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REVIEW
Vascular medicine

Clinical significance of the rivaroxaban–dronedarone interaction: insights from physiologically based pharmacokinetic modelling

Burkhard Hügl[1]*, Marc Horlitz[2], Kerstin Fischer[3], and Reinhold Kreutz [4]

[1]Clinic for Cardiology and Rhythmology, Marienhaus Klinikum St Elisabeth Neuwied, Neuwied, Germany; [2]Klinik für Kardiologie, Elektrophysiologie und Rhythmologie, Krankenhaus Porz am Rhein, Universität Witten/Herdecke, Köln, Germany; [3]Bayer AG, Research & Development, Pharmaceuticals Therapeutic Opportunity Expansion, Berlin, Germany; and [4]Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Clinical Pharmacology and Toxicology, Charité University Medicine, Berlin, Germany

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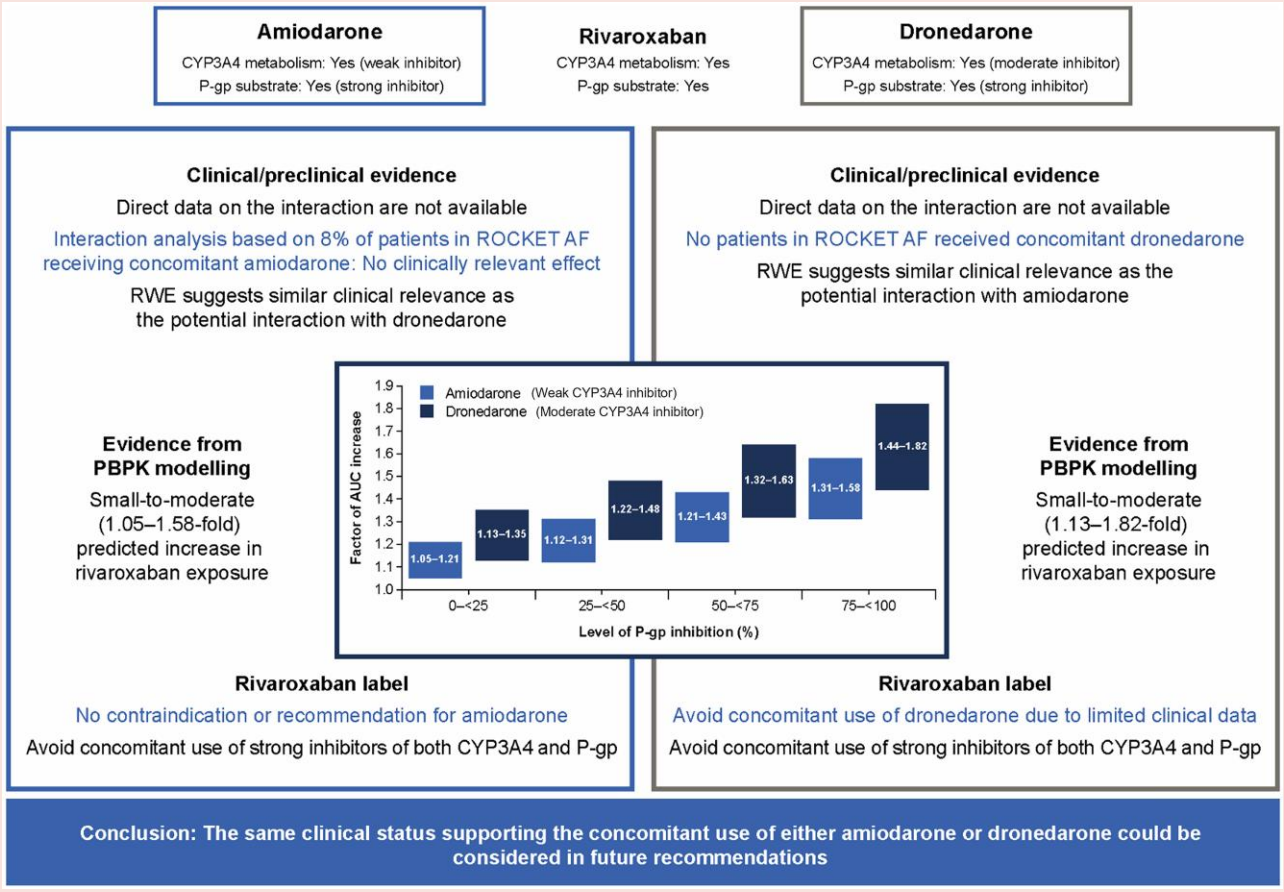
Patients with atrial fibrillation may require rhythm control therapy in addition to anticoagulation therapy for the prevention of stroke. Since 2012, the European Society of Cardiology and European Heart Rhythm Association guidelines have recommended non-vitamin K antagonist oral anticoagulants, including rivaroxaban, for the prevention of stroke in patients with atrial fibrillation. During the same period, these guidelines have also recommended dronedarone or amiodarone as second-line rhythm control agents in certain patients with atrial fibrillation and no contraindications. Amiodarone and dronedarone both strongly inhibit *P*-glycoprotein, while dronedarone is a moderate and amiodarone a weak inhibitor of cytochrome P450 3A4 (CYP3A4). Based on these data and evidence from physiologically based pharmacokinetic modelling, amiodarone and dronedarone are expected to have similar effects on rivaroxaban exposure resulting from *P*-glycoprotein and CYP3A4 inhibition. However, the rivaroxaban label recommends against the concomitant use of dronedarone, but not amiodarone, citing a lack of evidence on the concomitant use of rivaroxaban and dronedarone as the reason for the different recommendations. In this report, we discuss evidence from clinical studies and physiologically based pharmacokinetic modelling on the potential for increased rivaroxaban exposure resulting from drug–drug interaction between rivaroxaban and dronedarone or amiodarone. The current evidence supports the same clinical status and concomitant use of either amiodarone or dronedarone with rivaroxaban, which could be considered in future recommendations.

