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Evaluation of the dissertation

Title: Differences in hemocoagulation in patients with metabolic disorders
PhD Candidate: Jaka Fadraersada, M.Sc.
Supervisor: Prof. Přemysl Mladěnka, Pharm.D., Ph.D.
Consultant: Alejandro Carazo, Pharm.D., Ph.D.

Evaluation:

This study provides a comprehensive examination of the pharmacodynamic effects of direct oral anticoagulants (DOACs) in patients with metabolic disorders, such as familial hypercholesterolemia (FH) and type 1 diabetes mellitus (DMT1).

Mr. Jaka Fadraersada compared four DOACs, rivaroxaban, apixaban, dabigatran, and argatroban, in healthy individuals and patients, using ex vivo tests to determine their effects on coagulation parameters (PT/INR and aPTT). He also investigated the potential influence of anthropological and biochemical parameters like body mass index (BMI) and lipid levels, as well as the role of vitamin K in patients with metabolic diseases. The findings suggest that metabolic conditions may influence the efficacy of anticoagulation treatment.

The candidate published 5 papers related to the topics of his Ph.D. thesis. He is first author on one paper and co-author on the others. In the co-authorship papers the candidate clearly stated his contribution, that significantly contributed to his publications. Furthermore Mr. Jaka Fadraersada published two more papers with no direct relation to the topic of the thesis.

Strengths

1. Focus on Metabolic Disorders: The Ph.D. thesis addresses an important clinical issue how metabolic disorders like FH and DMT1 affect the coagulation process, and by extension, the efficacy of DOACs. The findings have significant implications for the management of thrombotic risks in patients with these conditions, particularly as metabolic diseases are highly prevalent.

2. Comparison of DOACs: The comparison of four clinically used DOACs offers valuable insights into the pharmacodynamics of these drugs, especially regarding their efficacy in different patient populations. The thesis revealed that rivaroxaban was the most active among the Factor Xa inhibitors, while dabigatran exhibited the highest activity among direct thrombin inhibitors (DTIs), a finding that aligns with some clinical outcomes.

3. Novel Insights on Vitamin K: The thesis provides novel insights into the role of vitamin K in patients with DMT1, highlighting lower levels of vitamin K in these patients, which may contribute to the observed differences in coagulation. This aspect of the thesis has potential clinical relevance for anticoagulation therapy in populations with metabolic disorders.

4. Use of Ex Vivo Methodology: The ex vivo approach, while having certain limitations (discussed below), allows for a controlled analysis of how different DOACs affect blood samples from diverse patient groups without the confounding variables that exist in *in vivo* studies. The chosen concentration of 1 μM was clinically relevant, allowing pharmacodynamic comparisons.

Weaknesses and Limitations

1. Ex Vivo Study Design: While the *ex vivo* design enabled control over certain variables, it lacks the complexity of *in vivo* conditions. Drug metabolism, absorption, distribution, and the body's physiological responses, particularly in patients with varying BMIs or lipid levels, were not accounted for. The candidate acknowledges this limitation.

2. Limited Scope of Inflammatory Markers: The study did not evaluate inflammatory markers, despite acknowledging that obesity and metabolic disorders are often accompanied by low-grade inflammation, which could significantly impact coagulation and the efficacy of anticoagulants. Future studies incorporating these factors would offer more insights.

3. Vitamin K Analysis Constraints: Although the study highlights the importance of vitamin K, it was limited by the inability to detect all vitamin K2 forms, particularly MK-9, due to the lack of standards. As vitamin K plays a key role in the synthesis of several coagulation factors, a more comprehensive analysis of its subtypes would have strengthened the conclusions of the thesis.

4. Study Population and FH Representation: The number of severe FH cases is relatively low considering that FH is underdiagnosed in clinical practice. The candidate notes that broader participation from other centers could have enhanced the statistical power and representation of this patient population.

5. Lack of Tailored Anticoagulant Therapy Evaluation: Although the thesis discusses the potential need for tailored anticoagulant therapy based on individual patient factors like BMI and lipid levels, it does not explore this in detail. A more detailed exploration of personalized anticoagulation strategies would have been a valuable addition to the thesis.

Mr. Jaka Fadraersada correctly identifies several areas for future research, including the need for *in vivo* studies to validate his *ex vivo* findings. The inclusion of inflammatory markers in future analyses is crucial to understanding how low-grade inflammation in obesity and other metabolic conditions affects the coagulation process.

In summary, this Ph.D. thesis offers valuable insights into the effects of DOACs in patients with metabolic diseases, demonstrating that metabolic conditions like FH and DMT1 can influence the efficacy of anticoagulant therapy. Future studies that incorporate *in vivo* methodologies, personalized therapy evaluations, and a more comprehensive analysis of vitamin K and inflammatory factors will be essential for fully understanding and optimizing anticoagulant therapy in patients with metabolic disorders.

In conclusion, the technical quality of Mr. Jaka Fadraersada's PhD thesis is of a high standard and its scientific contributions are outstanding. I strongly recommend the acceptance of this dissertation as the basis for awarding the candidate the Ph.D. title.

Vienna, October 1, 2024