Perspectives

Myths and challenges around anticoagulation in atrial fibrillation: A practicing clinician's perspective

K.E. Juhani Airaksinen, MD.[1] ORCID ID 0000-0002-0193-568X

Ville Langén MD.[2] ORCID ID 0000-0002-2382-7962

Konsta Teppo, MD.[1] ORCID ID 0000-0002-4460-0994

Gregory Y. H. Lip, MD.[3] ORCID: 0000-0002-7566-1626

[1]Heart Centre, Turku University Hospital and University of Turku, Turku, Finland

[2]Division of Medicine, Turku University Hospital and University of Turku, Turku, Finland

[3]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; Medical University of Bialystok, Bialystok, Poland.

Corresponding author:

Prof. K.E. Juhani Airaksinen, MD, PhD

Heart Centre, Turku University Hospital, Turku, Finland

Postal address: Hämeentie 11, PO Box 52, 20521 Turku

Email: juhani.airaksinen@tyks.fi; Tel. +358405876052

Abstract

Direct oral anticoagulants (DOACs) are currently the mainstream of long-term oral anticoagulation for patients with atrial fibrillation (AF). In spite of the active research in the field, many unanswered questions remain regarding the optimal use of DOACs and antithrombotic treatments in general. Some of the default approaches are still based on weak evidence and old 'traditions'. The general tendency has been to emphasize stroke prevention, with less attention given to bleeding problems and the net benefit of each antithrombotic regimen. Current practices seem to lead to potentially harmful overtreatment in some fragile patient groups. After recent observational and randomized studies, bleeding risk assessment has emerged as a new paradigm for maximizing the net benefit of antithrombotic treatments in patients with AF at high bleeding risk. Uninterrupted permanent anticoagulation is deeply rooted in clinical practice for all AF patients at risk of stroke solely based on their stroke risk score. This "one size fits all" principle may not be ideal for patients with low AF arrhythmia burden and rare AF attacks especially when combined with high bleeding risk.

In this narrative review, we take a critical perspective of some old myths and dogmas around antithrombotic treatments and focus on current challenges and "twilight zones" of DOAC use in indications with questionable net benefit.

KEY WORDS: atrial fibrillation, anticoagulation, stroke, thromboembolism, bleeding

1 Introduction

After the 50-year reign of warfarin, the advent of direct oral anticoagulants (DOACs) has made anticoagulation more convenient and accessible, and the multiple problems related to vitamin K antagonists (VKAs) concern now only a minority of patients with atrial fibrillation (AF). International guidelines have preferred DOACs over VKAs in the thromboembolic prophylaxis of patients with AF, but not for patients with mechanical heart valves, left ventricular assist devices, or moderate-to-severe mitral stenosis.[1,2,3] The VKAs remain the gold standard for managing antiphospholipid syndrome, especially in those with triple-positive syndrome, as evidenced by small studies indicating the inferior efficacy of DOACs compared to VKAs in preventing thromboembolism in this patient group.[4] The simple use of DOACs has facilitated their rapid and wide global uptake.[5] Importantly, the risk of intracerebral haemorrhage is lower when using DOACs, but unfortunately, the risk of gastrointestinal bleeds with some DOACs is increased during long-term treatment.[6,7]

In spite of the active research in the field, many unanswered questions and challenges remain regarding the use of DOACs and antithrombotic treatments in general.[8] Some of the default approaches are still based only on weak evidence and old traditions. The general tendency has been to emphasize anticoagulation for stroke prevention, with less attention given to bleeding issues and the net benefit of each treatment regimen. Dogmatic positions embraced by international guidelines, despite the lack of strong evidence, seem to have led to potentially harmful overtreatment in some patient groups.

In this narrative review, we take a critical perspective of some old myths and dogmas around antithrombotic treatments and focus on current challenges and “twilight zones” of DOAC use in indications with questionable net benefit. For the purpose of this article, all DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are discussed as a class, notwithstanding some differences between the agents in clinical pharmacology and (clinical trial or real-world) outcome data.

2 How low can we go with stroke risk?

2.1 Device-detected subclinical atrial fibrillation

Based on a Markov analysis, the DOACs have lowered the “tipping point” of stroke risk to ~0.9%/yr for starting anticoagulation in patients with AF.[9] This roughly equates to patients

with a single stroke risk factor, as traditionally assessed by stroke risk scores such as the CHA_2DS_2VASc score.[10] The recent 2024 ESC guidelines introduced the nonsex CHA_2DS_2VASc score (i.e. CHA_2DS_2-VA) with a Level of Evidence C "in the absence of other locally validated alternatives", since "the inclusion of gender complicates clinical practice … (and) omits individuals who identify as non-binary, transgender, or are undergoing sex hormone therapy".[1,10]

In a meta-analysis of the NOAH-AFNET 6 and ARTESiA trials, device-detected subclinical AF carries an overall low (~1%/yr) risk of ischaemic stroke, as well as a 32% reduction in ischaemic strokes and a 62% increase in major bleeding events with oral factor Xa inhibition compared with aspirin or placebo in patients with device-detected AF.[11] This 32% reduction in ischaemic stroke rate is in contrast to the 64% reduction in strokes with warfarin compared to control/placebo in the historical trials, or the 19% reduction in all strokes or systemic embolic events by DOACs compared to dose-adjusted warfarin.[12,13]

In previous trials on device-detected AF, episodes lasting >24 h were associated with a 3- to 5-fold increase in the risk of subsequent stroke or systemic embolism.[14,15] Current guidelines recommend individual risk assessment and shared decision-making in device-detected AF and recommend considering DOACs for patients with longer AF episodes and high CHA_2DS_2VASc/CHA_2DS_2VA scores. However, there is no strong support for these recommendations by the data from the two treatment trials, although the benefit of treatment with apixaban in preventing embolic events was greater than the risk of major bleeds in patients with CHA_2DS_2-VASc score >4 in the ARTESiA trial which enrolled subclinical AF patients (including those with atrial high rate episodes (AHRE) on cardiac devices).[16] Disappointingly, edoxaban had no significant effect on stroke risk in patients with CHA_2DS_2-VASc score >4 or in those with device-detected AHRE episodes >24 hours at baseline in the NOAH-AFNET 6 trial.[17] The statistical power of these analyses was limited, and more data are needed to identify circumstances when DOACs are of meaningful net benefit for these patients.

