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The American Journal of Hematology

ISSN 3064-6553

DIRECTIVE PUBLICATIONS

*Research Article*

# Systematic Review on New Anticoagulants and Their Reversibility, Studies on The Safety, Efficacy, and Antidotes of Direct Oral Anticoagulants (Doacs).

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## Abstract

Direct oral anticoagulants (DOACs) have revolutionized the prevention and treatment of non-valvular atrial fibrillation and venous thrombosis, offering similar or superior efficacy to warfarin with a lower risk of intracranial hemorrhage. However, the occurrence of major bleeding, particularly in the gastrointestinal tract and intracranial, remains a significant clinical challenge, reinforcing the need for effective reversal strategies.

**Objective:** To evaluate the scientific literature on the efficacy, safety, and reversibility of DOACs, highlighting specific antidotes (idarucizumab and andexanet alfa) and non-specific alternatives, and to discuss their clinical and regulatory impact.

**Methodology:** A systematic review was conducted following the PRISMA 2020 recommendations, including randomized clinical trials, meta-analyses, observational studies, and guidelines published between 2010 and 2025. The PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and Scopus databases were searched using descriptors related to DOACs, efficacy, safety, and reversal.

**Results:** The literature confirms that DOACs significantly reduce thromboembolic events, intracranial hemorrhage, and mortality compared to warfarin, although they present a variable risk of gastrointestinal bleeding among the different agents. Idarucizumab demonstrated immediate and sustained reversal of dabigatran, with high rates of hemostasis and clinical safety. Andexanet alfa showed hemostatic efficacy in severe bleeding due to factor Xa inhibitors, but was associated with a higher incidence of thrombotic events, with no proven benefit in mortality or functional disability in the ANNEXA-I study. Alternatives such as prothrombin complex concentrate (4F-PCC), hemodialysis (for dabigatran), and activated charcoal in recent ingestion remain relevant. Evidence also suggests that off-label doses increase the risk of complications, reinforcing the need for individualized adjustments.

**Conclusion:** DOACs represent a significant therapeutic advance, but their reversal remains a field of debate and development. Specific antidotes are already a clinical reality, albeit with limitations. Individualized strategies, institutional protocols, and future research on universal antidotes, such as ciraparantag, are essential to optimize safety and reduce morbidity and mortality in anticoagulated patients.

**Keywords** : Direct oral anticoagulants; Reversal; Idarucizumab; Andexanet alfa; Safety; Efficacy; Hemorrhage.

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**Received:** 26-August-2025, Manuscript No. TAJOH - 5083 **; Editor Assigned:** 29-August-2025 **; Reviewed:** 12-September-2025, QC No. TAJOH - 5083 **;**
**Published:** 17-September-2025, DOI: 10.52338/tajoh.2025.5083.
**Citation:** **Thiago Augusto Rochetti Bezerra.** Systematic Review On New Anticoagulants And Their Reversibility, Studies On The Safety, Efficacy, And Antidotes Of Direct Oral Anticoagulants (Doacs). The American Journal of Hematology. 2025 September; 13(1), doi: 10.52338/tajoh.2025.5083.
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## INTRODUCTION

Direct oral anticoagulants (DOACs) dabigatran (direct thrombin inhibitor) and factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) have transformed the prevention of thromboembolism in atrial fibrillation (AF) and the treatment of venous thrombosis (VT), offering predictable pharmacokinetics, fewer interactions, and no routine INR monitoring. In a meta-analysis of individual patient data from pivotal trials, DOACs (at standard doses) reduced stroke/systemic embolism and, above all, intracranial hemorrhage compared with warfarin, with lower overall mortality at the cost of higher bleeding profiles in the gastrointestinal tract in some subgroups (CARNICELLI et al., 2022).

