ISCHEMIC STROKE DUE TO ATRIAL FIBRILLATION:

ANTICOAGULATION STRATEGIES AND CLINICAL DECISION ALGORITHMS

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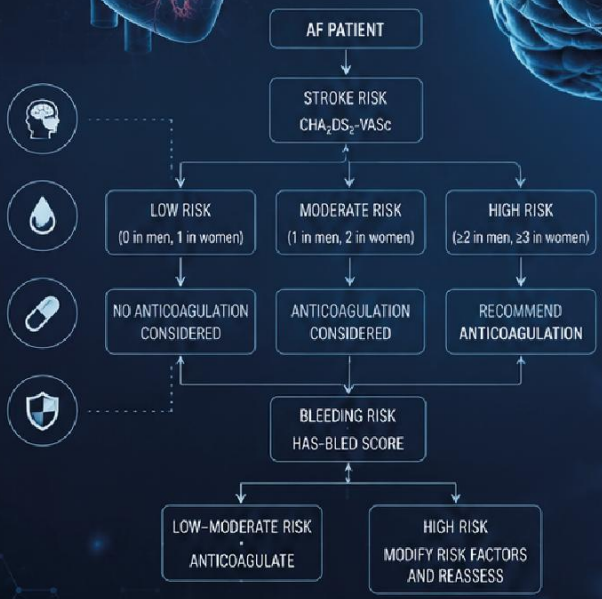

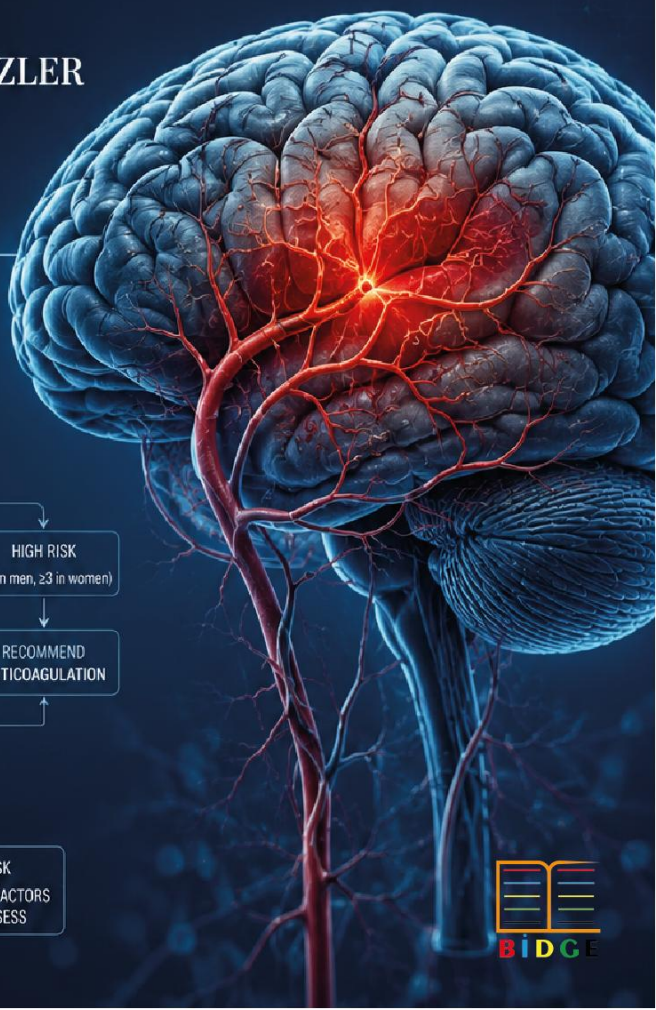

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İÇİNDEKİLER

INTRODUCTİON

ATRIAL FIBRILLATION

ATRIAL FIBRILLATION AND ISCHEMIC STROKE

ANTICOAGULATION THERAPY

Direct Oral Anticoagulants (DOACs) vs. Warfarin: A Contemporary Evidence-Based Review

PREFACE AND SCOPE

This book addresses the anticoagulation strategy for AF-related ischemic stroke from the perspective of current clinical evidence, guideline recommendations, and practical bedside decision-making. The target readership includes neurology residents and fellows, internal medicine trainees, and clinicians seeking to update their knowledge in this rapidly evolving field.

The content spans pathophysiology and risk stratification, the pharmacology of warfarin and each DOAC, pivotal clinical trial evidence, approaches to special patient populations, current international guidelines, and practical clinical decision algorithms. All recommendations are based on the 2024-2025 ESC, AHA/ACC, and ASA guidelines, as well as selected high-quality randomized controlled trials.

