Drug Trends in Cardiology

News from the European Society of Cardiology, and expert comment

Rivaroxaban in acute coronary syndromes and atrial fibrillation: rivaroxaban shown to reduce cardiovascular deaths in STEMI patients

The addition of rivaroxaban to dual therapy for ST-elevation myocardial infarction (STEMI) patients has been shown to reduce recurrent cardiovascular events and cardiovascular death without increasing fatal bleeding, although TIMI non-coronary artery bypass graft (CABG) major bleeding was increased.

Presenting the results of this pre-specified sub-group of the ATLAS ACS 2-TIMI 51 trial,1 Dr Jessica Mega, Brigham and Women’s Hospital, Boston, USA, noted that the primary-efficacy benefit, a significant 19% reduction in cardiovascular (CV) death, myocardial infarction (MI) or stroke emerged early in the first two to three weeks of rivaroxaban therapy. These results are consistent with the results from the overall ATLAS ACS 2-TIMI 51 phase III study. ‘The value of rivaroxaban relates to the blocking of excess thrombin generation, not only at the time of the index event but also over time’, Dr Mega said.

In the overall ATLAS ACS 2-TIMI trial, more than 15 000 patients with the whole spectrum of acute coronary syndrome (ACS) were recruited; 50.3% of patients presented with STEMI, 25.6% with non-STEMI (NSTEMI) and 24% with unstable angina. The 7 817 STEMI patients were stabilised according to the attending physician’s discretion, given aspirin 75–100 mg/day and randomised to placebo, or rivaroxaban 2.5 mg bid or 5 mg bid; 97% of patients were on either clopidogrel or ticlopidine, although some stopped taking this medication over the course of the study.

The primary efficacy endpoint was cardiovascular death, myocardial infarction (MI) or stroke. Safety was according to TIMI major bleeding not associated with CABG.

There was no reduction in cardiovascular death in patients receiving the 5-mg dose but there was a 40% reduction in CV deaths and a significant reduction in all-cause mortality in patients receiving the 2.5-mg dose of rivaroxaban. There was an increase in TIMI major and minor bleeding, with fewer bleeds on the lower dose. There was no increase in fatal bleeding on either dose. Dr Mega concluded that very low doses of rivaroxaban (2.5 mg twice daily) offer an effective treatment strategy to reduce thrombotic events in patients following STEMI (Table 1).

The use of the 2.5-mg bid rivaroxaban dose has been taken up in the new European Society of Cardiology (ESC) guidelines on STEMI with a class IIa, level 1B recommendation as follows: ‘In selected patients who do receive aspirin and clopidogral, lower-dose 2.5-mg rivaroxaban may be considered if the patient is at low bleeding risk.’

Taking clinical studies in stroke prevention in atrial fibrillation into practice

There is a high level of evidence to support the use of the new anticoagulants in stroke prevention in atrial fibrillation (AF). This has been taken up by the ESC in their newly released guidelines, which recommend the use of these novel agents as being broadly preferable to vitamin K antagonists for the majority of AF patients (level 1B recommendation).

This view was substantiated by Prof Robert M Califf, primary co-investigator of the ROCKET studies of rivaroxaban at a special symposium at the ESC, which evaluated the three series of studies in RE-LY, ROCKET and ARISTOTLE, involving dabigatran, rivaroxaban and apixaban, respectively. ‘Fundamentally, in my view, the data for these agents look more similar than different and without head-to-head comparisons in large populations, we will have to make appropriate decisions for individual patients based on our interpretation of the available data.’

The RE-LY study had the advantage of examining two doses of dabigatran compared to warfarin and was able to show equivalence at the lower dose (110 mg twice daily), with less bleeding than with warfarin. The higher dose (150 mg twice daily) was shown to be superior to warfarin in stroke prevention with the same level of bleeding complications but with fewer life-threatening major bleeds and somewhat higher gastrointestinal bleeding rates.

The ROCKET-AF trial was based on a single, once-daily dose of rivaroxaban (20 mg daily), which showed non-inferiority to warfarin with regard to the reduction of stroke and non-central nervous system embolism, with a decrease in serious bleeds such as intracranial and fatal bleeding, although overall bleeding rates were the same. It is important to note that the ROCKET trial intentionally included patients at considerable risk of stroke, and the overall risk score in ROCKET was much higher than in the other two trials.

| TABLE 1. ATLAS ACS 2-TIMI 51 RESULTS IN STEMI PATIENTS AT TWO YEARS |
|-------------------------------------------------|-----------------|
| Rivaroxaban 2.5 mg                              | Placebo         |
| CV death/MI/stroke                              | 8.7             | 10.6            |
| CV death                                       | 2.5             | 4.2             |
| All-cause death                                 | 3.0             | 4.7             |
| TIMI non-CABG major bleeding                    | 1.7             | 0.6             |

[1]"ACS 2-TIMI 51 trial"
Prof Werner Hacke, neurologist from Heidelberg University, Germany pointed out that the CHADS, score for ROCKET was 3.5, while average risk scores for RE-LY and ARISTOTLE were much lower at 2.1. Focusing on the neurologist’s experience of encountering AF patients only after they have experienced their first stroke, Prof Hacke presented important insights from the published data of the three trials in the pre-specified patient sub-group with prior stroke or transient ischaemic attack (TIA).