In recent years, scientific societies have published specific guidelines for DOAC reversal, structuring care pathways for life-threatening bleeding and urgent procedures. These documents emphasize rapid hemostatic assessment, preferential use of specific antidotes when available, and the importance of resuming anticoagulation as soon as safe to mitigate rebound thrombotic events (LEVY et al., 2024).

For dabigatran, the specific antidote idarucizumab (monoclonal antibody fragment) promotes immediate and complete neutralization of the anticoagulant effect. In the multicenter, cohort study RE-VERSE AD, 5 g of idarucizumab reversed 100% of anticoagulant activity within 4 hours, with hemostasis classified as normal or mildly abnormal in most cases and acceptable rates of subsequent thrombotic events (POLLACK et al., 2017). Subsequent real-world evidence has corroborated the high hemostasis rate and good safety profile in diverse populations, including thrombolysis settings for ischemic stroke (DAI et al., 2023).

For factor Xa inhibitors, andexanet alfa (a recombinant inactive FXa mimetic) rapidly reduces anti-Xa activity and is associated with good/excellent hemostatic control in most patients with major bleeding. In the final report of ANNEXA-4 (phase 3b/4, 479 patients), a ~93–94% reduction in anti-Xa activity was observed for apixaban/rivaroxaban and good/excellent hemostasis in ~ 80% of cases; thrombotic events occurred in ~10% during follow-up, reinforcing the need to reinstate anticoagulation when clinically safe (MILLING et al., 2023).

In the absence of a specific antidote or when it is unavailable, supportive management is recommended and, in some settings, the use of prothrombin complex concentrate (PCC/4F-PCC) as a non-specific strategy to reverse DOACs recognizing the limitations of comparative evidence and the prothrombotic potential. Hemostasis should be optimized with local and transfusion measures, and anticoagulation should be restarted in a timely manner (LEVY et al., 2024).

Adjuvant measures include activated charcoal when ingestion is very recent and, in particular, hemodialysis for overexposure to dabigatran due to its low plasma protein binding according to the updated regulatory label (UNITED STATES. FDA, 2024).

Finally, there is interest in “universal” antidotes. Ciraparantag (PER977), a small molecule that binds through non-covalent interactions to several anticoagulants, rapidly and sustainably reversed prolonged total clotting time in elderly volunteers anticoagulated with apixaban or rivaroxaban (phase 2 trials), with a favorable safety profile; However, clinical outcome data in critical bleeding situations are still needed before widespread adoption (ANSELL et al., 2021).

Given this scenario, a systematic review on the reversibility of DOACs considering the efficacy and safety of specific antidotes (idarucizumab, andexanet), the role of non-specific strategies (PPC/aPPC, dialysis for dabigatran, charcoal), target intervention times, and clinical outcomes is essential to inform institutional protocols and reduce morbidity and mortality associated with bleeding under anticoagulation.

## OBJECTIVES

### General objective

To conduct a systematic review of the literature to evaluate the safety, efficacy, and reversal strategies of direct oral anticoagulants (DOACs), including the impact of specific antidotes (idarucizumab, andexanet alfa) and non-specific measures (prothrombin complex concentrate, activated charcoal, hemodialysis).

### Specific objectives

1. Identify and analyze the main clinical trials and observational studies that investigated the efficacy of DOACs compared to vitamin K antagonists.
2. Evaluate safety data, focusing on major bleeding events and thrombotic complications after reversal.
3. Review the literature on the availability, mechanisms of action, and clinical effectiveness of specific antidotes for DOACs.
4. Synthesize the evidence on non-specific reversal alternatives in emergency settings.
5. Compare clinical outcomes of reversal in different scenarios (intracranial bleeding, gastrointestinal bleeding, urgent surgical need).

## METHOD

This systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020).

✓ Sources of information: The PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and Scopus databases will be systematically searched, in addition to gray literature (Google Scholar, ClinicalTrials.gov, medical society guidelines).

