Management of Complications in Anticoagulated Patients with Atrial Fibrillation

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Abstract

Oral anticoagulation is mandatory for patients at high risk of thromboembolism, but the risk of bleeding should also be taken into account. Direct oral anticoagulants are now recommended for non-valvular AF as a potential alternative to warfarin. In this article we discuss methods to assess the anticoagulant effect of these agents, specific and general antidotes, and management of complications such as embolic and haemorrhagic stroke, and significant bleeding.

Keywords

Atrial fibrillation, anticoagulation, ischaemic stroke, bleeding

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Atrial fibrillation (AF) is associated with a fivefold increased risk for stroke, a twofold increased risk for dementia, and a tripling of risk for heart failure,[1,2,3] while AF genetic risk is strongly associated with cardioembolic stroke.[4] In the Framingham Heart Study the percentage of strokes attributable to AF increases steeply from 1.5 % at 50–59 years of age to 23.5 % at 80–89 years of age.[5,6] In the Danish National Patient Registry, the 5-year risk of stroke for men aged 50 years with no risk factors was 1.1 %, and with AF alone without additional risk factors 2.5 %, with the great majority not being anticoagulated. In men aged 70 years, the corresponding risks were 4.8 % and 6.6 %.[7] Approximately 24 % of all strokes are due to AF,[3] and 10 % of ischaemic strokes are associated with AF first diagnosed at the time of stroke.[8] Numbers of AF-related incident ischaemic strokes at age ≥80 years have trebled over the last 25 years, despite the introduction of anticoagulants, and are projected to treble again by 2050.[9] In addition, extracranial systemic embolic events constitute 11.5 % of clinically recognised thromboembolic events in patients with AF, and are associated with a high morbidity and mortality, comparable to that of ischaemic stroke.[10] AF is the main cause of coronary embolism, being independently associated with an increased risk of myocardial infarction, especially non-ST-elevation myocardial infarction (NSTEMI) in women.[11,12]

Oral anticoagulation, therefore, is mandatory for patients at high risk of thromboembolism as expressed by a CHA_2DS_2VASc score >2, but the risk of bleeding, assessed by various schemes such as the HAS-BLED, ATRIA, HEMORR2HAGES, and ORBIT,[13,14] should also be taken into account. Low risk patients (score 0 for male and 1 for female) have a low risk of stroke (<1 % per year) and may be left without anticoagulation, since the benefit of anticoagulation does not outweigh the bleeding risk (net clinical benefit).[15] Anticoagulation in patients with one stroke risk factor (CHA_2DS_2VASc score 1 for men and 2 in women) should be individualised since there is a significant increase in events rate in the presence of an additional risk factor.[16–19] Direct oral anticoagulants (DOAC) are now recommended for non-valvular AF as a potential alternative to warfarin (see *Tables 1 and 2*).[20]

Assessment of Anticoagulant Effect and Antidotes of Specific Agents

Warfarin

The efficacy of the treatment with warfarin is directly related to the time in therapeutic range (TTR), that is, the percent time with international normalised ratio (INR) between 2.0 and 3.0. A target threshold TTR exists (estimated between 58 % and 65 %), below which there appears to be little benefit of oral anticoagulant (OAC) over antiplatelet therapy.[21] The SAMe-TT2R2 [Sex (female); Age, 60 years; Medical history (more than two comorbidities); Treatment (interacting drug, e.g. Amiodarone); Tobacco use (doubled), and Race (doubled)] score is useful in identifying individuals who will not have good INR control (score ≥2).[22]

For excessive INR in the absence of bleeding, the American College of Chest Physicians (ACCP) guidelines recommend oral vitamin K (phytomenadione, 1–2.5 mg) only when INR is >10.[23] IV vitamin K (1–2 mg) may also be given, although at 24 h oral vitamin K produces similar results. Oral dose is 2.5 mg or 1–2 mg of the IV preparation in a cup of orange juice. In the presence of major bleeding, four-factor prothrombin complex concentrate (4-PCC) is preferred to fresh frozen plasma since >1500 ml of fresh frozen plasma are needed to achieve a meaningful increase in coagulation factor levels.[24] In a trial for reversal of VKA-associated major bleeding, the reported efficacy of 4-PCCs was 72 %, with 8 % thrombotic events, and 6 % mortality.[25] The additional use of vitamin K 5 to 10 mg administered by slow IV injection is helpful in this setting.[26]

Dabigatran

Diluted thrombin time and ecarin clotting time or chromogenic assay are precise methods to assess the anticoagulant effect of dabigatran, but these methods are time-consuming and not widely available.[27]

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Table 1: Oral Anticoagulants for Atrial Fibrillation

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose	Variable once daily	150 twice daily 110 twice daily if CrCl <50 ml/min or >75 years of age 75 mg twice daily if CrCl 15–30 ml/min	20 mg once daily 15 mg once daily if CrCl 15–30 ml/min	5 mg twice daily 2.5 mg twice daily if two criteria of: • Cr ≥1.5 mg/dL, ≥80 years • Body weight ≤60 kg	60 mg once daily 30 mg once daily if CrCl ≤ 50 ml
Target	Vitamin K-dependent factors	Thrombin (Factor II)	Factor Xa	Factor Xa	Factor Xa
Half-life	40 h	12 h	9 h	12 h	10 h
Renal clearance	0	80 %	60 %	25 %	40 %
Onset of action inhibition	3–5 h	1 h	2 h	3 h	1 h
Anticoagulation monitoring	INR 2–3	Not required	Not required	Not required	Not required
Interactions	Multiple	P-gp	P-gp; CYP3A4	P-gp; CYP3A4	P-gp; CYP3A4
Antidote	Vitamin K	Idarucizumab; PCCs/aPCCs	Andexanet alfa; ciraparantag; PCCs/aPCCs	Andexanet alfa; ciraparantag; PCCs/aPCCs	Andexanet alfa; ciraparantag; PCCs/aPCCs

