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Efficacy of direct oral anticoagulants in plasma from patients with liver cirrhosis at high thrombotic risk

M.G. ZERMATTEN[1], M. FRAGA[2], D. BERTAGGIA CALDERARA[1], A. ALIOTTA[1], D. MORADPOUR[2] and L. ALBERIO[1]

[1]Division of Hematology and Central Hematology Laboratory and [2]Division of Gastroenterology and Hepatology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

canton de vaud | CHUV Centre hospitalier universitaire vaudois | UNIL | Université de Lausanne

HEMOSTASIS & PLATELET Research Laboratory Lausanne University Hospital

BACKGROUND AND OBJECTIVES

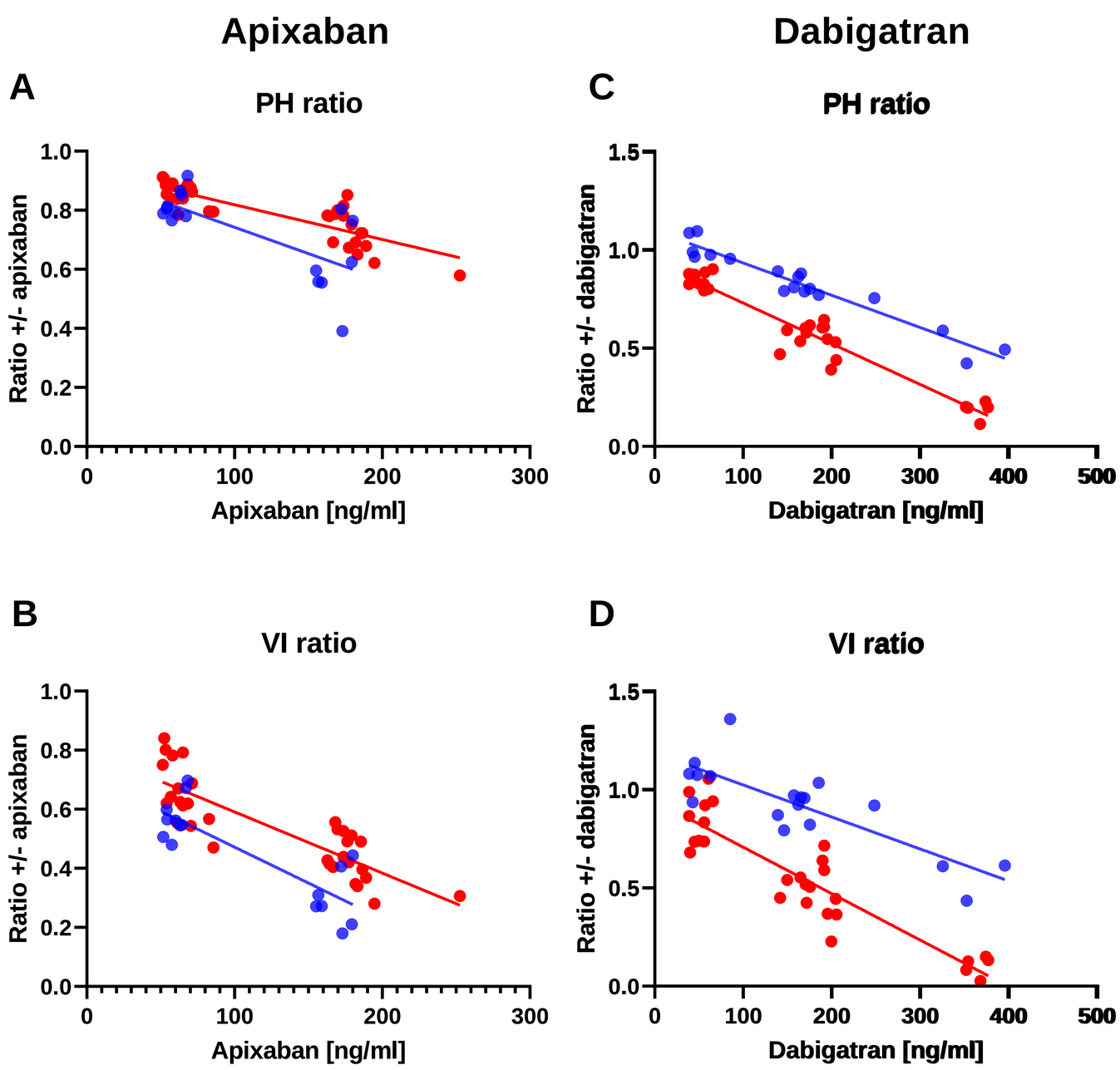
- Liver cirrhosis (LC) is a complex pathology which confers a prothrombotic state.
- The anticoagulation of LC-patients remains challenging because of the unknown efficacy of heparins and direct oral anticoagulants (DOACs), monitoring difficulty (particularly for coumarins), and alterations in drug metabolism.
- Among DOACs, apixaban and dabigatran seem to have the most adequate metabolic profile for LC-patients [Clin Pharmacokinet. 2013;52(4):243].
- We aimed to analyse the *in vitro* efficacy of these two anticoagulants in LC-patients at high thrombotic risk.

