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REVIEW

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Optimal management of cardiac surgery patients using direct oral anticoagulants: recommendations for clinical practice

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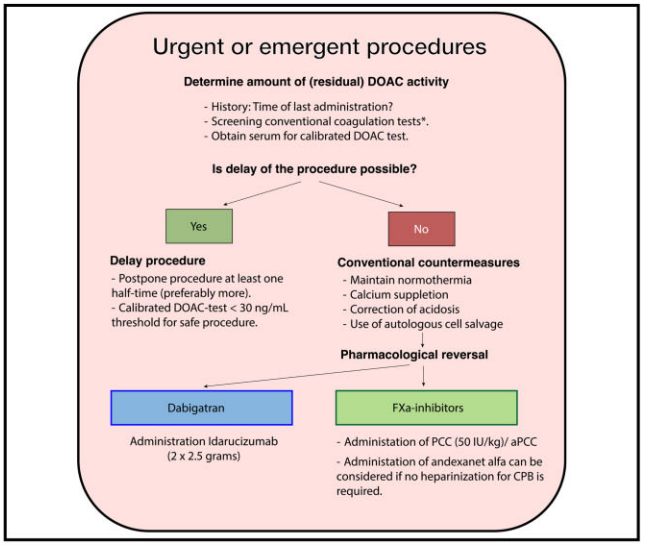
Optimal Management of Cardiac Surgery Patients Using Direct Oral Anticoagulants: Recommendations for Clinical Practice

Summary

DOACs have progressively replaced VKAs, also in patients undergoing cardiac surgery. For elective and urgent procedures, the cessation strategy can be adapted to the renal function. Emergent cases warrant particular attention as pharmacological reversal can be applied, but the use of and timing of reversal is heavily dependent on the type of DOAC and further need of heparinization



Abstract

OBJECTIVES: Literature is scarce on the management of patients using direct oral anticoagulants (DOACs) undergoing elective, urgent and emergency surgery. Therefore, we summarize the current evidence and provide literature-based recommendations for the management of patients on DOACs in the perioperative phase.

METHODS: A general literature review was conducted on the pharmacology of DOACs and for recommendations on the management of cardiac surgical patients on DOACs. Additionally, we performed a systematic review for studies on the use of direct DOAC reversal agents in the emergency cardiac surgical setting.

RESULTS: When surgery is elective, the DOAC cessation strategy is relatively straightforward and should be adapted to the renal function. The same approach applies to urgent cases, but additional DOAC activity drug level monitoring tests may be useful. In emergency cases, idarucizumab can be safely administered to patients on dabigatran in any of the perioperative phases. However, andexanet alfa, which is not registered for perioperative use, should not be administered in the preoperative phase to reverse the effect of factor Xa inhibitors, as it may induce temporary heparin resistance. Finally, the administration of (activated) prothrombin complex concentrate may be considered in all patients on DOACs, and such concentrates are generally readily available.

CONCLUSIONS: DOACs offer several advantages over vitamin K antagonists, but care must be taken in patients undergoing cardiac surgery. Although elective and urgent cases can be managed relatively straightforwardly, the management of emergency cases requires particular attention.

Keywords: Direct oral anticoagulants • Cardiac surgery • Emergency • Bleeding • Antidotes

ABBREVIATIONS

AF	Atrial fibrillation
(a)PCC	Activated prothrombin complex concentrate
AT	Antithrombin
CPB	Cardiopulmonary bypass
DOACs	Direct oral anticoagulants
F	Factor
LMWH	Low-molecular weight heparin
NVAF	Non-valvular atrial fibrillation
PCC	Prothrombin complex concentrate
UFH	Unfractionated heparin
VKAs	Vitamin K antagonists

INTRODUCTION

Direct oral anticoagulants (DOACs) have progressively replaced vitamin K antagonists (VKAs) in the treatment of venous thromboembolism and atrial fibrillation (AF). Widely recognized advantages of DOAC therapy over VKA include treatment simplification, pharmacological stability and a reduction in dietary restrictions [1, 2]. Inherently, the increasing use of DOACs in the general population is reflected in patients undergoing cardiac surgery [3]. Despite the advantages of DOAC therapy, the lack of routine laboratory monitoring and available antidotes led to significant bleeding complications in the perioperative phase [1, 4]. Nevertheless, recent advancements have resulted in the development of specific laboratory tests for DOACs as well as potent reversal agents [5–7], which may be of specific interest to the cardiac surgeon and the cardiac surgical patient. However, a basic understanding of the mechanisms of action of DOACs, their pharmacokinetics and indications and contraindications for the use of specific reversal agents is warranted. Therefore, the current review aims to provide an overview of these features of DOACs. Furthermore, we aim to present 10 literature-based practical recommendations for the strategy to interrupt DOACs in elective, urgent and emergency surgery, in conjunction with guidance on the use of reversal agents and mechanical drug removal devices.

METHODS

Ethical statement

Not applicable, since the current study comprises a literature review.

Search and study inclusion

Primarily, this article is a narrative review, which aims to provide the reader with an overview of literature regarding the mechanisms of action of DOACs and their reversal agents in general, and in patients undergoing cardiac surgery in particular. To the best of our knowledge, clinical studies evaluating the reversal of DOACs in such patients are yet to be published. However, several case reports and series have come to our attention, which prompted the current authors to perform this review. To guarantee transparency and reproducibility, a rapid systematic review of literature was performed to retrieve all cases of cardiac surgery patients treated with direct DOAC reversal agents. The details of this search are outlined below.

First, a general review of literature was conducted for information on the pharmacology of DOACs and for experiences with, as well as recommendations on, the general and therapeutic management of cardiac surgical patients on DOACs. Second, a rapid systematic literature review was performed through 3 electronic databases (PubMed, Embase, Cochrane) to retrieve cases on the use of direct DOAC reversal agents in the emergency cardiac surgical setting. The last search was performed on 3 June 2023. Of note, as the current rapid literature review only focused on case reports, it did not specifically adhere to the PRISMA 2020 statement. However, a systematic and reproducible search was conducted and presented in Supplementary Material 1. These search criteria included: 'cardiac surgery', 'cardiovascular surgery' (inclusive of alternative spelling and abbreviations) and 'idarucizumab', 'andexanet alfa' (inclusive of alternative spellings).

