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Article type: Review article

Received: May 1, 2026.

Revision accepted: June 3, 2026.

Published online: June 8, 2026.

ISSN: 1897-9483

Pol Arch Intern Med.

doi:10.20452/pamw.17319

Direct oral anticoagulants in older patients with atrial fibrillation and comorbidities: frailty, renal impairment, acute or chronic coronary syndromes, and acute stroke

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Abstract

Direct oral anticoagulants (DOACs) have been available since 2008, boosting appropriate anticoagulation and reducing intracranial hemorrhages compared to warfarin therapy. For older patients with atrial fibrillation (AF) and comorbidities, however, decisions on DOAC therapy may be challenging. In frail, stable-on-warfarin patients, the FRAIL-AF trial reported increased relevant bleeding with DOAC switching. However, subsequent individual patient-data analyses of the four pivotal DOAC-versus-warfarin AF trials confirmed overall advantages of DOACs over warfarin even among older, frail, warfarin-experienced individuals. Advanced age should not exclude the use of any DOAC for AF, but care is needed to adjust the doses, when indicated,

particularly by renal function. All DOACs undergo variable renal clearance and, in Europe, a creatinine clearance <30mL/min contraindicates dabigatran and <15mL/min the factor-Xa inhibitors. AF patients on DOACs presenting with an acute coronary syndrome and/or requiring percutaneous coronary interventions are generally managed by additional dual antiplatelet therapy for 1-4 weeks, followed by clopidogrel plus DOAC for up to 1 year. AF patients with chronic coronary syndromes should generally receive a DOAC without additional antiplatelet therapy, as this abates major bleeding and improves cardiovascular survival without evidence of increased ischemic risk. For AF patients who develop an acute ischemic stroke, recent exposure to a DOAC is a relative contraindication to intravenous thrombolysis, but the latter may be considered when clinically-relevant anticoagulation can be excluded. Finally, for AF patients who develop a non-severe hemorrhagic stroke during DOAC therapy, resuming a DOAC to prevent ischemic strokes is counterbalanced by considerably enhanced major bleeding, including intracranial.

Key words

acute stroke, atrial fibrillation, frailty, coronary syndrome, direct oral anticoagulant

Introduction

Direct oral anticoagulants (DOACs) have changed the way we prevent stroke-systemic embolism (stroke-SE) in patients with atrial fibrillation (AF) [1,2]. Compared to vitamin K antagonists (VKAs), DOACs are associated with fewer intracranial hemorrhages [3], have predictable pharmacokinetics, limited drug and food interactions, and do not require routine monitoring [4]; therefore, with few exceptions - such as patients with atrial fibrillation (AF) with severe mitral stenosis or a previously implanted mechanical heart valve - DOACs have largely replaced VKAs [1,2,4].

Many AF patients, however, are more complex than those included in the pivotal DOAC-versus-warfarin trials [3,5-7]: for older patients with frailty, renal failure, concomitant coronary syndromes, or acute ischemic or hemorrhagic stroke, decisions on type and timing of antithrombotic therapy may be challenging [5,6,8]. This narrative review-article summarizes key considerations and provides a focused update on DOAC use in these complex scenarios, taking into account prescribing differences across the world and major trial evidence published in the past ten years (Figure 1).

Direct oral anticoagulants in elderly patients with atrial fibrillation

Oral anticoagulation (OAC) in AF patients, compared to no anticoagulation, produces a 64% reduction in the relative risk of stroke [9]; thus, OAC is generally recommended for all AF patients with a CHA_2DS_2VA thromboembolic-risk score (1 point for Congestive heart failure, Hypertension, Age 65–74 years, Diabetes mellitus, and VAscular disease; 2 points for previous Stroke and Age ≥75 years) ≥2 [10]. AF is strongly age-dependent, and older people represent the fastest growing world-population subgroup [8,11-13]. Age ≥75 years is a generally accepted definition of 'elderly', although different thresholds have been used [8]. Compared to younger AF patients receiving OAC, elderly patients have increased rates of both stroke-SE and bleeding (so-called 'bi-risk') [3] (Figure 2), as well as prevalent multimorbidity, polypharmacy and frailty that complicate anticoagulant decision-making [8,11,12]. Despite these challenges, OAC remains the cornerstone of stroke prevention for older AF patients [8,10].

Four pivotal, DOAC-versus-warfarin, phase III, double-blind, randomized controlled trials (RCTs) - RE-LY, ROCKET AF, ARISTOTLE, ENGAGE-AF [14-17] – and subsequent trial-level and individual-patient data meta-analyses have consistently shown that DOACs are at least as effective as warfarin in preventing stroke-SE in older as in younger patients with

'nonvalvular' AF [3,8,12,13](Figure 2), with a ~50% relative risk reduction of intracranial hemorrhages (ICH) [3,8,12,13]. Moreover, on meta-analysis, a significant 10% relative risk reduction of all-cause death is seen across the spectrum of age [3,12,13]. Major extracranial bleeding rates are generally similar or lower with DOACs than with warfarin across age groups (Figure 2). An exception is gastrointestinal bleeding that occurs more often with dabigatran 150 mg twice daily (bid), rivaroxaban and edoxaban [8]. In contrast, apixaban and the 110 mg bid dose of dabigatran show similar gastrointestinal bleeding risks compared to warfarin [3,4,8].

Head-to-head comparisons between DOACs have not been conducted in AF populations; however, trial data for each DOAC show that apixaban resulted in reduced all-cause death compared to warfarin, and that both apixaban and dabigatran 110 mg bid resulted in an overall reduction in major bleeding [3,8]. Thus, for older AF patients, especially with a creatinine clearance <30 ml/min, apixaban represents a valuable choice.

In Europe, where the approved dabigatran doses are 150 and 110 mg bid, the 110 mg bid dosing is mandated for age >75 years or creatinine clearance 30-50 ml/min [4,10]. In the USA, where dabigatran 110 mg bid is not approved, 150 mg bid dosing applies to all age groups, provided creatinine clearance remains >30 ml/min; for a creatinine clearance of 15-30 ml/min instead, a dabigatran 75 mg bid dosing is recommended, regardless of age [18]. Two of three - among age $\geq$80 years, body weight $\leq$60 Kg or serum creatinine $\geq$1.5 mg/dl - mandate dose reduction of apixaban from 5 to 2.5 mg bid [4,8,19]. Thes dose-reduction criteria for edoxaban and rivaroxaban do not include age.