This book is intended as a clinical reference guide; individual patient management should always integrate personal clinical context with current guidelines.

CHAPTER I

INTRODUCTION — ATRIAL FIBRILLATION AND ISCHEMIC STROKE

1.1 Epidemiology and Global Burden

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide, affecting approximately 59.7 million individuals (GBD 2019 data). The condition carries a disproportionate burden of morbidity and mortality, with its consequences extending well beyond palpitations and hemodynamic compromise. AF-related stroke represents one of the most consequential complications: it accounts for 20-30% of all ischemic strokes globally, produces larger infarcts with greater functional disability, and is associated with nearly double the 30-day mortality compared with non-AF-related stroke.

The Global Stroke Atlas 2023 estimates that annual stroke incidence has plateaued or even increased in many low- and middle-income countries despite therapeutic advances in high-income settings. This disparity reflects the treatment gap in anticoagulation — the gap between patients who should receive oral anticoagulation

(OAC) and those who actually do. Studies across multiple countries consistently report anticoagulation rates of only 40-60% among eligible AF patients, leaving an enormous preventable disease burden.

1.2 Classification of Atrial Fibrillation

The 2020 ESC AF Guidelines and the 2023 AHA/ACC/HRS Guidelines classify AF by temporal profile as follows:

First-detected AF: First recognized episode; duration may be unknown.

Paroxysmal AF: Episodes terminating spontaneously or with intervention within 7 days; by definition, recurrent.

Persistent AF: Sustained >7 days, requiring pharmacologic or electrical cardioversion.

Long-standing persistent AF: Continuous AF >12 months when a rhythm-control strategy is pursued.

Permanent AF: The patient and clinician have jointly decided not to pursue rhythm control; a therapeutic attitude, not a pathophysiologic state.

Subclinical AF (AHRE): Detected by implanted devices or wearables without symptoms; CRYSTAL-AF and EMBRACE landmark trials.

1.3 Historical Perspective

The anticoagulation narrative in AF began in the 1950s with bishydroxycoumarin, but warfarin became the dominant agent through the landmark SPAF (Stroke Prevention in Atrial Fibrillation) trials conducted between 1989 and 1996. These pivotal studies demonstrated that adjusted-dose warfarin reduced stroke risk by approximately 64-67% compared with placebo. For nearly two decades, warfarin remained the sole oral anticoagulant option for AF, accepted despite its considerable pharmacologic limitations — narrow therapeutic index, multiple drug-food interactions,

unpredictable pharmacokinetics, and requirement for routine INR monitoring.

The paradigm shift came between 2009 and 2013, when four large-scale, phase III randomized controlled trials — RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 — evaluated non-vitamin K antagonist oral anticoagulants (DOACs) against warfarin. Their results collectively established the DOAC class as at least non-inferior and in several dimensions superior to warfarin, inaugurating a new era in AF stroke prevention.

CHAPTER II

PATHOPHYSIOLOGY AND RISK STRATIFICATION

2.1 Mechanisms of Thrombogenesis

Thromboembolic risk in AF is explained by all three components of Virchow's triad: (1) abnormal blood flow (stasis), (2) endothelial dysfunction, and (3) hypercoagulability. Loss of coordinated atrial contraction creates pronounced stasis, particularly in the trabeculated LAA. When flow velocity in the LAA falls below a threshold (typically <20 cm/s on TEE), spontaneous echocardiographic contrast ('smoke') develops — a marker that increases thrombus risk 4- to 5-fold and strongly predicts systemic embolism.

At the molecular level, AF induces a prothrombotic milieu characterized by increased thrombin generation, impaired fibrinolysis, elevated von Willebrand factor and tissue factor expression, and endothelial activation. Elevated P-selectin, thrombomodulin, and endothelin-1 reflect this endothelial dysfunction. Progressive atrial fibrosis and structural remodeling —

mediated by angiotensin II, TGF-beta, and galectin-3 — compound the electrical remodeling and perpetuate the thrombogenic substrate.

2.2 CHA2DS2-VASc Stroke Risk Score

The CHA2DS2-VASc score, introduced by Lip et al. in 2010, is the internationally endorsed tool for quantifying thromboembolic risk in AF. It has supplanted the earlier CHADS2 score due to improved discrimination in lower-risk patients. Component details are shown in the table below:

Interpretation: In male patients, a score >=2 warrants anticoagulation; in female patients, >=3. A score of 0 in males (or 1 in females counting only the sex criterion) is considered low risk and anticoagulation is not recommended. Annual stroke rates range from approximately 0.6% (score 1) to over 15% (score 9), underscoring the wide spectrum of risk within the AF population.