PHARMACOLOGY OF DIRECT ORAL ANTICOAGULANTS

Definition of direct oral anticoagulants

DOACs, also known as non-vitamin K or novel oral anticoagulants, comprise a pharmacological class of orally prescribed

Table 1: Overview of currently available direct oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Brand name	Pradaxa	Xarelto	Eliquis	Lixiana Savaysa
Approved in Europe since	2008	2008	2011	2015
Target factor	FIIa	FXa	FXa	FXa
Prodrug	Yes—dabigatran exelitate	No	No	No
Indications	NVAF VTE (treatment, recurrence, prophylaxis)	NVAF VTE (treatment, recurrence, prophylaxis) Chronic coronary syndromes and peripheral arterial disease	NVAF VTE (treatment, recurrence, prophylaxis)	NVAF VTE (treatment, recurrence, prophylaxis)
Contraindications	Moderate–severe renal failure MHVs Rheumatic heart disease Bleeding diathesis Severe hepatic failure Pregnancy APS	Severe renal failure MHVs Rheumatic heart disease Bleeding diathesis Severe hepatic failure Pregnancy APS	Severe renal failure MHVs Rheumatic heart disease Bleeding diathesis Severe hepatic failure Pregnancy APS	Severe renal failure MHVs Rheumatic heart disease Bleeding diathesis Severe hepatic failure Pregnancy APS
Regular dose (for NVAF)	150 mg twice daily	20 mg once daily	5 mg twice daily	60 mg twice daily

APS: antiphospholipid syndrome; MHVs: mechanical heart valves; NVAF: non-valvular atrial fibrillation; VTE: venous thromboembolisms.

medication developed for the direct inhibition of a specific coagulation factor (Table 1). The most common DOACs directly inhibit factor (F) Xa (rivaroxaban, apixaban, edoxaban) and thrombin (FIIa, dabigatran) [1]. Although several new agents—targeting other coagulation factors (FXIa)—are under investigation, these are beyond the scope of this current review [8].

Indications and contraindications for direct oral anticoagulants

A specific indication that may be encountered in patients undergoing cardiac surgery is the prevention of stroke or systemic thromboembolism in patients with non-valvular atrial fibrillation (NVAF) [9]. Table 1 provides an overview of currently available NOACs, their various other indications and contraindications. Of note, all DOACs are contraindicated in the presence of mechanical heart valves [10], a contraindication that was reconfirmed for newer-generation prostheses [11]. Moreover, DOACs led to significantly more cardiovascular events and deaths in patients with rheumatic heart disease and AF [12]—also known as valvular AF—as compared to VKAs [12].

Mechanisms of action

The DOAC drug effects are direct due to their direct selective coagulation factor inhibition, which is in sharp contrast with VKAs whose indirect mode of action results in a delay in onset and offset.

Dabigatran is the only approved direct thrombin (FIIa) inhibitor. Dabigatran etexilate (the prodrug), is converted to its active form (dabigatran) in the intestinal and hepatic environment after oral administration [13]. It binds to the active site of thrombin and prevents the conversion of fibrinogen (FI) to fibrin (FIa), subsequent platelet activation and the positive thrombin feedback mechanism on FV, FVIII and FXI (Fig. 1) [14]. Notably, its almost exclusive renal excretion necessitates dose adjustment in case of mild-to-moderate renal impairment, and prolonged cessation duration prior to high-risk surgery [15].

Direct FXa inhibitors, most commonly prescribed as rivaroxaban, apixaban and edoxaban, specifically target FXa, the gatekeeper of coagulation at the crossroads of the intrinsic and extrinsic pathway (Fig. 1) [16]. Once activated, FXa and cofactor FVa jointly form prothrombinase, which subsequently converts prothrombin (FII) to thrombin (FIIa). FXa inhibitors prevent the aforementioned amplification of the coagulation cascade by actively binding free and bound FXa, inhibiting the formation of prothrombinase [16]. The distinct FXa inhibitors slightly differ in their pharmacological properties, which is detailed in Table 2.

Measuring direct oral anticoagulant activity

There is little consensus on the indication to measure DOAC activity [17], and actual DOAC laboratory assays are not readily available in the emergency setting. Still, it can be helpful to assess anticoagulant activity in patients at a high risk of bleeding [18]. Historically, the prothrombin time and/or activated partial thromboplastin time have been used in such instances, but their reliability is questionable. For dabigatran, rivaroxaban and edoxaban, normal prothrombin time and activated partial thromboplastin time results generally rule out a substantial residual anticoagulant effect of these drugs, but this does not apply to apixaban. As such, specific tests may be more applicable in the clinical setting.

Indeed, for a precise and direct measurement of DOAC activity, specific anti-Xa tests can be used. Of note, for dabigatran, the diluted thrombin time (normal value <21 s) is more appropriate [19]. The different DOACs require calibrated anti-Xa tests to accurately measure the designated drug level. In general, drug levels <30 ng/ml are considered clinically insignificant in terms of bleeding risk [18, 20].

