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IM - DEBATE

Laboratory tests during direct oral anticoagulant treatment? No

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The anticoagulant effect of Dabigatran etexilate, Rivaroxaban, and Apixaban is dose-predictable, steady, and little influenced by diet and drugs [1]. Thus, similar to low-molecular weight heparin, laboratory tests have been unnecessary to evaluate such direct oral anticoagulant drugs (DOACs) in trials on thromboprophylaxis (Table 1). Nor such testing was needed in patients with atrial fibrillation (AF) receiving Dabigatran etexilate (RE-LY trial), Rivaroxaban (ROCKET AF trial) or Apixaban (ARISTOTLE trial). In the AF setting, vis-à-vis an at least as effective prevention of stroke and systemic embolism, the risk of intracranial hemorrhage was lower with DOACs than with INR-adjusted warfarin. Patients at high risk of bleeding are little represented in studies with DOACs [2, 3]. However, from October 2010 to December 2011, vis-à-vis 3.5 gastrointestinal bleedings and 2.4 intracranial hemorrhages/100,000 days at risk in new users of warfarin, 1.6 gastrointestinal bleedings and 0.8 intracranial hemorrhages/100,000 days at risk occurred among new users of Dabigatran in the every day practice in the USA [4].

At variance with the large majority of cases, there are special conditions and clinical settings (Table 2) in which the anticoagulant effect of DOACs should be measured [5]. However, peak concentrations of Rivaroxaban ($\approx$200 ng mL^{-1}) are determined by HPLC methods that are not suitable for routine practice [6]. On the other hand, in healthy volunteers, a 20 % prolongation of the aPTT has been observed for single Apixaban doses ranging from 25 to 50 mg [7]. Moreover, depending on the reagent employed, the concentrations of Rivaroxaban that double the aPTT range from 389 to 617 ng mL^{-1} [8]. Thus, the aPTT does not accurately assess the anticoagulant effect of Rivaroxaban or of Apixaban. A concentration-dependent prolongation of the aPTT occurs by spiking Dabigatran in human plasma [9]. However, such prolongation is linear only at Dabigatran concentrations >200 ng mL^{-1} (expected drug exposure being 50–300 ng mL^{-1}), and the effects on the aPTT vary up to 26 % between the most and least sensitive reagent [10]. Thus, the aPTT is not suitable for an accurate measurement of the anticoagulant effect of (high) Dabigatran concentrations.

At variance with Apixaban, Rivaroxaban prolongs the PT in a dose-dependent manner. However, at approved dose regimens (10–20 mg), the changes observed are small, and the results depend on the reagents employed. Accordingly, rather than quantitative, this accessible clotting method provides qualitative estimates of the anticoagulant effect of Rivaroxaban [11]. Likewise, significant effects in the PT-INR (i.e., INR >1.2) are only found in response to concentrations of Dabigatran >200 ng mL^{-1} [9]. Moreover, depending on the thromboplastin reagent used, major differences are observed in the results of the assays [10]. Thus, in its current form, the prothrombin time (PT), standardized as the International Normalized Ratio (INR), is not suitable for assessing the anticoagulant effect of Dabigatran. Nor is standardization between reagents and laboratories available for the very sensitive thrombin time (TT). [12] As a whole, while the PT and the aPTT provide little help distinguishing between treatment failure and non-adherence of patients, these routinely available clotting methods may be useful to establish whether the anticoagulant effect of a DOAC is higher than expected [an aPTT value twice the highest normal limit (i.e., >80 s) 12 h after the last administration of Dabigatran argues for

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Table 1 Clinical settings (randomized clinical trials of thromboprophylaxis) in which laboratory tests were unnecessary to evaluate the efficacy and safety of DOACs

Clinical setting	Numbers of patients in each arm of the studies (type of treatment)		
	DOACs	Competitor or placebo	Total
Venous thromboembolism[a]	17,772	16,925	34,722
Orthopedic surgery[b]	20,589	16,350	38,153
Arterial thromboembolism in atrial fibrillation (AF)[c]	31,943	25,027	57,040
Acute coronary syndrome (ACS)[d]	18,062	10,225	28,287
Total	88,366	68,527	158,202

[a] Combined data of patients from the following randomized studies: MAGELLAN; ADOPT; AMPLIFYEXTENTION; EINSTEIN PE; EINSTEIN DVT; REMEDY; RESONATE; RECOVER; RECOVER II

[b] Combined data of patients from the following randomized studies: BISTRO I; BISTRO II; REMODEL; REMOBILIZE; RENOVATE; RENOVATE 2; RECORD 1, 2,3, and 4; APROPOS; ADVANCE 1, 2 and 3

[c] Combined data of patients from the following randomized studies: PETRO; PETRO EXTENTION; RE-LY; ARISTOTLE; ROCKET AF; AVERROES

[d] Combined data of patients from the following randomized studies: REDEEM; ATLAS ACS TIMI 51; ATLAS ACS TIMI 46; APPRAISE 2