2.3 HAS-BLED Bleeding Risk Score

Bleeding risk must be assessed alongside thrombotic risk when initiating OAC. The HAS-BLED score was developed and validated to identify patients at elevated risk of major bleeding on anticoagulation:

IMPORTANT: A score >=3 designates 'high' bleeding risk. Current ESC 2024 and AHA 2023 guidelines emphasize that HAS-BLED should be used to identify and address modifiable bleeding risk factors — NOT as a reason to withhold anticoagulation. When high CHA2DS2-VASc and high HAS-BLED scores coexist, the net clinical benefit of anticoagulation remains positive; the appropriate response is to correct modifiable bleeding risk factors (hypertension control, medication review, alcohol cessation, INR optimization).

2.4 Stroke Subtypes and Their Association with AF

AF-related strokes are cardioembolic in mechanism and are characterized by: sudden-onset maximal neurological deficit, large vessel occlusion (particularly MCA-M1 and its branches), cortical

and deep white matter involvement, propensity for hemorrhagic transformation (especially in large infarcts with reperfusion), and consistently higher NIHSS scores compared with lacunar or atherothrombotic strokes. DWI patterns showing simultaneous bilateral or multiple territorial lesions are highly suggestive of a cardioembolic source. Among cryptogenic strokes meeting ESUS (Embolic Stroke of Undetermined Source) criteria, prolonged monitoring detects AF in 25-30% of cases.

CHAPTER III

WARFARIN — THE CORNERSTONE OF CLASSIC ANTICOAGULATION

3.1 Mechanism of Action and Pharmacology

Warfarin (acenocoumarin in some regions) is a coumarin-derivative oral anticoagulant that inhibits the hepatic carboxylation of vitamin K-dependent clotting factors (II, VII, IX, X) by blocking the enzyme vitamin K epoxide reductase (VKOR). It simultaneously suppresses the anticoagulant proteins C and S. This broad coagulation cascade inhibition renders warfarin potent but also pharmacodynamically complex. The drug is administered as a racemic mixture of S- and R-enantiomers; the more potent S-form is primarily metabolized by CYP2C9, while the R-form is metabolized by CYP3A4 and CYP1A2.

Polymorphisms in CYP2C9 and VKORC1 genes are the primary determinants of inter-individual dose variability — accounting for up to 40-50% of the dose variation observed in clinical practice. Patients with CYP2C9*2 or *3 alleles require significantly lower doses; VKORC1 promoter variants (1639 G>A)

are associated with warfarin sensitivity and increased bleeding risk at standard doses.

3.2 Pharmacokinetic Profile

Oral bioavailability: >95% (near-complete GI absorption)

Protein binding: >99% albumin-bound (displacement interactions clinically significant)

Onset of action: 36-72 hours (dependent on clotting factor half-lives)

Half-life: 20-60 hours (wide individual variation)

Metabolism: CYP2C9 (S-warfarin), CYP3A4/CYP1A2 (R-warfarin)

Elimination: Renal (~92% as inactive metabolites)

3.3 Target INR and Therapeutic Window

For AF stroke prevention, the target INR is 2.0-3.0. Interpretation of INR ranges: INR <2.0 indicates subtherapeutic anticoagulation with unprotected stroke risk; INR 2.0-3.0 represents the optimal therapeutic window; INR 3.0-4.0 signals over-anticoagulation with rising bleeding risk; INR >4.0 carries serious hemorrhagic risk requiring urgent correction. Time in Therapeutic Range (TTR) — the proportion of time the INR remains between 2.0 and 3.0 — is the single most important quality metric for warfarin therapy. A TTR >70% achieves optimal stroke protection while minimizing bleeding; TTR <65% is a strong indication to switch to a DOAC.

3.4 Clinical Efficacy: Key Evidence

SPAF I (1991) demonstrated that warfarin reduced stroke risk by 67% versus placebo in AF patients. The SPAF II and III trials established that aspirin was substantially inferior to warfarin, and that combining aspirin with low-intensity warfarin did not improve outcomes. The 2007 Cochrane meta-analysis by Hart et al. (12 RCTs,

n=12,963) confirmed that adjusted-dose warfarin reduced stroke risk by 64% relative to placebo and by 39% relative to antiplatelet therapy, at the cost of a 0.3% per year increase in major intracranial hemorrhage. The BAFTA trial (2007) established warfarin's superiority over aspirin in patients aged >75 years, definitively refuting the notion that age alone justifies aspirin monotherapy.

3.5 Limitations and Clinical Challenges

Narrow therapeutic window requiring routine INR monitoring — a significant logistical and patient burden.

Wide inter-individual pharmacokinetic variability driven by CYP2C9 and VKORC1 polymorphisms.