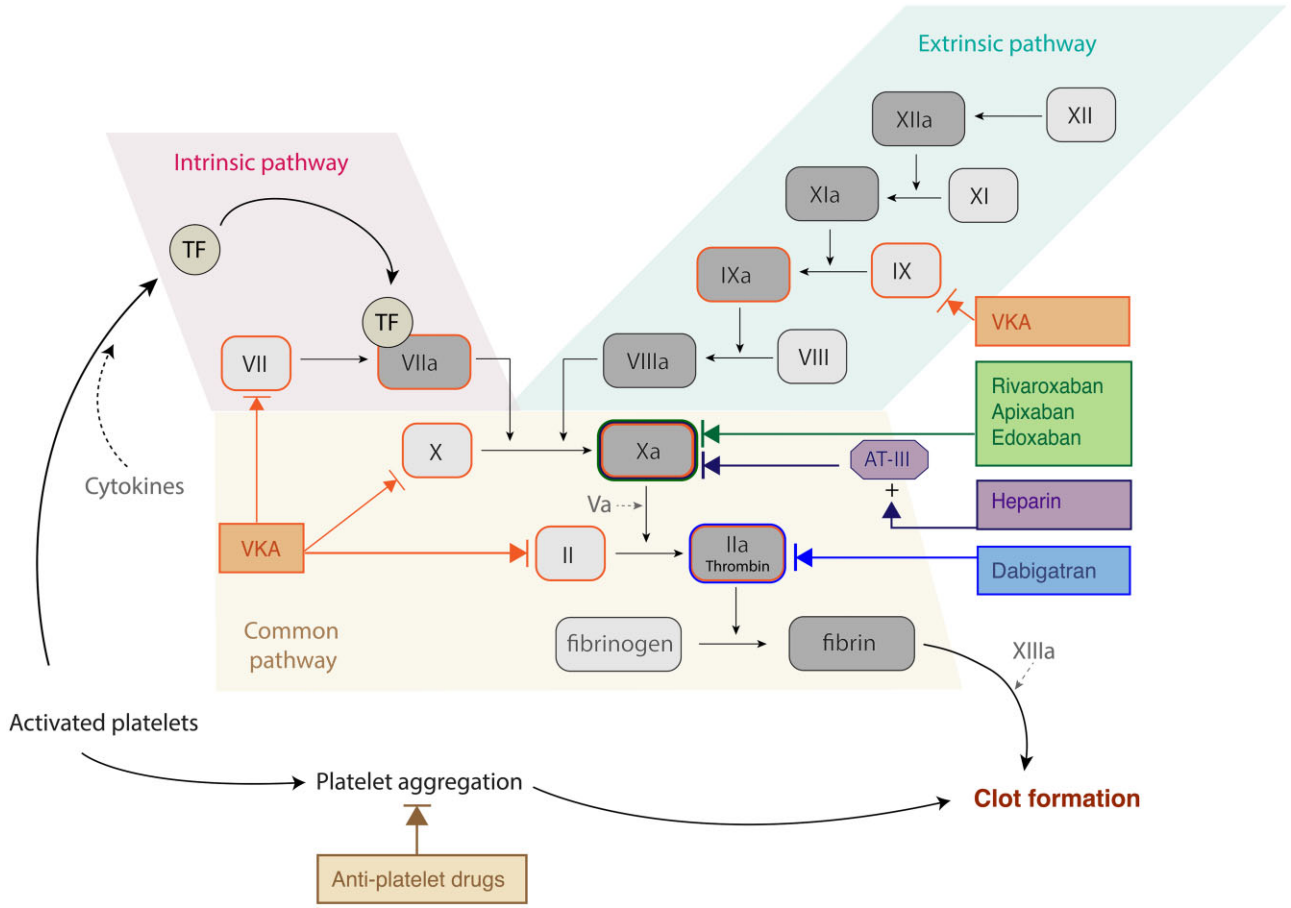


Figure 1: Schematic overview of the coagulation cascade and the mechanisms of action of the various anticoagulants. TF: tissue factor; VKA: vitamin K antagonist. Illustration by Barry van Varik (Pulse Medical Art).

Direct oral anticoagulant reversal agents

Previously, the absence of reversal agents was considered a limitation of DOAC therapy, but several direct antidotes have been introduced in recent years. Among these antidotes, 'Ciraparantag' and 'recombinant factor Xa' variants are still under development and being licenced [21, 22] and will therefore not be discussed in the current review.

Idarucizumab. Idarucizumab is a monoclonal antibody fragment that binds free and thrombin-bound dabigatran (Table 3), acting quickly within 10–30 min. By this binding mechanism, dabigatran's effect is reversed, reducing the risk of bleeding (Fig. 2). The beneficial effect of idarucizumab administration has been confirmed in bleeding patients and patients undergoing urgent surgery [23]. It is noteworthy that in the full-cohort analysis of the uncontrolled REVERSE-AD trial, thrombotic events only occurred in 4.8% of patients within 30 days [6].

Andexanet alfa. Andexanet alfa (Ondexxya, Andexxa) is a modified FXa protein that acts as a decoy by actively binding and sequestering FXa inhibitors, offsetting their anticoagulant mechanism within several min (Table 3). Furthermore, andexanet alfa competes with factor Xa for binding to the antithrombin (AT)–heparin complex [24], thus also neutralizing the effect of low-molecular weight heparin (LMWH) and unfractionated heparin (UFH), which will be elaborated on in the following sections [24]. In the ANNEXA-4 trial, 10% of patients developed a thromboembolic complication within 30 days, which could be due to late re-initiation of anticoagulation or a reflection of the reversible binding of andexanet alfa to tissue factor pathway inhibitor [24, 25]. Illustrating its efficacy, a recent comparison between indirect and direct reversal agents found andexanet alfa to be superior to conventional management [prothrombin complex concentrate (PCC)] in a matched study of patients with intracranial haemorrhage [26]. While the use of andexanet alfa for edoxaban reversal is not yet approved, studies have reported similar efficacy in reducing anti-Xa activity compared to patients on rivaroxaban and apixaban [27].