✓ Search strategy: Controlled descriptors (MeSH and Emtree) and free keywords in English and Portuguese were used, such as: "direct oral anticoagulants," "DOACs," "dabigatran," "apixaban," "rivaroxaban," "edoxaban," "reversal," "antidote," "idarucizumab," "andexanet alfa," "ciraparantag," "safety," and "efficacy."
✓ Boolean operators (AND, OR, NOT) were applied to combine terms.

✓ **Inclusion criteria**
- Randomized clinical trials (RCTs), cohort studies, case-control studies, and relevant case series;
- Adult population (≥18 years) using DOACs;
- Studies that evaluated the safety, efficacy, or reversibility of DOACs;
- Publications in English, Portuguese, or Spanish between 2010 and 2025.

✓ **Exclusion criteria**
- Studies exclusively in animal models or in vitro;
- Narrative reviews, editorials, letters to the editor;
- Duplicate studies or studies with insufficient data for extraction.

✓ **Data extraction and synthesis**
Information was collected on: study design, number of participants, drug used, type of reversal, primary outcomes (hemostatic effectiveness, laboratory reversal), and secondary outcomes (thrombotic events, mortality, re-exposure to anticoagulants).

✓ **Methodological quality assessment**
- For RCTs, the Cochrane Risk of Bias 2 (RoB 2) tool was used;
- For observational studies, the Newcastle-Ottawa Scale (NOS) tool was used.

✓ **Summary of results**
A qualitative analysis of the findings was performed. Given the sufficient homogeneity among the studies, a meta-analysis can be conducted using a random effects model, with calculation of relative risk (RR) or odds ratio (OR) and 95% confidence intervals.

## RESULTS

**Overall efficacy of DOACs compared to warfarin**
Direct oral anticoagulants (DOACs) have been shown to be superior to warfarin in terms of efficacy and safety in patients with non-valvular atrial fibrillation. A comprehensive meta-analysis based on individual data from four pivotal clinical trials involving 71,683 patients demonstrated that DOACs at standard doses significantly reduced the incidence of stroke (HR 0.81) and systemic thromboembolism (HR 0.81), in addition to decreasing the occurrence of intracranial hemorrhage (HR 0.45) and mortality (HR 0.92).
The risk of major bleeding was similar or slightly lower than that observed with warfarin. However, when reduced doses were used without formal indication or (e.g., without adjustment for renal function), safety was maintained, but there was a loss of efficacy in preventing stroke/TE. These results consolidate DOACs as the first choice in the treatment of atrial fibrillation (CARNICELLI et al., 2022).

**Safety of DOACs in relation to gastrointestinal bleeding**
Despite their overall efficacy, there are differences in the safety profile between molecules. A meta-analysis of 37 randomized clinical trials using Bayesian network analysis revealed that apixaban at a standard dose had the lowest risk of major gastrointestinal bleeding (MGB) when compared to rivaroxaban and dabigatran. Among reduced doses, edoxaban 30 mg/day had a lower risk of GIB compared to rivaroxaban 10 mg/day.
Overall, DOACs did not significantly increase the risk of GIB compared to conventional therapy, but these differences between agents and doses reinforce the importance of individualized drug selection (ZHANG et al., 2022).

**Reversal of dabigatran with idarucizumab**
The development of specific antidotes has led to important advances in the safety of DOAC use. Idarucizumab, a monoclonal antibody fragment, is used to reverse dabigatran. In the RE-VERSE AD study, which included 503 patients, reversal was complete within 4 hours in virtually all cases. In urgent surgery settings, hemostasis was classified as normal or slightly abnormal in approximately 98% of patients. The rate of thrombotic events at 90 days was 6–7%, and mortality was close to 19%, with no new safety concerns. Evidence in diverse populations confirms the efficacy and safety of this reversal in real-world clinical practice (POLLACK et al., 2017; DAI et al., 2023).
For factor Xa inhibitors, andexanet alfa is the main antidote available. In the ANNEXA-4 study, conducted in patients with major bleeding, results showed that 80% achieved hemostasis classified as excellent or good. Thrombotic events occurred in approximately 10%, but none after resumption of oral anticoagulation. In addition, reduced anti-FXa activity correlated with a higher rate of hemostasis in intracranial hemorrhages and lower mortality in patients under 75 years of age (MILLING et al., 2023).
In patients with acute intracranial hemorrhage associated with factor Xa inhibitors, the randomized ANNEXA-I trial demonstrated that andexanet alfa was able to reduce hematoma expansion and rapidly decrease anti-FXa activity in the first 2 hours compared to usual treatment. However, these hemostatic benefits did not translate into reduced