* Corresponding author. Tel: +492631 821212, Email: burkhard.huegl@marienhaus.de

Graphical Abstract



Clinical significance of the rivaroxaban–dronedarone interaction. AUC, area under the concentration–time curve; CYP3A4, cytochrome P450 3A4; PBPK, physiologically based pharmacokinetic; p-gp, p-glycoprotein; ROCKET AF, rivaroxaban once daily oral direct factor xa inhibition compared with vitamin k antagonism for prevention of stroke and embolism trial in atrial fibrillation; RWE, real-world evidence.

Keywords Physiologically based pharmacokinetic modelling • Drug–drug interaction • Rivaroxaban • Dronedarone • Amiodarone

Introduction

In addition to anticoagulation therapy to reduce the risk of stroke, patients with atrial fibrillation (AF) may require rhythm control therapy.[1–3] Since 2012, dronedarone and amiodarone have been recommended by the European Society of Cardiology (ESC) and European Heart Rhythm Association (EHRA) guidelines as second-line rhythm control agents in selected patients with AF.[1–6] The same guidelines have recommended the non-vitamin K antagonist oral anticoagulant (NOAC) rivaroxaban for the prevention of stroke in patients with AF since 2012, based on the results of the phase III Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) study.[1–3,6] The NOACs apixaban, dabigatran, and edoxaban are also recommended by the ESC/EHRA guidelines for the same indication.[2,3,6]

The concomitant use of rivaroxaban with either amiodarone or dronedarone has the potential for drug–drug interaction (DDI) because they share components of their elimination pathways [cytochrome P450 (CYP) 3A4 and *P*-glycoprotein (*P*-gp)].[4,7–9] However, not all DDIs are clinically significant; only concomitant medication that strongly inhibits both CYP3A4 and *P*-gp simultaneously is expected to lead to a clinically significant increase in rivaroxaban exposure and bleeding risk.[9–11] Amiodarone and dronedarone are strong inhibitors of *P*-gp, but dronedarone is a moderate inhibitor of CYP3A4, with a predicted increase in rivaroxaban exposure up to 1.82-fold, while amiodarone is a weak inhibitor of CYP3A4 with a predicted AUC (area under the curve) increase up to 1.58-fold.[4,5,12,13] Therefore, CYP3A4 and *P*-gp inhibition with either amiodarone or dronedarone is predicted to have a similar, small effect on rivaroxaban exposure.[13]

Despite this, both the rivaroxaban label and ESC/EHRA guidelines recommend against the concomitant use of dronedarone, but not amiodarone.[2,9] The reason for the different recommendations is that there is a lack of clinical evidence on the concomitant use of dronedarone and rivaroxaban.[2,9] However, in the ROCKET AF study, the expected increase in rivaroxaban exposure did not appear to be clinically relevant in the subset of patients ($n = 1144$) who received both rivaroxaban and amiodarone,[14] whereas no patients received dronedarone concomitantly with rivaroxaban in ROCKET AF.[14] Although there is limited pharmacokinetic data for some of these agents, the

ESC/EHRA guidelines do not recommend against the combination of amiodarone or dronedarone with other NOACs (however, concomitant use of dabigatran and dronedarone is contraindicated).[2] DDIs between dronedarone or amiodarone and other NOACs are possible to varying degrees[2] (*Table 1*).[2,15]

This review aims to synthesize the available evidence from clinical studies, as well as PBPK modelling, on the potential DDI between rivaroxaban and dronedarone, and place it in context of the evidence on the potential DDI between amiodarone and rivaroxaban.

DDIs exist between rivaroxaban and dronedarone or amiodarone due to their shared metabolic and elimination pathways

Rivaroxaban and other NOACs, such as apixaban, dabigatran, and edoxaban, can be used for the prevention of stroke in a broad population of patients with AF.[2,9] A subset of these patients are eligible for second-line rhythm control therapy with amiodarone or dronedarone. Patients with severe arrhythmia who have not responded to or tolerated other therapies, as well as patients with concomitant heart failure, may be eligible for amiodarone therapy.[3,5,6] Dronedarone has rhythm- and rate-controlling properties, but is indicated only to maintain sinus rhythm after successful cardioversion in clinically stable patients with paroxysmal or persistent (but not permanent) AF in whom other antiarrhythmics, such as flecainide or propafenone, cannot be used.[4,24] Dronedarone can be used in patients with or without structural heart disease, but not in patients with left ventricular systolic dysfunction or any history of heart failure.[4,25] In fact, dronedarone is a derivative of amiodarone designed to have an improved tolerability profile.[26] In one study, dronedarone use was shown not to be associated with an increased risk of death or liver disease in patients with AF in clinical practice compared with the general population.[27]

The reason for the potential DDI between rivaroxaban and amiodarone or dronedarone is that these agents share components of their elimination pathways, which may increase the plasma concentration of rivaroxaban.[4,7–9,15] Approximately two-thirds of each dose of rivaroxaban is metabolized by the cytochrome P450 enzymes CYP3A4 and CYP2J2, as well as CYP-independent pathways.[9,28] CYP3A4 contributes to 18% of rivaroxaban clearance and CYP2J2 accounts for 14%.[29] CYP-independent amide bond hydrolysis is responsible for 14% of rivaroxaban elimination; rivaroxaban is also a substrate of *P*-gp and breast cancer resistance protein (Bcrp) transporters.[7,9,28,29]