DIRECT ORAL ANTICOAGULANTS IN CARDIAC SURGERY PATIENTS

Numerous studies have addressed the safety of DOAC post-cardiac surgery, particularly for NVAF. These studies have consistently found that DOACs carry a similar or even a reduced risk of stroke without increasing the risk of bleeding, compared to VKAs [28, 29]. In a study conducted by the Virginia Cardiac Services Quality Initiative, which examined all patients between 2011 and 2018, 18% of patients were discharged on anticoagulation. Among these patients, 23% were prescribed DOACs. There was an approximate annual increase of 2% in the use of DOACs over

Table 2: Pharmacological characteristics of direct oral anticoagulants and considerations for dose adjustment, monitoring and reversal

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Half-life (h)	14–17	7–11	8–14	5–11
Tmax (h)	1–2	2–4	3–4	1–2
Time-to-peak effect (h)	1–3	2–4	1–2	1–2
Renal clearance (%)	80	33	27	50
Adjusted dose (for NVAF)	110 mg twice daily	15 mg once daily	2.5 mg twice daily	30 mg twice daily
Adjust when	CrCl <50 ml/min[a] Age >80 years Verapamil use	CrCl <50 ml/min	CrCl <30 ml/min Age >80 years Weight <60 kg	CrCl <50 ml/min Weight <60 kg Use of P-gp inhibitors
Cessation before high-risk surgery	CrCl >80 ml/min: 48 h	CrCl >50 ml/min: 48 h	CrCl >50 ml/min: 48 h	CrCl >50 ml/min: 48 h
Adjusted cessation	CrCl 50–80 ml/min: 72 h CrCl 30–49 ml/min: 96 h	CrCl 30–50 ml/min: 72 h	CrCl 30–50 ml/min: 72 h	CrCl 30–50 ml/min: 72 h
Monitoring DOAC activity				
Specific	Diluted TT	Anti-Xa[b]	Anti-Xa[a]	Anti-Xa[a]
Threshold drug calibrated	<21 s	<30 ng/ml	<30 ng/ml	<30 ng/ml
Threshold LMWH calibrated (IU/ml)	<0.1	<0.1	<0.1	<0.1
Non-specific	aPTT (PT secondary)	PT (aPTT secondary)	PT (aPTT secondary)	PT (aPTT secondary)
Non-specific countermeasures				
Primary	(a)PCC (50 IU/kg initial dose) Haemodialysis Ultrafiltration on CPB	(a)PCC (50 IU/kg initial dose)	(a)PCC (50 IU/kg initial dose)	(a)PCC (50 IU/kg initial dose)
Secondary	r-FVIIa	r-FVIIa	r-FVIIa	r-FVIIa
Specific reversal agents				
Generic drug name	Idarucizumab	Andexanet alfa	Andexanet alfa	Andexanet alfa

Based on European Association for Cardiothoracic Surgery (EACTS)/European Association for Cardiothoracic Anesthesiology (EACTA) guidelines on patient blood management for adult cardiac surgery [32] and partly adapted from Erdoes *et al.* [18].

[a]Contraindicated in moderate–severe renal impairment (CrCl <30 ml/min/m^2).

[b]It is recommended that these anti-Xa tests are calibrated for the specific DOAC [17].

(a)PCC: (activated) prothrombin complex concentrate; aPTT: activated partial thromboplastin time; CPB: cardiopulmonary bypass; CrCl: creatinine clearance; DOAC: direct oral anticoagulant; LMWH: low-molecular weight heparin; NVAF: non-valvular atrial fibrillation; P-gp: P-glycoprotein; PT: prothrombin time; r-FVIIa: recombinant FVIIa (novoseven); TT: thrombin time.

the course of the study period, which progressed from 10.3% in the first year to 35.4% in the last study year [3]. Although there is a scarcity of literature on the number of patients on DOACs before cardiac surgery, these data suggest that 42% of discharged patients on anticoagulation had a preoperative anticoagulation indication [3].

MANAGEMENT OF NON-EMERGENCY PATIENTS ON DIRECT ORAL ANTICOAGULANTS

Elective procedures

Several guidelines for discontinuation regimens of DOACs have been published. We based our recommendations on these consensus statements [18, 30, 31], in addition to contemporary literature. For patients with a normal renal function, DOACs can be ceased 48 h prior to cardiac surgery [32]. However, it is crucial to take additional precautions for patients with a compromised renal function, particularly in case of dabigatran use. In these cases, the cessation strategy must be adapted based on a recent assessment of the renal function (guided by the obtained CrCl). An overview of such an adjusted cessation strategy can be found in Table 2 [32].

There may be instances where DOACs need to be bridged with UFH or LMWH prior to the surgery. This decision is usually based on the thromboembolic risk estimation in cases where the indication is NVAF. According to the European Guidelines, for men with a CHA_2DS_2-VASc score of ≥2 and women with a score of ≥3, anticoagulation bridging with either UFH or LMWH is recommended [31, 32]. Other factors that necessitate bridging include recent thrombotic events (<4 weeks), and a high thromboembolic risk such as the presence of an intraventricular thrombus, AT 3 deficit or protein C/S deficiency [31].

Urgent procedures

For urgent cardiac surgery procedures, where the patient cannot be discharged without undergoing a surgical procedure, there are no specific guidelines concerning the use of DOACs [18, 33]. However, a similar cessation protocol to that used for elective patients can be applied. Since such patients are typically hospitalized for a longer period of time in the preoperative phase, this offers a sufficient period for DOAC cessation. If there is any doubt regarding residual DOAC levels and their activity, a calibrated activity test can be used [18]. According to the consensus statement by the European Association of Cardiothoracic Anaesthesiology, the pharmacological reversal of DOACs may be indicated in patients undergoing cardiac surgery with drug levels >30 ng/ml [18]. However, the indication for such a reversal is

Table 3: Pharmacological properties of idarucizumab and andexanet alfa

	Idarucizumab	Andexanet alfa
Brand name	Praxbind	Ondexxya Andexxa
Target	Dabigatran	Rivaroxaban Apixaban Edoxaban[a]
Mode of action	Non-competitive inhibitor	Decoy protein sequestering FXa inhibitors
Administration	Intravenous	Intravenous
Dosing	5 g in 2 separate vials (infusion within 15 min)	Low dose: 400 mg bolus, 2-h infusion 4 mg/min High dose: 800 mg bolus, 2-h infusion 8 mg/min
Specific dosing recommendations	NA	Last DOAC intake >8 h ago: low dose Last DOAC intake <8 h ago: high dose (rivaroxaban >10 mg, apixaban >5 mg), low dose (rivaroxaban <10 mg, apixaban <5 mg)
Onset	10–30 min	Within minutes
Half-life	45 min	5–7 h
Costs [51, 52][b]	€3000	€23 000 (low dose) €45 000 (high dose)

[a]Not (yet) approved for edoxaban, but studies have reported a similar efficacy for the reduction in anti-Xa activity, as compared to rivaroxaban and apixaban [27].
[b]References for the cost evaluation.
DOAC: direct oral anticoagulant; NA: not applicable.

dependent on the type of DOAC and the progressive urgency of the surgical indication.