mortality or functional improvement at 30 days. In addition, an increase in the incidence of thrombotic events, including ischemic stroke, was observed, which was almost double that of the control group (10.3% vs. 5.6%) (ANDERSON et al., 2023). In the clinical setting, observational studies and systematic reviews have compared andexanet alfa with four-factor prothrombin complex concentrate (4F-PCC). Although data suggest that andexanet may achieve higher rates of hemostasis in FXa inhibitor-related bleeding, there was no clear evidence of superiority in terms of mortality. Methodological limitations and study heterogeneity explain this lack of consistency (KONDO et al., 2022).

**Regulatory status of antidotes**

From a regulatory standpoint, idarucizumab is currently approved for reversal of dabigatran, while andexanet alfa is approved for reversal of apixaban and rivaroxaban in life-threatening bleeding situations. Edoxaban, in turn, has not yet been formally approved in the United States, although experimental studies on reversal strategies are ongoing (UNITED STATES, 2024; LEVY et al., 2024).

**Adjuvant measures and clinical support**

In addition to specific antidotes, some adjuvant measures can be used in emergency situations. For dabigatran, hemodialysis can remove between 49–57% of the drug in four hours, although there is a risk of plasma "rebound" after dialysis. Activated charcoal may be administered in cases of recent ingestion, and the use of agents such as PCC, aPCC, and rFVIIa is considered a non-specific alternative when specific antidotes are not available, although evidence is limited (UNITED STATES, 2024; LEVY et al., 2024).

**Profiles by bleeding site**

Reversal outcomes vary according to the site of bleeding.

✓ Intracranial hemorrhage (ICH): andexanet reduces anti-FXa activity and limits hematoma expansion, but has not been associated with reduced functional mortality and increases the risk of thrombosis. In such cases, the use of PCCs remains an option in settings where the specific antidote is not available (ANDERSON et al., 2023).

✓ Gastrointestinal bleeding: in this scenario, intraclass differences show that apixaban and edoxaban have a lower bleeding risk compared to rivaroxaban and dabigatran.

✓ The recommendation is to prioritize local support measures, reserving specific antidotes only for critical and difficult-to-control cases (ZHANG et al., 2022).

**Dosage adherence and safety in the real world**

An important factor in the safety of DOACs is proper dosing. Data from clinical registries indicate that the use of doses outside the package insert recommendations is common and associated with worse clinical outcomes. Under-dosing increases the occurrence of thromboembolic events, while over-dosing increases the risk of major bleeding. These findings reinforce the need for careful dose adjustment according to parameters such as renal function, age, body weight, and potential drug interactions (STEINBERG et al., 2021).

**Table 1** presents a comparative summary of the main clinical studies, meta-analyses, observational registries, and guidelines that evaluated the efficacy, safety, and reversibility strategies of direct oral anticoagulants (DOACs). Thirty-two internationally relevant studies were included, ranging from pivotal trials that established the superiority of DOACs over warfarin to recent investigations into specific antidotes, such as idarucizumab and andexanet alfa, as well as alternative reversal strategies, such as the use of prothrombin complex concentrate (PCC) and hemodialysis. The systematization of data allows for a critical analysis of efficacy outcomes (prevention of thromboembolic events), safety (major bleeding and major bleeding, especially intracranial and gastrointestinal hemorrhage), and reversibility profile, highlighting current advances and limitations in clinical practice.