In sum, available randomized trials and meta-analyses support the concept that advanced age *per se* does not represent a contraindication to anticoagulant therapy for AF patients, provided treatment is tailored to individual dose-reduction criteria and comorbidities [4,8,10].

Direct oral anticoagulants in patients deemed unsuitable for vitamin K antagonists or standard oral anticoagulants

Very old AF patients are greatly underrepresented in RCTs and are often deemed unsuitable for standard dose anticoagulation [3,11,20]. In the ELDERCARE-AF trial, 984 Japanese AF patients aged 80 years or above (mean 87±4 years), considered ineligible for standard OAC, were randomized to a very-low dose of edoxaban (15 mg once daily - od) or placebo [11]. Over a median of 1.3 years (accepting that 168 patients withdrew), this very-low dose of edoxaban yielded a 66% relative risk reduction in stroke-SE compared to placebo, without significant excess of major bleeding (3.3% vs 1.8% per year; p=0.09) but with more gastrointestinal bleeds (2.3% vs 0.8% per year; hazard ratio (HR) 2.85, 95% CI 1.03-7.88) [11] (Figure 3). This regimen is approved in Japan and Taiwan for patients ≥80 years with 'nonvalvular' AF who are deemed ineligible for standard-dose anticoagulants because of high bleeding risk, e.g., because of low body weight, low creatinine clearance, history of serious bleeding, or concomitant use of certain medications [21].

In the AVERROES trial, 5599 AF patients from four different continents, who were deemed unsuitable for VKA (mean age 70±9 years), were randomized to apixaban 5 mg bid or aspirin 81-324 mg od (mostly <162mg) [22]. Over a mean 1.1-year follow-up, apixaban resulted in a 55% relative risk reduction in stroke-SE (1.6% vs 3.7% events per year; p<0.001), without significant excess in major bleeding (1.4% vs 1.2% events per year; p=0.57) and without significant treatment-by-age interaction [22](Figure 3).

In sum, despite the age-related bleeding risk, the above findings support consideration of individualized anticoagulation, rather than none, in selected elderly patients deemed unsuitable for standard OAC or VKA [11,22,23].

Direct oral anticoagulants in frail patients with atrial fibrillation

Optimal management of frail AF patients may be challenging. The open-label, adaptive FRAIL-AF trial conducted in the Netherlands randomized 1323 elderly, frail AF patients who were stable on VKA (mean age 83±5 years, Groningen Frailty Indicator score ≥3) to DOAC switch or to continued VKA treatment [24]; over a mean follow-up of 344 days, those who switched experienced higher rates of major and relevant non-major bleeding (17.8% vs 10.5% per year, HR 1.69, 95% CI 1.23-2.32) without a significant reduction in thromboembolic events (2.6% vs 2.1% per year, HR 1.26, 95% CI 0.60-2.61), suggesting that routine switching may not benefit this specific population [24]. Of note, the Netherlands is a top-ranking country for optimal warfarin-dose control.

A retrospective study, based on a nation-wide Korean-claims database, identified 12,461 elderly frail AF patients (mean 80±4 years, Hospital Frailty Risk Score ≥5) who were prescribed warfarin without ever experiencing major bleeding or thromboembolic events; the effect of switching to a DOAC at least once (3349 patients) was evaluated by time-varying anticoagulant exposure [25]. During 11,842 person-years, DOAC treatment was associated with higher risks of major bleeding (HR 1.36, 95% CI 1.01-1.81), thromboembolic events (HR 1.61, 95% CI 1.30-2.00), net clinical outcome (HR 1.58, 95% CI 1.29-1.94) and all-cause death (HR 1.20, 95% CI 1.02-1.42) [25]. Reasons for switching and type of DOAC were not available; moreover, VKA-treated patients were selected for uneventful stability; moreover, 'bi-risk' patients were likely directed towards switching; thus, the above findings require careful interpretation.

The COMBINE-AF analysis of individual-patient data from the four pivotal DOAC-vs-warfarin trials has identified 5913 older, VKA-experienced, frail AF patients (mean age 80±4 years with ≥6 of 18 frailty index features) [26]. In these patients, DOAC initiation compared to warfarin continuation over a mean follow-up of 27 months was associated with significantly

lower rates of intracranial (0.38%/yr vs 1.33%/yr, HR 0.29, 95% CI 0.17-0.48) and fatal bleeding (0.24%/yr vs 0.54%/yr, HR 0.46, 95% CI 0.23-0.90), more gastrointestinal bleeds (3.37%/yr vs 1.85%/yr, HR 1.82, 95% CI 1.42-2.36), and similar rates of any major bleed (5.89%/yr vs 5.58%/yr, HR 1.06, 95% CI 0.90-1.25) or stroke-SE (1.99%/yr vs 2.39%/yr, HR 0.83, 95% CI 0.65-1.07) [26]. Of note, the composite primary endpoint of stroke-SE, major bleeding or death did not differ significantly between treatment arms in both the FRAIL-AF trial and the COMBINE-AF meta-analysis (see Figure 4).

Overall, despite some heterogeneity across studies and potential selection biases in observational data, the available evidence suggests that DOACs represent a viable alternative to warfarin in many frail elderly patients with 'nonvalvular' AF, provided bleeding prevention strategies are carefully implemented [24,26,27].

Direct oral anticoagulants in renally impaired patients with atrial fibrillation.

AF patients receiving OAC who have renal impairment are at increased risk for both ischemic stroke-SE and bleeding, compared to those with lesser renal impairment [3,12,13,19,23] (Figure 5). In such 'bi-risk' patients, multimorbidity and polypharmacy may further complicate anticoagulant decision-making. All DOACs undergo variable renal clearance, which is highest for dabigatran (80%) and edoxaban (50%), and lowest for rivaroxaban (35%) and apixaban (27%) [4,8,28]. The dose adjustments of each DOAC by renal function in Europe and in the USA are illustrated in Figure 6.