In the randomized LOOP trial, screening with an implantable loop recorder resulted in a threefold increase in AF detection and anticoagulation initiation in older individuals (mean age 75 years) with stroke risk factors, but no significant reduction in stroke risk was observed.[18] These findings are in line with the minimal effect size in the STROKESTOP and later negative large randomized AF screening trials (GUARD-AF, STROKESTOP II, VITAL-AF).[19,20,21,22] Current data indicate that short, infrequent episodes of device-

detected AF carry a low stroke risk and may not require anticoagulation therapy. Despite the limited evidence, screening for AF is increasingly applied with various devices, including smartphones and wearables.

Device-detected AF is a common finding, observed in roughly one-third of older individuals with an implanted rhythm device.[23] The risk of stroke in these patients is considerably lower than predicted by their mean CHA_2DS_2-VASc/CHA_2DS_2VA score, and the initiation of anticoagulation needs to be carefully balanced, considering not only the patient characteristics (stroke and bleeding risk factors) but also some measure of AF burden.

2.2 Paroxysmal atrial fibrillation and low AF burden

Anticoagulation does not prevent strokes in patients without AF, as shown by randomized trials in cryptogenic stroke, even in those with atrial cardiomyopathy.[24] The traditional binary (yes or no) definition of AF is simple at every level of health care, and the decision to initiate anticoagulant is currently based mainly on numerical values of patient characteristics by stroke risk scores such as CHA_2DS_2-VASc/CHA_2DS_2-VA score, with minimal weight placed on AF characteristics.

For example, anticoagulation is similarly recommended for a 65-year-old woman with hypertension whether she has a history of only one cardioversion for symptomatic AF attack many years earlier, repeated prolonged AF episodes with vague symptoms, or permanent AF. There are, however, increasing data that a more granular view on AF characteristics to integrate AF burden into treatment decisions has the potential for more precise stroke risk estimation.[23]

AF typically progresses from short infrequent paroxysms through self-terminating longer episodes to persistent AF. AF burden has been very low in screening trials and may explain their negative results in stroke prevention. The median AF burden in the LOOP trial was 0.13% and 0.46% in GUARD-AF trial compared with paroxysmal AF where the burden is usually 5-11%.[18,21,25] Antiarrhythmic drug therapy lowers the average AF burden to <3% and successful catheter ablation to <1%.[23]

AF burden is a composite of frequency and duration of AF episodes. It is challenging to incorporate AF burden into the treatment algorithms, since the burden thresholds to withhold anticoagulation therapy are not yet known. Also, arrhythmia burden is not static

but dynamic in nature, changing over time.[26] Based on current data, the risk of stroke increases together with AF burden: the risk is ~1%/yr in device-detected AF, ~2%/yr in paroxysmal AF, and ~3%/yr in chronic forms of AF in patients not using anticoagulation.[23]

The observational FinCV-4 study included 2,074 AF patients who were not using anticoagulation except for cardioversions.[27] The frequency of cardioversions – a rough clinical measure of AF burden in selected patients - was an independent strong predictor of stroke and systemic emboli (HR 2.87; $p = .002$) at 3 years. The risk of stroke and systemic thromboembolism was very low (0.08 per 100 patient-yrs) in patients with only one CHA_2DS_2-VASc point and low (0.48 per 100 patient-yrs) in patients with 2-3 CHA_2DS_2-VASc points who visited the emergency room for cardioversion less than once a year.

In the randomized EAST-AFNET 4 trial, early rhythm control therapy reduced AF burden, and the incidence of stroke was lower than in usual care (0.6% vs. 0.9%/100 patient-yrs) when the majority of patients were using anticoagulation.[28]

The assessment of AF burden as an additional risk factor may be valuable in patients with intermediate thromboembolic risk, i.e. those with CHA_2DS_2-VA score of 1 and those with a high risk of bleeding complications.[29] If an individual refrains from initiating anticoagulation after shared decision-making, careful follow-up with self-detection of AF using smartphones, other wearables or pulse palpation is advisable, since AF burden is a moving target and disease evolution is unpredictable. Whether oral anticoagulation is effective after successful AF ablation with low (<1%) AF burden is being investigated in the ongoing OCEAN trial.[30] Of note, the reduction of AF burden is already recognized as a therapeutic goal in the 2024 ACC/AHA/HRS AF guidelines.[2]

2.3 Cardioversion of AF

Cardioversion studies give clues about how the duration of AF paroxysms – the crucial component of AF burden – relates to stroke risk, since the risk is similar regardless of the mode (spontaneous or active cardioversion) of rhythm normalization. Prothrombotic changes (local platelet activation and increased thrombin generation) emerge rapidly after AF onset, and at 12 hours, a more comprehensive coagulability has been observed.[31] Second, the rhythm conversion from AF back to sinus rhythm results in mechanical stunning of the atria, providing a thrombogenic milieu especially in the left atrial appendage, but this phenomenon is also time-dependent and AF paroxysms lasting

less than 24 hours are not long enough to cause stunning.[32,33] Atrial stunning after an AF episode of less than one week usually resolves within 24 hours, but after longer episodes, the stunning and prothrombotic milieu are more profound, whereby restoration of atrial function takes up to 4 weeks.[32]

Based on this pathophysiology, the duration of AF episode and subsequent mechanical stunning of the atria are critical for the increased thromboembolic risk of AF paroxysms. Accordingly, in the ASSERT study, only those patients with AF episodes lasting over 24 hours were at higher immediate stroke risk than those without AF, while patients with AF episodes shorter than 24 hours were not at increased stroke risk.[14]