CONCLUSIONS

- Apixaban showed a slightly lower anticoagulant efficacy in plasma of LC patients compared to plasma of healthy donors.
- Dabigatran showed a clearly higher efficacy in plasma of LC patients compared to plasma of healthy donors.
- **Based on DOAC's metabolism and on these preliminary data showing a discordant anticoagulant effect of dabigatran versus apixaban in LC plasma, the latter appears to be the safest DOAC for LC-patients.**

RESULTS

At a target concentration of 150 ng/ml (representing peak level), in apixaban treated samples, the peak height (PH) ratio (Fig. A) (median 0.74 vs. 0.60, p-value 0.03) and the velocity index (VI) ratio (Fig. B) (0.42 vs. 0.27, p-value 0.008) were significantly higher in plasma of LC patients compared to plasma of healthy donors.



With dabigatran at the same target concentration of 150 ng/ml (representing peak level), both the peak height (PH) (Fig. C) and velocity index (VI) (Fig. D) ratios were significantly lower (0.58 vs. 0.80, p-value <0.0001; 0.51 vs. 0.94, p-value <0.0001) in plasma of LC patients compared to plasma of healthy donors.

Ratios for velocity index and peak height according to apixaban (A, B) and dabigatran (C, D) concentrations in patients with liver cirrhosis (red) and healthy donors (blue). The lines represent the linear regression lines. PH, peak height; VI, velocity index.

METHODS

We included 22 LC-patients identified as prothrombotic using *ex vivo* thrombin generation (ST Genesia with ThromboScreen reagents, Stago, Asnières-sur-Seine, France) and nine healthy donors. Plasma samples were spiked with either Owren's veronal buffer, apixaban, or dabigatran solutions (final target concentrations: 50, 150 ng/ml; additional concentration of 300 ng/ml for dabigatran). Concentrations were chosen according to the peaks and through levels observed in clinical studies of a therapeutic anticoagulation with both drugs. After spiking, apixaban and dabigatran concentrations were verified and *ex vivo* thrombin generation were analysed using ST Genesia with DrugScreen reagents (Stago). Ratios for velocity index and peak height assessed without and with anticoagulants were calculated, and compared between LC-patients and healthy donors for each target concentration using Mann-Whitney test.

CONTACT INFORMATION

Dr. med. Maxime G. Zermatten
maxime.zermatten@chuv.ch

Prof. Dr. med. Lorenzo Alberio
lorenzo.alberio@chuv.ch

Haemostasis and Platelet Research Laboratory
Division and Central Laboratory of Hematology / CHUV
Rue du Bugnon 27 SUD, CH-1011 Lausanne

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