Based on a study of the pharmacokinetics of rivaroxaban in healthy volunteers, only strong inhibitors of both CYP3A4 and *P*-gp or Bcrp are expected to increase rivaroxaban exposure to a clinically significant degree,[30] their concomitant use with rivaroxaban is not recommended.[9] In contrast, concomitant medications that inhibit only CYP3A4 or *P*-gp, but not both, and moderate inhibitors of CYP3A4, *P*-gp, or both are expected to cause smaller increases in rivaroxaban exposure that are unlikely to be clinically relevant, except in high-risk patients.[9,29] The concomitant use of these agents with rivaroxaban is not prohibited.[9]

Amiodarone is a weak inhibitor of CYP3A4 and a strong inhibitor of *P*-gp.[5,12,31] Although amiodarone is mainly metabolized by CYP3A4, CYP2C8 is also involved in its metabolism.[5,32] Interactions between amiodarone and other CYP enzymes, as well as transporters other than *P*-gp, have been demonstrated.[5] Concomitant treatment with amiodarone and rivaroxaban has been associated with increased plasma concentrations of rivaroxaban of almost two-fold [odds ratio (OR) 1.97, 95% confidence interval (CI), 1.04–3.72, $P = 0.036$] in clinical practice.[33] Dronedarone is also metabolized mainly by CYP3A4. It is a moderate inhibitor of CYP3A4 and a strong inhibitor of *P*-gp.[4] In addition, dronedarone is a mild inhibitor of CYP2D6 and may inhibit transport proteins other than *P*-gp.[4,13]

Therefore, neither amiodarone nor dronedarone strongly inhibits both CYP3A4 and *P*-gp. As demonstrated in *in vitro* assays and static modelling, the DDIs between rivaroxaban and amiodarone or dronedarone are expected to be weak and to result in similar increases in rivaroxaban exposure.[11] Despite this, the rivaroxaban label does not contraindicate the concomitant use of amiodarone or dronedarone with rivaroxaban, but cautions that concomitant use of dronedarone should be avoided due to the lack of clinical data.[9]

Other NOACS and their potential interactions with amiodarone and dronedarone

The label recommendations on the concomitant use of amiodarone or dronedarone with other NOACs vary according to their elimination pathways and the available evidence (*Table 1*). Apixaban is metabolized mainly by CYP3A4 and transported by both *P*-gp and Bcrp. However, although direct evidence on the DDIs between apixaban and amiodarone or dronedarone is not available,[2,19] the label does not contraindicate, or recommend a dose reduction with, the concomitant use of other medications that are not strong inhibitors of CYP3A4 as well as *P*-gp.[16] Dabigatran is metabolized independently of CYP3A4, but its plasma levels can be increased when administered concomitantly with a *P*-gp inhibitor.[17,34] Based on their effects on the plasma concentration of dabigatran, concomitant use of dronedarone is contraindicated and caution is advised when amiodarone is used.[17] Finally, edoxaban is a substrate for *P*-gp, but only a small proportion of edoxaban is metabolized by CYP3A4. Based on the effect of the rhythm control agents on edoxaban exposure *in vivo*, the label recommends halving the edoxaban dose when used in combination with dronedarone, but no dose reduction is required when co-administered with amiodarone.[18,20–22]

Current evidence suggests that DDIs with dronedarone or amiodarone and rivaroxaban are unlikely to increase the risk of clinical events.

Clinical evidence

The availability of evidence on the concomitant use of amiodarone, but not dronedarone, with rivaroxaban in the phase III ROCKET AF study accounts for this difference in the guideline recommendations.[2,14] In the ROCKET AF study, concomitant use of rhythm control agents was permitted at the discretion of the treating physician.[14] The risk of bleeding, death, and embolic events was not increased in the subset of patients who received rhythm control agents, including amiodarone, suggesting that the potential increase in rivaroxaban exposure with concomitant use of amiodarone and rivaroxaban may not be clinically relevant.[14] Furthermore, a meta-analysis of 4 randomized controlled trials showed that there was no significant difference in the risk of stroke or systemic embolism, major bleeding, or intracranial bleeding in patients receiving a NOAC with vs. without amiodarone.[35] Dronedarone use was not prohibited in the ROCKET AF study, but no patients in the study received dronedarone concomitantly with rivaroxaban.[14]

Real-world evidence

'Real-world' studies have been performed to address the lack of clinical evidence on the potential DDI between rivaroxaban and dronedarone, with varying results. A single-centre retrospective cohort study ($n = 226$) of patients with AF in the United States treated with rivaroxaban or apixaban showed that those receiving either concomitant amiodarone or dronedarone, diltiazem, or verapamil therapy had a higher risk of International Society on Thrombosis and Haemostasis

Table 1 Potential for DDI between dronedarone, amiodarone, and the NOACs, and the corresponding recommendations