Table 2 Laboratory tests for DOACs

Reasons why DOACs do not warrant laboratory monitoring in the large majority of patients	Settings and special populations in which the anticoagulant effect of DOACs should be measured
Short-half life	Thrombosis or hemorrhage while on treatment
Relatively wide therapeutic window	Need for immediate reversal of anticoagulation[a]
Clinical trials carried at a fixed dose	(Severe) renal/liver failure, drug interaction
Cost cutting	Extreme body weights
Easy management (for patients and physicians)	Special settings: pregnancy, children, elderly
Appealing (for patients and physicians)	To distinguish treatment failure from non-adherence, to administer t-PA to patients presenting with acute stroke while on DOACs

[a] To determine the offset of activity (invasive procedures, suspected overdose, suspect/known interaction with other drugs)

drug accumulation or overdose as being present], or is absent (major information needed when deciding for an invasive procedure). The sensitive modified (diluted) PT assay provides a reliable method to quantify the anticoagulant effect of Rivaroxaban or of Apixaban [12]. However, compared with the standard PT, a higher intra-individual variability is present in such test and the effects of Rivaroxaban vary from one PT reagent to the other [11]. Although attempts [5] have been made to normalize the PT results by calibrating different thromboplastin reagents versus Rivaroxaban alone, standardization efforts are needed to improve the clinical impact of this modified PT test.

Similar to the ecarin clotting time, the Hemoclot assay is a modified (diluted) TT provided with Dabigatran calibrators. While entirely insensitive to Rivaroxaban or Apixaban, it yields a very rapid linear ($r = 0.99$) relationship with plasma concentrations of Dabigatran that span the therapeutic range (50–2,000 ng mL^{-1}). However, similar to the modified (diluted) PT, this method is currently performed only in a few specialized centers. [13] As a whole, the inherent inter-laboratory variations, the need for ad hoc plasma calibrators and of protocols for interpreting some test results, the wide variations between peak and trough values, the lack of correlation between any given level of anticoagulation and efficacy/safety at the individual patient and population level, the lack of availability for 24 h a day in a general hospital laboratory, the limited number of patients who may need them and the high costs, greatly hamper the use of specific assays that measure DOACs accurately. By comparing the expected with the observed concentrations in plasma samples collected 2–4 h after drug administration, dosages of DOACs might be appropriately adjusted [14]. However, especially in asymptomatic stable patients, single results of one of such assays that slightly exceed/fall below the laboratory-based definition of "normal range", by no means allow physicians to adjust the approved schedules of DOACs [12].

Anti-FXa chromogenic assays have long been available for monitoring low-molecular weight heparin. Such assays employ routine automated coagulometers or manual spectrometers. Kits for anti-FIIa assays that measure Dabigatran levels and kits with Rivaroxaban calibrators are now commercially available. Anti-FXa activity linearly correlates with plasma concentrations of Rivaroxaban or of Apixaban throughout their therapeutic range [12].

However, no correlation has been identified between any of such tests and clinical outcomes in patients taking any of the DOACs. Thus, in addition to standardizing such assays and searching for their automation, validation is mandatory before they can be used to make clinical decisions.

Markov models have shown the cost effectiveness of Apixaban in the USA [15] and of Dabigatran in the Swiss context [16]. Compared with warfarin, the higher cost of such DOACs is balanced by savings in PT-INR monitoring, lower costs for clinical events and QALY-gains in such models. Such considerations further support the need to accurately measure DOACs only in special populations and settings.

In the large majority of patients, actions not confined to laboratory testing and mostly aimed at improving patient's awareness (e.g., optimal communication with doctors in every day practice) are requested to improve the choice between different DOACs and decide the optimal dose of a DOAC to be employed [17]: (1) Renal function should be assessed annually in patients with normal (GFR $\geq$80 mL/min) or mild (GFR 50–79 mL/min) renal impairment, and 2–3 times/year in patients with moderate (i.e., GFR 30–49 mL/min) renal impairment. Because of variations in plasma drug concentrations, a measurable proportion ($\approx$1/4) of patients on a fixed dose of Dabigatran will either achieve an insufficient or a supra-therapeutic drug level [18]. However, with the exception of renal function (in patients with GFR 15–30 mL/min receiving 75 mg BID, exposure to Dabigatran is comparable to that of those with normal GFR receiving 150 mg BID of such DOAC), no intrinsic (demographics, laboratory data, health status) or extrinsic (co-medications) factor affecting the AUCs in that model warrants dose adjustment; (2) Patients enrolled in RE-LY and in ARISTOTLE had a $CHADS_2$ score 2.1; those in the ROCKET-AF had a $CHADS_2$ score 3. Three or more risk factors for cerebrovascular disease ($CHADS_2$ score $\geq$3) were present in 87 % of patients in ROCKET-AF, in 33 % in RE-LY and in 30 % in ARISTOTLE; 64 % of the ROCKET AF patient population had some degree of heart failure; (3) In those $\geq$80 years of age, further help in the choice is driven by polypharmacy (Dabigatran exerts less pharmacological interactions than inhibitors of factor Xa) and by the individual adherence to treatment (the once-daily administration of Rivaroxaban facilitates adherence in AF patients with some degree of cognitive impairment) [19]; (4) In Re-LY, in addition to Dabigatran, 6,952 patients received aspirin $\pm$ clopidogrel. Compared with those who had received Dabigatran alone, the HR for major hemorrhages is higher in patients who receive the combination of Dabigatran plus aspirin $\pm$ clopidogrel (1.60, 95 % CI 1.41–1.81) [20]. This is in keeping with the elevated risk of bleeding in patients receiving Rivaroxaban plus aspirin $\pm$ clopidogrel in ROCKET-AF and the excess in major and intracranial bleedings in ACS patients receiving Apixaban (or Rivaroxaban) plus aspirin (or plus aspirin + clopidogrel). While the on-going use of platelet-active drugs should be taken into account to identify "high risk" patients and to handle "spontaneous" bleedings (e.g., in acute medicine), the risk of adding DOACs to aspirin + prasugrel (or to aspirin + ticagrelor) is presently unknown.