The thromboembolic risk of rhythm normalization is also time-dependent in cardioversion studies. In patients not using anticoagulation, the risk is low (0.3% within 30 days) when the duration of an AF episode is less than12 hours.[34] The risk is fourfold (1.2%) already in episodes of 12-48 hours, and rises up to 3.4-7% in longer AF episodes.[35] When using effective periprocedural anticoagulation with DOACs, elective cardioversion of AF is associated with a 0.4% risk of stroke within 30 days after rhythm normalization, and 80% of strokes occur during the first week.[36] This means that the first week after rhythm normalization is highly prothrombotic and carries a 20-fold risk of ischaemic stroke compared with an average week during DOAC treatment.[36,37]

On the basis of this pathophysiology and clinical studies, it seems reasonable to perform elective cardioversions as early as possible, since the overall risk of thromboembolic complications is only 0.1% when cardioversion is performed within 48 hours of AF onset in anticoagulated patients.[36] It is tempting to speculate—but almost impossible to show—that intensified anticoagulation during the first high-risk days after cardioversion could help to reduce stroke risk in those patients with high stroke risk as assessed by the CHA_2DS_2VASc/ CHA_2DS_2VA score.[35]

3 Anticoagulation in patients with high bleeding risk

3.1 End-stage kidney disease

AF is common in patients with chronic kidney disease. Evidence of net clinical benefit of DOACs for stroke prevention in patients with end-stage kidney disease (ESKD) and AF is

lacking because these patients have been excluded from the pivotal randomized DOAC trials.[6]

There are only three small randomized trials that compare apixaban or rivaroxaban with VKA, but these small trials have inadequate power to draw any firm conclusions regarding net benefit of DOACs in this fragile patient group.[38,39,40] Of note, clinically relevant bleeding events were approximately tenfold more frequent than strokes or systemic embolism among ESKD population on DOACs (Figure 1). In a recent meta-analysis - mainly based on observational data - there was no significant difference in all-cause death or thromboembolism between patients who did not receive anticoagulants and those who received DOACs.[41]

The lack of randomized trials comparing DOACs with no anticoagulation leaves uncertainty of any net benefit of chronic anticoagulation in this patient group. The DOACs seem to be to current choice of anticoagulation for the ESKD population with AF, with apixaban and rivaroxaban approved by the US FDA, but careful evaluation of stroke and bleeding risk is still needed in the treatment decision-making.

3.2 Cirrhosis

Anticoagulation is challenging in advanced liver disease due to coagulation abnormalities caused by cirrhosis, impaired hepatic clearance of DOACs, as well as the increased bleeding risk associated with oesophageal varices.[3]

In a recent study on two U.S. populations with cirrhosis and non-valvular AF, anticoagulation with rivaroxaban or VKA was associated with elevated rates of major bleeding events and similar rates of ischaemic stroke compared to apixaban treatment.[42] Most importantly, major bleeding events were approximately tenfold more frequent than ischaemic strokes (Figure 1). There are no head-to-head comparisons on DOACs and no data to compare DOACs to no anticoagulation in this fragile patient group, leaving clinicians without clear guidance on appropriate treatment decisions.[43]

Current guidance suggests that in liver disease, the use of VKAs in patients with advanced liver disease and coagulopathy is difficult due to intrinsically elevated INR values and difficulties in selecting appropriate VKA dosing. The DOACs are generally safe to administer in Child-Pugh class A liver disease. Apixaban, dabigatran, and edoxaban can be used with caution in Child-Pugh class B liver disease. However, all DOACs contraindicated in Child-Pugh class C liver disease.

3.3 Frailty

Many older AF patients have frailty syndrome, a clinical entity of multiple comorbidities, polypharmacy, and high biological vulnerability. The oldest individuals with AF and frailty were not included in the landmark trials on DOACs. In spite of that, a waning of the advantage of DOACs over VKAs in the oldest and most comorbid trial participants was observed.[6]

In the FRAIL-AF trial, frail patients (mean age 83 years) who were tolerant to VKA treatment were randomized to continue International Normalized Ratio (INR)-guided VKA treatment or switch to a DOAC[44]. In this trial setting where anticoagulation control with VKA was good, the DOACs were associated with more bleeding complications (hazard ratio 1.69) compared with continuing VKA treatment, and no reduction in thromboembolic complications was observed. The rate of major and clinically relevant bleeding - most of which were gastrointestinal - was 17.8 per 100 patient-yrs compared with the rate of ischaemic and haemorrhagic stroke of 2.3 per 100 patient-yrs (Figure 1). These findings are of importance when considering whether or not to switch a patient on stable VKA therapy (time in therapeutic range >70%) to a DOAC.

In practice, DOACs are often used with off-label reduced doses in this increasing patient group. Post hoc analysis of the ENGAGE AF-TIMI 48 trial in AF patients >80 years supports the concept that reduced-dose DOACs may be considered in older patients with AF also in the absence of dose-reduction criteria due to a lower risk of major bleeding events without an offsetting increase in ischaemic events in the edoxaban 30 mg group.[45] Similarly, a recent meta-analysis on observational studies covering 70,394 DOAC users showed no statistically significant increase in the risk of stroke/thromboembolism, no decrease in bleeding risk, nor a difference in the risk of all-cause mortality in patients with off-label use of low-dose DOACs.[46]

In the ELDERCARE-AF trial on elderly (>80 years) Japanese AF patients having bleeding risk factors, the annualized rate of stroke or systemic embolism was lower in the low-dose (15mg) edoxaban group compared with the placebo group (2.3% vs. 6.7%; P<0.001). The rate of major bleeding was 3.3% in the edoxaban group and 1.8% in the placebo group (P=0.09).[47]

Taken together, these results suggest that off-label use of low-dose DOACs may not always be harmful in fragile old patients and can be considered after careful judgment and shared decision-making. According to the 2024 ESC guidelines, a reduced dose DOAC therapy should be avoided (Class III recommendation), unless patients meet DOAC-specific criteria.[1]

3.4 Other gaps in evidence

We need prospective studies on the net benefit of DOACs in AF patients after successful AF ablation and in trigger-induced AF, although current guidelines recommend - based on observational data - that long-term oral anticoagulation should be considered in suitable patients at elevated thromboembolic risk.[1] There are also lack of high-quality data on DOAC use in AF patients with active cancer, adult congenital heart disease, and during breast feeding or pregnancy. There are also limited data on optimal timing of introducing DOACs after intracerebral haemorrhage or other major bleeding. The optimal dosing of DOACs in patients at extremes of weight needs also more research.[3]

Percutaneous left atrial appendage occlusion may be considered in patients with AF at high bleeding risk.[1,48] Ongoing randomized trials will clarify the position and indications of this invasive treatment strategy.