	CYP3A4 metabolism[9,16–18]	*P*-gp substrate[9,16–18]	Label recommendations[9,16–18]	ESC/EHRA guideline recommendations[2]	Evidence
Rivaroxaban	Yes	Yes	• Avoid concomitant use of strong inhibitors of both CYP3A4 and *P*-gp • No contraindication or recommendation for amiodarone • Avoid concomitant use of dronedarone due to limited clinical data	• Amiodarone: Consider dose adjustment or different NOAC, depending on other interactions • Dronedarone: Avoid concomitant use	• Amiodarone: Interaction analysis based on 8% of patients in ROCKET AF receiving concomitant amiodarone.[14] Direct data on the interaction are not available[2] • Dronedarone: No direct PK data on the interaction are available.[2] No patients in ROCKET AF received concomitant dronedarone[14]
Apixaban	Yes	Yes	• Avoid concomitant use of strong inhibitors of both CYP3A4 and *P*-gp[16] • No dose adjustment required with concomitant use of agents that do not strongly inhibit both CYP3A4 and *P*-gp[16]	• Amiodarone: Consider dose adjustment or different NOAC, depending on other interactions • Dronedarone: Use with caution and consider dose adjustment or different NOAC, depending on other interactions	• Amiodarone: Interaction analysis in ARISTOTLE.[19] Direct data on the interaction are not available[2] • Dronedarone: Direct data on the interaction are not available[2]
Dabigatran	No	Yes	• Concomitant amiodarone should be used with caution • Concomitant use of dronedarone is contraindicated	• Amiodarone: Consider dose adjustment or different NOAC, depending on other interactions • Dronedarone: Contraindicated	• Amiodarone: Increases dabigatran AUC 1.6-fold and C_{max} 1.5-fold[17] • Dronedarone: Increases dabigatran AUC 2.4-fold and C_{max} 2.3-fold[17]
Edoxaban	Minimal	Yes	• No dose reduction required with concomitant amiodarone • 50% dose reduction when co-administered with dronedarone	• Amiodarone: Consider dose adjustment or different NOAC, depending on other interactions • Dronedarone: Consider dose adjustment or different NOAC	• Amiodarone: Population PK analysis of phase I/II study data predicted a 1.4-fold increase in edoxaban AUC.[20,21] Amiodarone use in ENGAGE AF-TIMI 48 was not associated with an increased risk of major bleeding[22] • Dronedarone: DDI study in healthy individuals showed a 1.8-fold increase in edoxaban AUC.[21] No data from ENGAGE AF-TIMI 48 on patients receiving dronedarone and edoxaban[23]

ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; AUC, area under the concentration–time curve; C_{max}, maximum plasma concentration; CYP, cytochrome P450; DDI, drug–drug interaction; EHRA, European Heart Rhythm Association; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; ESC, European Society of Cardiology; NOAC, non-vitamin K antagonist oral anticoagulant; *P*-gp, *P*-glycoprotein; PK, pharmacokinetic; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

major, non-major, or minor bleeding compared with patients receiving only a NOAC.[36] A small observational study ($n = 23$) with a short follow-up period (mean 9.1 months) showed no thromboembolic or major bleeding events in patients with AF who received rivaroxaban and dronedarone.[37] In contrast, a large retrospective cohort study ($n = 91\ 330$) of patients with AF in the Taiwan National Health Insurance database who received apixaban, dabigatran, or rivaroxaban showed that the risk of major bleeding was significantly increased with concomitant amiodarone, but not significantly different with concomitant dronedarone, compared with patients receiving a NOAC alone.[38] Although the concomitant use of dronedarone and dabigatran is contraindicated,[39] this drug combination was reported in the study and reflects local clinical practice. The risk of major bleeding was increased with the combination of amiodarone and apixaban [rate ratio (RR) 1.30; $P \geq 0.01$], rivaroxaban (RR 1.38; $P < 0.01$), and dabigatran (RR 1.36; $P < 0.01$), but not increased with the combination of dronedarone with apixaban (RR 0.68; $P \geq 0.01$), dabigatran (RR 0.89; $P \geq 0.01$), or rivaroxaban (RR 0.92; $P \geq 0.01$).[38]

Although these studies acknowledged that their findings need to be confirmed with further analyses,[14,36–38] the limited available evidence from clinical studies suggests that the potential interaction of rivaroxaban with dronedarone is of similar clinical relevance to the interaction with amiodarone.

Evidence from PBPK modelling suggests no clinically significant increase in rivaroxaban exposure with amiodarone or dronedarone

Rationale for PBPK modelling

PBPK modelling is an established approach to estimate the pharmacokinetic effects of DDIs. It is used to guide drug development and in cases where clinical evidence is limited or where direct clinical studies are not feasible.[40,41] PBPK modelling can use information from *in vitro* and clinical studies to construct a whole-body model to predict complex aspects of the pharmacokinetics of a drug, including DDIs, in specific physiologic compartments, and models can be adapted to specific virtual patient populations based on their altered physiology.[42]

Because PBPK modelling requires detailed information about the drug as well as the physiologic or anatomical compartments of the system, it may be challenging to obtain all the parameters required to construct an accurate model.[40,43,44] Therefore, model performance should be assessed; sensitivity analysis can identify sources of uncertainty within a model, such as interactions between parameters or non-linear processes.[43] Model performance should also be validated with independent clinical data.[43] Any discrepancies between predicted and observed pharmacokinetics can guide further analyses to improve PBPK model performance.[44]

PBPK modelling studies have become an accepted source of evidence by regulatory authorities, and they are increasingly used in clinical development and to support drug label recommendations.[40,44,45] The US Food and Drug Administration (FDA) and European Medicines Agency have published guidance on the requirements for PBPK model analyses that are included in regulatory submissions[46,47] and provide guidance on the use of PBPK modelling and validation in various clinical scenarios, including DDI.[41,44,48,49] Many pharmaceutical companies use approaches such as PBPK modelling during drug development and to support regulatory submissions,[50] and a substantial proportion of regulatory submissions to the FDA that included PBPK modelling analyses focused on DDIs.[44]

While PBPK modelling is an important tool, there are limitations to this technique. Most importantly, the data provided by PBPK modelling is indirect as it does not involve actual patient data but rather relies on computational modelling.[13] In addition, a large number of parameters are required for this technique which means an accompanying sensitivity analysis must be completed to assess the unknown/uncertain parameters, their impact, and any other inferences that may be made regarding the PK of a drug.[13] PBPK models are also known to require substantially more data (both experimental and in silico) than static models.[40]