Renal function and its age-related decline must be measured regularly for DOAC eligibility and dose selection. Because the Cockcroft-Gault equation was used to assess creatinine clearance in the pivotal DOAC-vs-warfarin AF trials [3], this equation is recommended for dose selection, as follows [4,7,19]: (140 – age in years) x body weight in Kg / 72 x serum creatinine in mg/dl; the result is multiplied by 0.85 for female patients. A practical

rule of thumb for scheduling the next renal function check is to divide the patient's current creatinine clearance by 10 to obtain the monthly interval before the next check; e.g., with a creatinine clearance of 50 ml/min, the next check would be approximately after 50/10 = 5 months.

As stated, the Food and Drug Administration (FDA), but not the European Medicines Agency (EMA), recommend dabigatran 75 mg bid for patients with renal clearance between 15 and 30 ml/min [18]. Moreover, the FDA but not the EMA have approved the use of apixaban 5 mg bid in hemodialysis patients, with a reduction to 2.5 mg bid in the presence of one or two other reduction factors (body weight ≤60 Kg or age ≥80 years) [29] (Figure 6). According to the FDA [30], but not the EMA, edoxaban should not be used for patients with creatinine clearance >95ml/min [4].

Direct oral anticoagulants in patients with atrial fibrillation and coronary syndromes

AF patients presenting with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI) necessitate both long-term OAC as well as a variable duration of antiplatelet therapy (Figure 7).

For AF patients undergoing PCI, with or without ACS, four moderate-sized RCTs (RE-DUAL PCI, PIONEER AF-PCI, ENTRUST-AF PCI, AUGUSTUS) [31-34] have led the European Society of Cardiology guidelines to recommend short-term (1 to 4 weeks) triple therapy with OAC, aspirin and clopidogrel [10,35,36]. After a non-complex PCI procedure, aspirin should be discontinued early (≤1 week), followed by OAC plus clopidogrel for up to 6 months, in patients at lower ischemic risk, or up to 12 months, in those at higher ischemic risk, before transitioning to OAC alone [10,35,36] (Figure 7). In selected patients in whom the ischemic risk is estimated to outweigh the bleeding risk, extension of initial triple antithrombotic therapy up to 4 weeks may be considered [10,35-38]. For medically-managed

ACS patients, dual antithrombotic therapy with OAC and a single antiplatelet agent for up to 12 months is recommended, followed by OAC alone [10]. The use of ticagrelor or prasugrel as part of triple or dual antithrombotic therapy is generally discouraged, supporting clopidogrel as the preferred P2Y12 inhibitor in this setting [10,35,36]. The European guidelines support consideration of lower effective DOAC doses for AF during concomitant antiplatelet therapy, namely, rivaroxaban 15 mg od instead of 20 mg od, and dabigatran 110 mg bid instead of 150 mg bid [10,35,36]. During combination therapy, all bleeding mitigation strategies are strongly recommended [8].

For AF patients with chronic coronary syndrome (CCS) and a prior (≥6 months before) coronary-artery bypass or PCI or no prior revascularization, six small or moderate-sized RCTs (AFIRE, OAC-ALONE, PRAEDO, EPIC-CAD, AQUATIC, ADAPT AF-DES) have compared OAC monotherapy (mostly DOAC-based) to the combination of OAC plus an antiplatelet agent [39-44]. On meta-analysis, over a mean 1.8-year follow-up, OAC monotherapy showed a marked reduction in major bleeding (HR 0.59, 95% CI 0.44-0.79), no significant excess in ischemic events or deaths, and no significant treatment-by-age interaction [45-47]. A significantly lower cardiovascular mortality with OAC alone compared to OAC plus an antiplatelet agent was also reported in this setting [48]. Therefore, OAC monotherapy is generally recommended in the setting of AF and CCS (Figure 7).

In summary, combining antiplatelet agents with a DOAC is temporarily recommended in AF patients with ACS or recent PCI. For AF patients with CCS, only DOAC therapy is generally recommended, given reductions in bleeding and cardiovascular mortality compared to additional antiplatelet treatment [35,45-48].

Direct oral anticoagulant initiation after acute ischemic stroke

In AF patients with acute ischemic stroke, physicians may be uncertain on when to initiate OAC. In the OPTIMAS trial (the largest and longest in this setting), 3621 AF patients with acute ischemic stroke - for which physicians were uncertain of optimal DOAC timing - were randomized to early (≤4 days) or delayed (7-14 days) DOAC administration [49]. On admission, the median National Institutes of Health Stroke Scale score was 4 (interquartile 2-7), distributed as follows: 41% 0-4, 34% 5-10, 12% 11-15, 9% 16-21, 4% >21 or missing [49]. Early DOAC initiation was non-inferior to delayed initiation for the composite outcome of recurrent ischemic stroke, symptomatic ICH (sICH), unclassifiable stroke or systemic embolism at 90 days: 3.3% versus 3.3% (non-inferiority margin set at 3% absolute event difference) [49]. The findings suggest that earlier DOAC initiation is acceptable for patients with mostly-mild acute ischemic strokes.

Thrombolysis in patients atrial fibrillation with recent direct oral anticoagulant exposure

Intravenous thrombolysis (IVT) within 4.5 hours of symptom onset remains a cornerstone of therapy for patients with disabling acute ischemic stroke in the absence of absolute contraindications [50]. Because patients receiving OAC were excluded from pivotal thrombolytic trials, the safety of IVT in the setting of recent (<48 hours) DOAC use remains uncertain [50]. Observational data challenge the traditional view that recent DOAC exposure is an absolute contraindication to IVT.