MANAGEMENT IN EMERGENCY CASES

In emergency cases, specialized interventions may be necessary. These interventions could either be pharmacological or may involve the use of mechanical devices.

Pharmacological management

Depending on the renal function, it can take substantial time for the anticoagulant effects of DOACs to wear off. This delay may be unacceptable in emergency cases, prompting the use of pharmacological interventions. As such, clinicians should be aware of the conventional countermeasures that can be given to patients on DOACs.

First, general measures to reduce the risk of bleeding include the maintenance of normothermia, the suppletion of Ca^{2+}, the correction of possible acidosis and the use of autologous cell salvage (cell saver) [18]. Second, the administration of PCC and activated prothrombin complex concentrate [(a)PCC] may be indicated, replenishing the vitamin K-dependent factors FII, FVII, FIX, FX and protein C/S (Fig. 2A) [20]. A small randomized trial demonstrated that 2 PCC strategies markedly increased and normalized endogenous thrombin potential in patients using apixaban compared to placebo [34]. (a)PCC strategies are generally readily available and are known to be cost-effective [35]. Prior anaphylactic reactions to such concentrates are the most important contraindication for their use [36], and other relative contraindications are presumably less important in the light of the potential life-saving treatment effect. Current European guidelines recommend the use of (a)PCC in bleeding patients on FXa inhibitors, over direct FXa-reversal agents [37]. In such instances, the dose should be adapted to the patient's body weight (50 IU/kg, Table 3) [37]. The administration of fresh frozen plasma is not recommended, in the absence of a proven reversal effect [38]. Another alternative, and perhaps a last resort, is the use of recombinant FVIIa (r-FVIIa, 'novoseven'), which may be beneficial but carries a high financial cost [39].

Direct reversal agents. The rapid systematic literature review across 3 databases yielded 19 reports detailing cases of cardiac surgery patients where direct pharmacological reversal of DOACs was applied (Supplementary Material 1 and 2). The search led to the evaluation of 13 studies that reported on 84 patients undergoing cardiac surgery who were treated with idarucizumab (Fig. 2B), and 6 studies reporting on 9 cardiac surgery patients who were treated with andexanet alfa (Fig. 2B). A summary of these cases and their outcomes are presented in Supplementary Material 3 (idarucizumab) and Table 4 (andexanet alfa).

The use of idarucizumab in patients using dabigatran undergoing emergency cardiac surgery is supported by both European and American surgical guidelines [32, 40]. Also, most recent anaesthesiologic and intensive care guidelines recommend the use of idarucizumab as a primary line of treatment in bleeding surgical patients on dabigatran, over (a)PCCs [37]. As emergency surgery patients were also included in the REVERSE-AD trial [41], the use of idarucizumab is approved for this specific population. In our synthesis of available literature, 84 cardiac surgery patients received uneventful idarucizumab therapy during various perioperative phases, yielding favourable outcomes (Supplementary Material 3). None of these patients experienced complications related to heparinization and the initiation of cardiopulmonary bypass (CPB). Importantly, 7.5% of patients in the largest cohort within these 84 patients required surgical re-exploration for bleeding, and 66% of patients received any form of perioperative transfusion [42]. In particular, patients awaiting cardiac transplantation were reported to receive dabigatran therapy and subsequent reversal. Indeed, such patients may need anticoagulant therapy for a variety of indications. The unpredictability of donor availability and the emergent nature of transplantation when a