Conflict of interest GDM has served on advisory boards for and has received fees as a speaker at meetings organized by Boehringer-Ingelheim, Bristol-Myers Squibb, Pfizer and Daiichi Sankyo. The other authors have nothing to declare.

References

1. Coccheri S, Orlando D (2013) New oral anticoagulants in atrial fibrillation: a reappraisal of trial results looking at absolute figures. Intern Emerg Med 8:115–122
2. Ten Cate H (2012) Monitoring new oral anticoagulants, managing thrombosis, or both? Thromb Haemost 107:803–805
3. Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S et al (2012) Peri-procedural bleeding and thromboembolic events with dabigatran compared to warfarin: results from the RE-LY Randomized Trial. Circulation 126:343–348
4. Southworth MR, Reichman ME, Unger EF (2013) Dabigatran and postmarketing reports of bleeding. New Engl J Med 368(14): 1272–1274
5. Tripodi A (2013) The laboratory and the new oral anticoagulants. Clin Chem 59:2353–2362
6. Rohde G (2008) Determination of rivaroxaban—a novel, oral, direct factor Xa inhibitor—in human plasma by high-performance liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 872:43–50
7. Frost C, Wang J, Nepal S, Schuster A, Barrett YC, Mosqueda-Garcia R, Reeves RA, Lacreta F (2013) Apixaban, an oral, direct factor Xa inhibitor: single-dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br J Clin Pharmacol 75:476–487
8. Hillarp A, Baghaei F, Fagerberg Blixter I, Gustafsson KM, Stigendal L, Sten-Linder M, Strandberg K, Lindahl TL (2011) Effects of the oral, direct factor Xa inhibitor rivaroxaban on commonly used coagulation assays. J Thromb Haemost 9:133–139
9. Douxfils J, Mullier F, Robert S, Chatelain C, Chatelain B, Dogné JM (2012) Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. Thromb Haemost 107:985–997
10. Lindahl TL, Baghaei F, Blixter IF, Gustafsson KM, Stigendal L, Sten-Linder M, Strandberg K, Hillarp A (2011) Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. Thromb Haemost 105:371–378
11. Harenberg J, Marx S, Weiss C, Kramer R, Samama M, Schulman S (2012) Report of the Subcommittee of Control of Anticoagulation on the determination of the anticoagulant effects of rivaroxaban. J Thromb Haemost 10:1433–1436
12. Garcia D, Barrett YC, Ramacciotti E, Weitz JI (2013) Laboratory assessment of the anticoagulant effects of the next generation of oral anticoagulants. J Thromb Haemost 11:245–252
13. Helin TA, Pakkanen A, Lassila R, Joutsi-Korhonen L (2013) Laboratory assessment of novel oral anticoagulants: method suitability and variability between coagulation laboratories. Clin Chem (in press)

14. Samama MM, Céline G, Le Flem L (2012) Do new oral anticoagulants require laboratory monitoring? The clinician point of view. Thromb Res 130:S88–S89
15. Lee S, Mullin R, Blazawski J, Coleman CI (2012) Cost-effectiveness of apixaban compared with warfarin for stroke prevention in atrial fibrillation. PLoS One 7(10):e47473
16. Pletscher M, Plessow R, Eichler K, Wieser S (2013) Cost-effectiveness of dabigatran for stroke prevention in atrial fibrillation in Switzerland. Swiss Med Wkly 143:w13732
17. Di Minno MN, Russolillo A, Camera M, Parolari A, Tremoli E (2013) Direct anticoagulant drugs to overcome limitations of vitamin K antagonists. A critical appraisal of data in atrial fibrillation patients. Expert Opin Emerg Drugs 18(1):9–23
18. Liesenfeld KH, Lehr T, Dansirikul C et al (2011) Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. J Thromb Haemost 9:2168–2175
19. Mannucci PM (2013) Between scylla and charybdis: thromboprophylaxis in the oldest old with atrial fibrillation. Eur J Int Med (in press)
20. Di Minno G, Russolillo A, Gambacorta C, Prisco D (2013) Improving the use of direct oral anticoagulants in atrial fibrillation. Eur J Int Med (in press)