UMC Utrecht

Interference in lupus anticoagulant testing

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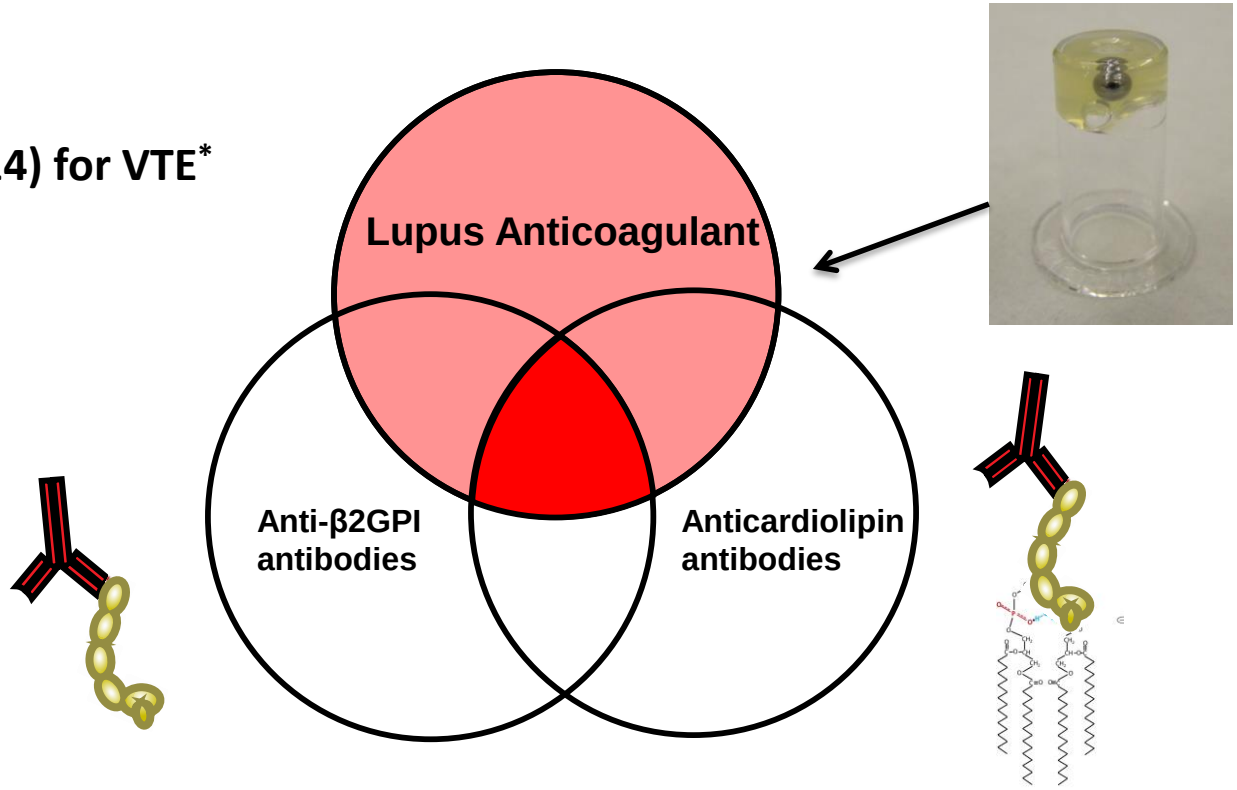
Disclosures for RT Urbanus

none

Antiphospholipid antibodies are risk factors for a first thrombotic event

HR: 3.9 (1.1-14) for VTE*

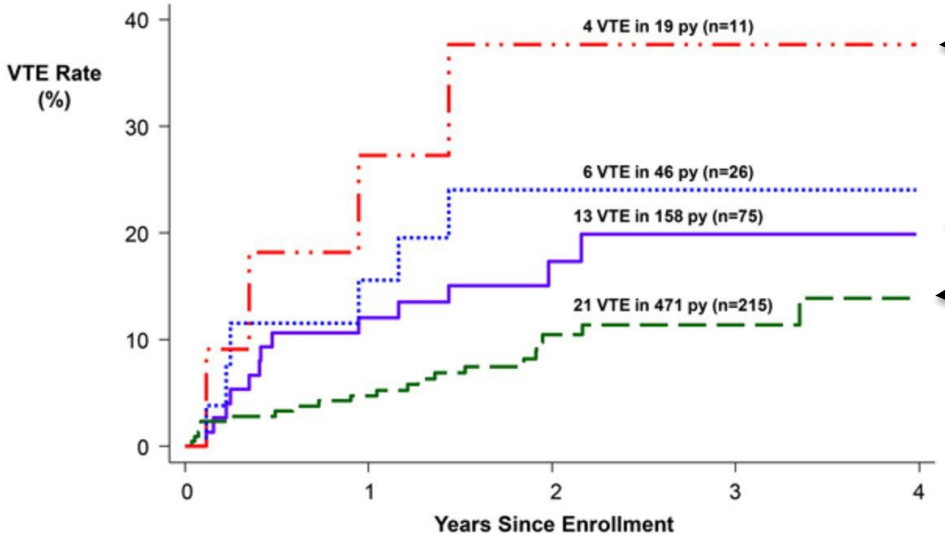


* Ruffatti et al. Ann Rheum Dis 2011;70:1083-1086

Miyakis et al. J Thromb Haemost 2006; 4:295-306

aPL are risk factors for recurrence as well

Recurrent VTE after stopping anticoagulants in unprovoked VTE patients with different APA findings



