comments: The investigators should be congratulated for this well-designed and nicely conducted landmark study. Overall, treating 54 patients for one year with ticagrelor instead of clopidogrel prevented one event of cardiovascular death, MI or stroke.

MI and bleeding: The authors used the new global MI definition and the trial design has been described previously (S James et al, Am Heart J 2009; 157: 599-605). A new definition of bleedings was used in PLATO. This definition seems appropriate and as good as the other 8-10 bleeding definitions that have been used in previous trials. There was no significant difference in PLATO or TIMI major bleedings between the two groups. However, there was an increased risk of non-CABG bleedings in the ticagrelor group, whereas the incidence of CABG-related bleedings did not differ. Patients with active bleeding, a bleeding history or severe anemia were excluded from the study, and therefore the bleeding profile of ticagrelor should also be tested in 'real' world ACS patients.

One of the major advantages of reversible inhibition of P2Y12 is indeed the possibility of reducing bleeding during surgery, and therefore it is not surprising that ticagrelor was not associated with an increased incidence of CABG related bleeds.

Dosing and duration: The dose of ticagrelor was chosen according to phase 2 trials (DISPERSE and DISPERSE-2) and clopidogrel was dosed according to guidelines. The inclusion of non-naïve clopidogrel patients in the study is appropriate as this is the real world, and because sub-analysis on these patients might provide useful information. Patients were included within the first 24 hours of ACS. In this phase, the risk of events is high, thus perhaps favouring the fast onset of strong platelet inhibition obtained with ticagrelor.

The ESC guidelines recommend dual anti-platelet therapy for 12 months in ACS. In PLATO, duration of treatment was 6 to 12 months. There was a significantly lower incidence of ischaemic events in the ticagrelor group both within the first 30 days and also in the period from 1 to 12 months. There is currently no evidence to recommend dual anti-platelet therapy beyond 12 month in ACS.

Side effects and compliance: The authors report an increase in the levels of uric acid, and also an increased frequency of dyspnoea and brady-arrhythmias in the ticagrelor group. Some of the side effects have been described in phase 2 studies with ticagrelor and were expected. No severe new side effects seemed to occur and only few patients had to stop ticagrelor due to side effects. The study drugs were discontinued prematurely in 23.4 and 21.5% of the patients in the ticagrelor and the clopidogrel groups, respectively.

Ticagrelor does not require metabolic activation, causes stronger platelet inhibition and has a fast onset of action. However, the reversible receptor binding and a 12 h half-life necessitate twice-daily dosing, which might be a problem in patients who are not fully compliant. The investigators reported that compliance was approximately 83% in each group. Implementation of ticagrelor might be troublesome in patients who are unable to fully adhere to the prescribed drug therapy, because insufficient platelet inhibition increases the risk of stent thrombosis and other ischaemic events.

This commentary accompanies a presentation given at the ESC Congress 2009. Written by the author, this report does not necessarily reflect the opinion of the European Society of Cardiology.

Reduction of the risk of heart failure with preventive cardiac resynchronisation therapy: MADIT-CRT trial

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This trial was designed to determine whether cardiac resynchronisation therapy would reduce mortality and heart failure events in patients with mild cardiac symptoms, reduced ejection fraction, and wide QRS complex

Methods: Over the course of 4.5 years, we enrolled and followed 1 820 patients with ischaemic or non-ischaemic cardiomyopathy, ejection fraction 0.30 or less, QRS 130 ms or more, and New York Heart class I or II symptoms. Patients were randomly assigned in a 3:2 ratio to receive cardiac resynchronisation therapy with defibrillator (1 089 patients) or an implanted defibrillator (731 patients). The primary end point was all cause mortality or heart failure event, whichever occurred first.

Results: During an average follow-up of 2.4 years, 17.2 percent of patients in the resynchronisation group and 25.3 percent in the defibrillator group experienced a primary end point. The hazard ratio in favor of resynchronisation therapy was 0.66 (95 percent confidence interval, 0.52 to 0.84; P=0.001), with similar benefit in patients with ischaemic and non-ischaemic cardiomyopathy. Superiority of cardiac resynchronisation therapy was driven by 41 percent reduction in the risk of a first heart failure event, a finding that was evident primarily in patients with QRS of 150 ms or more. Resynchronisation therapy was associated with significant reduction in left ventricular volumes and improvement in ejection fraction. Serious adverse events were infrequent.

Conclusion: Cardiac resynchronisation therapy decreases the risk of heart failure events in relatively asymptomatic patients with low ejection fraction and wide QRS complex. This therapy provides effective prevention for heart failure in these at-risk cardiac patients.