Evidence on rivaroxaban pharmacokinetics from PBPK modelling

PBPK modelling has been used to evaluate the pharmacokinetics of rivaroxaban in various clinical situations. In 2012, a semi-PBPK model assessed the effects of concomitant erythromycin, a moderate inhibitor of both CYP3A4 and *P*-gp, and varying degrees of renal impairment on rivaroxaban pharmacokinetics.[51] This analysis predicted that clinically relevant drug–drug–renal impairment interactions are possible in patients with mild-to-moderate renal impairment treated with rivaroxaban and erythromycin.[51] The model predictions were generally consistent with the available *in vivo* data.[51] Subsequently, an adult PBPK model of the pharmacokinetics of rivaroxaban was developed and scaled to a paediatric population. The results of this analysis were successfully used to guide dosing in subsequent clinical studies of rivaroxaban in paediatric patients, including the phase I Oral Rivaroxaban in Children With Venous Thrombosis (EINSTEIN-Jr) study.[52,53] A PBPK model was used to assess the effect of renal or hepatic dysfunction as well as concomitant use of strong CYP3A4/5, CYP2J2, or *P*-gp inhibitors on the pharmacokinetics of rivaroxaban.[54] This model also predicted the pharmacokinetics of rivaroxaban well compared with observations in healthy individuals and patients with renal or hepatic impairment.[54]

PBPK model analysis on the DDI between rivaroxaban and amiodarone predicted a 1.36-fold increase in rivaroxaban exposure in patients without renal impairment. Because this increase was within the predefined dose–exposure equivalence range, the authors concluded that it was unlikely to be clinically relevant.[55] Simulations in patients who also had mild or moderate renal impairment predicted larger increases in rivaroxaban exposure that were more likely to be clinically significant. The interaction between rivaroxaban and dronedarone was not assessed in the study.[55] Most recently, a rivaroxaban PBPK model was used to simulate the pharmacokinetics of rivaroxaban in patients with reduced rivaroxaban clearance, including DDIs with amiodarone or dronedarone.[13] This study showed that rivaroxaban exposure increased with the strength of CYP3A4 and *P*-gp inhibitors.[13] Importantly, the predicted increase in rivaroxaban exposure with concomitant amiodarone which represents weak CYP3A4 inhibition (1.05–1.58-fold) was similar and overlapping with the expected increase in rivaroxaban exposure with dronedarone which represents moderate CYP3A4 inhibition (1.13–1.82-fold) therapy and was small-to-moderate, depending on the level of *P*-gp inhibition (*Figure 1*).[13]

Implications of PBPK modelling for clinical use

The PBPK model assessing DDI between rivaroxaban and the rhythm control agents was based on standard dosages for all three drugs—rivaroxaban 20 mg od, dronedarone 400 mg bid, and amiodarone 200 mg od (maintenance dose)—in both healthy adults without conditions that may affect rivaroxaban elimination, and in patients with renal or hepatic impairment.[4,5,13] In general, patients with moderate to severe renal impairment [creatinine clearance (CrCl) 30–49 mL/min or CrCl 15–29 mL/min] require a reduced rivaroxaban dose because renal impairment itself may lead to increased rivaroxaban exposure. Other factors, such as frailty and advanced age, are not dose reduction criteria for rivaroxaban.[9,56] Similarly, no dose adjustment is required for dronedarone or amiodarone in elderly patients or patients with renal impairment (CrCl ≥30 mL/min).[4,5] However,

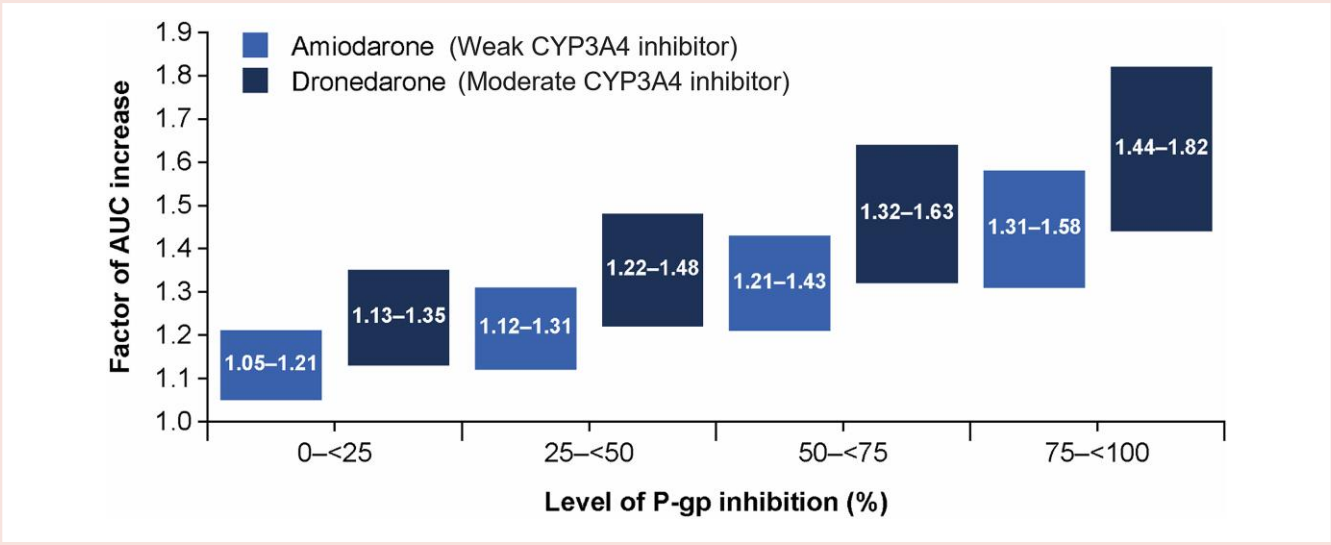


Figure 1 Predicted increases in rivaroxaban area under the concentration–time curve associated with concomitant amiodarone or dronedarone.[13] *P*-gp, *P*-glycoprotein.

frail or elderly patients may have coexisting conditions that could contribute to altered elimination of these medications.[9] RCTs investigating the use of NOACs in patients with AF exclude patients with severe chronic kidney disease; therefore, data on this population are scarce.[6,56] Further analyses would be needed to assess and model the impact of dronedarone or amiodarone use in patients with renal impairment receiving reduced dose rivaroxaban or in other challenging clinical scenarios.