Dabigatran is eliminated via the P-glycoprotein (P-gp) transporter, while the Xa inhibitors are eliminated via P-gp and cytochrome P450 (CYP) 3A4 activity. Their dosage should be reduced with co-administration of P-gp or CYP3A4 inhibitors, and they should be used with caution or avoided with administration of P-gp or CYP3A4 inducers. P-gp inhibitors include verapamil, diltiazem, amiodarone, dronedarone, quinidine, erythromycin, clarithromycin, ketoconazole, intraconazole, voriconazole, posaconazole, cyclosporine, grapefruit juice. P-gp inducers include rifampicin, St. John's wort, carbamazepine, phenytoin, phenobarbital and trazodone. CYP3A4 inhibitors include ketoconazole, intraconazole, voriconazole, posaconazole, fluconazole, chloramphenicol, clarithromycin, HIV protease inhibitors (e.g. ritonavir, atanazavir), verapamil and diltiazem. CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, rifampicin, and St. John's wort (Hypericum perforatum). aPCC = activated prothrombin complex concentrate; PCC = prothrombin complex concentrate. Source: Katritsis, et al., 2016.[75] Credit: p.589 Table 53.19, p.590 Table 53.20 & p.591 Table 53.22 from Chapter 53 'Atrial Fibrillation' from Clinical Cardiology: Current Practice Guidelines, Updated Edition by Katritsis, D.G., Gersh, B.J. & Camm, A.J. (2016). Free permission Author's own material, appr. HPL. By permission of Oxford University Press.

Individual NOAC Interactions
The dose of dabigatran or edoxaban should be reduced in patients taking verapamil.
No dose reduction is needed in patients taking rivaroxaban with verapamil.
Apixaban does not interact with amiodarone or verapamil.
Dabigatran is contraindicated in combination with dronedarone.
Edoxaban 30 mg should be used in patients on dronedarone.

Source: ¨Diene, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. *Eur Heart J 2017;38(12):860-868. By permission of Oxford University Press/European Society of Cardiology*

Activated partial thromboplastin time (*aPTT)* and prothrombin time (*PT)*, measured in samples soon after the last dose, are prolonged by dabigatran but the correlation is not linear to guide dosage.[28] However, in the presence of a normal aPTT, dabigatran is unlikely to contribute to bleeding, and aPTT can be used in emergencies as a rough estimate.[29]

Specific antidotes are under study.[30,31] Idarucizumab, a monoclonal antibody fragment, completely reverses the anticoagulant effect of dabigatran within minutes and has been shown to be effective in initial clinical trials (2.5 g IV infusions no more than 15 min apart).[32–34] In patients with acute major bleeding the reported efficacy was 71 %, with 10 % thrombotic events, and a mortality of 12 %.[32] Idarucizumab for reversal of dabigatran was approved by the FDA in October 2015. Ciraparantag binds in a similar way to the new oral factor Xa inhibitors, and to dabigatran, but further clinical experience is needed.

Non-specific haemostatic agents are prothrombin complex concentrates (PCCs) and activated prothrombin complex concentrates (aPCCs). PCCs are plasma-derived products that contain 3 (factors II, IX, and X) or 4 (addition of factor VII) clotting factors in addition to variable amounts of heparin and the natural coagulation inhibitors protein C and protein S. aPCC contains mostly activated factor VII along with mainly non-activated factors II, IX, and X. Recombinant activated factor VII may also reverse the effect of non-vitamin K antagonist oral anticoagulants (NOAC) but increases the risk of thromboembolic effects by >1 %.[31,35]

In emergencies, gastric lavage in recent drug ingestion, haemodialysis, oral charcoal within 2 h following dabigatran ingestion, desmopressin, packed red cells in anaemia, platelet transfusions in patients receiving concurrent antiplatelet therapies, and fresh frozen plasma in the presence of dilutional coagulopathy or disseminated intravascular coagulation may also be tried as general measures.[36] Prothrombin complex concentrates (PCCs and aPCCs) are more effective than fresh frozen plasma but they carry an absolute increase of thromboembolic events of 1 %.[31]

Factor Xa Inhibitors

Antifactor Xa assays may be used as an estimate of the anticoagulant effect.[27] aPTT and PT are prolonged by Xa inhibitors, but cannot be used to guide dosage since the correlation is not linear.[28] Diluted prothrombin time appears as the best test to use in emergency situations.[29]

Andexanet alfa, a recombinant protein that binds and sequesters factor Xa inhibitors has been successfully tried for apixaban and rivaroxaban (ANNEXA trials).[37,38] It is given as 300 mg IV bolus that can be followed by an infusion of 4mg/min for 120 min. In patients with acute major bleeding the reported efficacy was 79 %, with 18 % thrombotic events, and a mortality of 15 % reported.[38] Ciraparantag, (IV bolus of 100–300 mg), a synthetic molecule that binds specifically to unfractionated heparin and low-molecular-weight heparin, reversed edoxaban within 10–30 min,[39] and is under study.