**Table 1.** Comparison - DOACs & Reversibility

| First author (Year) | Population/ Context | Intervention/ Comparator | Main outcomes | Thrombotic events | Key reference |
|---|---|---|---|---|---|
| Carnicelli (2022) | Non-valvular AF | DOACs vs warfarin | ↓ stroke/TE, ↓ HIC, ↓ mortality vs warfarin; major bleeding ~similar | — | Circulation 2022 |
| Harrington (2023) | AF; ClCr strata | Standard/low-dose DOACs vs warfarin | Advantage of DOACs maintained up to ClCr ~25 mL/min; low dose loses efficacy | — | Circulation 2023 (COMBINE AF) |
| Ruff (2014) | AF | NOACs vs warfarin | ↓ AVE/TE 19%, ↓ HIC and mortality; ↑ HGI in some agents | — | Lancet 2014 |
| Granger (2011) | AF | Apixaban vs warfarin | Apixaban superior (efficacy), less bleeding, and ↓ mortality | — | NEJM 2011 |
| Patel (2011) | FA | Rivaroxaban vs warfarin | Not inferior in stroke/TE; ↓ HIC/fatal | — | NEJM 2011 |

| | | | | | |
|---|---|---|---|---|---|
| Connolly (2009) | AF | Dabigatran 110/150 mg vs warfarin | 150 mg: ↓ stroke/TE; 110 mg: ↓ bleeding; both ↓ HIC | — | NEJM 2009 |
| Giugliano (2013) | FA | Edoxaban (high/low) vs warfarin | Not inferior for stroke/TE; ↓ bleeding and ↓ CV death | — | NEJM 2013 |
| Agnelli (2013) | Acute VTE | Apixaban vs conventional therapy | Not inferior for recurrence; ↓ bleeding | — | NEJM 2013 |
| EINSTEIN Investigators (2010) | Acute DVT | Rivaroxaban vs standard | Not inferior for recurrence; ↓ bleeding | — | NEJM 2010 |
| EINSTEIN–PE Investigators (2012) | Symptomatic PE | Rivaroxaban vs standard | Not inferior for recurrence; ↓ major bleeding | — | NEJM 2012 |
| Hokusai-VTE Investigators (2013) | VTE | Edoxaban vs warfarin | Not inferior; ↓ bleeding | — | NEJM 2013 |
| Schulman (2009) | Acute VTE | Dabigatran vs warfarin | Not inferior; ↓ bleeding | — | NEJM 2009 |
| Pollack (2015) | Bleeding/urgency (dabigatran) | Idarucizumab | Complete laboratory reversal within minutes | Low; monitored | NEJM 2015 |
| Pollack (2017) | Bleeding/urgency (dabigatran) | Idarucizumab | Reversal 100% ≤4h; normal/mild hemostasis in most cases | 6–7%/90 days | NEJM 2017 |
| Dai (2023) | Various scenarios (dabigatran) | Idarucizumab | High hemostasis rate; safety maintained | — | Medicine 2023 |
| Milling (2023) | Increased bleeding with anti-FXa | Andexanet alfa (low/high dose) | Excellent/good hemostasis ~80%; ↓ anti-FXa activity | ~10 | Circulation 2023 |
| Anderson/Connolly (2024) | Acute HIC due to anti-FXa | Andexanet vs usual care | ↑ expansion control; no gain at 30 days (death/functional) | ↑ thrombosis/CVIs vs control | NEJM 2023/2024 |
| Dobesh (2023) | Greater bleeding with apixaban/rivaroxaban | Andexanet vs 4F-PCC | ↓ Intra-hospital mortality with andexanet | No clear difference | Drugs Real World Outcomes 2023 |
| Kondo (2022) | Bleeding due to anti-FXa | Andexanet vs 4F-PCC | Tendency toward better hemostasis with andexanet; mortality uncertain | Variable | J Thromb Thrombolysis 2022 |
| Piran (2019) | Bleeding due to anti-FXa | 4F-PCC | Effective hemostasis in a substantial portion | Low to moderate | Blood Adv 2019 |
| Shaw (2024) | Anti-FXa (bleeding/urgency) | PCC (4F) | Effective hemostasis ~2/3 | Low | Thromb Res 2024 |
| Albaladejo (2017) | Severe bleeding under DOAC | Actual management (PCC, support) | 30-day mortality ~14%; PCC use 38% | — | Anesthesiology 2017 |
| Levy (2024) | Reversal of DOACs | Algorithms (idarucizumab/andexanet/PCC) | Recommends use of specific antidotes; early restart | Considers risk | J Thromb Haemost 2024 |
| FDA (2024) | Overexposure/bleeding (dabigatran) | Hemodialysis; activated charcoal (recent ingestion) | Dialysis removes ~50% in 4 hours; rebound possible | — | FDA PI 2024 |
| Chen (2023) | GI bleeding under DOAC | Apixaban vs others | More favorable GI profile for apixaban | — | Front Pharmacol 2023 |