2 or more aPL HR 4.5 (95%-CI 1.5-13.0)

Any aPL HR 2.7 (95% CI, 1.1-6.7)

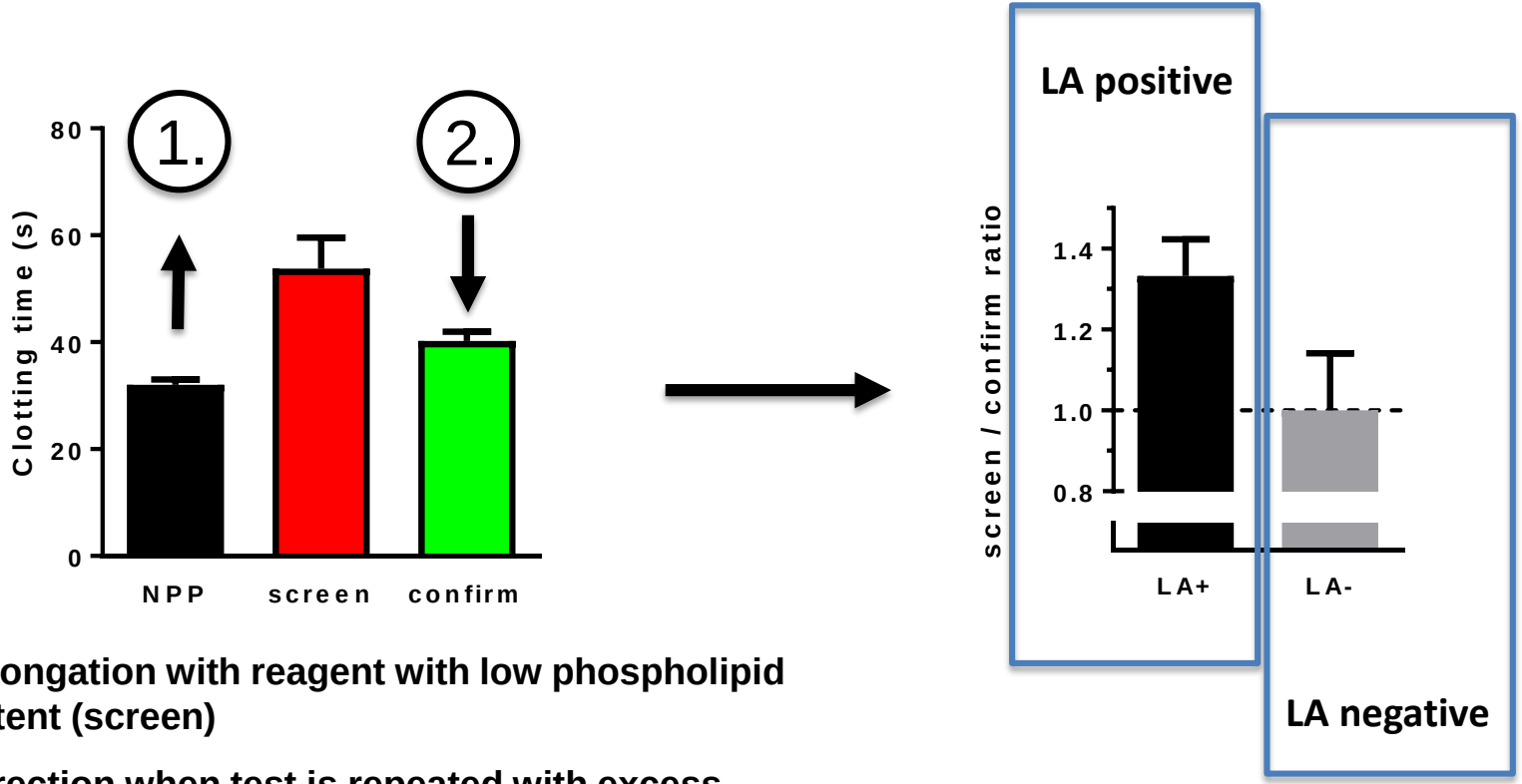
No aPL

79% of patients with aPL had LA

Increased risk of recurrent VTE in carriers of aPL after cessation of treatment

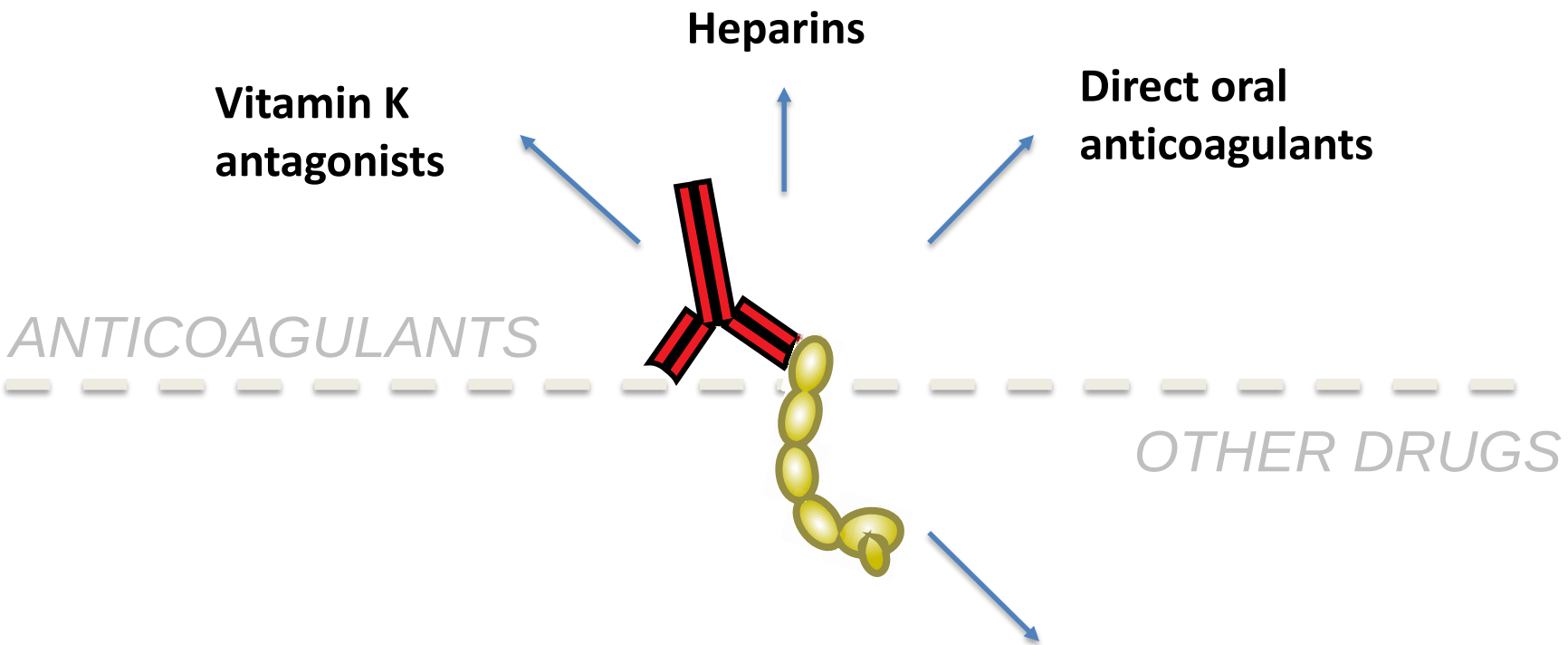
Kearon et al. Blood 2018; 131:2151-2160

