

Carbon footprint of direct oral anticoagulants in atrial fibrillation and venous thromboembolism

Anticoagulant therapies are used for the treatment and the prevention of venous thromboembolism (VTE) and stroke or systemic embolic events in atrial fibrillation (AF). Direct oral anticoagulants (DOAC) are now recommended by all major scientific guidelines as a first line therapy.^{1,2} DOAC including dabigatran, which inhibits thrombin; rivaroxaban, apixaban and edoxaban which inhibit factor Xa (FXa), are now widely used for oral anticoagulation due to their ease of administration, favorable pharmacological and safety profiles, and the absence of need for biological monitoring.³ DOAC, and in particular apixaban, are among the most prescribed drugs worldwide. DOAC have shown similar clinical efficacy and risk profiles in phase III trials in both VTE and AF indications.^{4,5} However, no randomized prospective trial has directly compared one DOAC with another and therefore a head-to-head comparison is not yet available. Available evidence is limited to registry-based studies, healthcare claims databases, and meta-analyses extrapolating data from trials using warfarin as a comparator and, confirms an overall reduced risk of bleeding but suggests an increased risk of bleeding with rivaroxaban compared with apixaban.⁶⁻⁹ In the absence of robust evidence-based superiority, international guidelines do not recommend one specific DOAC over another neither for AF nor for VTE. As a result, treatment choice depends largely on cost, dosing frequency (once-daily vs. twice-daily regimen), and physicians preferences, explaining national and international discrepancies in prescribing. In AF, patients usually receive lifelong treatment whereas in VTE, patients are usually treated for 3 to 6 months, or with long-term or indefinite anticoagulation in some cases of unprovoked VTE at high risk of recurrence, or in the context of cancer-associated VTE.^{1,10} Reduced-dose DOAC are recommended in AF in the context of renal impairment, low body weight, older age, or drug-drug interactions and according to each drug.² For VTE, recently, two randomized multicentric trials demonstrated the benefit of reduced-dose oral FXa inhibitors compared with standard-dose therapy after at least 6 months of full-dose anticoagulation, both in patients at high risk of recurrence and in those with cancer-associated thrombosis.^{11,12} Recently, Fan Bingwen *et al.*,¹³ in an international collaborative viewpoint, highlighted the importance of incorporating sustainability into anticoagulation care, aligning clinical excellence with climate responsibility, and suggested transitioning to lower-carbon anticoagulants. Given the near equivalence in efficacy and safety, and to provide an environmental perspective in treatment selection, the objective of this study was to compare greenhouse gas (GHG) emissions of three DOAC (dabigatran, apixaban and rivaroxaban) for use in VTE and AF, analyzed per molecule and per indication. The

second objective was to compare the GHG emissions of reduced dose in the context of extended VTE treatment. For each DOAC, we calculated GHG emissions in carbon dioxide equivalents (CO₂eq) using procurement data and published CO₂eq values from the latest life cycle assessments (LCA) available. Evaluated treatment durations included 1 year for AF and 6 months to 10 years for VTE, based on standard dosing regimens. Carbon footprint data were retrieved from two databases, respectively: Ecovamed (France, accessed April 17, 2025 and previously described here¹⁴) and Medicines Carbon Footprint (MCF) Classifier (UK, accessed March 13, 2025 and previously described here¹⁵). No human or animal data were used. Ethics approval was not required, and all procedures adhered to national ethical standards. Continuous data were expressed as median and range (min–max) according to methods of calculation. Descriptive analyses were performed using Prism (version 10.0; GraphPad). After extracting the estimation of carbon footprint data of DOAC regimens from the Ecovamed and MCF Classifier databases, we calculated the carbon footprint for each daily dose of rivaroxaban, apixaban, and dabigatran (Table 1). We

Table 1. Daily carbon footprint of direct oral anticoagulant regimens using Ecovamed and Medicine Carbon Footprint Classifier databases.