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Table 2: New Anticoagulants Versus Warfarin in Nonvalvular Atrial Fibrillation

Trial	Dose of NOAC	NOAC (%/y)	Warfarin (%/y)	p-value
		Stroke/systemic embolism		
RELY	Dabigatran 110 mg twice daily	1.53	1.69	0.34
	Dabigatran 150 mg twice daily	1.11	1.69	<0.001
ROCKET-AF	Rivaroxaban 15–20 mg once daily[a]	2.1	2.4	0.12
ARISTOTLE	Apixaban 2.5–5 mg twice daily[b]	1.27[c]	1.60[c]	0.01
ENGAGE-AF-TIMI 48	Edoxaban 60 mg once daily	1.57	1.8	0.08
	Edoxaban 30 mg once daily[d]	2.04	1.8	0.1
		Intracranial haemorrhage		
RELY	Dabigatran 110 mg twice daily	0.12	0.38	<0.001
	Dabigatran 150 mg twice daily	0.10	0.38	<0.001
ROCKET-AF	Rivaroxaban 15–20 mg once daily	0.5	0.7	0.02
ARISTOTLE	Apixaban 2.5–5 mg twice daily	0.24	0.47	<0.001
ENGAGE-AF-TIMI 48	Edoxaban 60 mg once daily	0.26	0.47	<0.001
	Edoxaban 30 mg once daily	0.16	0.47	<0.001
		Major bleeding		
RELY	Dabigatran 110 mg twice daily	2.71	3.36	<0.003
	Dabigatran 150 mg twice daily	3.11	3.36	0.31
ROCKET-AF	Rivaroxaban 20 mg once daily	3.6	3.4	0.58
ARISTOTLE	Apixaban 2.5–5 mg twice daily	2.13	3.09	<0.001
ENGAGE-AF-TIMI 48	Edoxaban 60 mg once daily	2.75	3.43	<0.001
	Edoxaban 30 mg once daily	1.61	3.43	<0.001
		Total mortality		
RELY	Dabigatran 110 mg twice daily	3.75	4.13	0.13
	Dabigatran 150 mg twice daily	3.64	4.13	0.051
ROCKET-AF	Rivaroxaban 20 mg once daily	4.5	4.9	0.15
ARISTOTLE	Apixaban 2.5–5 mg twice daily	3.52	3.94	0.047
ENGAGE-AF-TIMI 48	Edoxaban 60 mg once daily	3.99	4.35	0.08
	Edoxaban 30 mg once daily	3.80	4.35	0.006

a = 15 mg once daily if CrCl 40–49 ml/min; b = 2.5 mg twice daily if ≥2 of the following: age ≥80 y, BW <60 kg, creatinine ≥1.5 mg/dl; c = This number Includes both embolic and haemorrhagic strokes; d = 30 mg once daily if CrCl 30–50 ml/min, BW <60 kg, concomitant verapamil or quinidine; BW: body weight, CrCl: creatinine clerance; NOAC = nonvitamin K antagonist oral anticoagulants. Source: Katritsis, et al., 2016. Credit: p.589 Table 53.19, p.590 Table 53.20 & p.591 Table: 53.22 from Chapter 53 'Atrial Fibrillation' from Clinical Cardiology: Current Practice Guidelines, Updated Edition by Katritsis, D.G., Gersh, B.J. & Camm, A.J. (2016). Free permission Author's own material, appr. HPL. By permission of Oxford University Press.

Xa inhibitors are not removed by dialysis, being protein bound. Gastric lavage in recent drug ingestion, and platelet and fresh frozen plasma transfusions may also been tried as general measures. As noted, PCCs and aPCCs are more effective but they carry an absolute increase of thromboembolic events of 1 %.[31]

Management of Stroke

Ischaemic Stroke

Patients presenting within 4.5 h after the onset of ischaemic stroke should be considered for IV rt-PA (0.9 mg/kg, with 10 % bolus, and the remainder over 60 min, maximum dose 90 mg). Diffusion-weighted magnetic resonance imaging and non-enhanced computed tomography are the most sensitive and specific methods for detecting ischaemic stroke and excluding intracerebral haemorrhage.[40] They are necessary before intravenous rtPA to exclude intracranial haemorrhage (absolute contraindication) and to determine whether CT hypodensity of haemorrhage or MRI hyperintensity of ischaemia are present. Anticoagulation does not increase the risk of intracerebral haemorrhagic complications when INR is ≤1.7.[41] In patients who present with stroke while taking new anticoagulants, if the aPTT is prolonged in a patient taking dabigatran or the prothrombin time with an Xa inhibitor, it should be assumed that the patient is anticoagulated, and thrombolysis should probably not be administered.[40] However, in recent studies on patients with a ischaemic stroke and a NOAC taken within the last 48 h, thrombolysis with rt-PA or intra-arterial treatment had similar risk of symptomatic intracranial haemorrhage to that in patients on subtherapeutic VKA treatment (INR <1.7) or in those without previous anticoagulation.[42,43] Criteria for fibrinolysis are presented in *Table 3* and recommendations for secondary stroke prevention in *Table 4* and *Figure 1*. Of note, age >80 years is not an exclusion criterion, provided it can be given within the first 3 h. Tenecteplase (0.25 mg/kg, administered as a single bolus, with a maximum dose of 25 mg), a more fibrin-selective agent, is superior to alteplase in patients subjected to fibrinolysis within 6 h after the onset of ischaemic stroke,[44] but this was not verified in another comparison within 4.5 h after stroke.[45] Anticoagulants and antiplatelet agents should be withheld the first 24 h following fibrinolysis. Labetalol (10–20 mg IV over 1–2 min, may repeat 1 time), or nicardipine (5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h) are recommended only when the blood pressure exceeds 180/110 mmHg.[40] However, in patients who are not candidates for fibrinolysis, blood pressure lowering in acute stroke is not established to be useful with systolic blood pressure of 140 to 220 mmHg and without evidence of nonstroke end-organ damage, with the possible exception of an early (<6 h) BP lowering strategy.[46] Thus, treatment of hypertension in this setting should be individualised. In patients who are candidates for fibrinolysis a pre-treatment BP <180/110 mmHg is mandatory.