LA – a phospholipid-dependent coagulation inhibitor



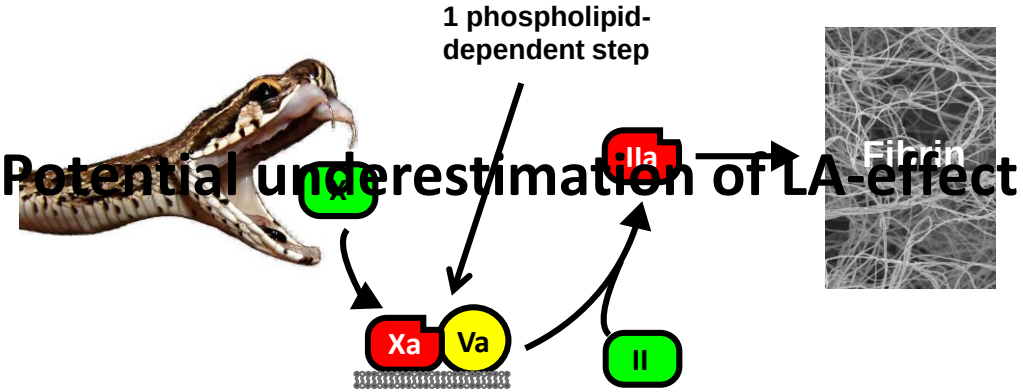
1. **Prolongation with reagent with low phospholipid content (screen)**
2. **Correction when test is repeated with excess phospholipid (confirm)**

Interference with lupus anticoagulant testing

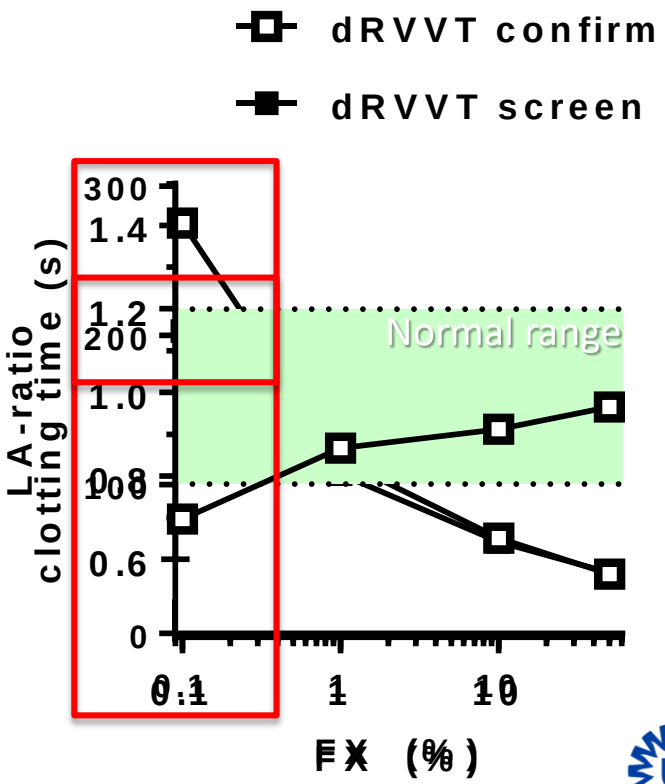


Rand et al. Blood. 2008;112:1687-95.