Direct oral anticoagulant	Dose mg	Dosing regimen	Indication	Daily carbon footprint (g CO ₂ eq)	
				Ecovamed	MCF classifier
Apixaban	10	BID	VTE	201.6	16.0
Apixaban	5	BID	AF & VTE	100.8	8.0
Apixaban	2.5	BID	AF & VTE	96.6	5.5
Rivaroxaban	20	OD	AF & VTE	92.3	16.9
Rivaroxaban	15	OD	AF	88.8	13.0
Rivaroxaban	15	BID	VTE	177.6	26.0
Rivaroxaban	10	OD	VTE	86.1	9.2
Dabigatran	150	BID	AF & VTE*	338.8	290.8
Dabigatran	110	BID	AF & VTE*	273.8	214.0

Median daily carbon footprint (g CO₂eq) of direct oral anticoagulant (DOAC) regimens according to the Ecovamed and Medicine Carbon Footprint (MCF) Classifier databases. *For the treatment of venous thromboembolism (VTE), dabigatran requires an initial 5 to 10 days of parenteral anticoagulation, the carbon footprint of which is not included here; calculations are based on atrial fibrillation (AF) treatment. BID: twice daily; OD: once daily; g CO₂e: grams of carbon dioxide equivalent.

observed differences in the total carbon footprint between the two databases, but a similar trend: a higher carbon footprint for dabigatran compared with apixaban and rivaroxaban, and a lower daily carbon footprint with reduced-dose regimens of each molecule. Using the Ecovamed database, we were able to analyze the partitioning of the carbon footprint of DOAC by emission source (Figure 1). We observed that, for oral FXa inhibitors, about 70% of emissions originated from corporate activities, compared with 22.0% for dabigatran. Regarding emissions from the active pharmaceutical ingredient (API), these accounted for 67.4% for dabigatran, *versus* 10.2% for rivaroxaban and 5.5% for apixaban. In terms of manufacturing, emissions represented 18.5% for apixaban, compared with 9.9% for rivaroxaban and 7.2% for dabigatran. Partitioning of the carbon footprint was not available in the MCF due to the method. Next, we analyzed the carbon footprint of DOAC for 1 year of treatment in AF. According to the Ecovamed database, the median carbon footprints per year at standard dose of rivaroxaban, apixaban, and dabigatran were 33.7 kg CO₂eq (range, 6.7–60.7), 36.8 kg CO₂eq (range, 10.3–63.3), and 123.7 kg CO₂eq (range, 74.2–173.2), respectively (Figure 2A). The median carbon footprints per year of the reduced-dose rivaroxaban, apixaban, and dabigatran were 32.4 kg CO₂eq (range, 5.5–59.3), 35.3 kg CO₂eq (range, 7.8–62.8), and 99.9 kg CO₂eq (range, 59.9–139.9), respectively. According to the MCF Classifier database, the median carbon footprints per year at standard dose were 6.2 kg CO₂eq (range, 3.5–8.9) for rivaroxaban, 2.9 kg CO₂eq (range, 1.9–3.9) for apixaban, and 106.1 kg CO₂eq (range, 69.0–143.2) for dabigatran, respectively (Figure 2B). The median carbon footprints per year of the reduced-dose rivaroxaban, apixaban, and dabigatran were 4.8 kg CO₂eq (range, 3.1–6.5), 2.0 kg CO₂eq (range, 1.3–2.7), and 78.1 kg CO₂eq (range, 50.8–105.4), respectively. Both databases showed no notable difference between the two oral anti-FXa inhibitors. However, dabigatran exhibited a significant environmental disadvantage, with carbon emissions 3 to 36 times higher than those of rivaroxaban or apixaban for 1 year of AF treatment. The large discrepancies between the