Fibrinolysis offers recanalisation rate of <50 %, and large thrombi in vessels such as the distal internal carotid artery or the first segment of the middle cerebral artery respond poorly.[47] Intra-arterial, catheter-based treatment administered within 6 h after acute ischaemic stroke

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Table 3: Management of Acute Ischaemic Stroke

AHA/ASA 2013 Guidelines on Acute Ischemic Stroke. Inclusion and Exclusion Characteristics of Patients with Ischemic Stroke who Could Be Treated with IV rtPA Within 3 Hours from Symptom Onset
Inclusion criteria
Diagnosis of ischaemic stroke causing measurable neurological deficit
Onset of symptoms <3 h before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid haemorrhage
Arterial puncture at non-compressible site within previous 7 days
History of previous intracranial haemorrhage
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic ≥185 mmHg or diastolic ≥110 mmHg)
Active internal bleeding
Acute bleeding diathesis, including, but not limited to:
Platelet count ≤100 000/mm^3
Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant, with INR >1.7 or PT >15 s
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
Blood glucose concentration <5O mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative exclusion criteria
Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV alteplase administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract haemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

1. The checklist includes some FDA-approved Indications and contraindications for administration of IV alteplase for acute ischaemlc stroke. Recent guideline, revisions have modified the original FDA-approved Indications. A physician with expertise in acute stroke care may modify this list. Onset time is defined as either the witnessed onset of symptoms or the time last known normal If symptom onset was not witnessed. In patients without recent use of oral anticoagulants or heparin. treatment with IV alteplase can be initiated before availability of coagulation test results but should be discontinued If INR is >1.7 or PT is abnormally elevated by local laboratory standards. In patients without, history of thrombocytopenia, treatment with IV alteplase can be initiated before availability of platelet count but should be discontinued if platelet count is <100 000/mm^3. aPTT = indicates activated partial thromboplastin time; CT = computed tomography; ECT ecarin clotting time; FDA = Food and Drug Administration; INR = international normalized ratio; IV = Intravenous; PT = partial thromboplastin time; and TT = thrombin time. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Source: [77]Jauch, et al. AHA/ASA 2013 Guideline for the Early Management of Patients With Acute Ischemic Stroke Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870–947. http://stroke.ahajournals.org/content/44/3/870

2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke (A Summary of Recommendations)

Endovascular Interventions	
1. Patients eligible for intravenous r-tPA should receive IV r-tPA even if endovascular treatments are being considered.	I-A
2. Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria: a. Prestroke mRS score 0–1; b. Acute ischaemic stroke receiving IV r-tPA within 4.5 h of onset according to guidelines from professional medical societies; c. Causative occlusion of the ICA or proximal MCA (M1); d. Age ≥18 years; e. NIHSS score ≥6; f. ASPECTS ≥6; and g. Treatment can be initiated (groin puncture) within 6 h of symptom onset.	I-A
3. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible and within 6 h of stroke onset.	I-B-R
4. When treatment is initiated beyond 6 h from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischaemic stroke who have causative occlusion of the ICA or proximal MCA (M1).	IIb-C
5. Endovascular therapy with stent retrievers completed within 6 h of stroke onset in carefully selected patients with anterior circulation occlusion who have contraindications to intravenous r-tPA.	IIa-C
6. Use of endovascular therapy with stent retrievers for carefully selected patients with acute ischaemic stroke in whom treatment can be initiated (groin puncture) within 6 h of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.	IIb-C
7. Endovascular therapy with stent retrievers may for some patients <18 years of age with acute ischaemic stroke who have demonstrated large-vessel occlusion in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset.	IIb-C

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2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke (A Summary of Recommendations): Cont.

Endovascular Interventions	
8. Endovascular therapy with stent retrievers for patients with acute ischaemic stroke in whom treatment can be initiated (groin puncture) within 6 h of symptom onset and who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6 and causative occlusion of the ICA or proximal MCA (M1).	IIb-B-R
9. Observing patients after IV r-tPA to assess for clinical response before pursuing endovascular therapy is not recommended.	III-B-R
10. Use of stent retrievers in preference to the MERCI device.	I-A
The use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances.	IIb-B-NR
11. Use of a proximal balloon guide catheter or a large-bore distal-access catheter rather than a cervical guide catheter alone in conjunction with stent retrievers may be beneficial.	IIa-C
12. The technical goal of the thrombectomy procedure should be a TICI grade 2b/3 angiographic result to maximize the probability of a good functional clinical outcome.	I-A
Use of salvage technical adjuncts, including intra-arterial fibrinolysis, to achieve these angiographic results if completed within 6 h of symptom onset.	IIb-B-R
13. Angioplasty and stenting of proximal cervical atherosclerotic stenosis or complete occlusion at the time of thrombectomy may be considered, but the usefulness is unknown.	IIb-C
14. Initial treatment with intra-arterial fibrinolysis for carefully selected patients with major ischaemic strokes of <6 h duration caused by occlusions of the MCA.	I-B-R
A clinically beneficial dose of intra-arterial r-tPA is not established, and r-tPA does not have FDA approval for intra-arterial use. Thus, endovascular therapy with stent retrievers is recommended over intra-arterial fibrinolysis as first-line therapy.	I-E
15. Intra-arterial fibrinolysis initiated within 6 h of stroke onset in carefully selected patients who have contraindications to the use of IV r-tPA.	IIb-C
16. Favour conscious sedation over general anaesthesia during endovascular therapy for acute ischaemic stroke.	IIb-C
Imaging	
1. Emergency imaging of the brain before any specific treatment for acute stroke is initiated. In most instances, nonenhanced CT will provide the necessary information to make decisions about emergency management.	I-A
2. If endovascular therapy is contemplated, a noninvasive intracranial vascular study during the initial imaging evaluation should not delay IV r-tPA if indicated.	I-A
3. The benefits of additional imaging beyond CT and CTA or MRI and MRA such as CT perfusion or diffusion- and perfusion-weighted imaging for selecting patients for endovascular therapy are unknown.	IIb-C