Phospholipid concentration modulates coagulation reactions



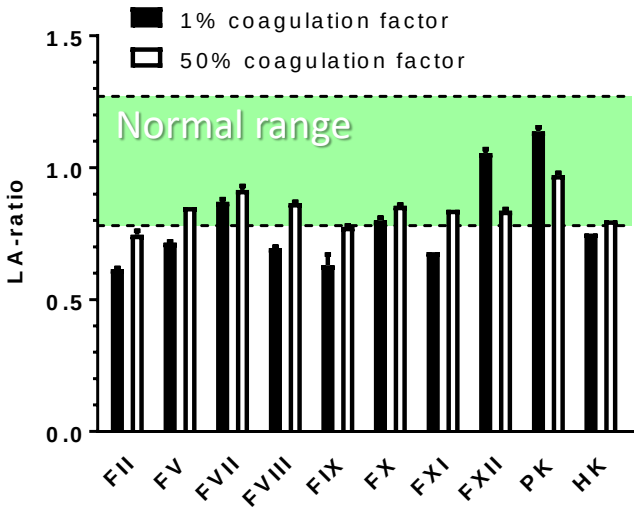
Potential underestimation of LA-effect



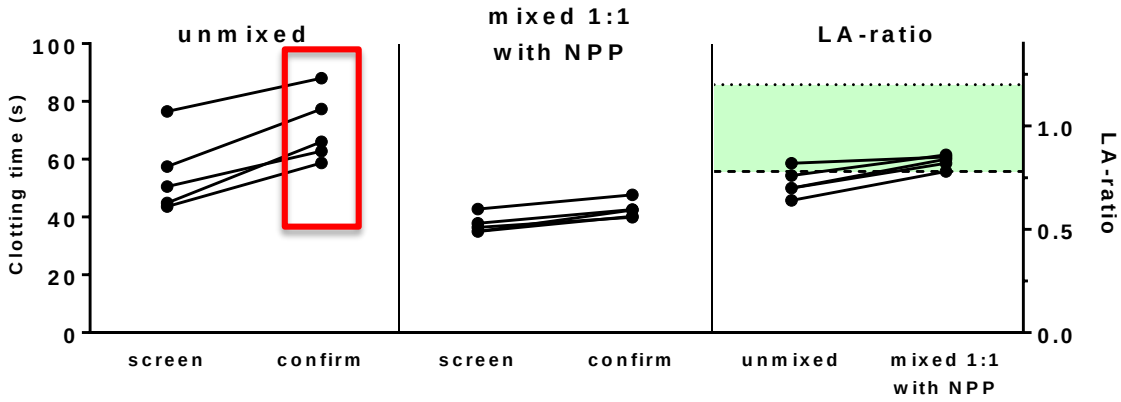
Pennings et al. Thromb Haemost. 2014;112:736-42