This evaluation of secondary prevention shows that in prior stroke patients in RE-LY and ARISTOTLE, some 20% of patients had higher CHADS scores and were more comparable to the overall ROCKET experience with its inclusion of patients at higher stroke risk. ‘In this group of patients who are more vulnerable to a further stroke and experience almost twice as many strokes as the stroke-naive patients, the higher dose of dabigatran loses its superiority in stroke prevention to warfarin but is still better than warfarin with regard to reducing intracranial bleeds. This is in concordance with the overall results of the RE-LY trial.’

‘Similarly, if the data from the ARISTOTLE trial with apixaban is analysed with regard to these patients, the stroke rate was three times higher than in those without a prior stroke. Apixaban for these patients was shown to be non-inferior to warfarin with fewer haemorrhagic strokes and intracranial bleeding events. Again concordance is seen with regard to the overall results of ARISTOTLE.’

‘ROCKET-AF included 55% of patients with prior stroke or TIA and most patients were at risks above 2; only 13% had a CHADS score of 2 and few had a score of 1. Prof Hacke noted that the patients with a prior stroke in ROCKET were at even higher risk of stroke (CHADS score > 4) than the already high risk levels within the ROCKET patient cohort who had to have had a stroke, TIA or systemic embolism or at least two risk factors for inclusion in the trial.’ In these very vulnerable patients, there were once again twice as many strokes as in stroke-naive patients, and rivaroxaban treatment reduced the number of strokes, with a clear trend towards lower rates of intracranial and fatal bleeding’, he noted.

**Practical advice on use of these novel agents**

The importance of counselling patients when prescribing these new agents was stressed by Prof Jafna Cox, Canada, who noted that patients should be instructed to not stop the drug without prior consultation with their physician. Also they need to be told how to manage a missed dose of dabigatran using the six-hour rule, and with rivaroxaban to just take the drug even if later on the same day. Not doubling the dose is an essential warning for all of these agents.

‘Inevitably, as we treat these patients, we encounter patients with recent ACS and they require on-going surveillance. I avoid dabigatran in this situation, rather choosing rivaroxaban but nonetheless keeping a watchful, concerned eye over developments.’

Withdrawal of these agents may not always be necessary, particularly when patients are undergoing low-risk procedures. If there is bleeding on an anticoagulant, tests such as the aPTT for dabigatran and PT for rivaroxaban are useful, as higher values indicate the patient is still taking the drug. Action can be initiated as for any bleeding event.

**Expert comments**

**Dr Mike Bennett, Wilgers Hospital, comments on the developments related to novel anticoagulant use in AF**

Atrial fibrillation patients are poorly treated. Physicians are afraid of warfarin side effects and patients on warfarin are often poorly controlled. They face limitations with regard to diet and lifestyle, with the required regular monitoring intruding on their peace of mind. The new oral agents are simple to use and as safe as warfarin. It comes as no surprise to me that the new ESC guidelines recommend their use above warfarin for most patients. It is absolutely clear that aspirin has no place in stroke prevention in AF, yet it is still commonly prescribed in South Africa. Other absolutes for me in stroke prevention in AF are that patients older than 75 years and those of any age who have had a stroke require oral anticoagulation. With regard to stroke patients, the absence of any remaining symptoms of the incident does not mean that the patient does not require anticoagulation; the risk of a second stroke remains.

The elderly are at particularly high risk for a stroke and warfarin presents particular challenges, so it is often not prescribed. The older patient is usually on multiple other medications, may have cognitive problems and if living in a retirement or old-age home is dependent on others to give the medication. They are dependent on their carers to get them to clinics or doctors’ rooms where the INR checks are done and their time in therapeutic range (TRT) is frequently less than ideal.

With regard to rivaroxaban, it is attractive as a once-daily, fixed dose, it requires no monitoring, is as safe and as effective as warfarin, while also reducing the risk of intracranial bleeds. It has no food or drug interactions and allows the patient to live without continually being concerned about its use. Affordability is an issue but this needs to be evaluated against the significant healthcare costs of warfarin.