Direct-acting oral anticoagulants: Less is not always more

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SOUHRN

Popisujeme případ, kdy bylo snížení dávky perorálního přímého inhibitoru faktoru Xa rivaroxabanu samotným pacientem spojeno s neobvyklou tromboembolickou komplikací v podobě akutního infarktu myokardu s elevacemi úseku ST (ST-segment elevation myocardial infarction, STEMI) při nestabilních renálních funkcích a odhadované glomerulární filtraci pohybující se v i mimo rozmezí, kdy se doporučuje snížení dávky rivaroxabanu. Popisovaný případ zdůrazňuje důležitost správného dávkování rivaroxabanu u pacientů, jejichž doporučený dávkovací režim se pohybuje v blízkosti mezních hodnot, protože je sice dobře známo riziko krvácení při poklesu hodnot CrCl < 30 ml/min, ale zdá se, že v případě zlepšení hodnot CrCl hrozí zase nebezpečí poddávkování. Vzhledem k výše uvedenému je třeba pečlivě zvážit buď alternativní postup, nebo důsledné monitorování renálních funkcí, aby se předešlo potenciálně život ohrožujícím komplikacím v důsledku poddávkování nových perorálních antikoagulancií.

Keywords:
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ABSTRACT

We report a case in which self-prescribed dose reduction of the orally active, direct factor Xa inhibitor, rivaroxaban, was associated with the unusual thrombo-embolic complication of acute ST-segment elevation myocardial infarction (STEMI) in the setting of a fluctuating renal function and estimated glomerular filtration falling in and out of the range where dose reduction of rivaroxaban is suggested. The case highlights the importance of dosing of rivaroxaban in those patients who sit around the recommended dosage regimen cut offs as they are well known to be at risk of bleeding should their CrCl fall <30 mL/min, but they also appear at risk of under-dosing should their CrCl improve. Due to the above-mentioned issue, careful consideration should be given to either alternative choices or close renal function monitoring, to avoid potentially life-threatening complications due to under-dosing of new oral anticoagulants.

We report a case in which dose reduction of the orally active, direct factor Xa inhibitor, rivaroxaban, was associated with the unusual thrombo-embolic complication of acute ST-segment elevation myocardial infarction (STEMI). A 74-year-old woman presented with sudden onset central chest pain and ST-segment elevation in the inferior leads of her initial ECG (Fig. 1A). Salient medical history included distant breast cancer with ongoing tamoxifen, hypertension, stage III chronic kidney disease (CKD) and permanent atrial fibrillation (AF), for stroke risk reduction due to AF, she was prescribed rivaroxaban. Admission blood tests revealed a creatinine clearance (CrCl) of 52 mL/min (Cockcroft-Gault) and normal aPTT, PT, and INR. She had experienced recurrent epistaxis six months prior and given a labile CrCl hovering between 40 and 60 mL/min, a decision was made then to reduce her dose of rivaroxaban to 15 mg. The patient reported less than ideal compliance to rivaroxaban, with the last dose taken more than 24 h leading up to her current presentation.

Our patient underwent emergent primary percutaneous intervention. Coronary angiography revealed an acute occlusion of the mid segment of the Left Circumflex (LCx) artery (Fig. 1B) with otherwise angiographically 'smooth' left anterior descending and right coronary arteries. Manual aspiration thrombectomy was performed with a 6Fr Export catheter (Medtronic, Minneapolis, USA) retrieving a large burden of soft, acute thrombus (Fig. 1D) with subsequent improvement of coronary flow. As residual thrombus was still evident, further aspiration was performed revealing an angiographically 'smooth' culprit site without evidence of underlying atherosclerotic plaque rupture (Fig. 1E). The patient had complete resolution of chest pain, together with normalization of her ST segments.