Extensive drug interactions: antibiotics (especially fluoroquinolones, metronidazole), NSAIDs, antifungals, antiepileptics, statins, amiodarone.

Dietary interactions: vitamin K-rich foods (dark leafy vegetables) reduce INR; dietary inconsistency causes instability.

Delayed onset and offset of anticoagulant effect; bridging anticoagulation often required perioperatively.

Reversal challenges: vitamin K (slow onset), fresh frozen plasma (volume, infection risk), or PCC (preferred for ICH).

Patient adherence: monitoring burden, dietary restrictions, and frequent dose adjustments undermine long-term compliance.

CHAPTER IV

DIRECT ORAL ANTICOAGULANTS (DOACs)

4.1 Pharmacologic Classification and General Properties

Direct oral anticoagulants (DOACs) — formerly termed NOACs (Non-vitamin K antagonist Oral Anticoagulants) — are a class of agents that directly and specifically inhibit defined coagulation enzymes, thereby interrupting the coagulation cascade at targeted nodal points. Two mechanistic classes exist:

Direct thrombin inhibitors (DTIs): Dabigatran — inhibits both free and clot-bound thrombin

Factor Xa inhibitors: Rivaroxaban, Apixaban, Edoxaban — inhibit both free and prothrombinase-bound factor Xa

Compared with warfarin, DOACs offer predictable pharmacokinetics, fixed dosing without routine coagulation monitoring, fewer drug-drug and drug-food interactions, rapid onset and offset of action, and the availability of specific reversal agents. These properties have translated into improved real-world adherence and outcomes in observational registries.

4.2 Comparative Pharmacology

*Rivaroxaban bioavailability increases to >80% when taken with food, making coadministration with the main meal of the day mandatory at doses >=10 mg.

4.3 Dabigatran — RE-LY Trial

Dabigatran etexilate is a prodrug converted to active dabigatran by esterase-mediated hydrolysis. The RE-LY trial (2009, Connolly et al., NEJM) was an open-label, randomized comparison of two fixed dabigatran doses against dose-adjusted warfarin in 18,113 patients with AF and at least one additional stroke risk factor (median CHADS2 score 2.1).

Dabigatran 150 mg BID vs. warfarin: Stroke/SE 1.11% vs. 1.69%/year (34% RRR, p<0.001); Major bleeding: similar (3.11% vs. 3.36%); ICH: 0.32% vs. 0.76%

Dabigatran 110 mg BID vs. warfarin: Stroke/SE: Non-inferior; ICH: 0.23% vs. 0.76% (69% RRR, p<0.001); Major bleeding: 2.71% vs. 3.36% (p=0.003)

GI bleeding was significantly higher with dabigatran 150 mg, particularly in patients >75 years

A modest signal for increased myocardial infarction was observed but attenuated in subsequent analyses

The specific reversal agent idarucizumab (Praxbind, 5 g IV) received FDA approval in 2015 and provides complete and rapid reversal of dabigatran within minutes — a critical advantage in emergent surgery or life-threatening hemorrhage.

4.4 Rivaroxaban — ROCKET-AF Trial

ROCKET-AF (2011, Patel et al., NEJM) was a double-blind, randomized trial of rivaroxaban 20 mg once daily versus dose-adjusted warfarin in 14,264 patients. Notably, the trial enrolled a higher-risk population than other DOAC trials (mean CHADS2 3.5,

55% with prior stroke or TIA), which may have influenced the magnitude of observed treatment differences.

Stroke/SE: Rivaroxaban 1.7% vs. warfarin 2.2%/year (non-inferiority $p<0.001$; superiority $p=0.12$)

ICH: 0.5% vs. 0.7% (31% RRR, $p=0.02$)

Major bleeding: similar overall; GI bleeding higher with rivaroxaban

Once-daily dosing and no dietary restrictions (except the requirement to take with food) support adherence

4.5 Apixaban — ARISTOTLE Trial

ARISTOTLE (2011, Granger et al., NEJM) was a double-blind, randomized trial comparing apixaban 5 mg BID against warfarin in 18,201 patients. The trial achieved a remarkable four-domain superiority over warfarin — simultaneously demonstrating better stroke prevention, fewer deaths, less major bleeding, and dramatically fewer intracranial hemorrhages.

Stroke/SE: Apixaban 1.27% vs. warfarin 1.60%/year (21% RRR, $p=0.01$) — superiority over warfarin

ICH: 0.33% vs. 0.80% (58% RRR, $p<0.001$) — largest ICH reduction among all DOAC trials

Major bleeding: 2.13% vs. 3.09% (31% RRR, $p<0.001$)

All-cause mortality: 3.52% vs. 3.94% (11% RRR, $p=0.047$)

GI bleeding: similar to warfarin — unique among DOACs

AVERROES (2011) complemented ARISTOTLE by demonstrating apixaban's significant superiority over aspirin in patients unsuitable for warfarin, without a significant increase in major bleeding. This established apixaban as the preferred agent in patients unable to tolerate vitamin K antagonists.