4 Old dogmas - difficult to tackle

4.1 Heparin bridging

Heparin bridging established its leading status in the routine perioperative management of VKA treatment decades ago. The only evidence to support this strategy was the fear of uncontrollable haemorrhage during uninterrupted VKA treatment, which appears exaggerated. Furthermore, rapid and precise reversal of VKA anticoagulation can be achieved using prothrombin complex concentrate unlike the incomplete reversal of low-molecular weight heparin (LMWH) effect by protamine. However, numerous studies showed that uninterrupted VKA treatment is a safe option for most cardiac interventions.[49,50,51,52]

Also, randomized trials have been performed showing that heparin bridging increases bleeding risks and provides no benefit on thromboembolic risks in non-cardiac surgery and

interventions.[53,54,55] This is not a surprise, since VKAs reduce the synthesis of active clotting factors while LMWHs inhibit clotting factors. It is challenging to control over the dynamic changes in both the synthesis and activity of clotting factors during bridging and to avoid periods of sub- and supratherapeutic anticoagulation and consequent thrombotic and bleeding risks.[56] Wide fluctuations in INR are common and long-lasting after VKA interruption, and warfarin re-initiation may cause a transient prothrombotic state due to protein C and S suppression.

At present, heparin bridging of VKA treatment is still included in the guidelines with a conditional recommendation and very low certainty of evidence.[54] When using DOACs, there are no indications for heparin bridging.[57]

4.2 Acute and chronic coronary syndromes

The 12-month duration of dual antiplatelet therapy (DAPT) in acute coronary syndromes is still the default Class I recommendation in the international guidelines based on three historical studies, none of which were designed to assess the optimal duration of DAPT.[1,58] Later, numerous studies have evaluated optimal DAPT duration and various de-escalation strategies. Not surprisingly, they have not shown net benefits of 12-month DAPT compared with abbreviated DAPT regimens.[58] Based on higher bleeding risk caused by prolonged DAPT, alternative approaches with shorter DAPT are now included in the international guidelines, especially for patients with high bleeding risk, but with a lower Class IIa level of evidence.[59]

In line with this history, the exaggerated fear of stent thrombosis led to introduction of triple therapy (DAPT plus warfarin) for up to 6-12 months as the default approach for AF patients after coronary stenting and in acute coronary syndromes.[60] This strategy was first challenged in the randomized WOEST trial where 44% of patients in the triple therapy group suffered a bleeding event within one year, while the incidence of definite stent thrombosis was not lower (1.1%) than in patients treated with anticoagulation and clopidogrel only (0.4%).[60] Randomized studies showing adverse net effects of triple therapy, with no advantage in ischaemic events, were repeated after the introduction of DOACs (Figure 2).[61,62]

From a philosophical point of view, it is noteworthy that the primary endpoint in these trials was a major or clinically relevant non-major bleeding event during follow-up. In other words, the goal was to reduce the harm caused by the recommended treatment, rather than showing a benefit in terms of initial treatment targets – protection against thrombotic and thromboembolic complications.[61] The current treatment strategy after hospital discharge includes DOAC plus clopidogrel, and, importantly, with a shorter and individualized duration of antiplatelet treatment.[1,63]

Similarly, in patients with AF and stable coronary artery disease, the randomized AFIRE and EPIC-CAD trials have shown that DOAC monotherapy is sufficient for the prevention ischaemic events and leads to a lower risk of bleeding complications than previously used long term dual antithrombotic therapy.[64,65]

5 Future perspectives - less is more?

These examples from different research areas show the general tendency of cardiological community to start the antithrombotic treatments from the “deep end”, using drug regimens with maximal effect on thromboembolic and thrombotic events. This principle raises a risk of overtreatment, especially in older patients having comorbidities which increase their bleeding risks. After recent observational and randomized studies, bleeding risk assessment has emerged as a new paradigm for maximizing the net benefit of antithrombotic treatments in AF patients at high bleeding risk.

Second, based on early anticoagulation trials, uninterrupted permanent anticoagulation is deeply rooted in clinical practice for all AF patients at risk of stroke solely based on their CHA_2DS_2-VASc/CHA_2DS_2-VA score. This “one size fits all” principle may not be ideal for patients with low AF burden and rare AF attacks, since uninterrupted anticoagulation is not without risks even in this population with low stroke risk. The technological evolution enables widespread screening for early AF and more patients with low AF burden and stroke risk are uncovered emphasizing the need of research on optimal treatment of this growing patient group. This phenomenon may contribute to the recent observations on declining overall trends in stroke risk of non-anticoagulated of AF patients.[66] Whether a low arrhythmia burden is a justification to reduce therapy is being tested in ongoing studies.[30] Interestingly, the REACT-AF trial is comparing continuous anticoagulation with a smartwatch-guided intermittent anticoagulation regimen that is confined to periods of high

AF burden.[67] These personalized medicine strategies - if proven safe and effective - could maintain the benefits while reducing the risks of DOACs.

Figure 1. **Stroke and bleeding rates in diverse patient populations with AF receiving DOACs**. Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; RCT, randomized controlled trial. Outcome definitions: Subclinical AF 1, ischaemic stroke and major bleeding; DOAC RCTs 2, Ischaemic stroke or systemic embolism and major bleeding; Cirrhosis 3, Ischaemic stroke and major bleeding; Frailty 4, any stroke and major or clinically relevant nonmajor bleeding; Hemodialysis 5, any stroke or systemic embolism and major or clinically relevant non-major bleeding.

