



Updates

TREAT

Ticagrelor in patients with STEMI treated with pharmacological thrombolysis trial

JAMA cardiology –March 2018.

This trial attempts to answer the doubts regarding the safety and efficacy of converting to ticagrelor in patients already on clopidogrel after thrombolysis.

The trial results suggest that bleeding events are not statistically increased in the patient population converted to ticagrelor. It also reported that death, MI, stroke, recurrent ischaemia and TIA were not different in the groups treated with clopidogrel or ticagrelor.

The current STEMI guidelines do not permit the concomitant use of ticagrelor with thrombolytics. At present clopidogrel is the sole drug approved as an add on antiplatelet agent to aspirin in the context of thrombolysis.

With the prominence given to the pharmaco-invasive treatment strategy in treating acute ST elevation myocardial infarction, the question of the best antiplatelet agent to use with either streptokinase or tenecteplase has no doubt gained greater relevance in current practice. Ticagrelor is accepted as the antiplatelet agent with equiipoised anti-thrombotic and pro-hemorrhagic effects. Hence its use in the pharmaco-invasive treatment strategy is a valid clinical query to consider. The TREAT trial provides the answer as to the safety and efficacy of ticagrelor in this scenario.

The question which is important in the Sri Lankan context is whether we need to replace clopidogrel with ticagrelor in our patients undergoing pharmaco-invasive therapy. The answer is probably in the negative. The reason is that the TREAT trial showed no benefit of ticagrelor in preventing major cardiac events.

Practice Points from Late Breaking Clinical trials

From the Editorial desk

It could well be that the benefit is present and was not revealed in TREAT, as it was primarily a non-inferiority trial concerning bleeding. Further large scale studies are needed for full resolution of the query. At present, in the Sri Lankan context we probably could continue with clopidogrel in the pharmaco-invasive strategy unless the attending cardiologist decides on ticagrelor, based on findings during coronary intervention.

MANAGE

Management of myocardial injury after non cardiac surgery (MINS)

ACC march -2018 and Canadian Journal cardiology 2018.

Patients who are at higher risk of vascular disease appear to suffer a greater number of heart attacks in the post-operative period of non-cardiac surgery.

MINS is defined as clinical MI or isolated troponin elevations up to ischaemic levels within 30 days of non-cardiac surgery.

The statistics quoted inform us that out of the approximately 200 million non cardiac surgeries performed worldwide annually, 8 million suffer some form of myocardial injury in the post-operative phase. This works out to 4% which may not seem much as a statistical figure but the actual numbers are phenomenal.

The study population of MANAGE consisted largely of patients at higher risk for vascular disease and diabetes mellitus.

Myocardial injury was diagnosed by the presence of new myocardial infarction (20%) or isolated elevation of a troponin performed 1-3days in the postoperative phase (80%). 91% had no symptoms suggestive of myocardial injury and troponin assays were performed routinely as per study protocol.



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The trial tested whether treating these patients with a NOAC, namely dabigatran 110mg bd would prevent major vascular outcomes – i.e nonfatal MI, non-hemorrhagic stroke, peripheral arterial thrombosis, amputations, venous thromboembolism and vascular mortality, all of which appear to be more frequent in the follow up phase of MINS sufferers.

The MANAGE trial reported that 24 MINS patients needed to be treated to prevent one major vascular complication. There can be no doubt that this NNT could be of great clinical significance.

Current data suggests that 10% of MINS patients will die in the first 30 days following surgery. The increased risk of death persists for one year.

Cardiac troponin is certainly not routinely measured after non cardiac surgery and hence we are undoubtedly missing a large number of MINS patients.

Should we measure troponin in all patients undergoing non cardiac surgery? A more realistic approach would be to do the troponin levels on patients with prior arterial disease of any type, patients >65 years and diabetics. This recommendation however is not based on the trial data.

It must be said that commencing dabigatran soon after surgery would raise serious concerns regarding bleeding complications. However the MANAGE trial reported no increase of hemorrhagic events compared to placebo. The critical bleeding sites recorded in the MANAGE trial were intracranial, intraocular, intraspinal, pericardial and retroperitoneal.

How long should we continue dabigatran? This question remains unanswered but in MANAGE the average duration was 16 months. However its safety is not established as 14% discontinued the drug due to a major complication.

The evidence from MANAGE is far from conclusive and the trial methodology has been heavily criticized mainly because of the very high rates of withdrawal. However it gives clinicians some evidence to commence anticoagulation in the post op period in patients who are diagnosed with MINS.

