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Response to Comment on: "Carbon footprint of direct oral anticoagulants in atrial fibrillation and venous thromboembolism"

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VM: Conceptualization, investigation, writing – original draft writing – review and editing.

Both authors contributed to the scientific discussion and interpretation of the literature, critically revised the manuscript, and approved the final version.

We thank the correspondents for their thoughtful comment[1] on our recent study quantifying the carbon footprint of direct oral anticoagulants (DOACs) in atrial fibrillation and venous thromboembolism (VTE)[2]. We fully agree with their central message: comparing environmental estimates requires aligned functional units and system boundaries, and transparency is what makes such comparisons scientifically defensible.

Their hemophilia example illustrates a general principle that applies to the entire thrombosis and haemostasis community, and particularly to anticoagulants, its most widely prescribed drug class. Indeed, anticoagulation provides a strong case study of an environmental incorporation into therapeutic decision, when clinical equipoise between agents offers opportunity for environmental optimization. As authors suggested, this approach could be extended to other areas of haemostasis, such as recombinant factor VIII, but also into laboratory-intensive diagnostics, blood products, haemostatic therapies, or complex interventional procedures. Our observations with oral anticoagulants, aligns with recent consensus statement to promote lower-carbon strategies maintaining clinical excellence. Once efficacy and safety are ensured, clinicians may consider the environmental efficiency of medical interventions without compromising quality of care[3]. However, as highlighted by the correspondents, therapeutic decisions should consider the entire care pathway to meaningfully affect environmental impact: from optimizing complications (bleeding and recurrent thrombosis), reducing rehospitalizations (i.e. perioperative management), as well as minimizing biological monitoring. Therefore, a sustainable anticoagulation should not be considered independently of clinical effectiveness, patient safety, resource availability and access to care.

We would like to push the argument one step further, from transparency of estimates to action within anticoagulation care. Methodological heterogeneity should not become a reason for inac-

tion. The observation from the correspondent that our two estimation tools (Ecovamed and the MCF Classifier) yielded divergent results for the same DOAC, and converged once boundaries were harmonized, is important. We reported both estimates to ensure the reproducibility of our conclusions and let clinicians appreciate their discrepancy. This is why we disclosed our functional unit (one treatment course per patient), our boundaries, and the emission categories included, so that other groups can reproduce, challenge, or extend our calculations. Compared to MCF, Ecovamed used a Life Cycle Assessment (LCA) methodology measuring medicine carbon footprint from its manufacturing to direct-to-consumer delivery. Notably, it encompasses the carbon footprint of corporate activities, defined as all activities not directly related to the manufacturing and transport of the medicine (research, development, sales, marketing, regulatory affairs, general administration, etc.)[4]. Indeed, one of our main findings was that corporate activities accounted for 70% of the total footprint of apixaban and rivaroxaban. Thus, with the development of generic drugs in the coming years (already available in Europe), we hope that the global carbon footprint of DOACs will substantially decrease. Still, the entire anticoagulation lifecycle, from manufacturing, laboratory diagnostics, therapeutic monitoring, complication management, and long-term follow-up, is associated with CO_2 emissions. Interestingly, a UK single-centre study showed that the switch from warfarin to DOACs reduced the carbon footprint of the elective direct current cardioversion care pathway[5]. Also, reduced-dose DOACs are emerging strategies after an initial 6 months of full-dose anticoagulation, in patients with cancer-associated thrombosis or at high risk of recurrence[6,7] and our observations support the ecological effectiveness of such reduced-dose regimens. Using the Ecovamed database, dose reduction was associated with modest reductions in carbon footprint, from 3.9% to 6.4% at 10 years, a difference that is possibly underestimated, since reduced dosing may also prevent bleeding events and the care they require[2,8]. However, further studies should evaluate the additional reduction in the carbon

footprint of reduced-dose DOACs, in terms of fewer bleeding events. LCA in England reported an estimate of 7.56 kg CO_2-equivalent per red cell unit transfused[9], mostly generated by transportation and refrigeration.

We think that larger environmental gains in anticoagulation also require eliminating low-value care. Unnecessary coagulation testing in patients on DOACs, whose results cannot be interpreted and may mislead clinicians; non-recommended periprocedural interruptions or bridging; or parenteral therapy (heparins, fondaparinux) continuation despite oral alternative, are all actionable targets, irrespective of which LCA database one uses. We also share their skepticism toward equating fewer administrations with lower impact. The administration step is a minor contributor to the footprint of DOACs. Indeed, in our analysis, apixaban twice daily yielded to similar findings than rivaroxaban once daily whereas the active substance dominates. Conversely, despite long-acting effect observed with some injectable therapies, patient transportation and hospital visits represent additional ecological expense.

Recently, Lana Roberts et al. challenged the routine use of elastic stockings, or antiembolism stockings, in contemporary VTE prevention[10]. Although inexpensive individually, their widespread use represents over £63 million annually in England, for surgical patients alone. The authors also highlighted their environmental impact. They are typically made from non-recyclable synthetic materials, and contamination with body fluids often requires disposal through clinical waste streams, including incineration, adding to the healthcare carbon footprint.

We therefore support the correspondents' call for reporting requirements in sustainable healthcare research: functional unit, system boundaries, emission categories, allocation rules, and reference year. In the thrombosis and haemostasis field, including haemophilia, where many

drugs with different mechanisms of action have been developed over the last 10 years, manufacturers should publish manufacturing emissions per commercial presentation, not only per molecule, since real-world dosing and packaging combinations contributes to the measurable footprint of a treatment course. Beyond anticoagulation, sustainability must extend to bleeding disorders and the broader therapeutic landscape of haemostasis, as well as laboratory-intensive burden, where diagnosis, treatment monitoring, and follow-up often require repeated testing. Haemophilia care increasingly relies on complex and expensive recombinant factor concentrates, extended-half-life products, non-factor therapies, and gene therapy. These innovations have transformed clinical outcomes, but they introduce complex manufacturing, storage, distribution, and administration pathways, and must be carefully weighted with the expected benefit, issued from robust evidence of randomized controlled trials.

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