Monitoring rivaroxaban plasma levels during concomitant use of rhythm control agents to avoid an excessive increase in bleeding risk would not be feasible because no known plasma level thresholds are available. Rivaroxaban plasma levels were found to be highly variable between patients with AF in the ROCKET AF trial; it was found that monitoring rivaroxaban levels in patients was unlikely to offer benefits compared to monitoring other patient factors.[57] This analysis demonstrated no obvious lower limit of rivaroxaban exposure that culminated in any loss of efficacy, further showing the wide therapeutic range that exists for rivaroxaban in patients with non-valvular atrial fibrillation. Any potential gain from measuring rivaroxaban levels would be limited.[57]

Furthermore, the rivaroxaban label states that monitoring of exposure or coagulation parameters is not required when used concomitantly with amiodarone[5,9] If rivaroxaban and amiodarone can be used in combination without monitoring plasma levels, and amiodarone and dronedarone have similar effects on rivaroxaban plasma levels, the same approach is expected to apply to the concomitant use of rivaroxaban and dronedarone.

Conclusion/learning points

The available evidence from clinical studies complemented by PBPK modelling suggests that the potential for increased rivaroxaban exposure due to DDIs with the combination of dronedarone and rivaroxaban is similar to that with amiodarone. Depending on individual factors and comorbidities, these DDIs may be associated with an increase in the risk of bleeding, as previously suggested for all NOACs (*Table 1*). Thus, other factors affecting the risk of bleeding should be considered in individual patients. The available evidence, based on PBPK modelling and real-world studies, suggests that concomitant use of dronedarone with rivaroxaban should have the same clinical status as concomitant amiodarone.

Lead author biography

Burkhard Hügl has been the Head of the department of Cardiology/Rhythmology of the Marienhaus St. Elisabeth Hospital in Neuwied since 2008. He worked as a senior research fellow at the University of Leipzig Heart Center and in the Cardiology Department at the Heart Center Bad Berka. He is one of the leading users of robotic navigation to treat arrhythmias in the cath lab. His main research topics are arrhythmias in combination with mapping systems or device therapies.

Data availability

No new data were generated or analysed in support of this research.

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References

1. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T,

Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Vardas P, Al Attar N, Alfieri O, Angelini A, Blomstrom-Lundqvist C, Colonna P, De Sutter J, Ernst S, Goette A, Gorenek B, Hatala R, Heidbuchel H, Heldal M, Kristensen SD, Kolh P, Le Heuzey JY, Mavrakis H, Mont L, Filardi PP, Ponikowski P, Prendergast B, Rutten FH, Schotten U, Van Gelder IC, Verheugt FWA. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;**33**:2719–2747.

2. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbuchel H; ESC Scientific Document Group. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;**39**:1330–1393.
3. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
4. Sanofi-aventis groupe. Multaq (dronedarone) Summary of Product Characteristics. 2022. https://www.medicines.org.uk/emc/product/13964/smpc#gref (19 July 2022).
5. Accord Healthcare Limited. Amiodarone 200 mg Summary of Product Characteristics. 2022. https://www.medicines.org.uk/emc/product/13964/smpc#gref (19 July 2022).
6. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL; ESC Scientific Document Group. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498.
7. Gnoth MJ, Buetehorn U, Muenster U, Schwarz T, Sandmann S. *In vitro* and *in vivo* P-glycoprotein transport characteristics of rivaroxaban. *J Pharmacol Exp Ther* 2011; **338**:372–380.
8. Perzborn E, Roehrig S, Straub A, Kubitza D, Mueck W, Laux V. Rivaroxaban: a new oral factor Xa inhibitor. *Arterioscler Thromb Vasc Biol* 2010;**30**:376–381.
9. Bayer AG. Xarelto® (rivaroxaban) Summary of Product Characteristics. 2021. https://www.ema.europa.eu/documents/product-information/xarelto-epar-product-information_en.pdf (19 July 2022).
10. Gronich N, Stein N, Muszkat M. Association between use of pharmacokinetic-interacting drugs and effectiveness and safety of direct acting oral anticoagulants: nested case-control study. *Clin Pharmacol Ther* 2021;**110**:1526–1536.
11. Cheong EJ, Goh JJ, Hong Y, Venkatesan G, Liu Y, Chiu GN, Kojodjojo P, Chan EC. Application of static modeling in the prediction of in vivo drug-drug interactions between rivaroxaban and antiarrhythmic agents based on in vitro inhibition studies. *Drug Metab Dispos* 2017;**45**:260–268.
12. Wessler JD, Grip LT, Mendell J, Giugliano RP. The P-glycoprotein transport system and cardiovascular drugs. *J Am Coll Cardiol* 2013;**61**:2495–2502.
13. Willmann S, Coboeken K, Kapsa S, Thelen K, Mundhenke M, Fischer K, Hügl B, Mück W. Applications of physiologically based pharmacokinetic modeling of rivaroxaban—renal and hepatic impairment and drug-drug interaction potential. *J Clin Pharmacol* 2021;**61**: 656–665.
14. Steinberg BA, Hellkamp AS, Lokhnygina Y, Halperin JL, Breithardt G, Passman R, Hankey GJ, Patel MR, Becker RC, Singer DE, Hacke W, Berkowitz SD, Nessel CC, Mahaffey KW, Fox KA, Califf RM, Piccini JP; ROCKET AF Steering Committee and Investigators. Use and outcomes of antiarrhythmic therapy in patients with atrial fibrillation receiving oral anticoagulation: results from the ROCKET AF trial. *Heart Rhythm* 2014;**11**:925–932.
15. Barrios V, Masjuan J. Use of direct oral anticoagulants in patients with nonvalvular atrial fibrillation according to clinical profile. *Future Cardiol* 2017;**13**:49–64.
16. Bristol Myers Squibb, Pfizer EEIG. Eliquis® (apixaban) Summary of Product Characteristics. 2022. https://www.ema.europa.eu/documents/product-information/eliquis-epar-product-information_en.pdf (19 July 2022).
17. Boehringer Ingelheim International GmbH. Pradaxa® (dabigatran etexilate) Summary of Product Characteristics. 2022. https://www.ema.europa.eu/documents/product-information/pradaxa-epar-product-information_en.pdf (19 July 2022).
18. Daiichi Sankyo Europe GmbH. Lixiana® (edoxaban) Summary of Product Characteristics. 2021. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf (19 July 2022).
19. Flaker G, Lopes RD, Hylek E, Wojdyla DM, Thomas L, Al Khatib SM, Sullivan RM, Hohnloser SH, Garcia D, Hanna M, Amerena J, Harjola VP, Dorian P, Avezum A, Keltai M, Wallentin L, Granger CB; ARISTOTLE Committees and Investigators. Amiodarone, anticoagulation, and clinical events in patients with atrial fibrillation: insights from the ARISTOTLE trial. *J Am Coll Cardiol* 2014;**64**:1541–1550.
20. Salazar DE, Mendell J, Kastrissios H, Green M, Carrothers TJ, Song S, Patel I, Bocanegra TS, Antman EM, Giugliano RP, Kunitada S, Dornseif B, Shi M, Tachibana M, Zhou S, Rohatagi S. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. *Thromb Haemost* 2012;**107**:925–936.
21. Mendell J, Zahir H, Matsushima N, Noveck R, Lee F, Chen S, Zhang G, Shi M. Drug-drug interaction studies of cardiovascular drugs involving P-glycoprotein, an efflux transporter, on the pharmacokinetics of edoxaban, an oral factor Xa inhibitor. *Am J Cardiovasc Drugs* 2013;**13**:331–342.
22. Steffel J, Giugliano RP, Braunwald E, Murphy SA, Atar D, Heidbuchel H, Camm AJ, Antman EM, Ruff CT. Edoxaban vs. warfarin in patients with atrial fibrillation on amiodarone: a subgroup analysis of the ENGAGE AF-TIMI 48 trial. *Eur Heart J* 2015;**36**: 2239–2245.
23. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.
24. Page RL, Connolly SJ, Crijns HJ, van Eickels M, Gaudin C, Torp-Pedersen C, Hohnloser SH; ATHENA Investigators. Rhythm- and rate-controlling effects of dronedarone in patients with atrial fibrillation (from the ATHENA trial). *Am J Cardiol* 2011;**107**: 1019–1022.
25. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, Amlie J, Carlsen J, Dronedarone Study G. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–2687.
26. Kozlowski D, Budrejko S, Lip GYH, Mikhailidis DP, Rysz J, Raczak G, Banach M. Dronedarone: an overview. *Ann Med* 2012;**44**:60–72.
27. Friberg L. Safety of dronedarone in routine clinical care. *J Am Coll Cardiol* 2014;**63**: 2376–2384.
28. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin Pharmacokinet* 2014;**53**:1–16.
29. Mueck W, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. *Br J Clin Pharmacol* 2013;**76**:455–466.
30. Mueck W, Schwers S, Stampfuss J. Rivaroxaban and other novel oral anticoagulants: pharmacokinetics in healthy subjects, specific patient populations and relevance of coagulation monitoring. *Thromb J* 2013;**11**:10.
31. Ohyama K, Nakajima M, Suzuki M, Shimada N, Yamazaki H, Yokoi T. Inhibitory effects of amiodarone and its N-deethylated metabolite on human cytochrome P450 activities: prediction of *in vivo* drug interactions. *Br J Clin Pharmacol* 2000;**49**:244–253.
32. Wu Q, Ning B, Xuan J, Ren Z, Guo L, Bryant MS. The role of CYP 3A4 and 1A1 in amiodarone-induced hepatocellular toxicity. *Toxicol Lett* 2016;**253**:55–62.
33. Kaserer A, Schedler A, Jetter A, Seifert B, Spahn DR, Stein P, Studt JD. Risk factors for higher-than-expected residual rivaroxaban plasma concentrations in real-life patients. *Thromb Haemost* 2018;**118**:808–817.
34. Delavenne X, Ollier E, Basset T, Bertoletti L, Accassat S, Garcin A, Laporte S, Zufferey P, Mismetti P. A semi-mechanistic absorption model to evaluate drug-drug interaction with dabigatran: application with clarithromycin. *Br J Clin Pharmacol* 2013;**76**:107–113.
35. Lupercio F, Romero J, Peltzer B, Maraboto C, Briceno D, Villablanca P, Ferrick K, Gross JN, Kim S, Fisher J, Di Biase L, Krumerman A. Efficacy and safety outcomes of direct oral anticoagulants and amiodarone in patients with atrial fibrillation. *Am J Med* 2018;**131**: 573.e1–573.e8.
36. Hanigan S, Das J, Pogue K, Barnes GD, Dorsch MP. The real world use of combined P-glycoprotein and moderate CYP3A4 inhibitors with rivaroxaban or apixaban increases bleeding. *J Thromb Thrombolysis* 2020;**49**:636–643.
37. Escobar C, Arceluz M, de Oca R M, Mori R, López-Sendón JL, Merino JL. Concomitant rivaroxaban and dronedarone administration in patients with nonvalvular atrial fibrillation. *Rev Esp Cardiol (Engl Ed)* 2017;**70**:121–122.
38. Chang SH, Chou IJ, Yeh YH, Chiou MJ, Wen MS, Kuo CT, See LC, Kuo CF. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. *JAMA* 2017;**318**: 1250–1259.
39. Chiang CE, Wu TJ, Ueng KC, Chao TF, Chang KC, Wang CC, Lin YJ, Yin WH, Kuo JY, Lin WS, Tsai CT, Liu YB, Lee KT, Lin LJ, Lin LY, Wang KL, Chen YJ, Chen MC, Cheng CC, Wen MS, Chen WJ, Chen JH, Lai WT, Chiou CW, Lin JL, Yeh SJ, Chen SA. 2016 guidelines of the Taiwan heart rhythm society and the Taiwan society of cardiology for the management of atrial fibrillation. *J Formos Med Assoc* 2016;**115**:893–952.
40. Sager JE, Yu J, Ragueneau-Majlessi I, Isoherranen N. Physiologically based pharmacokinetic (PBPK) modeling and simulation approaches: a systematic review of published models, applications, and model verification. *Drug Metab Dispos* 2015;**43**:1823–1837.
41. Varma MV, Pang KS, Isoherranen N, Zhao P. Dealing with the complex drug-drug interactions: towards mechanistic models. *Biopharm Drug Dispos* 2015;**36**:71–92.