Mixing studies to correct factor deficiency in VKA samples

Silica clotting time



LA-ratio in LA negative samples on VKA

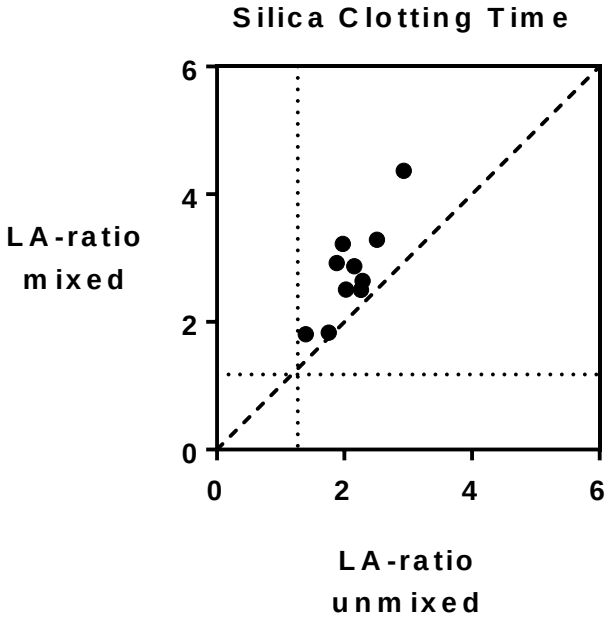


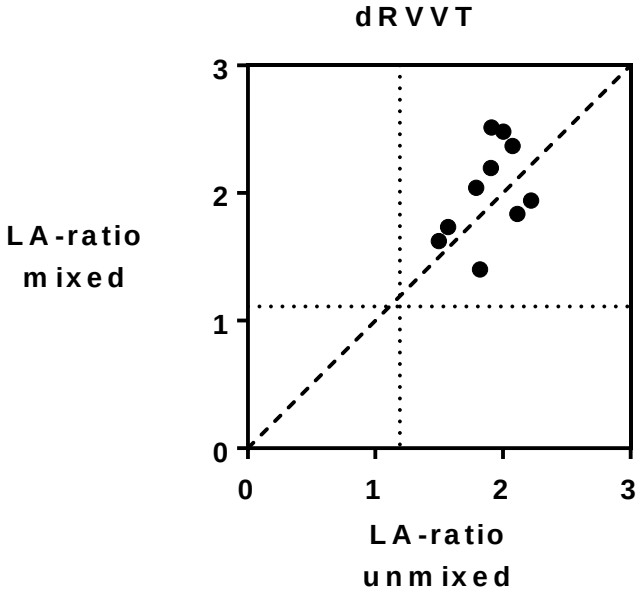
Effect more pronounced in confirm test, leading to underestimation of LA

Mixing with normal plasma corrects VKA effects

Pennings et al. Thromb Haemost. 2014;112:736-42

VKA: false negative LA





Underestimation of LA in samples with INR>2

Pennings et al. Thromb Haemost. 2014;112:736-42

VKA: false positive LA

BRIEF REPORT

Mixing studies in lupus anticoagulant testing are required at least in some type of samples

K. M. J. DEVREESE* and B. DE LAAT†‡

Patients receiving VKA treatment

Patients remaining LA positive after mixing test: 64/113

Direct oral anticoagulants and APS

Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial

Hannah Cohen, Beverley J Hunt, Maria Efthymiou, Deepa R J Arachchill
Maria L Bertolaccini, Maria Ruiz-Castellano, Nicola Muirhead, Caroline

Lancet Haematol. 2016;3: e426

Conclusions RAPS trial:

Rivaroxaban not non-inferior to VKA in low risk APS patients, but no events during (short term) follow-up

DOACs are rapidly becoming drug of choice for secondary thromboprophylaxis in VTE

CLINICAL TRIALS AND OBSERVATIONS

Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

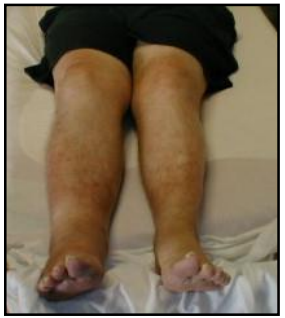
Vittorio Pengo,[1] Gentian Denas,[1] Giacomo Zoppellaro,[1] Seena Padayattil Jose,[1] Ariela Hoxha,[2] Amelia Ruffatti,[2] Laura Andreoli,[3] Angela Tincani,[3] Caterina Cenci,[4] Domenico Prisco,[4] Tiziana Fierro,[5] Paolo Gresele,[5] Arturo Cafolla,[6] Valeria De Micheli,[7] Angelo Ghirarduzzi,[8] Alberto Tosetto,[9] Anna Falanga,[10] Ida Martinelli,[11] Sophie Testa,[12] Doris Barcellona,[13] Maria Gerosa,[14] and Alessandra Banzato[1]

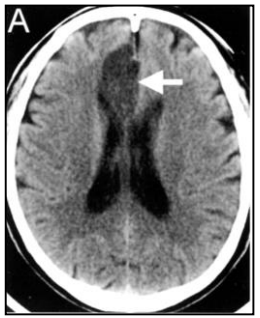
Blood. 2018; 132:1365-1371

TRAPS trial:

Trial terminated prematurely due to high number of thrombotic events in rivaroxaban users (n=7, 12%) compared with VKA users (0%)

First clinical manifestation of APS

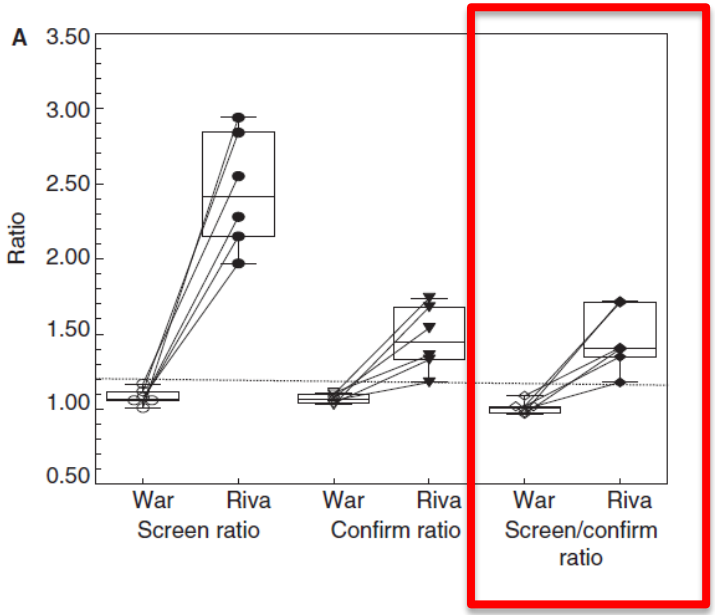




Manifestation at disease onset	% of patients
Venous thromboembolism *Deep vein thrombosis, pulmonary embolism*	46.7
Arterial thrombosis *stroke, myocardial infarction, TIA, amaurosis fugax*	25.6
Fetal loss	8.3

