ROCKET AF:
Rivaroxaban? What does it mean to pharmacist?

In November, 2010, a new oral anticoagulant drug, rivaroxaban, was “landed on earth” with a high profile presentation at the American Heart Association (AHA) 2011 at Chicago, which is the study based on the Rivaroxaban Once daily Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). [1] Confirmed with the preliminary results presented at the conference, the ROCKET-AF study was recently published in the New Journal of Medicine (10 August 2011). [2] Meanwhile, the United Kingdom Clinical Pharmacy Association has issued guidance on the appropriate use of new oral anticoagulant medicines for the prevention of stroke for patients with atrial fibrillation and expected to be licensed for this indication in 2011/2012.So, what is the pharmacology of rivaroxaban? what is the ROCKET-AF study about? And what are the actual potential advantages of this new anticoagulant to the clinical pharmacy practice? Does it mean warfarin can be put “to an end”?

Since the 1960s, warfarin has been the only anticoagulant drug in regular use for treating patients with thromboembolic disease. It is until 2008, rivaroxaban, (one of the new anticoagulant, the other one is dabigatran) was registered in Australia for the prevention of venous thrombosis after elective knee or hip replacement therapy. [3] [4] And since then, rivaroxaban is believed to be effective anticoagulants which offer potential advantages over heparin and warfarin. Pharmacologically, rivaroxaban is a competitive reversible antagonist of activated factor X (Xa). Factor Xa is the active component of the prothrombine complex that catatlyses the conversion of prothrombin (factor II) to thrombin (factor IIa).[5]

The purpose of the Rocket-AF study was to compare once-daily rivaroxaban with dose-adjusted warfarin for the prevention of stroke and systemic embolism in patients with non-valvular trial fibrillation who were at moderate-to-high risk for stroke. The primary hypothesis was that rivaroxaban would be non-inferior to warfarin for the prevention of stroke or systemic embolism. Warfarin requires frequent coagulation monitoring and subsequent dose adjustments, whereas rivaroxaban may provide more consistent and predictable anti-coagulation, and is therefore more “patient” friendly. In this double-blinded trial, researches randomised 14264 patients with non-valvular AF and a moderate-to-high risk of stroke (i.e. CHADS2 score of 2 or more) to receive rivaroxaban 15mg daily, rivaroxaban 20mg daily or dose-adjusted wafarin (target international normalised ration 2-3). The primary efficacy end-point was stroke or systemic embolism and it occurred in 188 patients taking rivaroxaban and 241 patients receiving warfarin ($p<0.001$ for non-inferiority). The secondary efficacy end-point included primary end-point or death from cardiovascular cause. For this secondary efficacy outcomes, mycocardial infarction occurred in 101 patients (0.9% per year) in the rivaroxaban group and in 126 patients (1.1% per year) in the warfarin group. There were 208 deaths (1.9% per year) in the rivaroxaban group and 250 deaths (2.2% per year) in the warfarin group. Furthermore, the study also investigate the primary safety outcome, a composite of major and non-major clinically relevant bleeding events. This occurred in 475 patients in the rivaroxaban group and 1449 patients in the warfarin group ($p=0.04$).

Though the study didn't show that rivaroxaban was inferior to warfarin in the prevention of subsequent stroke or systemic embolism, the study revolutionise treatment of patients with AF compared with warfarin. In fact there are many potential and advantages of this direct factor Xa inhibitor:[6]

1. Fast onset and offset of action
2. Few drug an food interactions
3. Fixed dosage and no regular monitoring for dose adjustments
4. Potentially have a lower risk of major bleeding
5. Increase prescribing anticoagulant
6. Increased used in elderly

Having said that, however, many critical issues have been found out for the drug as well: [6]

1. Potential for lack of emphasis on education and bleeding risk with new anticoagulants
2. Lack of routine monitoring will lead to less warning regarding bleeding events (e.g. in people with worsening renal function or commencing interacting medications

3. More frequent dosing leads to reduced adherence
4. Lack of monitoring may significantly reduce persistence; cessation of new anticoagulants may not be clear to prescriptions, as patients often don't tell their doctors when they become non-persistent
5. No antidote has been developed so far to reverse the condition of over-anticoagulated

Therefore, as a conclusion, direct factor Xa inhibitor represents a new and potentially exciting development in anti-thrombosis therapy. They have the potential to be as effective, safer and easier to use than conventional drugs, which is warfarin. However, clinical evidence has not yet shown superiority to older anti-coagulants in all aspects and problems like management of bleeding and adherence are the most concern of this new medication. Therefore, it's still early to say "warfarin can be put to end" as we still need more evidence-based data for the safety and compliance issues of the drug.

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References

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DO YOU KNOW.....?

....what is the Chinese name of Medication reconciliation?

Medication reconciliation is (? or was) a hot topic in Hong Kong and it is also a medication safety goal of a lot of countries. In English-speaking world, we, of course, have no problem at all though the term is still a little too long. Folks in the states like to call it "med rec", where we like to call it MR in Hong Kong (though we also call "mental retardation" as MR, hahaha)

Well, Hong Kong is definitely a metropolitan. We cannot survive here if we can just speak one language. Chinese and English are equally important in our daily life. Therefore, we NEED a Chinese term for medication reconciliation. It is convenient for us to communicate among ourselves so as to communicate with our counterparts in China. It was then discussed seriously in the Medication Reconciliation Interest Group under the clinical pharmacy subcommittee of the Hospital Authority (HA).

Quite a lot of suggestions were brought up in the meeting including the followings.

協調 which was used in the previous presentation in China,
修和 which is used by Catholics when talking about relationship with god,
執正 which carries the meaning of bringing chaotic things into order
理順 which implies that we are just matching the drug list but also to solve drug-related problems,
用藥總歸戶 which is quoted from a Taiwanese website
用藥持續性照顧 from a Taiwanese website as well
藥物整合 from Mainland and Taiwanese website
調解、調停、修正、執正、整理、整頓 are all other possible choices.

To be continued on P.5