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LETTER TO THE EDITOR

Response to paper by Douxfils *et al.* Oestradiol is not the Holy Grail in the quest for the ideal oestrogen therapy

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We express our deep thanks to all distinguished colleagues for their careful reading of our paper (Menopause Rev 2022; 21: 197-199) and for writing their thoughtful and valuable commentary (Menopause Rev 2023; 22: 117-119). We would like to take this opportunity to address some of the issues they have raised.

The aim of our paper was to present the most recently published clinical data on the safety profile of oral oestrogen-progestogen hormone therapies with respect to the venous system provided by studies conducted in standard real-world clinical practice. We did not address in our paper estetrol-containing drugs simply because no such studies exist, and the presentation and detailed discussion of basic science findings was out of our paper's scope. The end-point of both studies discussed by us was exclusively the thromboembolism risk measured by epidemiological and not biochemical parameters. These clinical data, for obvious reasons, cannot be directly confronted with pharmacodynamic (PD) or pharmacokinetic (PK) findings. We fully agree with Douxfils *et al.* in their statement that PD and PK characteristics of estetrol, especially with regard to activated protein C resistance, are very promising, although the clinical relevance of these findings remains to be confirmed by clinical studies using randomized controlled trials or real-world evidence methodology. We are awaiting with great interest the results of such studies.

According to the brilliant remark of our distinguished colleagues addressing the famous biblical relic, we would like to express our firm conviction that the chase for the Holy Grail in the quest for the ideal oestrogen therapy will never end because you cannot search for something that does not exist.

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