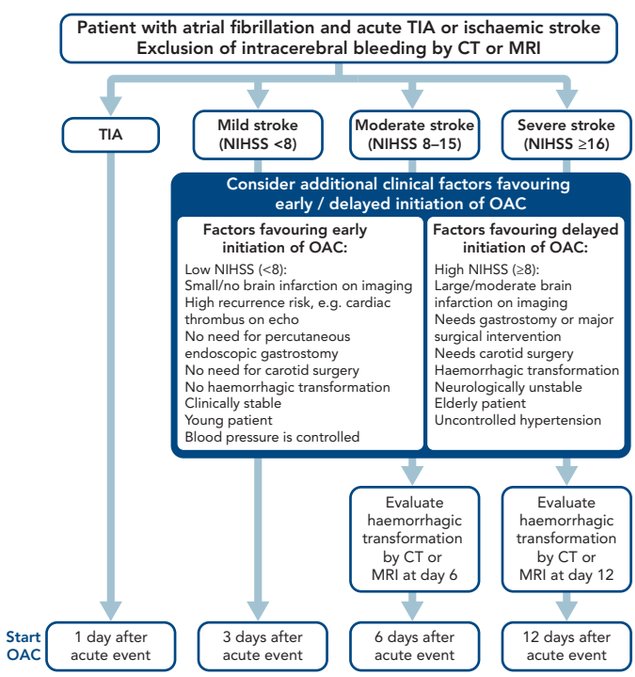
ASPECTS = Alberta Stroke Program Early CT Score; CT = computed tomography; CTA = computed tomography angiography; FDA = Food and Drug Administration; ICA = internal carotid artery; MCA = middle cerebral artery; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; r-tPA = recombinant tissue-type plasminogen activator; TICI = thrombolysis in cerebral infarction. Source: Powers, et al. 2015[75]. Credit: American Heart Association, Inc.

Table 4: ESC 2016 Guidelines on Atrial Fibrillation. Recommendations for Secondary Stroke Prevention

Anticoagulation with heparin or LMWH immediately after an ischaemic stroke is not recommended.	III-A (harm)
In TIA or stroke while on anticoagulation, adherence to therapy should be assessed and optimized.	IIa-C
In moderate-to-severe ischaemic stroke while on anticoagulation, anticoagulation should be interrupted for 3–12 days based on a multidisciplinary assessment of acute stroke and bleeding risk.	IIa-C
Following a stroke, aspirin should be considered for secondary prevention until the initiation or resumption of oral anticoagulation.	IIa-B
Systemic thrombolysis with rtPA is not recommended if the INR is above 1.7 (or, for patients on dabigatran, if aPTT is outside normal range).	III-C (Harm)
NOACs are preferred to VKAs or aspirin in AF patients with a previous stroke.	I-B
After TIA or stroke, combination therapy of OAC and an antiplatelet is not recommended.	IIII-B (harm)
After intracranial haemorrhage, oral anticoagulation in patients with AF may be reinitiated after 4–8 weeks provided the cause of bleeding or the relevant risk factor has been treated or controlled.	IIb-B

aPTT = activated partial thromboplastin time; AF = atrial fibrillation; INR = international normalized ratio; LMWH = low-molecular weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; rtPA = recombinant tissue plasminogen activator; TIA = transient ischaemic attack; VKA = vitamin K antagonist.
Source: Kirchhof, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962. Published with permission of the European Society of Cardiology.

Figure 1: Initiation or Continuation of Anticoagulation in Atrial Fibrillation Patients After a Stroke or Transient Ischaemic Attack



This approach is based on consensus rather than prospective data. AF = atrial fibrillation; CT = computed tomography; MRI = magnetic resonance imaging; NIHSS = National Institutes of Health stroke severity scale (available at http://www.strokescenter.org/wp-content/uploads/2011/08/NIH_Stroke_Scale.pdf); OAC = oral anticoagulation; TIA = transient ischaemic attack. Source: Kirchhof, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962. Published with permission of the European Society of Cardiology.

using aspiration and stent retrievers has improved neurologic recovery, and reduced mortality compared to IV fibrinolysis, especially in the presence of a proximal cerebral arterial occlusion, and a small infarct or salvageable brain tissue on CT.[48] It can be delivered with or without