In a large, international, retrospective analysis of over 33,000 consecutive patients with acute ischemic stroke receiving IVT, 832 patients with documented DOAC use within 48 hours were compared to 32,375 non-anticoagulated controls [51]. At 36-hour imaging, sICH occurred in 2.5% of patients with recent DOAC exposure versus 4.1% in the control group (adjusted odds ratio 0.57, 95% CI 0.36-0.92) [51]. The prospective RASUNOA-Prime study enrolled

2737 acute ischemic stroke patients with or without prior OAC (1066 DOAC, 695 VKA, 976 no OAC); IVT and 120-hour imaging for sICH were performed in 63, 104 and ~450 patients respectively; the risk of sICH was not increased compared to patients without OAC (odds ratio for DOAC 0.56, 95% CI 0.17-1.89; p=0.34; odds ratio for VKA 0.95, 95% CI 0.31-2.92; p=0.92) after adjusting for thrombectomy [52].

The latest European Stroke Organisation (ESO) guidance dating 2021 allows IVT after DOAC use when clinically relevant anticoagulant activity can be reliably excluded, that is, with a thrombin time <60 seconds (or more specific assays such as dilute thrombin time or ecarin clotting time) for dabigatran, and with anti-Xa activity <0.5 U/mL for factor-Xa inhibitors [53]. For those with recent dabigatran exposure, the 2021 ESO guidance states that rapid reversal with idarucizumab plus IVT, over no IVT, is backed by insufficient evidence for or against [53]; two small cohort studies (120 and 51 patients, respectively) suggest satisfactory results with reversal strategies, including reversal of factor-Xa inhibitor activity with andexanet alfa [53].

The 2026 American Heart Association/American Stroke Association guidelines recommend cautious individualized decisions on IVT for stroke in patients with recent DOAC exposure, taking into account timing of last DOAC dose, renal function, stroke severity, availability of reversal drugs and specific coagulation assays [50]. Importantly, mechanical thrombectomy is not contraindicated in patients receiving DOAC therapy and should not be withheld when otherwise indicated, i.e., for acute ischemic stroke caused by large vessel occlusion in patients presenting within 6 hours of symptom onset, or up to 24 hours in selected patients with favorable imaging [50].

Direct oral anticoagulants in patients with atrial fibrillation and acute hemorrhagic stroke

A key unresolved question is whether OAC should be resumed in anticoagulated AF patients who develop an ICH. In the European, open-label, PRESTIGE-AF trial, 319 AF survivors following a non-severe ICH (modified Rankin Scale score ≤4) were randomized to DOAC or none [54]. Before the index ICH, 84% of patients were on anticoagulation. Randomization was stratified by sex and ICH location (lobar vs non-lobar). DOAC was started from 14 days to 12 months after the index ICH. In the no-DOAC arm, 33% received an antiplatelet agent according to local practice. Over a median of 1.4 years, DOAC prescription markedly reduced the cumulative rates of ischemic stroke, particularly in the first year (0.83%/year vs 8.60%/year, P <0.001), but increased recurrent ICH (unrelated to ICH location or randomization onset: 5.00%/year vs 0.82%/year) and any type of major bleeding (7.75%/year vs 2.05%/year), with non-significant differences in all-cause mortality (6.67%/year vs 8.6%/year) [54]. These findings indicate an uncertain risk/benefit balance in AF patients surviving an ICH, with ischemic stroke prevention by DOAC largely offset by increased risks of ICH and other major bleeds. For AF patients with spontaneous ICH in whom the decision is made to restart anticoagulation, the 2022 AHA/ASA guidelines state that "initiation of anticoagulation ~7 to 8 weeks after ICH may be considered after weighing specific patient characteristics to optimize the balance of risks and benefits" [55].

Non-pharmacological alternatives to OAC, such as left atrial appendage closure (LAAC), have been considered to abate bleeding complications. Two recent trials tested the noninferiority of LAAC versus medical therapy alone (mostly DOAC) in AF patients who were either at high-bleeding risk (CLOSURE-AF, N=912 out of 1512 initially planned, mean 78±7 yrs,) or OAC-eligible (CHAMPION-AF, N=3000, mean 72±78 yrs) [56,57]. In the investigator-initiated, German CLOSURE-AF trial, LAAC was followed by DAPT for at least 3 months, and then SAPT for at least 6 months [56]. High bleeding risk was defined as a HAS-BLED

score ≥3, stage IV CKD, prior intracranial or spinal or serious ocular bleed, or recurrent bleeding precluding long-term anticoagulation [56]. At a median follow-up of 3 years, LAAC compared to medical therapy resulted in a comparable rate of ischemic stroke (1.8% vs 1.5%), but was not noninferior for the composite primary endpoint of stroke (ischemic or hemorrhagic), systemic embolism, BARC 3-5 major bleeding, or cardiovascular or unexplained death: Kaplan-Meier estimates 16.8% vs 13.3%; restricted mean survival time -0.36, P=0.44 for noninferioriy (margin = HR 1.3) [56]. In the company-sponsored, multinational CHAMPION-AF trial, LAAC was followed by 3 months of either DAPT, DOAC plus aspirin, or DOAC alone, followed by SAPT. After 3 years of follow-up, the occurrence of the primary efficacy endpoint (cardiovascular death, stroke, or systemic embolism) was noninferior (P<0.001; margin 4.8 percentage points): Kaplan-Meier estimate 5.7% vs 4.8%; non-procedure-related bleeding was abated after LAAC (Kaplan-Meier estimate 10.9% vs 19.0%; HR 0.55; 95% CI, 0.45 to 0.67; P<0.001 for superiority) [57].Given the apparent diverging results of these recent trials, partly related to differences in population type and sample size, further investigations may be needed to fully establish the indication for LAAC among high hemorrhagic risk AF patients.

Conclusions Complex scenarios involving AF patients who are very old, frail, renally impaired, affected by concomitant acute or chronic coronary syndromes, or by acute ischemic or hemorrhagic stroke are not rare in clinical practice and require careful decisions regarding the type and timing of antithrombotic therapy (Figure 1). For the majority of cases, recent-trial evidence and international scientific guidance support DOAC prescription, provided bleeding prevention strategies are adopted, and regular checks are carefully carried out for renal function, as well as for ischemic and bleeding risks. Polypharmacy may complicate DOAC therapy, enhancing bleeding risk in case of concomitant antiplatelet, non-steroidal anti-inflammatory or CYP3A4 inhibitor drugs, and directly affecting long-term adherence. In such multimorbid

patients, significant gaps in evidence are present. Future research priorities should include geriatric-focused clinical trials and optimal healthcare-resource allocation in ageing populations.