4.6 Edoxaban — ENGAGE AF-TIMI 48 Trial

ENGAGE AF-TIMI 48 (2013, Giugliano et al., NEJM) was a double-blind, randomized trial of two edoxaban doses versus

warfarin in 21,105 patients — the largest AF anticoagulation trial by enrollment. A unique dose-modification algorithm halved the dose in patients with CrCl 15-50 mL/min, body weight <=60 kg, or concomitant use of p-gp inhibitors.

Edoxaban 60 mg vs. warfarin: Stroke/SE non-inferior; ICH 0.39% vs. 0.85% (47% RRR); Major bleeding 2.75% vs. 3.43% (20% RRR)

Edoxaban 30 mg vs. warfarin: Stroke/SE non-inferior (numerically slightly higher strokes); ICH 0.26% vs. 0.85% (54% RRR); Lowest absolute bleeding rate

The 60 mg dose is standard in clinical practice; dose reduction criteria apply in specific circumstances

CHAPTER V

COMPARATIVE EFFICACY AND SAFETY

5.1 Pivotal Randomized Controlled Trials — Summary

Abbreviations: SE=Systemic embolism; ICH=Intracranial hemorrhage; RRR=Relative risk reduction. Annual stroke/SE rates shown are for the respective DOAC arm of each trial.

5.2 Meta-Analyses and Network Meta-Analyses

The landmark meta-analysis by Ruff et al. (2014, Lancet), pooling all four pivotal trials (n=71,683 patients), established the class-level superiority of DOACs versus warfarin: 19% reduction in stroke/SE ($p<0.0001$), 52% reduction in intracranial hemorrhage ($p<0.0001$), 10% reduction in all-cause mortality ($p=0.0003$), and a 25% increase in GI bleeding ($p=0.043$). The critical clinical message is that the DOAC class as a whole demonstrates net clinical benefit over warfarin, irrespective of which individual agent is selected.

Indirect network meta-analyses comparing DOACs against one another (Lip et al. 2018, Wang et al. 2021) suggest that apixaban may offer the most favorable combined efficacy-safety profile,

dabigatran 150 mg provides the strongest stroke prevention, and edoxaban and dabigatran 110 mg carry the lowest bleeding risk. However, the absence of head-to-head randomized trials mandates that these rankings be interpreted cautiously.

5.3 Real-World Evidence

Observational registries and health database analyses in unselected clinical populations have generally confirmed and extended the findings of randomized trials:

XANTUS (2016): Real-world rivaroxaban registry (n=6,784); bleeding rates lower than ROCKET-AF, consistent efficacy

GARFIELD-AF (2015-2021): 35 countries, 57,000 patients; DOAC adoption associated with improved stroke and bleeding outcomes prospectively

ARISTOPHANES (2019): Medicare database, n=233,000; apixaban associated with lowest rates of stroke and major bleeding among all DOACs and warfarin

GLORIA-AF (2018-2022): Global prospective AF registry; DOAC use increased from 55% to 70% during observation period, warfarin use correspondingly declined

IMPACT-AF (2020): Developing nations cohort; documented persistently low anticoagulation rates and high stroke burden, highlighting the global treatment gap

5.4 Intracranial Hemorrhage: The Critical Safety Differentiator

ICH is the most feared complication of anticoagulant therapy, carrying approximately 50% mortality and severe disability in survivors. The ICH rate with warfarin (0.7-1.0%/year) consistently exceeds that of all DOACs (0.3-0.5%/year) across all trials and real-world registries. Proposed mechanisms for DOAC superiority include less accumulation in CNS tissue, better preservation of the balance between pro- and anticoagulant forces in the brain, and

possibly reduced microhemorrhage progression. This differential ICH risk has become one of the most compelling arguments for preferring DOACs over warfarin in all suitable patients.

CHAPTER VI

ANTICOAGULATION IN SPECIAL POPULATIONS

6.1 Special Situation Reference Table

6.2 Chronic Kidney Disease

CKD is independently associated with both increased thromboembolic risk and increased major bleeding risk, creating a high-stakes clinical dilemma. DOACs differ substantially in their degree of renal elimination: dabigatran 80%, edoxaban 50%, rivaroxaban 35%, apixaban 27%. Consequently, apixaban accumulates least in CKD and has the most extensive clinical data in moderate-to-severe CKD. ARISTOTLE subgroup analyses confirmed consistent efficacy and safety of apixaban across all eGFR categories. For patients on hemodialysis, randomized evidence is extremely limited; the RENAL-AF and AXADIA trials were underpowered and inconclusive. Current guidelines cautiously allow apixaban or warfarin in dialysis patients based on observational data.