Ecovamed and MCF Classifier results, particularly for the two oral anti-FXa inhibitors, are explained by the different LCA system boundaries. Notably, the MCF Classifier does not include corporate activities (such as Research & Development, sales, marketing, administration, or regulatory processes). When both datasets are adjusted to the same boundaries, the results are consistent (Figure 2C). Next, we analyzed the carbon footprint of rivaroxaban and apixaban for the first 6 months of treatment for VTE. According to the Ecovamed database, the median carbon footprints of rivaroxaban was 18.4 kg CO₂eq (range, 3.4–33.4) and for apixaban was 18.8 kg CO₂eq (range, 5.3–32.3), respectively (Figure 2D). According to the MCF Classifier database, the median carbon footprints was 3.2 kg CO₂eq (range, 2.1–4.3) for rivaroxaban and 1.5 kg CO₂eq (range, 1.0–2.0) for apixaban, respectively (Figure 2E). The carbon footprint after 6 months of initial VTE treatment and over 6 months, 2, 5, and 10 years with both databases is shown in Figure 2F, G. After 1 year and 10 years of treatment, the use of reduced-dose rivaroxaban, following 6 months of initial therapy, reduced CO₂eq emission by 21.9% and 43.1% with the MCF Classifier, and by 3.1% and 6.4% with Ecovamed. After 1 year and 10 years of treatment the use of reduced-dose apixaban following 6 months of initial therapy, reduced CO₂eq emission by 15.0% and 29.1% with the MCF Classifier, and by 2.2% and 3.9% with Ecovamed.

In this study, we provide an environmental perspective based on GHG emissions to help guide clinicians in the choice between DOAC in both AF and VTE indication at equivalent doses. Using two methods, we observed that dabigatran has a clearly higher GHG impact compared with apixaban and rivaroxaban in both AF and VTE. The carbon footprint of dabigatran is mainly linked to the API, in contrast to other DOAC. Conversely, corporate activities account for approximately 70% of the total impact of oral FXa inhibitors. The GHG impact of apixaban and rivaroxaban appears to be similar across indications. Reduced-dose DOAC for extended VTE treatment decreases bleeding risk while maintaining similar efficacy in preventing recurrent events,^{11,12} thereby improving

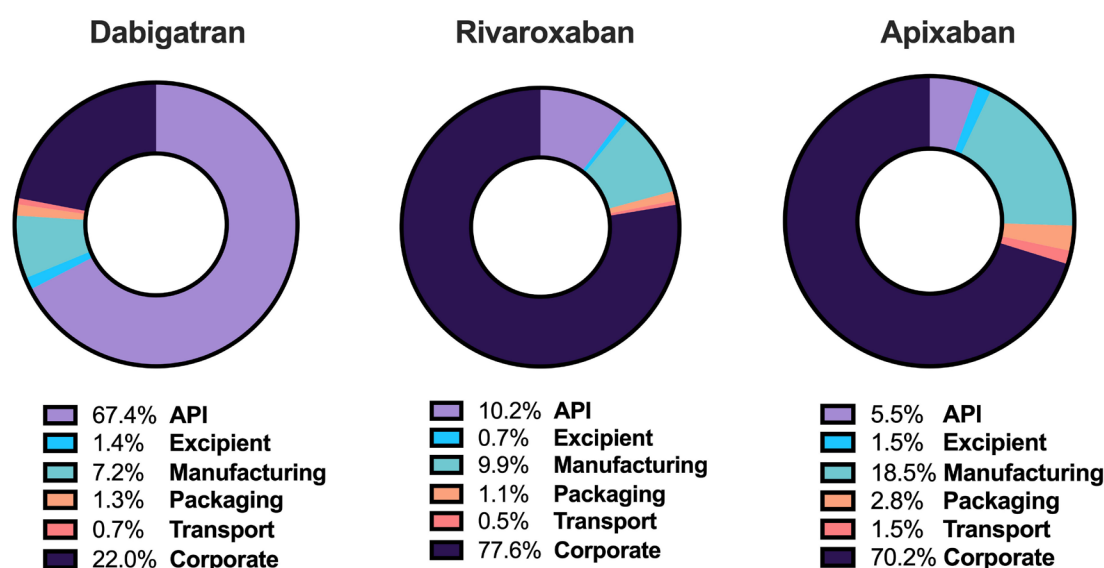


Figure 1. Distribution of the carbon footprint of direct oral anticoagulants by emission source (Ecovamed data). API: active pharmaceutical ingredient

the environmental impact. As expected, reduced-dose DOAC for extended treatment duration lowered the GHG emissions of each drug. GHG emissions were reduced by about 30%

when using the MCF Classifier and by around 3-5% with Ecovamed. The smaller reductions observed with Ecovamed, compared with MCF, are due to the high contribution of cor-