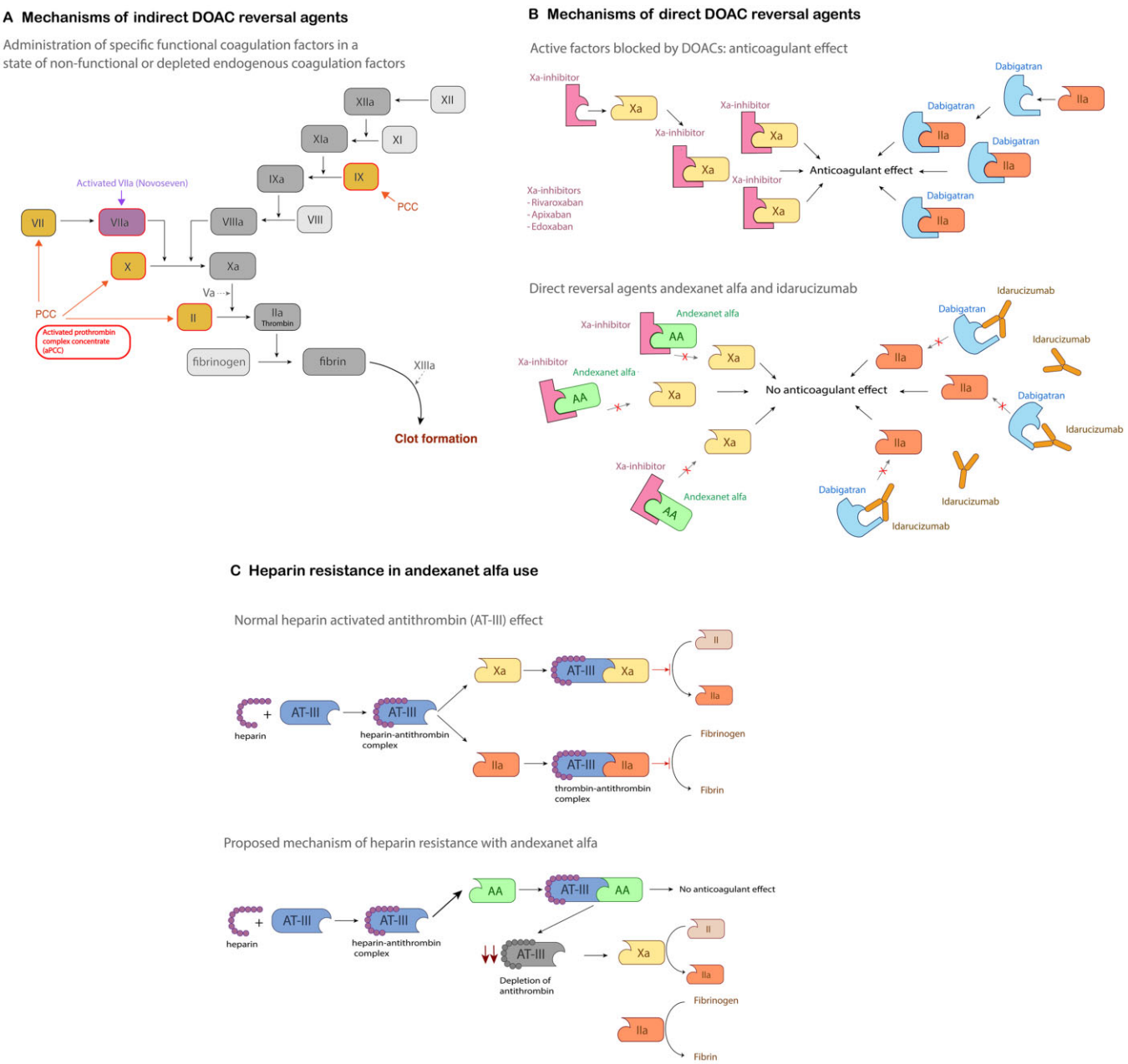


Figure 2: Mechanisms of actions of the various indirect (**A**) and direct (**B**) DOAC reversal agents, and a visual representation of the heparin resistance hypothesis (**C**). AA: andexanet alfa; AT: antithrombin; DOAC: direct oral anticoagulant; PCC: prothrombin complex concentrate. Illustration by Barry van Varik (Pulse Medical Art).

donor becomes available warrant an immediately accessible and reliable antidote.

As for andexanet alfa, literature is scarce regarding its indication and timing of administration, particularly in the perioperative phase. Moreover, andexanet alfa was not yet approved when the European guidelines on perioperative blood management were published [32]. However, more recent American guidelines recommend the administration of andexanet alfa in patients on rivaroxaban or apixaban who require emergency cardiac surgery [40]. Remarkably, surgical patients were excluded from the ANNEXA-4 trial and its use is actually not approved in emergency surgical patients [43] and therefore considered off-label.

Several trials have demonstrated the efficacy of andexanet alfa in patients at high risk of bleeding [5], but concerning cases have been reported in patients undergoing cardiac surgery [44–49]. As shown in Table 4, andexanet alfa was safely administered to patients after weaning off CPB. However, important issues regarding heparinization were reported in all patients treated with andexanet alfa during the preoperative phase. Most likely, heparin resistance led to significant clot formation in the CPB circuit, resulting in compromised outcomes in several instances. Therefore, the recommendation to administer andexanet alfa preoperatively, as stated in the American guidelines [40], may be flawed. Following these clinical observations, the European Medicines Agency even issued a warning, advising to 'avoid the

Table 4: Tabular overview of reported cases in patients undergoing cardiac surgery with FXa inhibitor reversal

Author	Year	Number of patients	DOAC	Reversal agent and timing	Type of intervention	Details	Clinical outcome
Al-Attar *et al.* [44]	2023	3	Rivaroxaban (1), edoxaban (2)	Andexanet alfa, preoperatively (1), post-CPB (2)	Emergency surgery for ATAAD	Heparin resistance in the patient with preoperative andexanet alfa administration	Survived (3)
Apostel *et al.* [45]	2021	1	Apixaban	Andexanet alfa, preoperatively	Surgical management of LV free wall rupture	Heparin resistance and clot formation in the CPB circuit counteracted with AT administration	Survived
Brenner *et al.* [46]	2022	2	Apixaban (2)	Andexanet alfa, intra-operatively on-CPB (1), intra-operatively pre-CPB (1)	Emergency surgery for ATAAD	Heparin resistance in both patients, with significant CPB clot formation in 1 patient	Survived (1) Deceased (1)
Flaherty *et al.* [47]	2019	1	Apixaban	Andexanet alfa, preoperatively	Emergency root repair for pseudo-aneurysm	Heparin resistance, overcome by administration of 80 000 IU of UFH achieving an ACT of 434 s	Survived
Honda *et al.* [48]	2023	1	Edoxaban	Andexanet alfa, preoperatively	Emergency aortic arch surgery	Heparin resistance, counteracted by 60 000 IU of UFH and 3000 IU of AT	Unknown
Kainz *et al.* [49]	2021	1	Apixaban	Andexanet alfa, intra-operatively, post-CPB and post-protamine administration	Emergency surgery for ATAAD	Administration of andexanet alfa on V-A ECMO. Uneventful initiation of UFH on POD1	Survived

ACT: activated clotting time; AT: antithrombin; ATAAD: acute type A aortic dissection; CPB: cardiopulmonary bypass; DOAC: direct oral anticoagulant; LV: left ventricular; POD: postoperative day; UFH: unfractionated heparin; V-A ECMO: veno-arterial extracorporeal membrane oxygenation.

use of andexanet alfa before heparinization' [50]. Furthermore, the European Medicines Agency stated that the results of coagulation tests are not reliable when andexanet alfa is administered, particularly in combination with heparin [50]. In contemporary European anaesthesiology guidelines, the administration of (a)PCCs is therefore also favoured over andexanet alfa, in bleeding surgical patients on FXa inhibitors. Finally, an important issue is the high financial cost of these agents, applying to andexanet alfa in particular (Table 3). The literature on the cost-effectiveness is scarce, and primarily focuses on non-surgical patients (i.e. patients with intracranial haemorrhage) [51–53]. As cost-effectiveness is yet to be demonstrated, specifically in surgical patients, this issue should also be heavily weighed when considering the indication for the administration of these reversal agents.