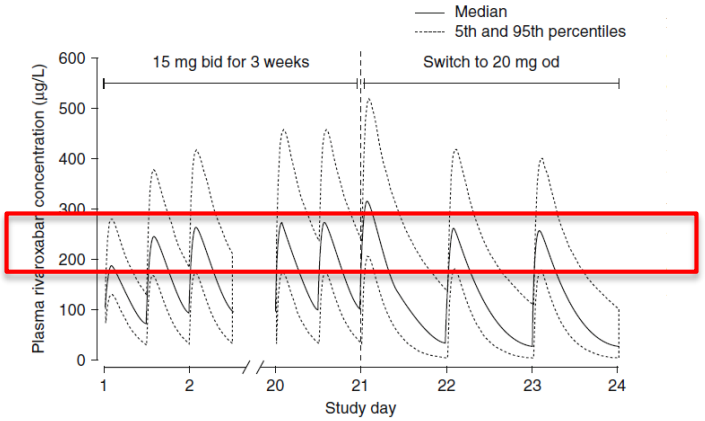
Cervera et al. Arthritis Rheum 2002; 46: 1019-27

Measurement of LA during DOAC treatment.



False positive LA

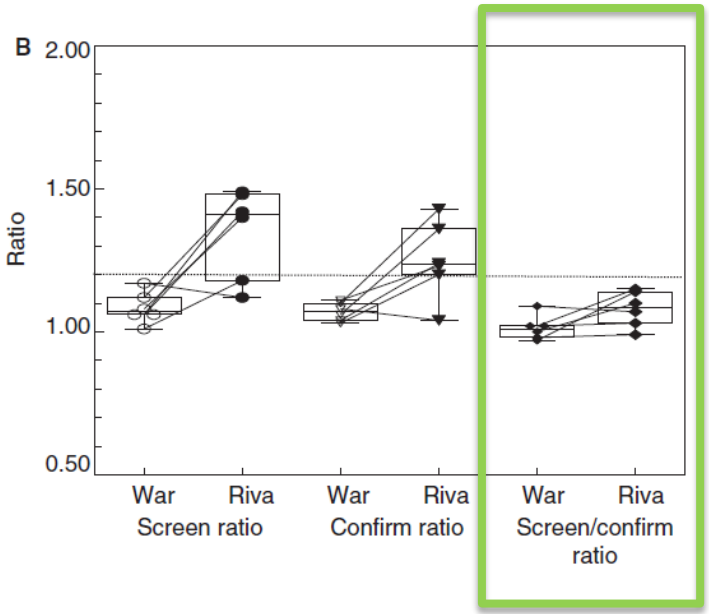
- **6 LA negative patients**
- **Baseline on Warfarin (war)**
- **At least 30 days on rivaroxaban (riva)**
- **Peak levels 240 µg/L, CI 165–270 µg/L**



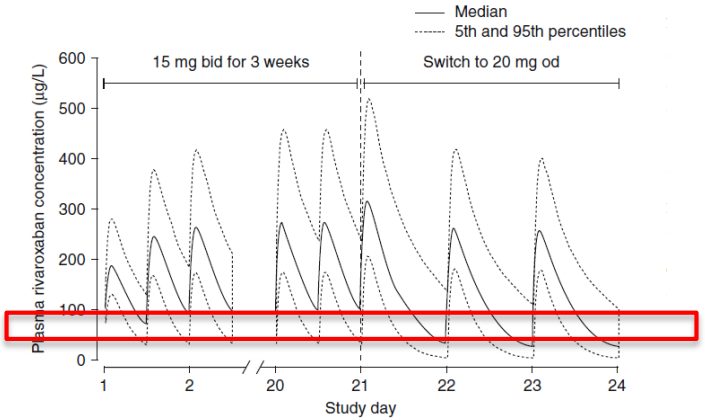
Arachchillage et al. J Thromb Haemost 2015; 13: 1264–73.

Mueck et al. Clin Pharmacokinet 2011; 50: 675-686

Measurements possible at trough levels?



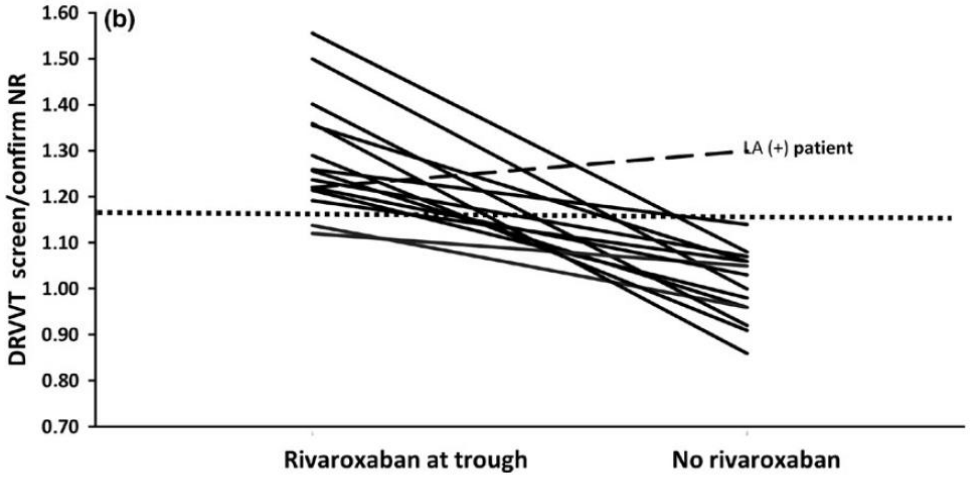
- 6 LA negative patients
- Baseline on Warfarin (war)
- At least 30 days on rivaroxaban (riva)
- Trough levels 55 µg/L, CI 36–80 µg/L



Arachchillage et al. J Thromb Haemost 2015; 13: 1264–73.