Commentary on the MADIT-CRT trial

Guenter Breithardt

Cardiac resynchronisation therapy (CRT) induces progressive reverse LV remodelling and slows disease progression in patients with NYHA class III or IV heart failure. Whether it may also be beneficial in patients with less severe heart failure was tested in the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronisation Therapy) presented by A. Moss during the Hotline Session. The trial randomised 1820 NYHA class I or II patients to CRT or no CRT. All patients were candidates for an ICD, had to have a QRS width of 0.13s or greater and a left ventriclar ejection fraction of 0.30 or less.

During follow-up, 17.2% of patients in the resynchronisation group and 25.3 % in the ICD group experienced the primary end point of all cause mortality or a heart failure event whichever occurred first (Hazard Ratio 0.66, 95% confidence interval 0.52 to 0.84; P=0.001), with similar benefit in patients with ischaemic and non-ischaemic cardiomyopathy (10). Superiority of resynchronisation therapy was driven by a 41% reduction in the risk of a first heart failure event without an effect on the 3% annual mortality in each treatment group. Resynchronisation therapy was associated with significant reduction in left ventricular volumes and improvement in ejection fraction.

Conclusion: MADIT-CRT has shown that CRT may delay disease progression in heart failure class I or II patients through left ventricular remodeling. This is consistent with a prior smaller trial (REVERSE, 610 patients), which, however, did not reach statistical significance of a heart failure clinical composite response that compared only the percentage of patients worsened (primary endpoint). However, secondary endpoints were in line with the much larger MADIT-CRT trial results concerning left ventricular remodelling and reduction in the need for heart failure hospitalisations. CRT is an effective therapy in improving heart failure-related manifestations in patients with poor left ventricular function (EF <0.30 like in MADIT-CRT or <0.40 like in REVERSE) who frequently are eligible for primary prevention ICD implantation with an ischaemic or non-ischaemic aetiology and broad QRS complexes of >0.12 s (REVERSE) or >0.13 s (MADIT-CRT) but with no or only minimal symptoms.

Open issues: Is the evidence similarly strong for class I and II patients? This and other questions might be answered by merging the original data from both trials into a meta-analysis. Patient characteristics were not much different from previous ICD trials, especially with regard to ejection fraction. Should we re-define the present guidelines for primary ICD implantation to include CRT and, if so, to all patients with a QRS duration of >0.13s (or >0.12s like in REVERSE)? Or should there be a cut-off of about 0.15s as suggested by the subgroup analyses in both trials? Should parameters of dyssynchrony be added?

Mortality in class I and II heart failure patients is low. However, if progression of the disease on the long-term is retarded by CRT, does this translate into a lower mortality as the disease would normally progress and as long as no competing risks occur? It may be difficult to find an answer to this issue since the present data by MADIT-CRT but also REVERSE may make it at least difficult if not impossible to do another randomised trial with and without CRT which, as a mortality trial, would require a very large population.

This commentary accompanies a presentation given at the ESC Congress 2009. Written by the author, this report does not necessarily reflect the opinion of the European Society of Cardiology.w

The risk of cardiovascular event for patients treated with clopidogrel or prasugrel in combination with a Proton Pump Inhibitor: Results from the TRITON-TMI 38 trial

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Background: Prasugrel significantly reduces cardiovascular events as compared with clopidogrel in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI), but with an increased risk of bleeding. Proton pump inhibitors (PPI) are often prescribed to patients in combination with thienopyridines to help reduce the risk of gastrointestinal bleeding. Some data suggest that many PPIs may reduce the antiplatelet effects of clopidogrel by inhibiting CYP2C19 and thus the conversion of clopidogrel to its active metabolite. The clinical implications of co-administration of a PPI with either clopidogrel or prasugrel remain undefined.

Methods: The TRITON-TIMI 38 trial randomised 13,608 subjects with ACS and planned PCI to prasugrel or clopidogrel, in addition to standard therapy. The primary endpoint of the trial was cardiovascular death, MI or stroke. The decision to treat with a proton pump inhibitor was left to the discretion of the treating physician and was captured on the case-report forms. A multivariable Cox proportional hazards model was used to evaluate the association between use of a PPI at randomisation and the risk of long-term clinical outcomes. The multi-variable model included potential confounders and a propensity score constructed with 15 variables associated with use of a PPI. Further sensitivity analyses were performed to evaluate the association between use of a PPI at different timepoints during follow-up, different types of PPIs, and the risk of short- or long-term cardiovascular events.