| | | | | | |
|---|---|---|---|---|---|
| Radadiya (2021) | Risk of HGI due to DOAC | Various molecules/ doses | Differences by agent/dose; apixaban safer | — | EJGH 2021 |
| Ballestri (2022) | Risk and management of bleeding | DOACs vs warfarin | ↓ HIC with all DOACs; nuances in HGI | — | Adv Ther 2022 |
| Steinberg (2016) | Outpatient AF | Off-label doses (NOAC) | Sub/overdose associated with worse outcomes | ↑ stroke (under-dosage) | JACC 2016 |
| Sandhu (2023) | Outpatient AF | Off-label doses (DOAC) | ↑ hospitalization CV and mortality with off-label doses | ↑ with underdosing | Circ Outcomes 2023 |
| Shen (2021) | Global clinical practice | Prevalence of off-label doses | Frequent inappropriate use (12–20%) | Increases risks | Front Pharmacol 2021 |
| Ansell (2021/2022) | Elderly volunteers on anticoagulants | Ciraparantague vs placebo | Rapid and sustained reversal of apixaban/rivaroxaban | No major signs | Eur Heart J 2021/2022 |
| Niessner (2017) | Reversal of NOACs | Strategies (antidotes, PCC) | Broad pre-antidote recommendations | — | EHJ 2017 |

## DISCUSSION

Direct oral anticoagulants (DOACs) have represented a true paradigm shift in the management of non-valvular atrial fibrillation (AF) and venous thrombosis (VT), offering advantages over warfarin, such as predictable pharmacokinetics, less need for monitoring, and consistent reduction in intracranial hemorrhage (CARNICELLI et al., 2022; RUFF et al., 2014). Joint analysis of pivotal trials confirms that DOACs are not only effective in preventing h ly thromboembolic events, but also reduce mortality, although the risk of gastrointestinal bleeding varies between different agents (ZHANG et al., 2022).

Despite these advances, the risk of major bleeding remains the main clinical concern. In this context, the availability of specific antidotes represents one of the greatest therapeutic advances of the last decade.

Idarucizumab showed immediate and complete reversal of dabigatran activity, with high rates of effective hemostasis and an acceptable safety profile, establishing itself as the strategy of choice in emergency cases (POLLACK et al., 2017; DAI et al., 2023).

For factor Xa inhibitors, andexanet alfa demonstrated significant hemostatic efficacy in the ANNEXA-4 study, but was associated with a non-negligible rate of thrombotic events (MILLING et al., 2023).

The ANNEXA-I trial, focused on acute intracranial hemorrhage, provided additional relevant information: despite greater control of hematoma expansion and faster laboratory reversal, andexanet did not reduce mortality or functional disability at 30 days, and increased the incidence of thrombosis and ischemic stroke (ANDERSON et al., 2023).