6.3 Mechanical Heart Valves

The RE-ALIGN trial (2013) was terminated early due to significantly higher rates of thromboembolic events and major bleeding with dabigatran versus warfarin in patients with mechanical prosthetic valves. The FDA issued a black-box warning, and all current guidelines classify all DOACs as contraindicated (Class III, Harm) in mechanical valve patients. Target INR for these patients is valve- and position-specific: bileaflet aortic prostheses require INR 2.0-3.0, while mitral mechanical valves and high-risk configurations require INR 2.5-3.5.

6.4 Elderly Patients (>=75 years)

Advanced age simultaneously increases both thromboembolic risk (CHA2DS2-VASc score) and hemorrhagic risk (HAS-BLED score). The BAFTA trial definitively established warfarin's superiority over aspirin in patients >75 years. DOAC subgroup analyses in elderly patients demonstrate favorable profiles for apixaban (consistent efficacy-safety across age strata in ARISTOTLE) and dabigatran 110 mg (non-inferior stroke prevention with significantly less ICH and major bleeding in patients >=80 years). Practical considerations in geriatric patients include: fall risk (NOT a contraindication to anticoagulation per se; approximately 200 falls/year would be required to offset the net clinical benefit of anticoagulation), renal function monitoring (CrCl declines with age, necessitating at least annual reassessment), polypharmacy and drug interactions, and frailty-adjusted dosing.

6.5 Timing of Anticoagulation After AF-Related Stroke

The '1-3-6-12 rule' (EHRA consensus) provides practical guidance for initiating OAC after acute AF-related ischemic stroke:

TIA: Start within 1 day (often same day if imaging excludes hemorrhage)

Minor stroke (NIHSS <8): Start on day 3

Moderate stroke (NIHSS 8-15): Start on day 6

Large stroke (NIHSS >=16 or >1/3 hemisphere): Start on day 12

The TIMING trial (2023, Lancet) and ELAN trial (2023, NEJM) significantly challenged the conservative approach by demonstrating that early DOAC initiation (within 4 days) did not increase symptomatic ICH or hemorrhagic transformation compared with later initiation (7-14 days), and may reduce recurrent embolic events in minor-moderate strokes. These findings are influencing ongoing guideline updates toward earlier anticoagulation initiation.

6.6 Management of Anticoagulant-Related Bleeding

Warfarin reversal: IV vitamin K 5-10 mg (onset 6-12h), fresh frozen plasma (immediate but volume-limited), 4-factor PCC (25-50 IU/kg; preferred for ICH — faster and more complete INR reversal). Dabigatran reversal: Idarucizumab 5 g IV (single dose) — complete reversal within minutes, independent of renal function. Factor Xa inhibitor reversal: Andexanet alfa (recombinant modified human fXa decoy; FDA/EMA approved) — high-dose or low-dose bolus plus infusion; 4-factor PCC 25-50 IU/kg if andexanet unavailable (off-label but widely used). The ANNEXA-4 trial confirmed hemostatic efficacy of andexanet alfa in factor Xa inhibitor-related major bleeding.

CHAPTER VII

DOSING, DRUG INTERACTIONS, AND PRACTICAL CONSIDERATIONS

7.1 DOAC Dose Reduction Criteria

*Apixaban dose reduction: Apply if >=2 of the following 3 criteria: age >=80 years, body weight <=60 kg, serum creatinine >=1.5 mg/dL. Using only 1 criterion does not warrant dose reduction.

7.2 Drug Interactions

Dabigatran

Dabigatran is a P-glycoprotein (p-gp) substrate but NOT metabolized by CYP enzymes. P-gp inhibitors (amiodarone, verapamil, quinidine, dronedarone, ketoconazole, clarithromycin): increase dabigatran plasma levels significantly -> dose reduction may be required (consider 110 mg BID). P-gp inducers (rifampicin, carbamazepine, phenytoin, St. John's Wort): reduce dabigatran exposure substantially -> avoid combination; loss of anticoagulant efficacy.