Figure 2: **Outcomes of double and triple therapy in patients using oral anticoagulant therapy undergoing percutaneous coronary intervention**. Double therapy: oral anticoagulant plus ADP receptor antagonist (mainly clopidogrel). Triple therapy. oral anticoagulant plus ADP receptor antagonist (mainly clopidogrel) and ASA.

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DATA AVAILABILITY STATEMENT

Perspective article is based on interpretation of the articles in the reference list. Data used to support the findings of this study are available from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

KEJA wrote the draft of this paper. VL, KT and GYHL contributed to substantive revision of the paper. All authors read and approved the final manuscript. KEJA is the guarantor of this paper.

REFERENCES

1. Van Gelder IC, Rienstra M, Bunting K V, et al. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. Published online August 30, 2024. doi:10.1093/EURHEARTJ/EHAE176

2. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149(1):E1-E156. doi:10.1161/CIR.0000000000001193

3. Bejjani A, Khairani CD, Assi A, et al. When Direct Oral Anticoagulants Should Not Be Standard Treatment: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2024;83(3):444-465. doi:10.1016/J.JACC.2023.10.038

4. Gullapalli K, Prasad RM, Al-abcha A, et al. Efficacy and Safety of Direct Oral Anticoagulants in Patients With Antiphospholipid Syndrome: A Systematic Review and Meta-Analysis. *Cureus*. 2022;14(9). doi:10.7759/CUREUS.29449

5. Frost L, Halminen O, Lehto M, et al. Geographical Variation in the Use of Oral Anticoagulation and Clinical Outcomes among Patients with Atrial Fibrillation in Denmark, Sweden, and Finland. *TH open companion J to Thromb Haemost*. 2023;7(2):e133-e142. doi:10.1055/A-2080-6171

6. Carnicelli AP, Hong H, Connolly SJ, et al. Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex. *Circulation*. 2022;145(4):242-255. doi:10.1161/CIRCULATIONAHA.121.056355

7. Patel SM, Braunwald E, Steffel J, et al. Efficacy and Safety of Non-Vitamin-K Antagonist Oral Anticoagulants Versus Warfarin Across the Spectrum of Body Mass Index and Body Weight: An Individual Patient Data Meta-Analysis of 4 Randomized Clinical Trials of Patients With Atrial Fibrillation. *Circulation*. 2024;149(12):932-943.

doi:10.1161/CIRCULATIONAHA.123.066279

8. Airaksinen KEJ, De Sensi F. Ten years of direct oral anticoagulants: lessons learned and challenges ahead. *Eur Heart J*. 2024;45(25):2178-2180. doi:10.1093/EURHEARTJ/EHAE061

9. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2011;4(1):14-21. doi:10.1161/CIRCOUTCOMES.110.958108

10. Potpara TS, Romiti GF, Sohns C. The 2024 European Society of Cardiology Guidelines for Diagnosis and Management of Atrial Fibrillation: A Viewpoint from a Practicing Clinician's Perspective. *Thromb Haemost*. 2024;124(12). doi:10.1055/A-2434-9244

11. McIntyre WF, Benz AP, Becher N, et al. Direct Oral Anticoagulants for Stroke Prevention in Patients With Device-Detected Atrial Fibrillation: A Study-Level Meta-Analysis of the NOAH-AFNET 6 and ARTESiA Trials. *Circulation*. 2024;149(13):981-988. doi:10.1161/CIRCULATIONAHA.123.067512

12. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857-867. doi:10.7326/0003-4819-146-12-200706190-00007

13. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet (London, England)*. 2014;383(9921):955-962. doi:10.1016/S0140-6736(13)62343-0

14. Van Gelder IC, Healey JS, Crijns HJGM, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J*. 2017;38(17):1339-1344. doi:10.1093/EURHEARTJ/EHX042

15. Singer DE, Ziegler PD, Koehler JL, Sarkar S, Passman RS. Temporal Association Between Episodes of Atrial Fibrillation and Risk of Ischemic Stroke. *JAMA Cardiol*. 2021;6(12):1364-1369. doi:10.1001/JAMACARDIO.2021.3702

16. Lopes RD, Granger CB, Wojdyla DM, et al. Apixaban vs Aspirin According to CHA2DS2-VASc Score in Subclinical Atrial Fibrillation: Insights From ARTESiA. *J*

Am Coll Cardiol. 2024;84(4):354-364. doi:10.1016/J.JACC.2024.05.002

17. Becher N, Toennis T, Bertaglia E, et al. Anticoagulation with edoxaban in patients with long atrial high-rate episodes ≥24 h. *Eur Heart J*. 2024;45(10):837-849. doi:10.1093/EURHEARTJ/EHAD771

18. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *Lancet (London, England)*. 2021;398(10310):1507-1516. doi:10.1016/S0140-6736(21)01698-6

19. Svennberg E, Friberg L, Frykman V, Al-Khalili F, Engdahl J, Rosenqvist M. Clinical outcomes in systematic screening for atrial fibrillation (STROKESTOP): a multicentre, parallel group, unmasked, randomised controlled trial. *Lancet (London, England)*. 2021;398(10310):1498-1506. doi:10.1016/S0140-6736(21)01637-8

20. Corica B, Bonini N, Imberti JF, et al. Yield of diagnosis and risk of stroke with screening strategies for atrial fibrillation: a comprehensive review of current evidence. *Eur Hear J open*. 2023;3(2). doi:10.1093/EHJOPEN/OEAD031

21. Lopes RD, Atlas SJ, Go AS, et al. Effect of Screening for Undiagnosed Atrial Fibrillation on Stroke Prevention. *J Am Coll Cardiol*. Published online September 2024. doi:10.1016/J.JACC.2024.08.019

22. Kemp Gudmundsdottir K, Svennberg E, Friberg L, et al. Randomized Invitation to Systematic NT-proBNP and ECG Screening in 75-Year Olds to Detect Atrial Fibrillation -STROKESTOP II. *Circulation*. Published online September 2024. doi:10.1161/CIRCULATIONAHA.124.071176