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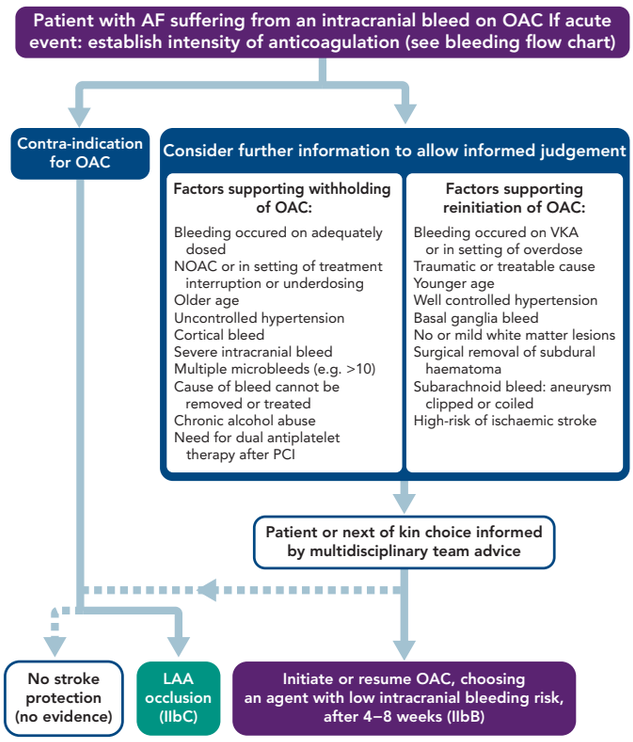
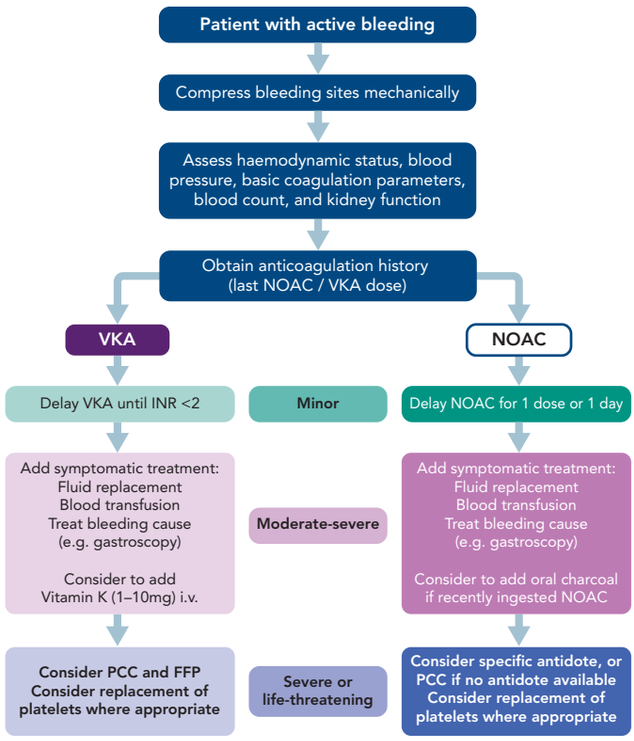
Figure 2: Initiation or Resumption of Anticoagulation in Atrial Fibrillation Patients After an Intracranial Bleed



This approach is based on consensus opinion and retrospective data. In all patients, evaluation by a multidisciplinary panel is required before treatment (stroke physician/neurologist, cardiologist, neuroradiologist, and neurosurgeon). AF = atrial fibrillation; LAA = left atrial appendage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist. Source: Kirchhof, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962. Published with permission of the European Society of Cardiology.

Figure 3: Management of Active Bleeding in Patients Receiving Anticoagulation



Institutions should have an agreed procedure in place. FFP = fresh frozen plasma; INR = international normalized ratio; i.v. = intravenous; NOAC = non-vitamin K antagonist oral anticoagulant; PCC = prothrombin complex concentrated; VKA = vitamin K antagonist. Source: Kirchhof, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962. Published with permission of the European Society of Cardiology.

Table 5: ESC 2016 Guidelines on Atrial Fibrillation. Recommendations for Management of Bleeding

Blood pressure control in hypertensive patients	IIa-B
When dabigatran is used, a reduced dose (110 mg twice daily) in patients >75 years to reduce the risk of bleeding.	IIb-B
In patients at high-risk of gastrointestinal bleeding, a VKA or another NOAC preparation should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily.	IIa-B
Avoid alcohol excess in all AF patients considered for OAC.	IIa-C
Genetic testing before the initiation of VKA therapy is not recommended.	III-b (no benefit)
Reinitiation of OAC after a bleeding event in all eligible patients by a multidisciplinary AF team, considering different anticoagulants and stroke prevention interventions, improved management of factors that contributed to bleeding, and stroke risk.	IIa-B
In AF patients with severe active bleeding events, interrupt OAC therapy until the cause of bleeding is resolved.	I-C

AF = atrial fibrillation; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; VKA = vitamin K antagonist. Source: Kirchhof, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962. Published with permission of the European Society of Cardiology.

concomitant IV fibrinolysis, and preliminary data suggest that they might be useful up to 8 h[49] or even 12 h[50] after symptoms onset. Re-initiation of anticoagulation following a non-fibrinolysed ischaemic stroke should be within 14 days after the onset of symptoms (AHA/ASA 2014 GL for prevention of stroke IIa-B), since the risk of early recurrence is as high as 8 %.[50] In patients with a TIA, anticoagulation can be initiated 1 day after the onset of neurological symptoms, 3 days following small, non-disabling infarcts, 5–7 days following moderate infarcts, and 12–14 days following severe strokes.[52,41] In the presence of high risk for haemorrhagic conversion (i.e. large infarct, haemorrhagic transformation on initial imaging, uncontrolled hypertension, or haemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days (AHA/ASA 2014 GL for prevention of stroke IIa-B).[51] If anticoagulation is unsuitable or not feasible, dual antiplatelet therapy is recommended for secondary prevention (Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack [CHANCE] trial).[53] Since dabigatran 150 mg twice daily resulted in a significant reduction in both ischaemic and haemorrhagic stroke, should the acute ischaemic stroke occur while the patient is taking dabigatran 110 mg twice daily, or rivaroxaban or apixaban (neither of which significantly reduced ischaemic stroke compared with warfarin, in their respective trials), the use of dabigatran 150 mg twice daily instead, may be reasonable, but no direct data exist.[54] Elective non-cardiac surgery may best be avoided for 9 months following a stroke, if possible.[55]