Despite these concerns, in some cases, such as an iatrogenic tamponade with persistent bleeding following any transcatheter intervention, andexanet alfa may have already been administered in the referring centre. When an emergency surgical intervention is indicated to resolve the bleeding despite the reversal of an FXa inhibitor, heparin resistance can be anticipated.

Heparin resistance and its management. The possible mechanism of heparin resistance following andexanet alfa administration is elegantly described by Apostel *et al.* [45], and the concept is further commented on by Erdoes *et al.* [54] (a visualization of this concept is presented in Fig. 2C). Typically, when UFH is used to achieve an adequate activated clotting time (ACT) for the safe initiation of CPB, UFH enhances the activity of AT. These UFH–AT complexes then inactivate thrombin (FIIa) and activated factors IX, X, XI and XII, thereby halting the coagulation cascade and preventing consumptive coagulopathy on CPB (Fig. 1). Although *in vitro* and clinical data are scarce [55], it is most likely that andexanet alfa also serves as a decoy protein for the UFH–AT complexes, thereby inhibiting their anticoagulant effect [56]. This heparin ineffectiveness is an example of the condition more commonly known as 'heparin resistance' [57]. In the cases referenced, the absolute or relative AT depletion was counteracted by the administration of additional recombinant AT, with a favourable effect in 2 reports [45, 48]. Interestingly, in another case, the administration of 80 000 IU UFH ultimately achieved an adequate ACT [47]. Alternatively, bivalirudin or argatroban can be considered a useful alternative anticoagulant strategy when andexanet has already been administered [58–60]. Lastly, device-based haemoadsorption can be considered, with several options available.

Mechanical device management

An intuitive method for mechanical filtration of any drug is the implementation of haemodialysis. This might be particularly

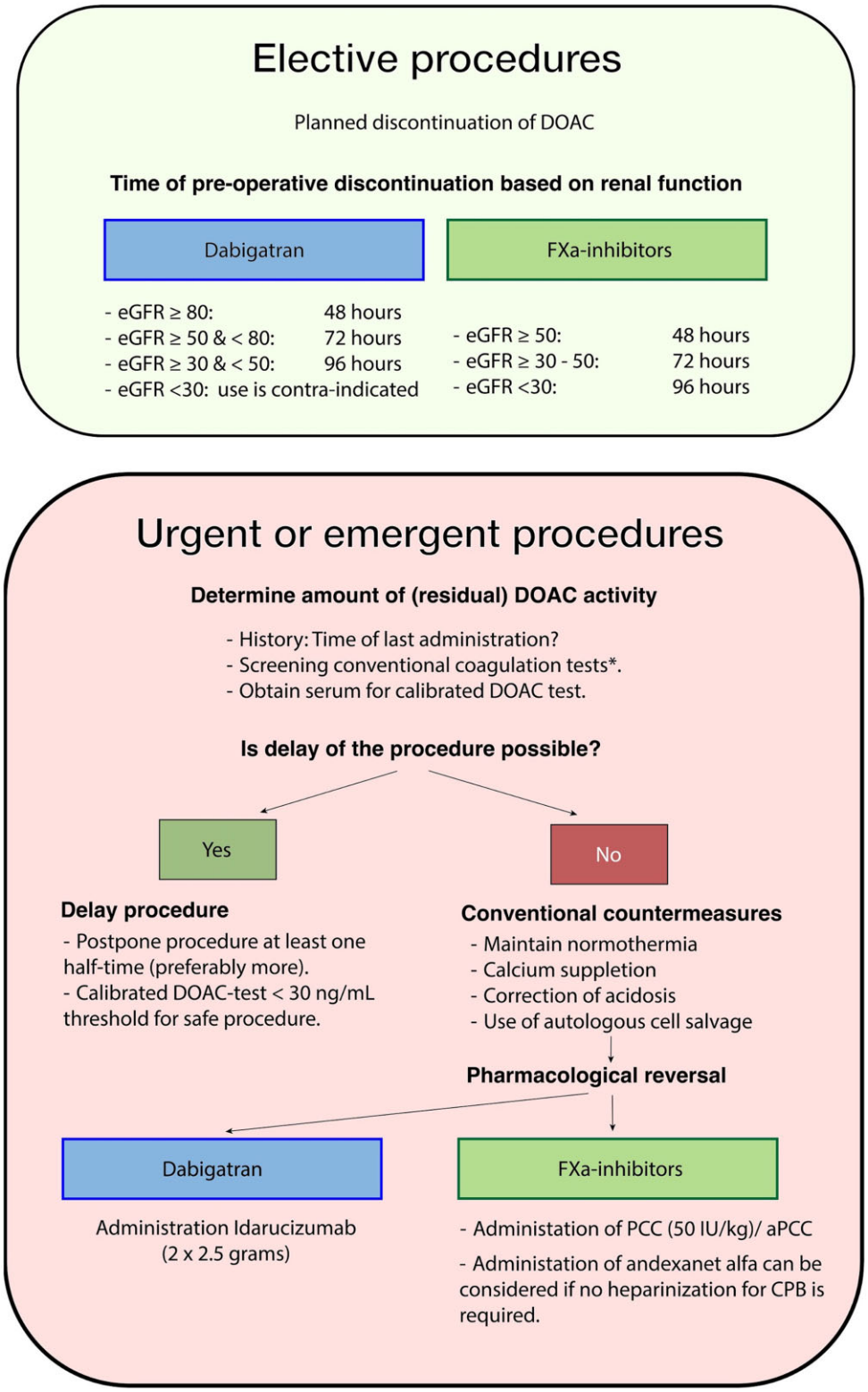


Figure 3: Clinical decision pathway for perioperative management of cardiac surgery patients using DOACs. *Conventional screening tests may not be reliable. CPB: cardiopulmonary bypass; DOACs: direct oral anticoagulants; eGFR: estimated glomerular filtration rate; PCC: prothrombin complex concentrate. Illustration by Barry van Varik (Pulse Medical Art).