Rivaroxaban, Apixaban, Edoxaban

These agents are substrates of both CYP3A4 and p-gp. Strong combined CYP3A4 + p-gp inhibitors (ketoconazole, itraconazole, ritonavir, indinavir): increase rivaroxaban and apixaban exposure 2-4-fold -> CONTRAINDICATED with rivaroxaban and apixaban. Strong CYP3A4 + p-gp inducers (rifampicin, phenytoin, carbamazepine, St. John's Wort): markedly reduce exposure of all three agents -> avoid combination. Moderate inhibitors (fluconazole, diltiazem, verapamil, amiodarone): require dose adjustment or cautious use.

7.3 Perioperative Management

DOACs do not require routine 'bridging' anticoagulation in the perioperative period — the BRIDGE trial and subsequent evidence established that bridging with LMWH increases bleeding without reducing thromboembolism in warfarin-treated patients, and the principle applies equally to DOACs. Interruption timing is guided by renal function, procedural bleeding risk, and drug half-life. For high-bleeding-risk procedures:

Dabigatran: Normal renal function -> 24-48h; CrCl 30-50 -> 48-72h; High-risk procedure -> up to 96h

Rivaroxaban / Apixaban / Edoxaban: 24h for standard procedures; 48h for high-bleeding-risk procedures

For emergency procedures: idarucizumab for dabigatran; andexanet alfa or PCC for fXa inhibitors.

7.4 Switching from Warfarin to DOAC

The transition from warfarin to a DOAC is INR-guided. INR <2.0: DOAC can be started immediately. INR 2.0-2.5: DOAC may be initiated for most agents; check individual SmPC. INR 2.5-3.0: Re-check INR in 24 hours; initiate DOAC when <2.5. INR >3.0: Await INR to fall below therapeutic range before starting DOAC.

There is no washout period required; the DOAC's anticoagulant effect commences within hours of the first dose.

CHAPTER VIII

CURRENT CLINICAL GUIDELINES AND RECOMMENDATIONS

8.1 2024 ESC Atrial Fibrillation Guidelines

The European Society of Cardiology's 2024 AF Guidelines (van Gelder et al., Eur Heart J) represent the most comprehensive contemporary framework for AF management. Key anticoagulation recommendations:

CHA2DS2-VASc >=2 (male) / >=3 (female): OAC recommended — Class I, Level A

DOACs are preferred over VKAs in all patients eligible for OAC, except those with mechanical valves or moderate-severe rheumatic MS — Class I, Level A

Anticoagulation strategy does not differ by AF type (paroxysmal, persistent, permanent) — Class I, Level B

The 'ABC-AF' integrated care pathway: A=Anticoagulation, B=Better symptom management (rate/rhythm control), C=Cardiovascular risk and comorbidity management

Subclinical AF (AHRE >=24h duration + high stroke risk): Individualized OAC decision — Class IIa, Level B

LAA occlusion (Watchman device): Reasonable alternative for patients unable to take OAC — Class IIb, Level B

8.2 2023 AHA/ACC/ACCP/HRS AF Guidelines

The American Heart Association's 2023 comprehensive AF guidelines (Joglar et al., J Am Coll Cardiol) provide the following key anticoagulation recommendations:

CHA2DS2-VASc >=2 (male) / >=3 (female): OAC is recommended — Class I (Strong Recommendation), Level A

DOAC is preferred over warfarin in patients with non-valvular AF who can tolerate anticoagulation — Class I, Level A

Warfarin is indicated only for mechanical prosthetic heart valve or moderate-severe rheumatic mitral stenosis — Class I, Level B

CHA2DS2-VASc 0 (male) / 1 (female, sex-only score): OAC is NOT recommended — Class III, Harm

Continuation of long-term OAC after catheter ablation of AF in patients at low stroke risk: uncertain benefit — Class IIb

Perioperative OAC continuation during catheter ablation: recommended — Class I

8.3 2021 AHA/ASA Ischemic Stroke Prevention Guidelines

The American Stroke Association's 2021 Guideline for Prevention of Stroke in Patients with Stroke and TIA (Kleindorfer et al., Stroke) provides the following recommendations for AF-related cardioembolic stroke:

OAC for cardioembolic stroke/TIA attributable to AF: Class I, Level A

Timing of OAC initiation: 2-14 days depending on stroke size (the 1-3-6-12 rule provides practical guidance) — Class IIb

DOAC over warfarin (target INR 2-3) for non-valvular AF: Class I, Level A

Antiplatelet therapy combined with OAC is NOT recommended routinely — Class III

In patients with mechanical prosthetic valve and AF, warfarin remains mandatory — Class I

8.4 European Heart Rhythm Association (EHRA) Practical Guide

The 2021 EHRA Practical Guide on DOAC use in AF patients (Steffel et al., Europace) provides detailed clinical guidance including:

Systematic renal function assessment: CrCl-guided dosing; monitoring frequency: CrCl/10 months (e.g., CrCl 30 -> monitor every 3 months)