23. Becher N, Metzner A, Toennis T, Kirchhof P, Schnabel RB. Atrial fibrillation burden: a new outcome predictor and therapeutic target. *Eur Heart J*. 2024;45(31). doi:10.1093/EURHEARTJ/EHAE373

24. Kamel H, Longstreth T, Tirschwell DL, et al. Apixaban to Prevent Recurrence After Cryptogenic Stroke in Patients With Atrial Cardiopathy: The ARCADIA Randomized Clinical Trial. *JAMA*. 2024;331(7):573-581. doi:10.1001/JAMA.2023.27188

25. Singer DE, Atlas SJ, Go AS, et al. Atrial Fibrillation Burden on a 14-Day ECG Monitor: Findings From the GUARD-AF Trial Screening Arm. *JACC Clin*

Electrophysiol. Published online September 2024. doi:10.1016/J.JACEP.2024.08.010

26. Imberti JF, Bonini N, Tosetti A, et al. Atrial High-Rate Episodes Detected by Cardiac Implantable Electronic Devices: Dynamic Changes in Episodes and Predictors of Incident Atrial Fibrillation. *Biology (Basel)*. 2022;11(3). doi:10.3390/BIOLOGY11030443

27. Jaakkola S, Kiviniemi TO, Jaakkola J, et al. Frequency of cardioversions as an additional risk factor for stroke in atrial fibrillation - the FinCV-4 study. *Ann Med*. 2022;54(1):1452-1458. doi:10.1080/07853890.2022.2077430

28. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med*. 2020;383(14):1305-1316. doi:10.1056/nejmoa2019422

29. Komen JJ, Pottegård A, Mantel-Teeuwisse AK, et al. Oral anticoagulants in patients with atrial fibrillation at low stroke risk: a multicentre observational study. *Eur Heart J*. 2022;43(37):3528-3538. doi:10.1093/EURHEARTJ/EHAC111

30. Verma A, Ha ACT, Kirchhof P, et al. The Optimal Anti-Coagulation for Enhanced-Risk Patients Post-Catheter Ablation for Atrial Fibrillation (OCEAN) trial. *Am Heart J*. 2018;197:124-132. doi:10.1016/J.AHJ.2017.12.007

31. Sohara H, Amitani S, Kurose M, Miyahara K. Atrial Fibrillation Activates Platelets and Coagulation in a Time-Dependent Manner: A Study in Patients With Paroxysmal Atrial Fibrillation. *J Am Coll Cardiol*. 1997;29(1):106-112. doi:10.1016/S0735-1097(96)00427-5

32. Khan IA. Atrial stunning: Basics and clinical considerations. *Int J Cardiol*. 2003;92(2-3):113-128. doi:10.1016/S0167-5273(03)00107-4

33. Antonielli E, Pizzuti A, Dogliani S, Stasi M, Bassignana A, Doronzo B. Absence of left atrial stunning after cardioversion of recent-onset atrial fibrillation in patients at low-stroke risk. *Eur J Emerg Med*. 2017;24(3):217-223. doi:10.1097/MEJ.0000000000000333

34. Nuotio I, Hartikainen JEK, Grönberg T, Biancari F, Airaksinen KEJ. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA - J*

Am Med Assoc. 2014;312(6):647-649. doi:10.1001/jama.2014.3824

35. Airaksinen KEJ. How to Optimize Cardioversion of Atrial Fibrillation. *J Clin Med*. 2022;11(12). doi:10.3390/JCM11123372

36. Jaakkola S, Kiviniemi TO, Airaksinen KEJ. Cardioversion for atrial fibrillation - how to prevent thromboembolic complications? *Ann Med*. 2018;50(7):549-555. doi:10.1080/07853890.2018.1523552

37. Itäinen-Strömberg S, Lehto M, Halminen O, et al. Thromboembolic and bleeding complications after elective cardioversion of atrial fibrillation: a nationwide cohort study. *Europace*. 2024;26(6). doi:10.1093/europace/euae131

38. Pokorney SD, Chertow GM, Al-Khalidi HR, et al. Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial. *Circulation*. 2022;146(23):1735-1745. doi:10.1161/CIRCULATIONAHA.121.054990

39. Reinecke H, Engelbertz C, Bauersachs R, et al. A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study. *Circulation*. 2023;147(4):296-309. doi:10.1161/CIRCULATIONAHA.122.062779

40. de Vriese AS, Caluwé R, Pyfferoen L, et al. Multicenter Randomized Controlled Trial of Vitamin K Antagonist Replacement by Rivaroxaban with or without Vitamin K2 in Hemodialysis Patients with Atrial Fibrillation: the Valkyrie Study. *J Am Soc Nephrol*. 2020;31(1):186-196. doi:10.1681/ASN.2019060579

41. Kao TW, Chen ZW, Lin YH. Anticoagulation for Patients With Concomitant Atrial Fibrillation and End-Stage Renal Disease: A Systematic Review and Network Meta-Analysis. *J Am Heart Assoc*. 2024;13(8):e034176. doi:10.1161/JAHA.123.034176

42. Simon TG, Singer DE, Zhang Y, et al. Comparative Effectiveness and Safety of Apixaban, Rivaroxaban, and Warfarin in Patients With Cirrhosis and Atrial Fibrillation : A Nationwide Cohort Study. *Ann Intern Med*. 2024;177(8). doi:10.7326/M23-3067

43. Steffel J, Collins R, Antz M, et al. 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(10):1612-1676.

doi:10.1093/EUROPACE/EUAB065

44. Joosten LPT, Van Doorn S, Van De Ven PM, et al. Safety of Switching From a Vitamin K Antagonist to a Non-Vitamin K Antagonist Oral Anticoagulant in Frail Older Patients With Atrial Fibrillation: Results of the FRAIL-AF Randomized Controlled Trial. *Circulation*. 2024;149(4):279-289. doi:10.1161/CIRCULATIONAHA.123.066485