Intracerebral Haemorrhage

In the case of intracerebral haemorrhage, reversal of anticoagulation (INR <1.3) is needed with vitamin K 10 mg IV, to be repeated if the INR remains >1.4 at 24–48 h.[56] If INR remains >1.4, four-factor PCCs are preferred to fresh frozen plasma. In patients receiving a DOAC, a specific antidote such as idarucizumab for dabigatran and andexanet alfa for Xa inhibitors

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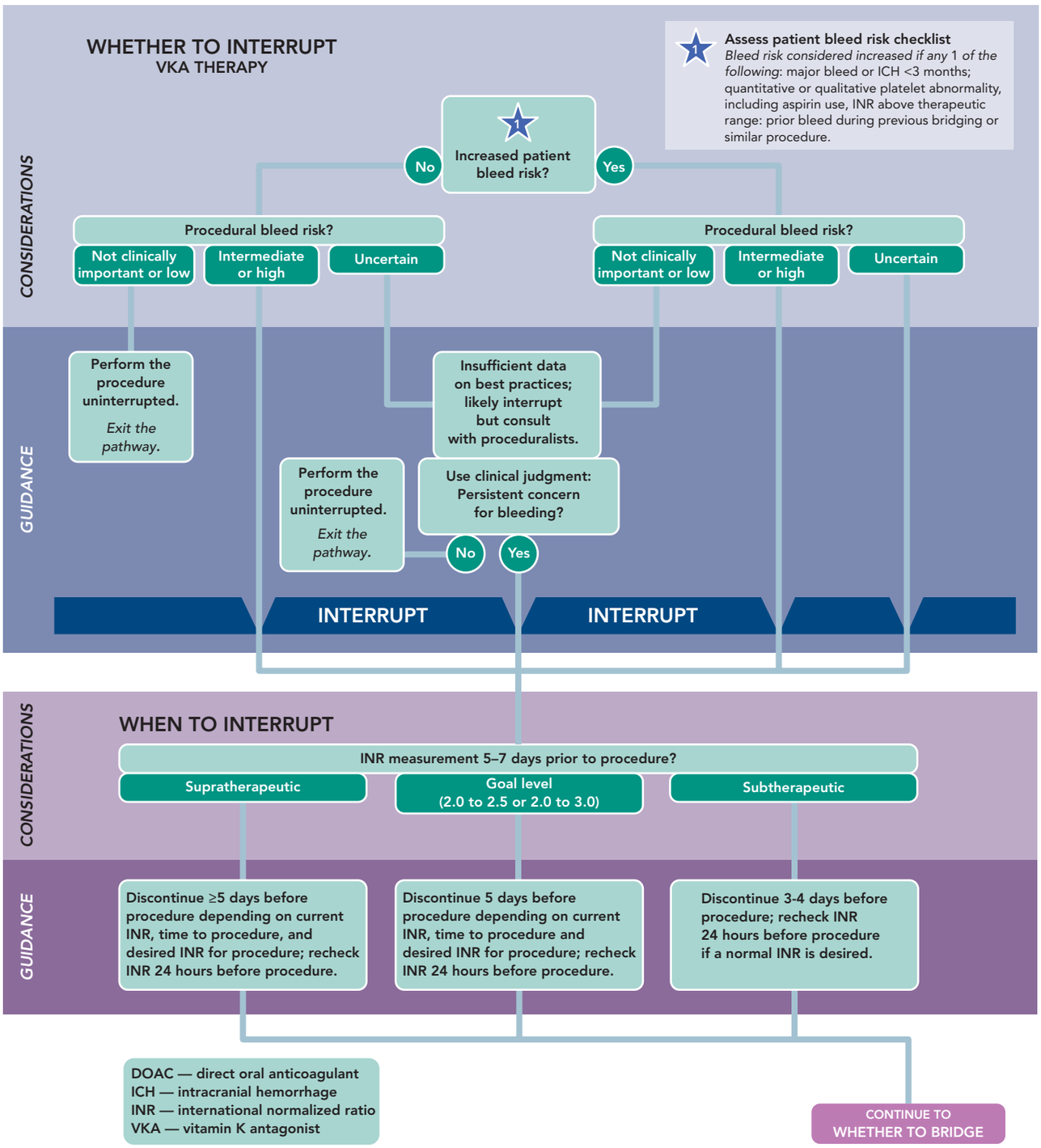
Figure 4: Whether to Interrupt and How to Interrupt for Vitamin K Antagonists



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are preferable, but if not available four-factor PCCs should be used. Protamine (1 mg for every 100 units of unfractionated heparin [UFH]) is used for unfractionated as well as for LMW heparin, and cryoprecipitate should be administered to patients who have received thrombolytics. Platelet transfusions are not recommended for patients who take antiplatelet agents, unless neurosurgical procedures are needed.[56] Intensive treatment to lower the blood pressure with a target systolic level of <180 mmHg is recommended,[57] but there has been evidence that values <160–140 mmHg may reduce haematoma enlargement and improve functional outcomes.[58,59] After documentation of cessation of bleeding, low-dose heparin may be started 1–4 days from onset.[57] The timing of resumption of oral anticoagulant is controversial (*Figure 2*). However, it may be started within 2 weeks since it is associated with a significant reduction in ischaemic stroke/all-cause mortality rates.[60] DOAC are probably preferred if the haemorrhage happened on warfarin. In Asian patients, where the prevalence of intracranial haemorrhage is