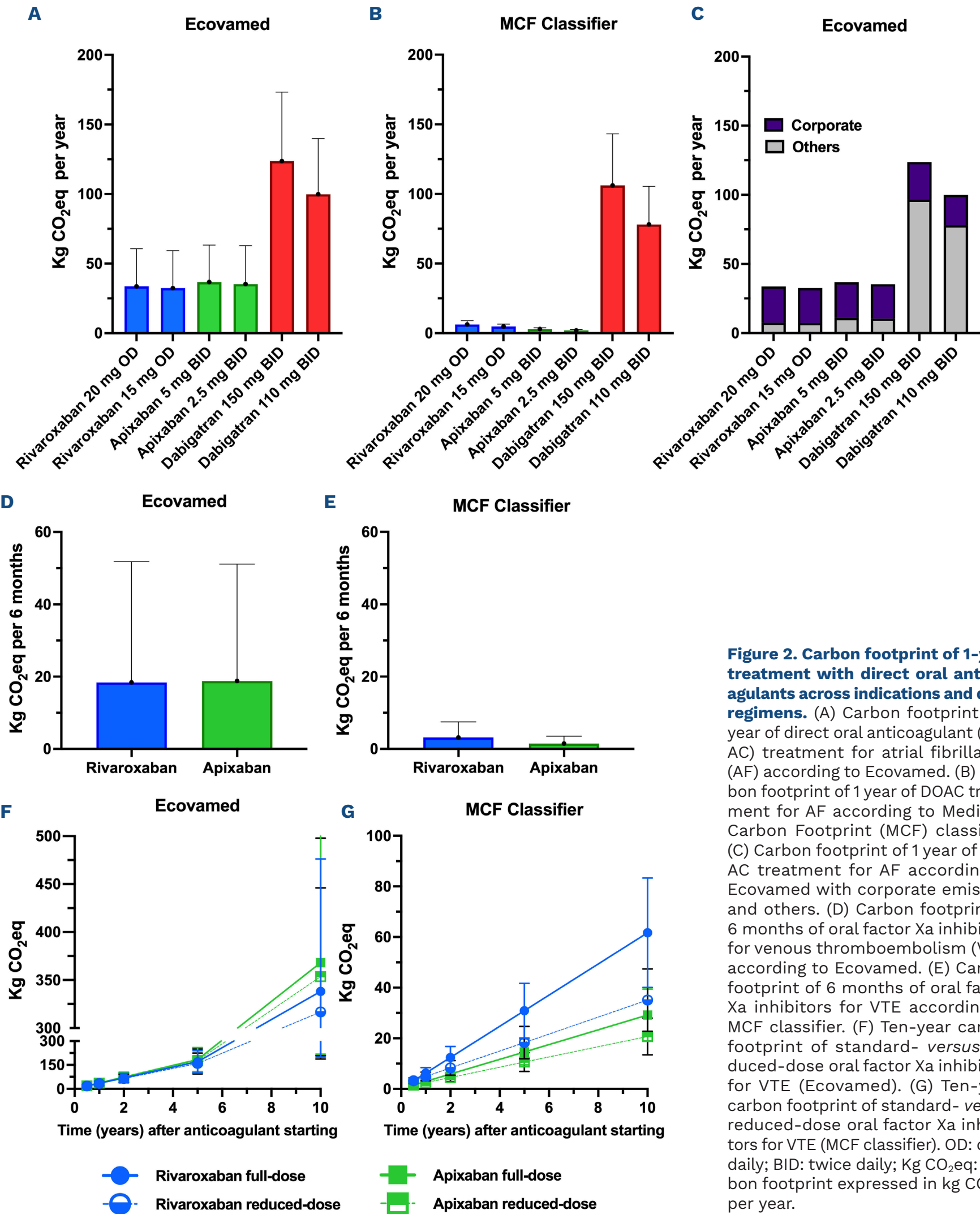


Figure 2. Carbon footprint of 1-year treatment with direct oral anticoagulants across indications and dose regimens. (A) Carbon footprint of 1 year of direct oral anticoagulant (DOAC) treatment for atrial fibrillation (AF) according to Ecovamed. (B) Carbon footprint of 1 year of DOAC treatment for AF according to Medicine Carbon Footprint (MCF) classifier. (C) Carbon footprint of 1 year of DOAC treatment for AF according to Ecovamed with corporate emission and others. (D) Carbon footprint of 6 months of oral factor Xa inhibitors for venous thromboembolism (VTE) according to Ecovamed. (E) Carbon footprint of 6 months of oral factor Xa inhibitors for VTE according to MCF classifier. (F) Ten-year carbon footprint of standard- versus reduced-dose oral factor Xa inhibitors for VTE (Ecovamed). (G) Ten-year carbon footprint of standard- versus reduced-dose oral factor Xa inhibitors for VTE (MCF classifier). OD: once daily; BID: twice daily; Kg CO₂eq: carbon footprint expressed in kg CO₂eq per year.

porate activities, which remain stable across doses, unlike API, excipients, and manufacturing, and are not reported in the MCF Classifier. Our results should encourage guidelines to promote low carbon footprint therapies (oral FXa inhibitors) in clinical decision making, encourage reduced-dose strategies when clinically indicated and encourage manufacturers to provide more transparency in their carbon footprint. To the best of our knowledge, this is the first study evaluating the carbon footprint of DOAC. We acknowledge some limitations. First, both methods are validated for DOAC prescriptions in France (Ecovamed) and in UK (MCF), which limits the applicability of our observations beyond Western Europe. Second, the carbon footprint values in the MCF Data Extract are modeled predictions rather than measured emissions using a cradle-to-gate carbon footprint assessment that follows the principles of ISO 14040-14044 and complies with the GHG Protocol. Third, our data do not include edoxaban, which is not available in France, nor account for the use of parenteral heparin therapy recommended for 5 days prior to dabigatran initiation in VTE.