Perioperative management algorithm based on renal function and procedure bleeding risk

Specific guidance for conversion between anticoagulants, cardioversion, and catheter ablation

Drug interaction tables with specific clinical recommendations for commonly co-prescribed medications

CHAPTER IX

CLINICAL DECISION ALGORITHM AND SUMMARY

9.1 Step-by-Step Anticoagulation Decision Algorithm

The following six-step algorithm applies to all newly diagnosed or re-evaluated AF patients:

STEP 1 — Diagnosis and risk stratification: Calculate CHA2DS2-VASc score. Male >=2 or Female >=3: anticoagulation indicated. Male 0 or Female 1 (sex-only): anticoagulation not recommended.

STEP 2 — Contraindication screening: Active major bleeding? -> Defer OAC, identify and control source. Mechanical heart valve? -> Warfarin mandatory. Moderate-severe rheumatic mitral stenosis? -> Warfarin. Pregnancy? -> LMWH (second and third trimester); neither warfarin nor DOAC recommended in first trimester.

STEP 3 — DOAC selection: Assess renal function (CrCl by Cockcroft-Gault). Review concomitant medications for interactions. Check age and weight for dose reduction criteria. Consider once-

daily (rivaroxaban, edoxaban) vs. twice-daily (dabigatran, apixaban) based on patient preference and adherence profile.

STEP 4 — Follow-up plan: DOACs: annual kidney function (CrCl), liver function, CBC. Warfarin: target INR 2-3; weekly INR initially, then monthly when stable; aim TTR >70%.

STEP 5 — Bleeding risk management: Calculate HAS-BLED score. Score >=3: target modifiable risk factors — blood pressure control (SBP <140 mmHg), medication review (NSAIDs, antiplatelets), alcohol cessation, labile INR management (switch to DOAC).

STEP 6 — Patient education: Drug mechanism in lay terms, dosing instructions, missed dose protocol, bleeding warning signs, perioperative disclosure, emergency anticoagulant alert card.

9.2 Quick DOAC Selection Guide

9.3 Emerging Evidence and Future Directions

Several trials and developments from 2023-2025 are actively shaping the next iteration of clinical guidelines:

NOAH-AFNET 6 (2023): Edoxaban did not demonstrate superiority over aspirin in patients with subclinical AF (AHRE); the question of anticoagulation in this population remains unresolved.

ARTESIA (2024): Apixaban significantly reduced stroke risk versus aspirin in patients with device-detected subclinical AF (>6 min episodes), but at the cost of more major bleeding. Net clinical benefit remains uncertain and guidelines are cautious.

CHAMPION-AF (ongoing): Head-to-head comparison of Watchman LAA occlusion device vs. DOAC in standard-risk AF patients; results expected to influence device recommendations substantially.

Factor XIa inhibitors (asundexian, milvexian): Theoretically lower bleeding risk by targeting thrombus formation without

substantially impairing physiologic hemostasis; phase III trials in AF ongoing.

Pharmacogenomics-guided warfarin dosing: CPIC guidelines incorporate CYP2C9 and VKORC1 genotype information into starting dose algorithms; cost-effectiveness in AF populations under evaluation.

Wearable technology and digital AF detection: Photoplethysmography-based AF detection (Apple Watch, Kardia Mobile) and AI-powered ECG interpretation are expanding the diagnostic reach, particularly for subclinical and early AF.

9.4 Conclusion

AF-related ischemic stroke is, to a very substantial extent, a preventable disease. More than three decades of rigorous clinical investigation have unequivocally established that oral anticoagulation dramatically reduces stroke risk in AF patients. Warfarin, with its half-century of clinical experience, remains a viable option in specific circumstances — but the emergence of DOACs has constituted a genuine paradigm shift in antithrombotic therapy.

The four pivotal phase III randomized trials (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48), corroborated by extensive real-world evidence, demonstrate that DOACs offer comparable or superior efficacy in stroke prevention, significantly reduced intracranial hemorrhage risk, and a more convenient therapeutic profile — without the necessity of routine coagulation monitoring. The 2024 ESC, 2023 AHA/ACC, and 2021 ASA guidelines unanimously recommend DOACs as the first-line anticoagulant choice in all eligible patients with non-valvular AF.

The clinician's task is to individualize: to calculate CHA2DS2-VASc and HAS-BLED scores precisely, to select the DOAC that best fits the patient's renal function, drug interactions, and adherence profile, and to maintain a structured long-term follow-

up plan. Closing the anticoagulation treatment gap — particularly in regions where it remains wide — represents one of the highest-yield interventions in contemporary stroke prevention medicine.

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