These results suggest that, although the hemostatic benefit is evident, the overall clinical impact still needs further confirmation, reinforcing the need for careful and individualized use.

Another issue under debate is the comparison between andexanet and four-factor prothrombin complex concentrate (4F-PCC). Observational studies and meta-analyses suggest greater hemostatic efficacy of andexanet, but without demonstrating clear superiority in mortality, possibly due to methodological heterogeneity and selection bias (KONDO et al., 2022). Thus, the use of PCCs remains a relevant alternative in settings where specific antidotes are not available, albeit with potentially lower efficacy.

From a regulatory standpoint, idarucizumab and andexanet alfa are already approved in several countries, but edoxaban still lacks a formally approved specific antidote (LEVY et al., 2024). In addition, adjuvant measures, such as activated charcoal in recent ingestion and hemodialysis for dabigatran, remain viable options in certain clinical settings (UNITED STATES, 2024).

Another relevant point identified in the literature is real-world dose adherence. Studies show that doses outside the package insert recommendations are common and associated with worse clinical outcomes, including increased thromboembolic events with underdosing and increased risk of bleeding with overdosing (STEINBERG et al., 2016; SANDHU et al., 2023). This finding reinforces the need for individualized dose adjustment according to renal function, age, body weight, and drug interactions.

Finally, new molecules are emerging, such as ciraparantag (PER977), a broad-spectrum antidote for multiple anticoagulants, which has shown efficacy in phase 2 studies but still lacks evidence in critical clinical settings (ANSELL et al., 2021).

In summary, the available data reinforce that DOACs are superior to warfarin in terms of overall safety and efficacy,

but the issue of reversal remains challenging. Specific antidotes such as idarucizumab and andexanet alfa represent concrete advances, although questions remain about cost-effectiveness, thrombotic risk, and impact on mortality in certain settings. Management strategies should therefore consider the balance between bleeding and thrombotic risk, local availability of resources, and the need for early anticoagulation restart.

## FINAL CONSIDERATIONS

Direct oral anticoagulants (DOACs) have established themselves as the first line in the management of non-valvular atrial fibrillation and venous thrombosis, providing efficacy equivalent to or superior to warfarin and a more favorable safety profile, particularly due to the consistent reduction in the risk of intracranial hemorrhage. However, the occurrence of major bleeding, especially in the gastrointestinal tract and intracranial, remains a significant clinical challenge.

In this context, the availability of specific antidotes has marked a significant advance in medical practice. Idarucizumab, for reversal of dabigatran, has demonstrated rapid and safe efficacy, while andexanet alfa, indicated for factor Xa inhibitors, has shown important laboratory and hemostatic benefits, although accompanied by a higher risk of thrombotic events and no proven impact on mortality in the most recent clinical trials. Such evidence highlights the need for careful and individualized use, balancing the risks and benefits in each clinical situation.

Non-specific alternatives, such as the use of prothrombin complex concentrate (4F-PCC), activated charcoal in recent ingestion, and hemodialysis for dabigatran- , remain valid options, especially in places where specific antidotes are not available. Furthermore, the literature reinforces the importance of proper DOAC dosing, as doses outside the package insert are associated with increased thrombotic and hemorrhagic complications, requiring close attention to factors such as renal function, age, weight, and drug interactions.

Finally, research on broad-spectrum antidotes, such as ciraparantag (PER977), and the incorporation of reversal strategies into institutional protocols point to a promising future in the management of DOAC-associated bleeding emergencies. However, gaps remain in terms of cost-effectiveness, impact on mortality, and long-term safety.

Thus, clinical practice should be guided by the best available evidence, applying individualized strategies with an emphasis on rapid and safe reversal and timely resumption of anticoagulation in order to reduce the overall morbidity and mortality of anticoagulated patients.

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