42. Edginton AN, Willmann S. Physiology-based simulations of a pathological condition: prediction of pharmacokinetics in patients with liver cirrhosis. *Clin Pharmacokinet* 2008;**47**:743–752.
43. McNally K, Cotton R, Loizou GD. A workflow for global sensitivity analysis of PBPK models. *Front Pharmacol* 2011;**2**:31.
44. Jamei M. Recent advances in development and application of physiologically-based pharmacokinetic (PBPK) models: a transition from academic curiosity to regulatory acceptance. *Curr Pharmacol Rep* 2016;**2**:161–169.
45. EFPIA Mid Workgroup, Marshall SF, Burghaus R, Cosson V, Cheung SY, Chenel M, DellaPasqua O, Frey N, Hamren B, Harnisch L, Ivanow F, Kerbusch T, Lippert J, Milligan PA, Rohou S, Staab A, Steimer JL, Tornoe C, Visser SA. Good practices in model-informed drug discovery and development: practice, application, and documentation. *CPT Pharmacometrics Syst Pharmacol* 2016;**5**:93–122.
46. European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. 2018. https://www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation (19 May 2022).
47. US Food and Drug Administration. Physiologically based pharmacokinetic analyses—format and content. 2018. https://www.fda.gov/media/101469/download (19 May 2022).
48. European Medicines Agency, Committee for Human Medicinal Products. Guideline on the investigation of drug interactions. CPMP/EWP/560/95/Rev.1 Corr.2. 2012. https://www.ema.europa.eu/documents/scientific-guideline/guideline-investigation-drug-interactions_en.pdf (19 May 2022).
49. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Clinical drug interaction studies—study design, data analysis, and clinical implications. 2017. https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093606.htm (19 May 2022).
50. Schuck E, Bohnert T, Chakravarty A, Damian-Iordache V, Gibson C, Hsu CP, Heimbach T, Krishnatry AS, Liederer BM, Lin J, Maurer T, Mettetal JT, Mudra DR, Nijsen MJ, Raybon J, Schroeder P, Schuck V, Suryawanshi S, Su Y, Trapa P, Tsai A, Vakilynejad M, Wang S, Wong H. Preclinical pharmacokinetic/pharmacodynamic modeling and simulation in the pharmaceutical industry: an IQ consortium survey examining the current landscape. *AAPS J* 2015;**17**:462–473.
51. Grillo JA, Zhao P, Bullock J, Booth BP, Lu M, Robie-Suh K, Berglund EG, Pang KS, Rahman A, Zhang L, Lesko LJ, Huang SM. Utility of a physiologically-based pharmacokinetic (PBPK) modeling approach to quantitatively predict a complex drug-drug-disease interaction scenario for rivaroxaban during the drug review process: implications for clinical practice. *Biopharm Drug Dispos* 2012;**33**:99–110.
52. Willmann S, Becker C, Burghaus R, Coboeken K, Edginton A, Lippert J, Siegmund HU, Thelen K, Mück W. Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. *Clin Pharmacokinet* 2014;**53**:89–102.
53. Kubitza D, Willmann S, Becka M, Thelen K, Young G, Brandao LR, Monagle P, Male C, Chan A, Kennet G, Martinelli I, Saracco P, Lensing AWA. Exploratory evaluation of pharmacodynamics, pharmacokinetics and safety of rivaroxaban in children and adolescents: an EINSTEIN-jr phase I study. *Thromb J* 2018;**16**:31.
54. Xu R, Ge W, Jiang Q. Application of physiologically based pharmacokinetic modeling to the prediction of drug-drug and drug-disease interactions for rivaroxaban. *Eur J Clin Pharmacol* 2018;**74**:755–765.
55. Cheong EJY, Goh JJN, Hong Y, Kojodjojo P, Chan ECY. Rivaroxaban with and without amiodarone in renal impairment. *J Am Coll Cardiol* 2018;**71**:1395–1397.
56. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Vanassche T, Potpara T, Camm AJ, Heidbüchel H. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace* 2021;**23**:1612–1676.
57. Zhang L, Yan X, Fox KAA, Willmann S, Nandy P, Berkowitz SD, Hermanowski-Vosatka A, Weitz JI, Solms A, Schmidt S, Patel M, Peters G. Associations between model-predicted rivaroxaban exposure and patient characteristics and efficacy and safety outcomes in patients with non-valvular atrial fibrillation. *J Thromb Thrombolysis* 2020;**50**:20–29.