Authors

Laurence Chery,^{1,2} Zahra Hassani,^{2,3} Lise Durand,^{2,4} Dorothée Boisseau,^{2,5} Victorien Monguillon,⁶ David Grimaldi,⁷ Sebastien Taillemite,⁸ Benjamin de Sainte Marie⁹ and Nicolas Gendron^{2,10-12}

¹Pharmacy Department, Groupe Hospitalier UNEOS, Metz-Vantoux;

²The Shifters Association, Cercle Thématique Santé, Paris; ³SESAME, One Health Medical Education, Prades-le-Lez; ⁴Pharmacy Department, Centre Hospitalier Universitaire de Rennes, Rennes; ⁵Department of Infectious Disease, St Nazaire Hospital, Saint-Nazaire; ⁶Sorbonne Université, ACTION Study Group, INSERM UMRS 1166, Institut de Cardiologie, Hôpital Pitié-Salpêtrière (AP-HP), Paris; ⁷The Shift Project, Paris; ⁸Ecovamed, Paris; ⁹Department of Internal Medicine, Centre Hospitalier Universitaire de La Timone, Marseille; ¹⁰Hematology Department, Hôpital Européen Georges Pompidou, Assistance

Publique Hôpitaux de Paris-Centre, Université Paris Cité (APHP-CUP), Paris; ¹¹Paris Cité University, INSERM, Paris Cardiovascular Research Center, Team Endotheliopathy and Hemostasis Disorders, Paris and ¹²Investigation Network on Venous Thrombo-Embolism - French Clinical Research Infrastructure Network, Saint-Étienne, France

Correspondence:

N. GENDRON - nicolas.gendron@aphp.fr

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Contributions

LR, ZH, ST and NG collected data, analyzed data and wrote the manuscript. LR, ZH, LD, DB, VM, DG, ST, BST, and NG contributed to data analysis and manuscript revision.

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Data-sharing statement

The datasets generated and/or analyzed during the current study are not publicly available due to contractual restrictions with data providers. Data cannot be shared.

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