Article information

Acknowledgments None.

Funding None.

Contribution statement [xxx add].

Conflict of interest FA reports receiving personal fees from Amgen, Menarini, Novo Nordisk and Servier, outside the present work. LC reports receiving a fellowship grant from Abiomed outside the present work. FB reports receiving speaker fees from Abbott, Abiomed, Edwards, Medtronic and Terumo, outside the present work. All other authors report no known potential conflict related to the present work.

AI statement Artificial intelligence was not used in preparation of this manuscript.

How to cite Andreotti F, Balaji AN, Cappannoli L, et al. Direct oral anticoagulants in older patients with atrial fibrillation and comorbidities: frailty, renal impairment, acute or chronic coronary syndromes, and acute stroke. Pol Arch Intern Med. 2026; XX: 17319. doi:10.20452/pamw.17319

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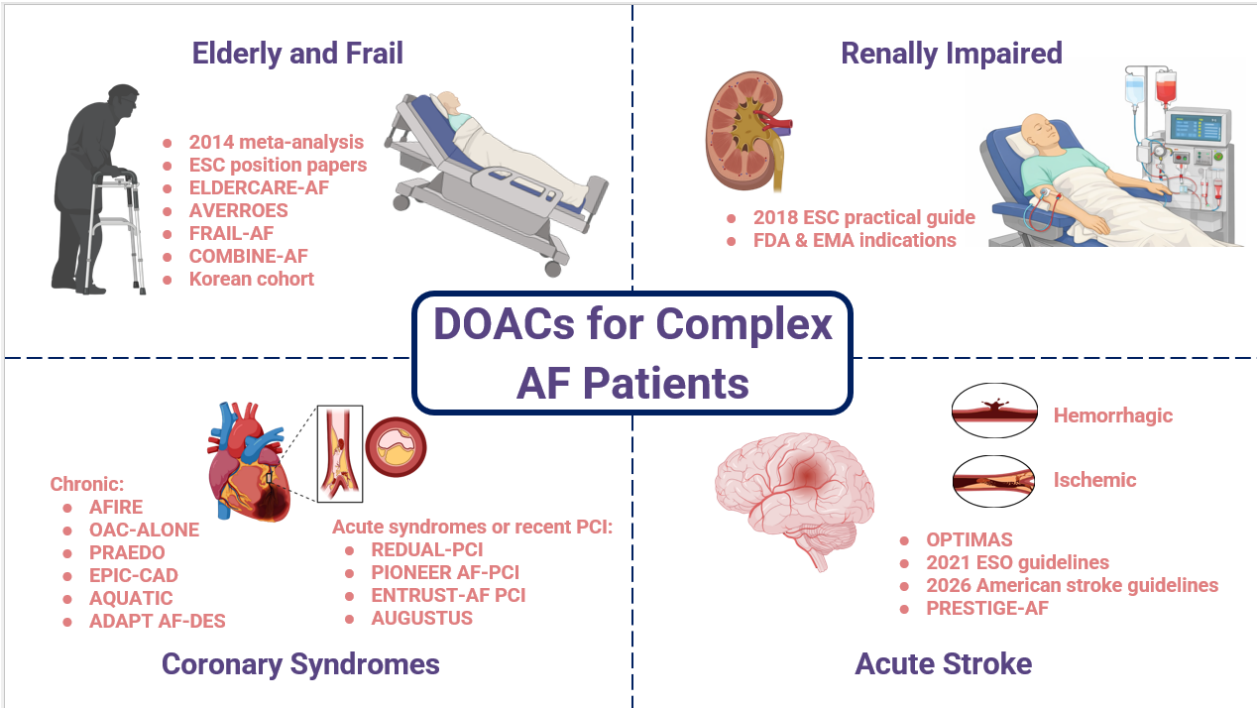

Figure 1 DOACs in older patients with AF and comorbidities: frailty, renal impairment, acute or chronic coronary syndromes, and acute stroke.

Key articles guiding the use of the four direct oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban) in each of the four clinical scenarios are listed.

Abbreviations: ADAPT AF-DES, Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents in Atrial Fibrillation; AFIRE, Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease; AQUATIC, Assessment of Quitting versus Using Aspirin Therapy in Patients with Stabilized Coronary Artery Disease after Stenting Who Require Long-Term Anticoagulation; AUGUSTUS, An Open-Label, 2×2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K

Antagonist and Aspirin Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment bid: bis in die (twice daily); COMBINE-AF, A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulation Use in Atrial Fibrillation; DOAC, direct oral anticoagulant; ELDERCARE-AF, Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients; EMA, European Medicines Agency; ENTRUST-AF PCI, Edoxaban Treatment vs Vitamin K Antagonist in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; EPIC-CAD, Edoxaban versus Edoxaban With Antiplatelet Agent in Patients with Atrial Fibrillation and Chronic Stable Coronary Artery Disease; ESC, European Society of Cardiology; ESO: European Stroke Organisation; FDA, Food and Drug Administration; FRAIL-AF, Frail Atrial Fibrillation; OPTIMAS, OPTIMAal timing of anticoagulation after acute ischaemic Stroke; PCI, percutaneous coronary intervention; PIONEER AF-PCI, An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; PRAEDO, Prospective RAndomized study of safety outcomes treated with EDOxaban in patients with stable CAD and atrial fibrillation; PRESTIGE AF, PREvention of STroke in Intracerebral haemorrhaGE survivors with Atrial Fibrillation; RE-DUAL PCI, Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