How soon after surgery could we commence on dabigatran? There is no clear answer except that it is apparently safe to start within the first 35 days with the concurrence of the surgeon.

Could warfarin sodium be used instead of dabigatran? The answer is probably yes. Warfarin sodium has been studied in non-surgical patients, comparing aspirin alone or aspirin plus warfarin sodium (keeping the INR at 2-3).

The composite aspirin plus warfarin sodium was superior in reducing all-cause mortality, nonfatal myocardial infarction and nonfatal embolic stroke. However aspirin plus warfarin sodium was associated with a higher risk of major bleeds. Hence in the post-surgical setting dabigatran alone would be a better option.

All patients with MINS in the MANAGE study received aspirin as well as a statin. Dual antiplatelet therapy was not initiated.

CANTOS

(Canakinumab anti-inflammatory thrombosis outcome Study)
NEJM 2017

Canakinumab is a monoclonal antibody targeting the inflammatory molecule interleukin 1 β inhibiting the interleukin 1 β mediated innate immunity pathway.

The CANTOS study population consisted of 10,061 patients who had suffered a myocardial infarction and who had elevated hs-CRP levels over 2mg/L. Canakinumab was administered subcutaneously at three monthly intervals.

The median follow up was 3.7 years. The study reported a 0.6% absolute reduction in MI, Stroke and CV death. The main reduction was in the incidence of MI. Hospital readmission for unstable angina was a secondary endpoint which was also favorably affected by canakinumab therapy.



A concern which arises with inhibition of the interleukin system is the possibility of higher rates of infection. Canakinumab therapy does show a trend towards higher incidence of sepsis although not statistically significant.

The JUPITER trial (2008), addressed the question as to whether statin therapy in patients with normal or low LDL levels (<130mg%) but with high hs-CRP (>2mg%) would lead to any benefit. At a follow-up of approximately two years 20mg of rosuvastatin showed a significant reduction in the primary end point (i.e. composite of MI, stroke, CV death, unstable angina and revascularization) associated with reduction of LDL- C (by 50%) as well as hs-CRP level (by 37%). In this case the reduction in the primary endpoint could have been due to either or both biochemical effects.

The MESA study (Multi-ethnic study of atherosclerosis) suggested that hs-CRP was elevated across ethnicity. Smaller Indian studies indicate that hs-CRP is elevated in diabetics, pre diabetics, metabolic syndrome in addition to coronary artery disease and stroke.

The CANTOS trial is important in that it provides evidence suggesting the importance of inflammation in the pathogenesis and value of anti-inflammatory agents in the therapy of atherosclerosis. However the CANTOS trial demonstrates only modest benefit of therapy and hence clinical significance remains to be further established.

ODYSSEY -Out comes

(Evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab).

ACC 2018

The results were made public at the annual scientific session of the American College of Cardiology 2018. The trial recruited patients who had suffered an acute coronary syndrome one year prior.

The drug alirocumab was administered subcutaneously to patients randomized to receive it, on a bi weekly basis.

The dose of alirocumab was titrated so as to keep the LDL-C at 25-50mg% but not permitted to go below 15mg%. The follow up was for 4years. The principal findings were very encouraging & are summarized below.

	Alirocumab	Placebo	P
MACE	9.5%	11%	0.0003
MI	6.6%	7.6%	0.0006
Ischemic stroke	1.2%	1.6%	0.01
Unstable angina	0.4%	0.6%	0.02
Coronary deaths	2.2%	2.3%	0.38
Death, MI, stroke	10.3%	11.9%	0.0003
Coronary revascularization	7.7%	8.8%	0.009
All cause mortality	3.5%	4.1%	0.026

The greatest number to derive benefit from alirocumab were the patients whose LDL-C was $\geq 100\text{mg\%}$ at base line even with intensive statin therapy.

Even though all-cause mortality was reduced, the coronary death reduction did not reach statistical significance in accordance with the predetermined statistical analysis plan. Hence the drug cannot be promoted as reducing cardiovascular mortality.

The other trial with the PCSK9 inhibitor evolocumab was FOURIER which did not show any mortality benefit. Although meta-analysis of cholesterol lowering trials suggest that coronary events reduce by 22% for every 1mmol/L ($=38\text{mg\%}$) reduction in LDL-C, the ODYSSEY- outcomes trial data does not demonstrate a reduction of commensurate magnitude. Alirocumab being a monoclonal antibody, may lead to the development of neutralizing antibodies which could attenuate its action as a late effect.