45. Zimerman A, Braunwald E, Steffel J, et al. Dose Reduction of Edoxaban in Patients 80 Years and Older With Atrial Fibrillation: Post Hoc Analysis of the ENGAGE AF-TIMI 48 Randomized Clinical Trial. *JAMA Cardiol*. 2024;9(9). doi:10.1001/JAMACARDIO.2024.1793

46. Joosten LPT, Van Maanen R, Van Den Dries CJ, et al. Clinical consequences of off-label reduced dosing of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. *Open Hear*. 2023;10(1). doi:10.1136/OPENHRT-2022-002197

47. Okumura K, Akao M, Yoshida T, et al. Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation. *N Engl J Med*. 2020;383(18):1735-1745. doi:10.1056/NEJMOA2012883

48. Potpara T, Grygier M, Haeusler KG, et al. An International Consensus Practical Guide on Left Atrial Appendage Closure for the Non-implanting Physician: Executive Summary. *Thromb Haemost*. Published online December 10, 2024. doi:10.1055/A-2469-4896

49. Karjalainen PP, Vikman S, Niemelä M, et al. Safety of percutaneous coronary intervention during uninterrupted oral anticoagulant treatment. *Eur Heart J*. 2008;29(8):1001-1010. doi:10.1093/eurheartj/ehn099

50. Annala A-P, Karjalainen PP, Porela P, Nyman K, Ylitalo A, Airaksinen KEJ. Safety of Diagnostic Coronary Angiography During Uninterrupted Therapeutic Warfarin Treatment. *Am J Cardiol*. 2008;102(4):386-390. doi:10.1016/j.amjcard.2008.04.003

51. Airaksinen KEJ, Biancari F, Karjalainen P, et al. Safety of coronary artery bypass surgery during therapeutic oral anticoagulation. *Thromb Res*. 2011;128(5):435-439. doi:10.1016/j.thromres.2011.05.021

52. Jamula E, Lloyd NS, Schwalm J-D, Airaksinen KEJ, Douketis JD. Safety of uninterrupted anticoagulation in patients requiring elective coronary angiography with or without percutaneous coronary intervention: A systematic review and metaanalysis. *Chest*. 2010;138(4):840-847. doi:10.1378/chest.09-2603

53. Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation. *N Engl J Med*. 2015;373(9):823-833. doi:10.1056/NEJMOA1501035

54. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative Management of Antithrombotic Therapy: An American College of Chest Physicians Clinical Practice Guideline. *Chest*. 2022;162(5):e207-e243. doi:10.1016/J.CHEST.2022.07.025

55. Douketis JD, Spyropoulos AC. Perioperative Management of Patients Taking Direct Oral Anticoagulants: A Review. *JAMA*. 2024;332(10). doi:10.1001/JAMA.2024.12708

56. Airaksinen KEJ, Schlitt A, Rubboli A, Karjalainen P, Lip GYH. How to manage antithrombotic treatment during percutaneous coronary interventions in patients receiving long-term oral anticoagulation: To “bridge” or not to “bridge”? *EuroIntervention*. 2010;6(4):520-526. doi:10.4244/EIJ30V6I4A86

57. Douketis JD, Spyropoulos AC, Duncan J, et al. Perioperative Management of Patients with Atrial Fibrillation Receiving a Direct Oral Anticoagulant. *JAMA Intern Med*. 2019;179(11):1469-1478. doi:10.1001/jamainternmed.2019.2431

58. Valgimigli M, Landi A, Angiolillo DJ, et al. Demystifying the Contemporary Role of 12-Month Dual Antiplatelet Therapy After Acute Coronary Syndrome. *Circulation*. 2024;150(4):317-335. doi:10.1161/CIRCULATIONAHA.124.069012

59. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J*. 2023;44(38):3720-3826. doi:10.1093/EURHEARTJ/EHAD191

60. Dewilde WJM, Oirbans T, Verheugt FWA, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet (London, England)*. 2013;381(9872):1107-1115. doi:10.1016/S0140-6736(12)62177-1

61. Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med*. 2017;377(16):1513-1524. doi:10.1056/NEJMOA1708454

62. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med*. 2020;383(14):1305-1316. doi:10.1056/NEJMOA2019422

63. Byrne RA, Rossello X, Coughlan JJ, et al. [2023 ESC Guidelines for the management of acute coronary syndromes]. *G Ital Cardiol (Rome)*. 2024;25(2 Suppl 2):1e-112e. doi:10.1714/4191.41785

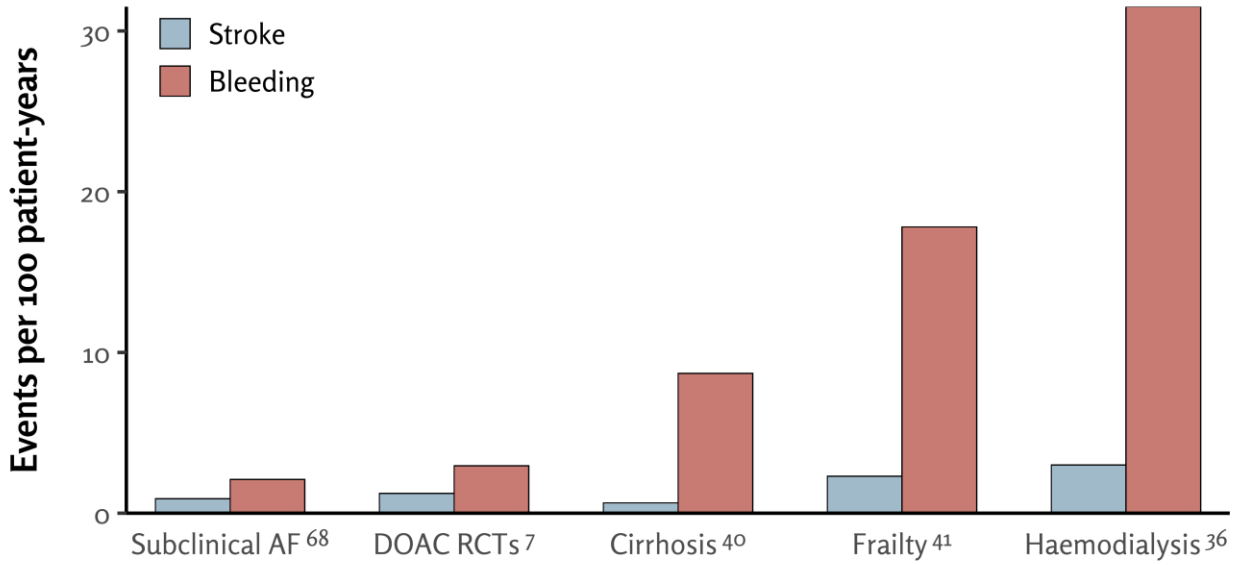
64. Yasuda S, Kaikita K, Akao M, et al. Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease. *N Engl J Med*. 2019;381(12):1103-1113. doi:10.1056/NEJMOA1904143