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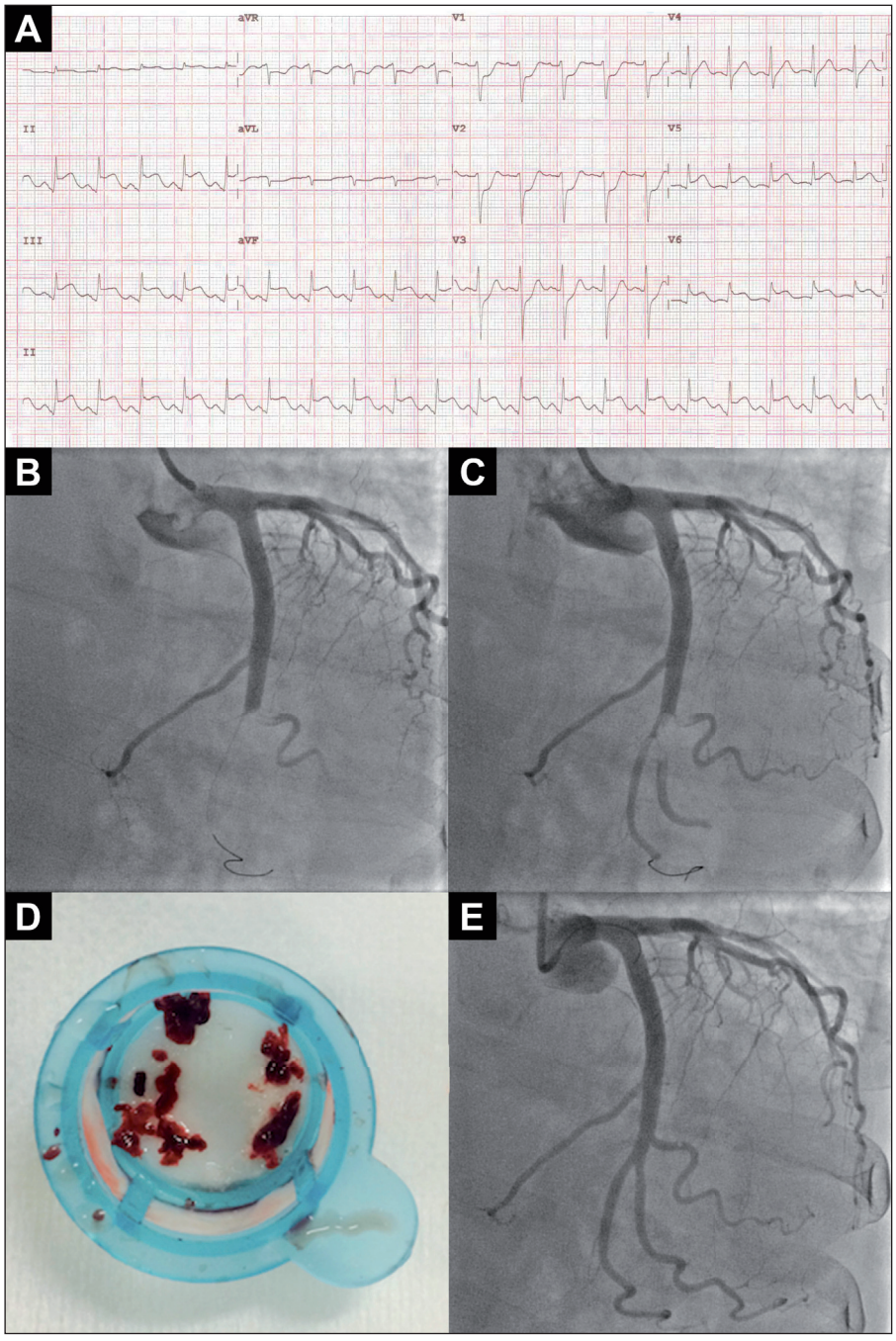

Fig. 1 – (A) ECG demonstrating ST elevation in inferior–lateral leads, (B, C) angiography showing acute occlusion of the Left Circumflex and obtuse marginal arteries, (D) acute thrombus extracted on manual aspiration, (E) post manual thrombectomy angiography showing non-obstructive left coronary system.

Transthoracic echocardiography demonstrated akinesia of her anterolateral wall with overall moderate left ventricular dysfunction and no evidence of left ventricular thrombus. In view of a past history of breast cancer, computed tomography imaging and biomarkers for recurrent malignancy were unrevealing. The cause for the extensive intracoronary thrombus was attributed to AF and in the setting of a labile CrCl, under-dosing of her Xa inhibitor was the most likely culprit and thus was switched to warfarin with enoxaparin bridging. The patient remains well at 6-month follow up with a stable INR and no further bleeding or thromboembolic episodes.

Discussion

Based on earlier pharmacokinetic studies the phase III trial for rivaroxaban (ROCKET AF)[1] included a reduced dose for patients with a CrCl 30–49 mL/min and the phase III studies for apixaban (AVERROES vs. aspirin and ARISTOT-

LE[2] vs. warfarin) included a composite of serum creatinine, age and weight to qualify for the reduced dose. In the phase III study of dabigatran (RE-LY) however, both doses of dabigatran (110 mg and 150 mg) were trialled in a blinded fashion, thus exposing patients with a normal GFR to a 'reduced' dose and those with renal impairment to the 'standard' dose. Evaluated in pre-specified groups, event rates in those with preserved renal function (CrCl >80 mL/min) who received the 110 mg dose (0.94%/year) were higher than those who received the 150 mg dose (0.75%/year) intimating they were likely to have been under-dosed.

This observation has important implications for those patients who sit around the recommended dosage regimen cut-offs as they are well known to be at risk of bleeding should their CrCl fall <30 mL/min, but they also appear at risk of under-dosing should their CrCl improve. A number of guidelines recommend at least annual review of renal function although in the setting of labile readings, this should be more frequent. Indeed with persistently low or labile CrCl readings, most Society Guidelines recommend moving back to warfarin given the ability to measure therapeutic concentrations and attenuate bleeding risk. If a DOAC remains the preferred option in the setting of renal impairment, apixaban may be advisable as it is least renally cleared and its composite use of age and weight may provide a complete stratification of bleeding risk.

As this case documents, DOAC dosing at each end of the spectrum should be approached with caution. Our patient's renal function had slowly improved over 6 months, and coupled with patient concerns over bleeding, was switched to a well-intentioned, but ultimately subtherapeutic dose of rivaroxaban leaving her at risk for systemic embolisation.

Conflict of interest
The authors state no conflict of interest.

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Ethical statement
The authors state that the publication was made in accordance with ethical standards.

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