Results: Of the 13,608 subjects enrolled in TRITON-TIMI 38, 33% of subjects were being treated with a PPI at randomisation. For patients randomised to clopidogrel, the rate of the primary endpoint through long-term follow-up was 11.8% in subjects on a PPI and 12.2% in subjects not on a PPI (HR 0.98, 95% CI 0.84-1.14, P=0.80). For patients randomised to prasugrel, the rate of the primary endpoint was 10.2% in subjects on a PPI and 9.7% in subjects not on a PPI (HR 1.05, 95% CI 0.89-1.23, P=0.58). After adjusting for known confounders and the propensity to treat with a PPI, there remained no significant association between the use of a PPI and the risk of the primary endpoint, both for patients treated with clopidogrel (adjusted HR 0.94, 95% CI 0.80-1.11) or for those treated with prasugrel (adjusted HR 1.00, 95% CI 0.84-1.20). Similarly, the use of a PPI was not associated with an increased risk of MI, stent thrombosis, or urgent revascularisation, or a decreased risk of bleeding, for patients treated with either clopidogrel or prasugrel (Table). Sensitivity analyses demonstrated consistency of the results based on use of PPI at different timepoints during follow-up, different types of PPIs, and varying durations of follow-up.

Conclusion: In a large population of subjects treated with clopidogrel or prasugrel, the use of a PPI was not associated with an increased risk of cardiovascular events.

	Clopidogrel (n=6795)			Prasugrel (n=6813)		
	Treated with a PPI (n=2257)	Not treated with a PPI (n=4538)	Adjusted HR (95% CI)	Treated with a PPI (n=2272)	Not treated with a PPI (n=4541)	Adjusted HR (95% CI)
CV death, MI or stroke	11.8%	12.2%	0.94 (0.80-1.11)	10.2%	9.7%	01.00 (0.84-1.20)
Myocardial infarction	9.5%	9.8%	0.98 (0.82-1.17)	7.7%	7.3%	1.02 (0.84-1.25)
Stent thrombosis (ARC definite or probable)	2.4%	2.3%	1.08 (0.75-1.55)	1.1%	1.1%	1.03 (0.60-1.76)
TIMI major bleeding	2.4%	1.6%	1.20 (0.80-1.79)	2.5%	2.4%	0.97 (0.67-1.39)
Net clinical outcome (death, MI, stroke or TIMI major non-CABG bleeding)	13.9%	13.8%	0.96 (0.83-1.12)	12.6%	12.1%	0.99 (0.85-1.17)

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Commentary on the TRITON-TIMI 38 trial - Combination of Proton Pump Inhibitor and clopidogrel or prasugrel

Kurt Huber

Background: In this interesting study the authors investigated by retrospective analysis of patients of the TRITON TIMI-38 trial whether the use of proton pump inhibitors (PPI) negatively influences clinical outcome compared with non-use. Controversial data of clinical outcome from other authors as well as studies, which demonstrated a reduced action of clopidogrel on in vitro testing of platelet function when PPIs, especially omeprazole, were used, were the background of the investigation. Of special interest was the opportunity to test the potential influence of PPIs on prasugrel, a new thienopyridine, which showed favorable effects over clopidgrel in the TRITON TIMI-38 trial.

Methods and statistics: The TRITON-TIMI 38 trial randomised 13,608 subjects with ACS and planned PCI to prasugrel or clopidogrel, in addition to standard therapy, of which 4,538 (20%) were being treated with a PPI at randomisation. Use of a PPI was at the discretion of the treating physician and not randomised. A multi-variable Cox proportional hazards model, which included potential confounders and a propensity score constructed with 15 variables associated with use of a PPI, was used to evaluate the association between use of a PPI at randomisation and the risk of long-term clinical outcomes.

Results: After adjusting for known confounders and the propensity to treat with a PPI, there remained no significant association between the use of a PPI and the risk of the primary endpoint, either for patients treated with clopidogrel (adjusted HR 0.94, 95% CI 0.78-1.13) or for those treated with prasugrel (adjusted HR 0.94, 95% CI 0.77-1.16).

Comments: Contrary to several other investigations with higher patient numbers, in this population of subjects treated with clopidogrel or prasugrel, the use of a PPI was not associated with an increased risk of cardiovascular events. What are the differences between TRITON TIMI-38 and other investigations, which make the results more reliable for clinical practice? Based on the fact that patients were not randomised to receive or not to receive a PPI in all studies published so far, different inclusion bias might have triggered the different clinical outcomes. In addition, the current data come from a prospective randomised trial with a well-defined study population. This might be different to the study populations of other trials and registries including patients with higher age and more co-morbidities - which is frequently the reason for using PPIs - and therefore at higher risk for clinical events. Differences in outcome might also be explained by different statistical approaches. Also the consistent use of PPIs during dual antiplatelet therapy might have impacted on clinical outcome. It would be interesting to know whether the authors have performed in vitro platelet function testing and whether the test results are related with the clinical outcome. Unfortunately, also the TRITON TIMI-38 substudy on the impact of use or non-use of PPIs on clinical outcome in clopidogrel or prasugrel-treated patients does not fully answer the still open questions. Only a prospective randomised trial of PPI use will be capable of establishing the safety of PPIs in combination with thienopyridines.

This commentary accompanies a presentation given at the ESC Congress 2009. Written by the author, this report does not necessarily reflect the opinion of the European Society of Cardiology.