Mueck et al. Clin Pharmacokinet 2011; 50: 675-686

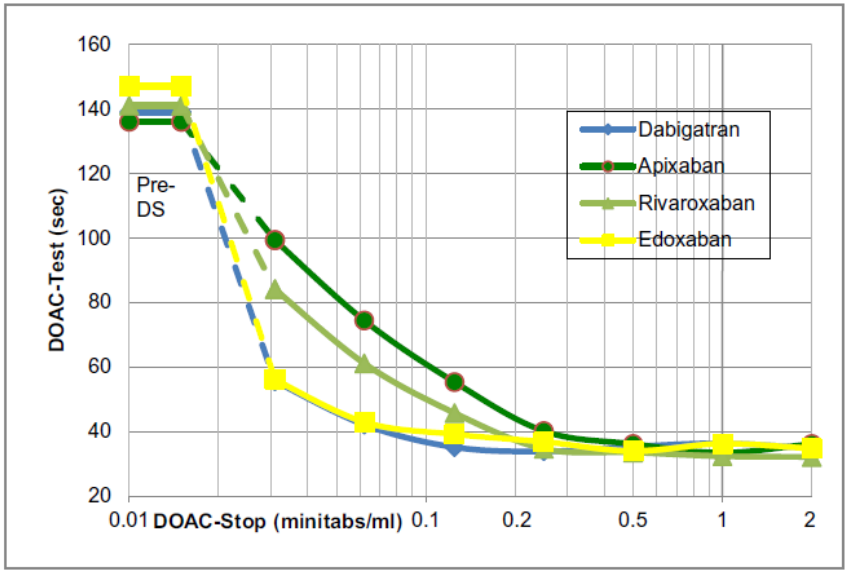
However, false positive LA are still reported at trough levels