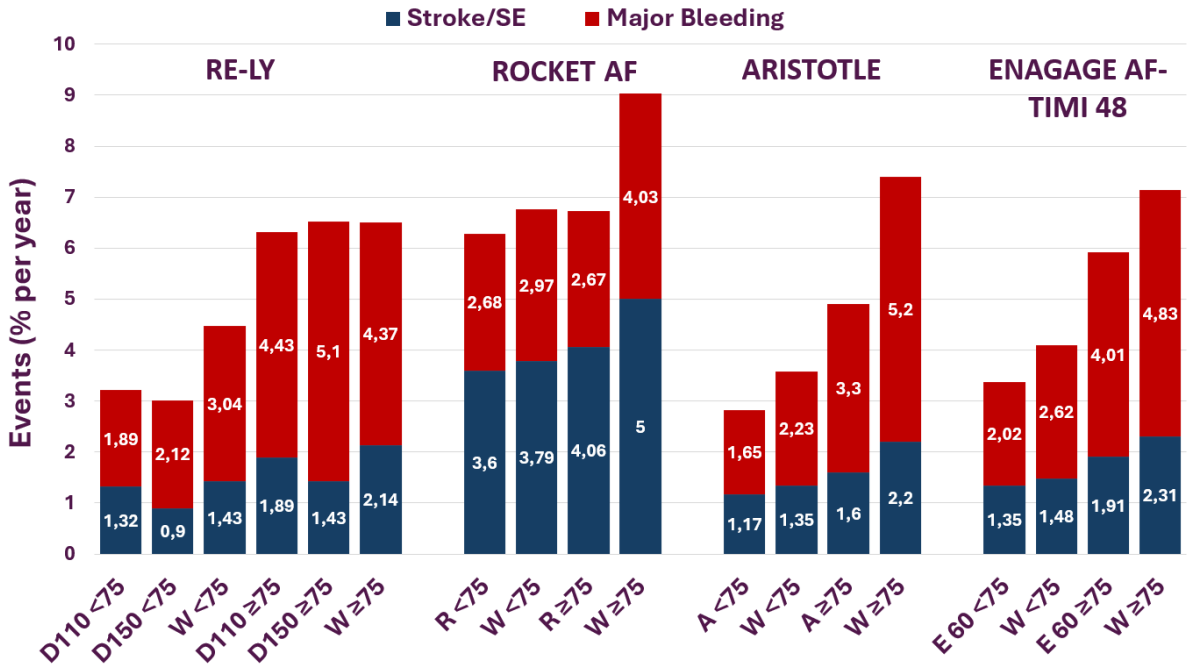

Figure 2 Stroke-systemic embolism and major bleeding by treatment and age.

Data are from the four pivotal DOAC-versus-warfarin AF trials. Patient event rates are presented as % per year of follow-up. Age is stratified as <75 and ≥75 years.

Abbreviations: A, apixaban; D, dabigatran; E, edoxaban; R, rivaroxaban; SE, systemic embolism, W, warfarin

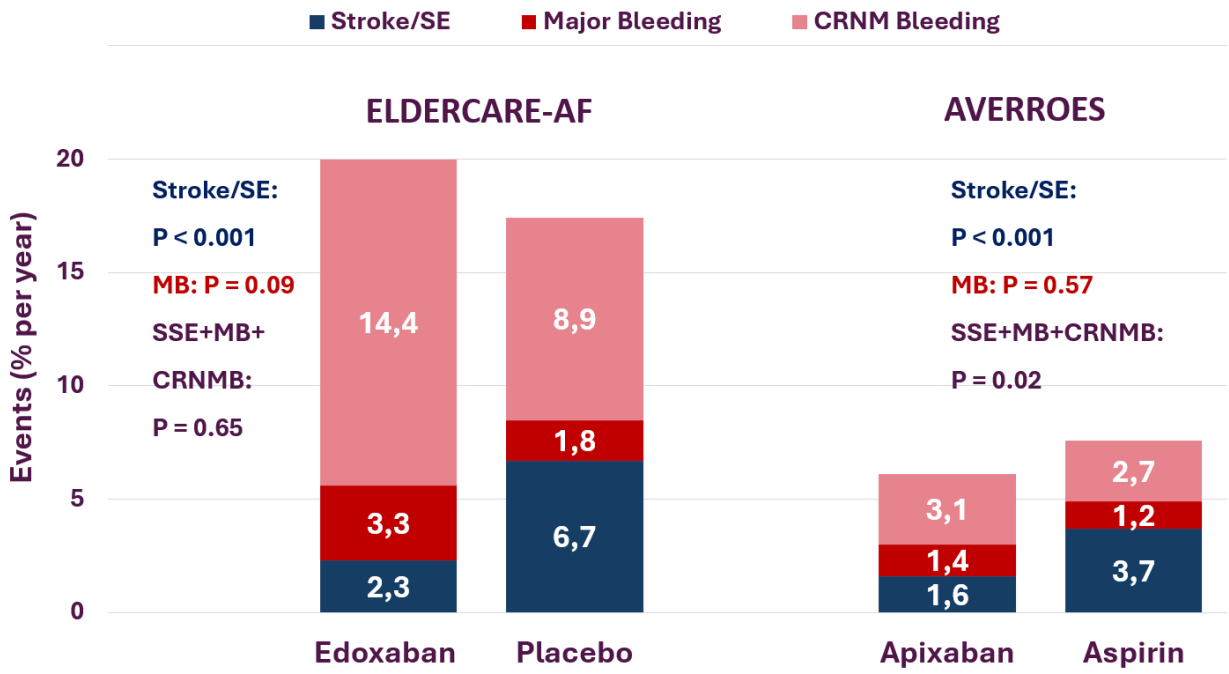

Figure 3 Clinical outcomes stratified by treatment in AF patients judged unsuitable for VKA or standard OAC.

In ELDERCARE-AF, edoxaban dose is 15 mg od. In AVERROES, apixaban dose is 5 mg bid and aspirin dose is 81-324 mg od (mostly <162 mg). Patient event rates are % per year of follow-up. Multiple events in the same patient are included.