applicable to patients using dabigatran, as dabigatran is only partially protein bound (35%). Of note, haemofiltration can also be considered during CPB. Four hours of haemodialysis has been shown to reduce dabigatran drug levels by >50% [61, 62]. However, it is important to note that the FXa inhibitors are highly protein-bound, rendering haemodialysis ineffective [18]. Moreover, applying haemodialysis could further compromise the haemodynamic status of an already unstable patient [63], and the

Table 5: Ten practical recommendations for the perioperative management of patients using direct oral anticoagulants

	Recommendations	Refs.
1.	DOACs are safe to prescribe for patients scheduled for elective cardiac surgery	[28, 29]
2.	For elective procedures, the discontinuation strategy should take into account the renal function. This particularly applies to dabigatran, which is renally excreted and requires a different discontinuation regimen compared to other DOACs	[15, 30] [32]
3.	In urgent scenarios, a similar protocol can be used. If there is any uncertainty regarding residual DOAC activity, a calibrated DOAC activity test can be performed. A drug level of <30 ng/ml is considered a safe threshold in terms of bleeding risk	[18]
4.	Conventional coagulation tests, such as PT and aPTT, lack specificity and may not accurately reflect the residual anticoagulant drug effect	[17, 18]
5.	In emergency cases, pharmacological reversal might be indicated, but the decision and timing of reversal depend on the specific DOAC in use	[32, 40]
6.	Dabigatran can safely and effectively be reversed by idarucizumab during any perioperative phase, without important side effects or heparinization issues	[42]
7.	Therefore, dabigatran might be the DOAC of choice for patients on waiting lists with an impending emergency indication for cardiac surgery, such as cardiac transplant recipients	[42]
8.	Andexanet alfa should never be administered before or during surgery when CPB is still required, due to its impact on heparinization. The administration of (a)PCC is favoured over andexanet. Yet, in cases with persistent bleeding after weaning from CPB, andexanet alfa can be used at that stage or anytime thereafter.	[44–50]
9.	When andexanet alfa is administered in the preoperative phase and heparinization is still warranted, antithrombin has been used to achieve desired ACT levels. Alternatively, bivalirudin or argatroban can be used instead of heparin to safely commence CPB	[45, 48, 54, 58–60]
10.	DOACs can also be mechanically removed by haemodialysis (dabigatran) or designated filters (FXa inhibitors). However, literature on this strategy is limited, rendering it only applicable in specific cases	[61, 62, 64, 66]

(a)PCC: activated prothrombin complex concentrate; ACT: activated clotting time; aPTT: activated partial thromboplastin time; CPB: cardiopulmonary bypass; DOACs: direct oral anticoagulants; F: factor; PT: prothrombin time.

time required to arrange haemodialysis may not always align with the emergent nature of the procedure.

More contemporary solutions for mechanical drug removal are being developed, among which filtration by CytoSorb (CytoSorbents Inc., USA) is the most commonly applied device. This device is integrated into the CPB circuit, positioned between the oxygenator and the venous reservoir. CytoSorb has been reported to effectively clear rivaroxaban (and ticagrelor) and has improved clinical outcomes in general cardiac surgery patients and patients with acute type A aortic dissection [64, 65]. In addition, a recent case report confirmed the potential of CytoSorb in apixaban clearance as well [66]. However, it should be noted that the CytoSorb device relies on the CPB circuit and cannot counteract potential heparin resistance if andexanet alfa is administered during the preoperative phase. Finally, providing specific recommendations on mechanical device management of DOACs in emergency patients can be challenging as literature is scarce and the technique is still in its infancy. As such, larger trials are currently being conducted [66].

GENERAL RECOMMENDATIONS FOR PERIOPERATIVE MANAGEMENT OF DIRECT ORAL ANTICOAGULANTS IN CARDIAC SURGERY

Our goal was to present clinicians with 10 practical recommendations for managing patients on DOACs in the acute setting cardiac surgical setting. These insights, drawn from available literature and clinical experience, are depicted in Fig. 3 and presented in Table 5.

CONCLUSION

DOACs are increasingly prescribed for patients undergoing cardiac surgery. For elective and urgent cardiac surgery procedures, the cessation strategy is relatively straightforward and can be guided by the renal function and, in some instances, by DOAC activity monitoring. However, for patients with an emergency indication for cardiac surgery, additional interventions such as pharmacological reversal may be warranted. The use of idarucizumab appears to be safe in any periprocedural phase, but the preoperative administration of andexanet alfa likely leads to significant clinical problems and should be avoided. Literature on mechanical device management in DOAC use is limited, underscoring the need for future research to definitely determine its role in the perioperative management of these patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: Dr. Bart Maesen is a consultant for Medtronic and Atricure, not related to this work. The other authors report no conflict of interest.

DATA AVAILABILITY

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

Author contributions

Samuel Heuts: Conceptualization; Formal analysis; Investigation; Methodology; Visualization; Writing—original draft; Writing—review & editing. **Angelique Ceulemans:** Methodology; Supervision; Validation; Writing—review & editing. **Gerhardus J.A.J.M. Kuiper:** Supervision; Validation; Writing—review & editing. **Jan U. Schreiber:** Supervision; Validation; Writing—review & editing. **Bernard J. van Varik:** Supervision; Validation; Visualization; Writing—

review & editing. **Renske H. Olie:** Supervision; Validation; Writing—review & editing. **Hugo Ten Cate:** Supervision; Validation; Writing—review & editing. **Jos G. Maessen:** Supervision; Validation; Writing—review & editing. **Milan Milojevic:** Conceptualization; Supervision; Validation; Writing—original draft; Writing—review & editing. **Bart Maesen:** Conceptualization; Methodology; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

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