16 patients, 1 LA positive

Martinuzzo et al. Int J Lab Hem. 2018;40:e99–e101

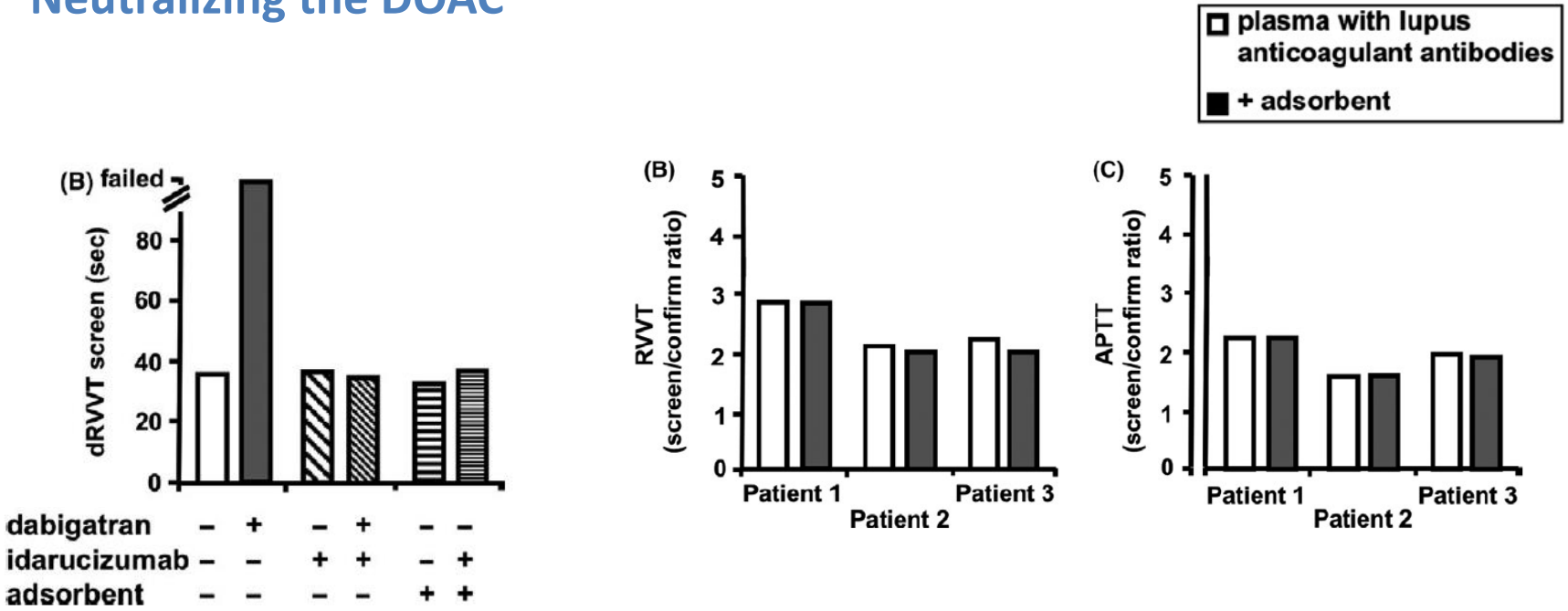
Adsorption of DOAC from samples



DOAC-STOP, Haematex

Exner et al. Thromb Res. 2018;63:117–122

Neutralizing the DOAC

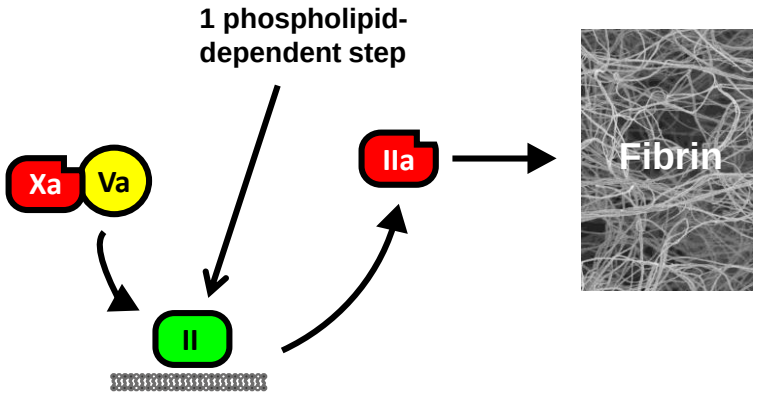


Needs evaluation in larger cohorts

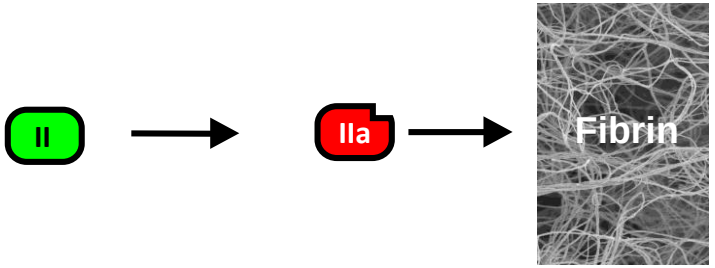
Jacquemin et al. Int J Lab Hem. 2018;40:442–447.

Alternative assays: TSVT / Ecarin time ratio

Taipan snake venom time



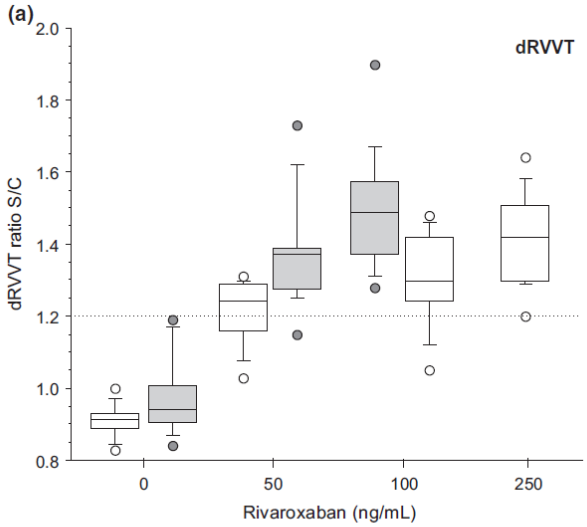
Ecarin time

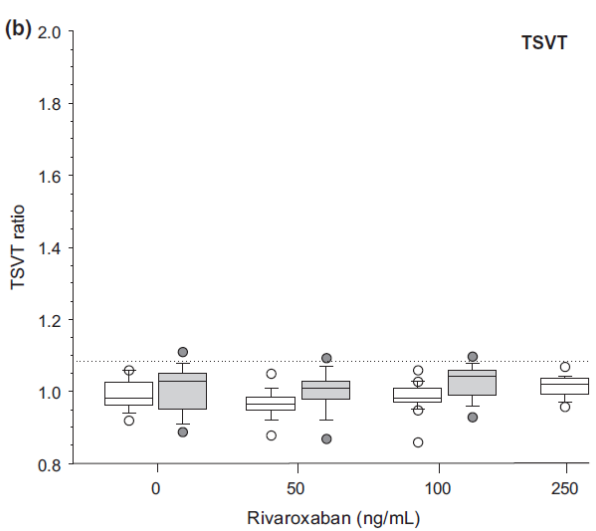


TSVT-Xa component insensitive to direct Xa-inhibitors

No false positive LA with rivaroxaban

Detection of lupus anticoagulant in the presence of rivaroxaban using Taipan snake venom time





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ersity Medical Center,
e Netherlands

Larger studies are needed to confirm the applicability of the TSVT/ET ratio

Pouplard et al. Int J Lab Hematol. 2017;39:e60-e63.

In conclusion

- Anticoagulant treatment interferes with LA detection
- Use samples collected prior to start anticoagulation treatment, or sufficiently long after cessation of treatment for LA assessment
- Effects of VKA can be corrected by mixing sample 1:1 with normal plasma, but interpretation is difficult when INR > 3.
- No solutions for LA assessment in samples containing DOACs yet, but promising alternatives are under investigation