Abbreviations: CRNM, clinically relevant non-major; MB, major bleeding; OAC, oral anticoagulation; SE, systemic embolism; SSE, stroke or systemic embolism; VKA, vitamin K antagonist

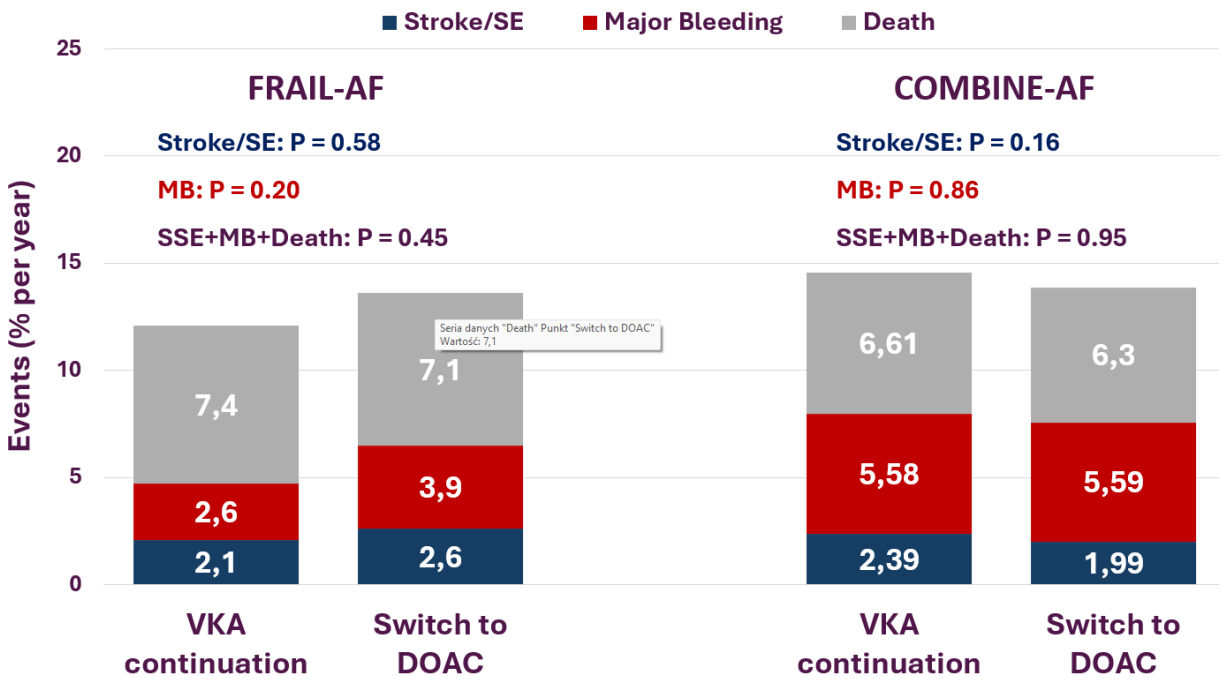

Figure 4 Clinical outcomes stratified by treatment in stable, VKA-experienced, frail AF patients.

The composite of stroke-SE, major bleeding or death, which was the primary endpoint of the COMBINE-AF analysis, did not differ significantly between treatments in both FRAIL-AF and COMBINE-AF. Patient event rates are % per year of follow-up. Multiple events in the same patient are included.

Abbreviations: CRNM, clinically relevant non-major; DOAC, direct oral anticoagulant; MB, major bleeding; SE, systemic embolism; SSE, stroke or systemic embolism; VKA, vitamin K antagonist

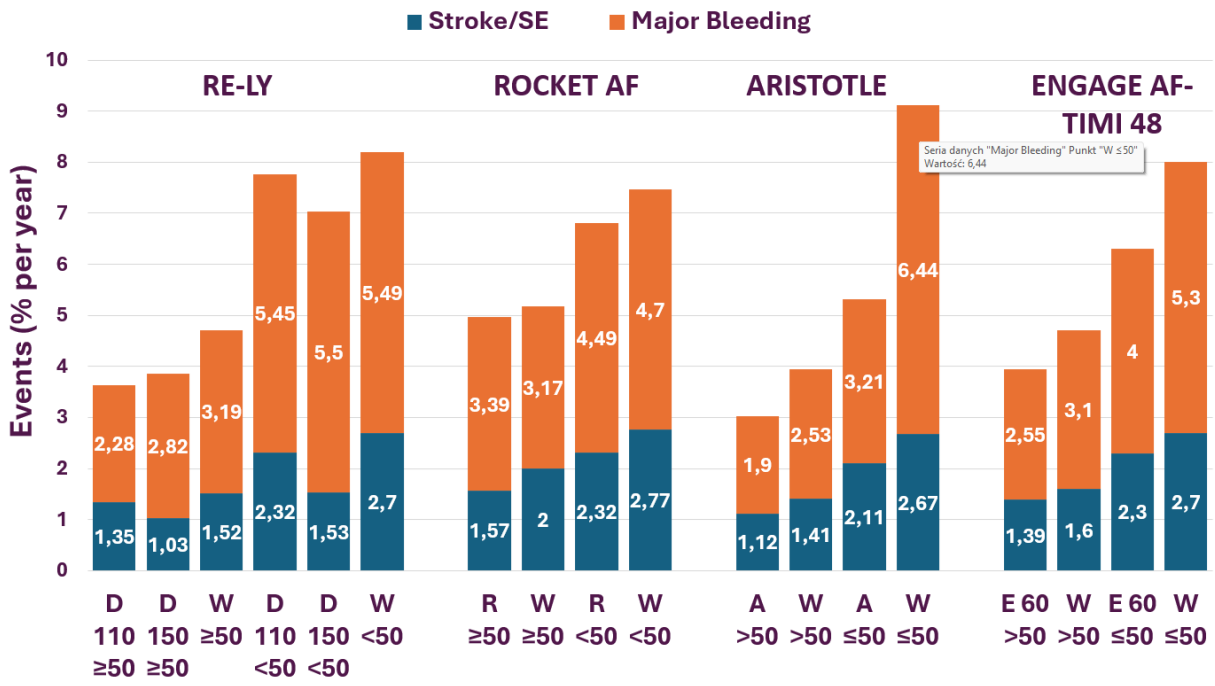

Figure 5 Stroke-systemic embolism and major bleeding by treatment and creatinine clearance. Data are from the four pivotal DOAC-versus-warfarin AF trials. Patient event rates are % per year of follow-up. Reduced clearance defined as <50 ml/min or ≤50 ml/min in different trials. Creatinine clearance estimated by the Cockcroft-Gault equation.

Abbreviations: A, apixaban; D, dabigatran E, edoxaban; R, rivaroxaban; SE, systemic embolism, W, warfarin.