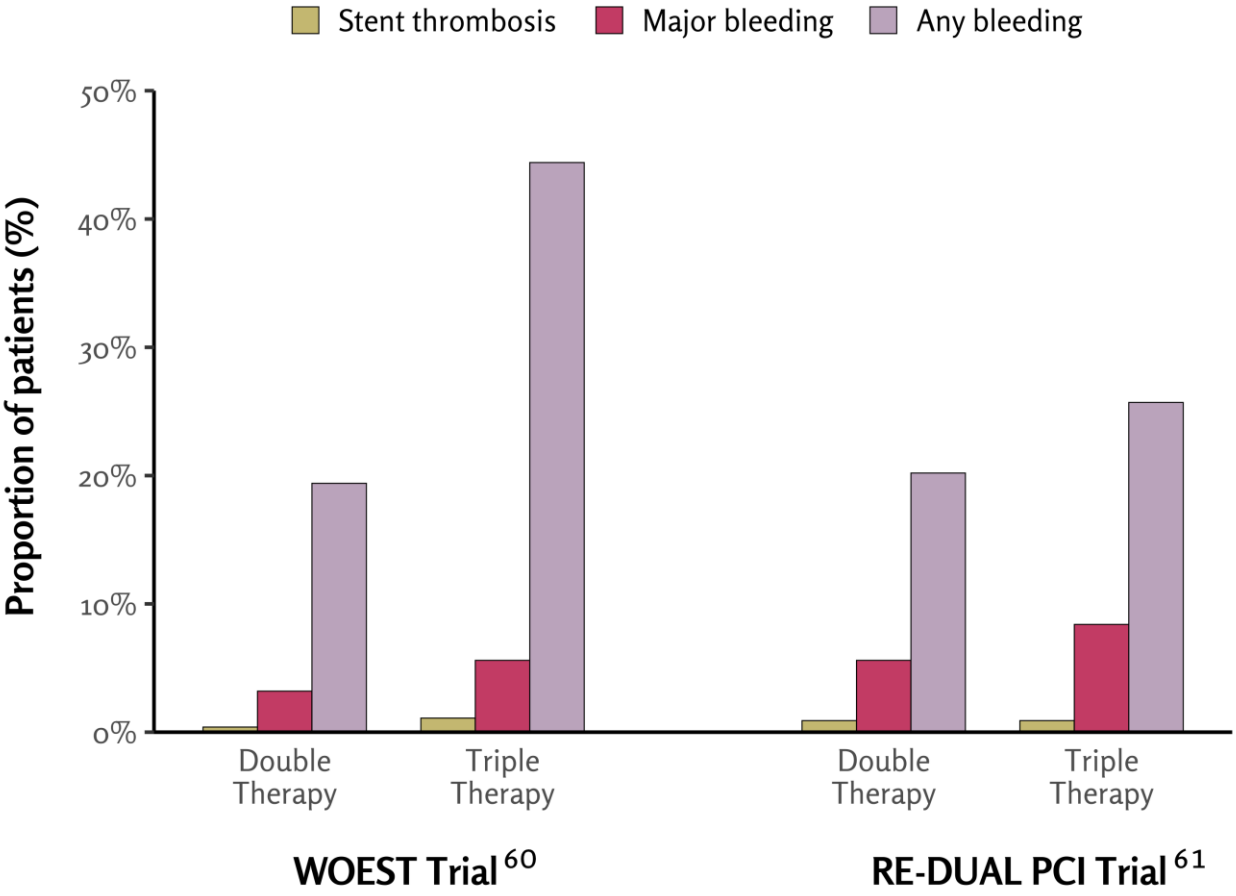
65. Cho MS, Kang D-Y, Ahn J-M, et al. Edoxaban Antithrombotic Therapy for Atrial Fibrillation and Stable Coronary Artery Disease. *N Engl J Med*. Published online September 2024. doi:10.1056/NEJMOA2407362

66. Teppo K, Lip GYH, Airaksinen KEJ, et al. Comparing CHA2DS2-VA and CHA2DS2-VASc scores for stroke risk stratification in patients with atrial fibrillation: a temporal trends analysis from the retrospective Finnish AntiCoagulation in Atrial Fibrillation (FinACAF) cohort. *Lancet Reg Heal Eur*. 2024;43. doi:10.1016/J.LANEPE.2024.100967

67. Peigh G, Passman RS. “Pill-in-Pocket” anticoagulation for stroke prevention in atrial fibrillation. *J Cardiovasc Electrophysiol*. 2023;34(10):2152-2157. doi:10.1111/JCE.15866

68. P. Kirchhof, T. Toennis, A. Goette, et al. Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes. *N Engl J Med*. 2023;389(13),1167-1179. https://doi.org/10.1056/NEJMoa2303062


Stroke
Bleeding
Events per 100 patient-years
30
20
10
0
Subclinical AF 68
DOAC RCTs 7
Cirrhosis 40
Frailty 41
Haemodialysis 36


Stent thrombosis
Major bleeding
Any bleeding
Proportion of patients (%)
50%
40%
30%
20%
10%
0%
Double Therapy
Triple Therapy
Double Therapy
Triple Therapy
WOEST Trial 60
RE-DUAL PCI Trial 61