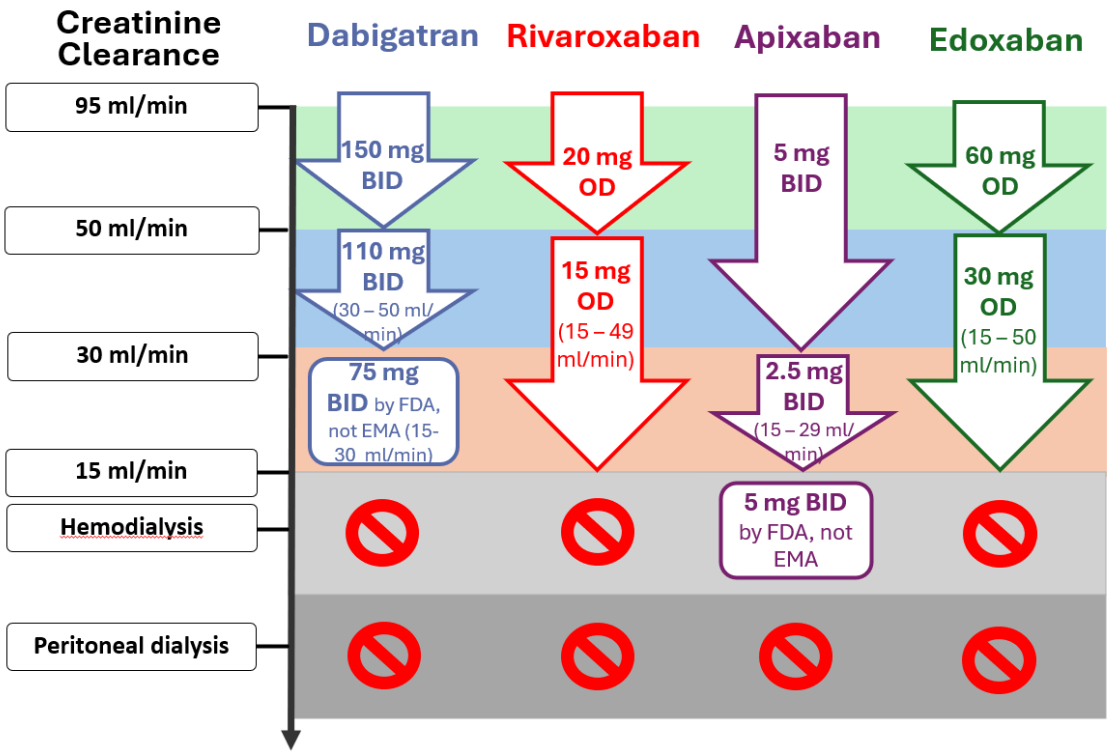

Figure 6 DOAC indications and doses based on creatinine clearance.

Creatinine clearance estimated by Cockcroft-Gault equation. Dose reduction for rivaroxaban is <50 ml/min and for edoxaban ≤50 ml/min.

Abbreviations: BID, bis in die (twice daily); EMA, European Medicines Agency; FDA, Food and Drug Administration; OD, once daily.

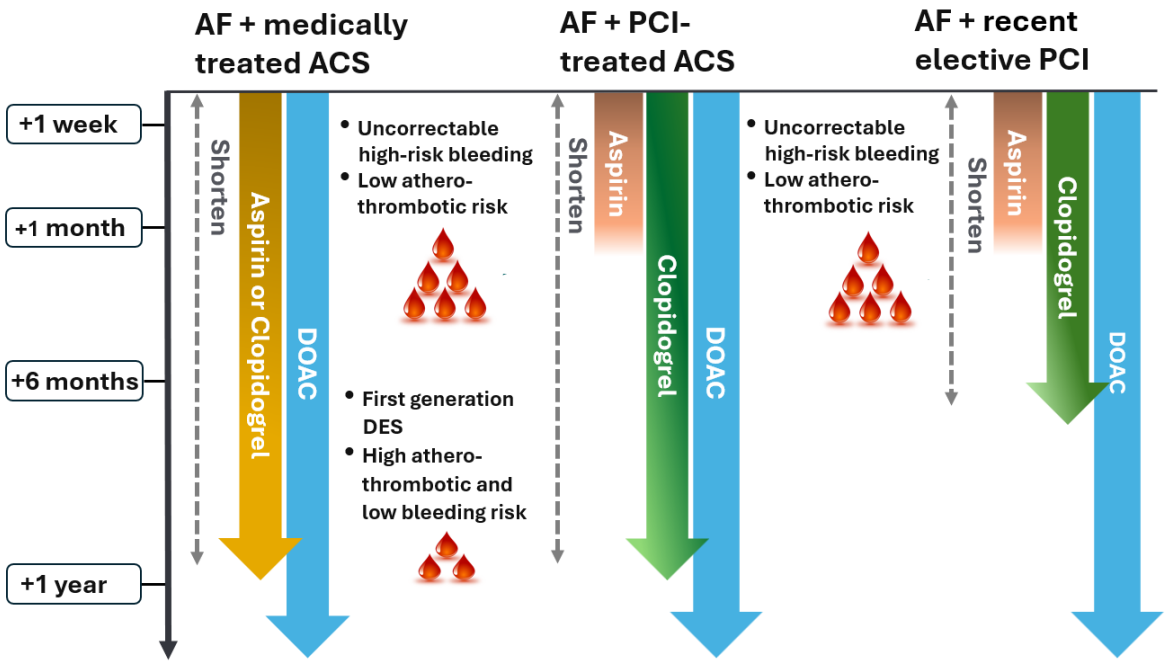

Figure 7 Antiplatelet regimens in DOAC-treated AF patients with coronary syndromes.

Antiplatelet drugs for a limited time are recommended in combination with a DOAC for AF patients presenting with ACS (with or without PCI) and for CCS patients undergoing elective PCI.

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; CCS, chronic coronary syndrome; DES, drug-eluting stent; DOAC, direct oral anticoagulant; PCI, percutaneous coronary intervention

Short title: DOACs across complex clinical scenarios