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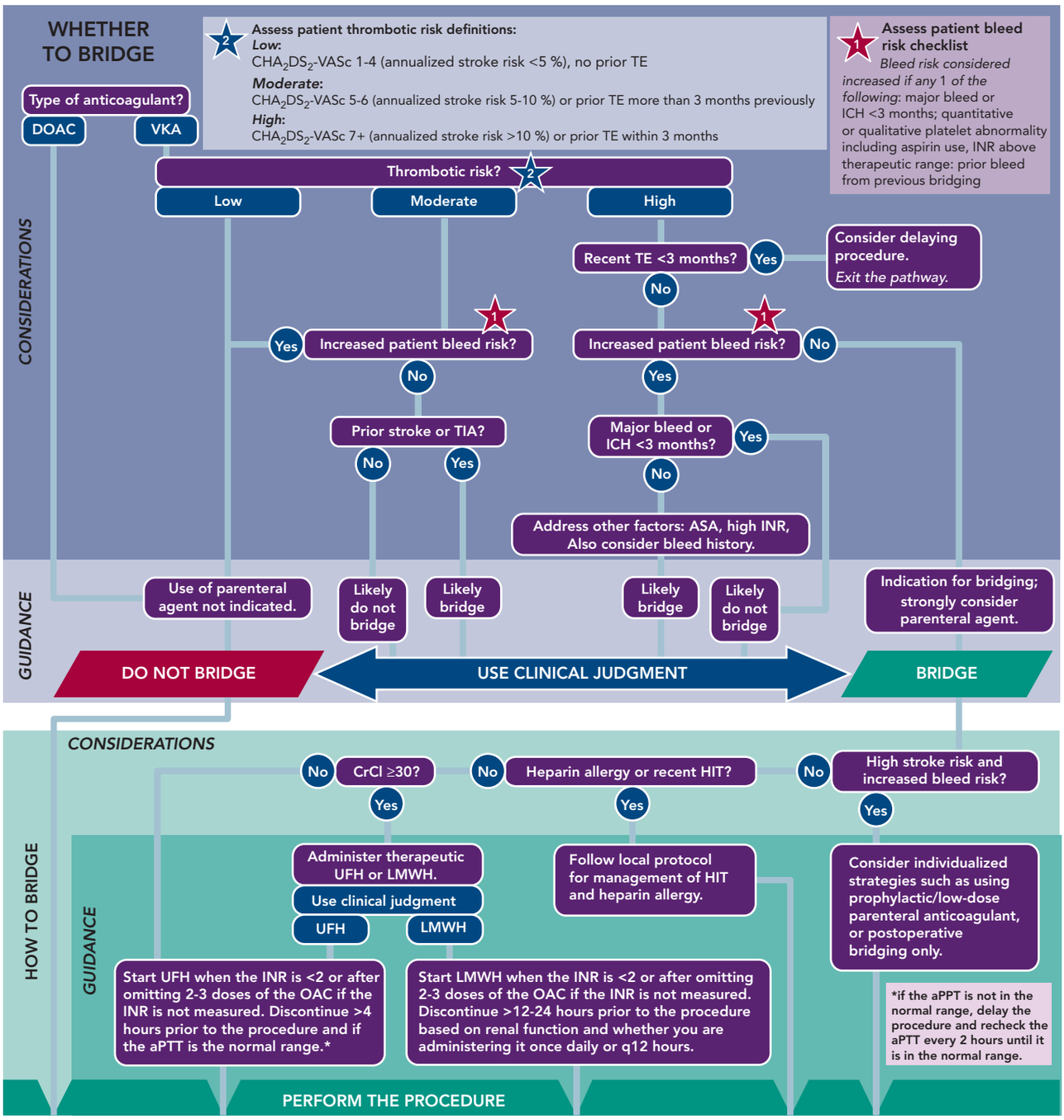
Figure 5: Whether to Bridge and How to Bridge for Direct Oral Anticoagulants and Vitamin K Antagonists



aPTT = activated partial thromboplastin time assay; ASA = acetylsalicylic acid (aspirin); DOAC = direct oral anticoagulant; HIT = heparin-induced thrombocytopenia; ICH = intracranial hemorrhage; INR = international normalised ratio; LMWH = low-molecular-weight heparin; OAC = oral anticoagulation; TE = thromboembolic event; TIA = transient ischemic attack; UFH = unfractionated heparin; VKA = vitamin K antagonist. Reprinted from Doherty, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69:871–98. With permission from the Journal of the American Society of Cardiology

much higher than in non-Asians, warfarin was found beneficial following an event only in patients with CHA_2DS_2-VASc score ≥6.[61]

Management of Bleeding

Antidotes and general measures as discussed, are summarised in *Table 5* and *Figure 3*. Recent data suggest that anticoagulation should be restarted following discharge after an episode of GI bleeding.[62] However, this study was too small for definitive conclusions.

Perioperative Anticoagulation

Warfarin

Usually major surgical procedures require an INR of at least <1.5. Warfarin has a half-life of 36–42 h and should be stopped for 3–4 days before surgery when the INR is <2 and 5 days when it is >2 (*Figure 4*).[63] In urgent cases oral or IV vitamin K (1–2 mg) may be considered. In need of urgent reversal, prothrombin plasma concentrate may also be added, and is preferable to fresh frozen plasma.[64] Bridging to UFH

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Table 6: AHA/ACC 2017 Update of the 2014 Guidelines on Valve Disease. Bridging Therapy for Prosthetic Heart Valves

Continuation of VKA with a therapeutic INR in patients with mechanical heart valves undergoing minor procedures (such as dental extractions or cataract removal).	I-C
Temporary interruption of VKA, without bridging agents while the INR is subtherapeutic, in patients with a bileaflet mechanical AVR and no other risk factors for thrombosis who are undergoing invasive or surgical procedures.	I-C
Bridging anticoagulation therapy during the time interval when the INR is subtherapeutic preoperatively on an individualized basis, with the risks of bleeding weighed against the benefits of thromboembolism prevention, for patients who are undergoing invasive or surgical procedures with a 1) mechanical AVR and any thromboembolic risk factor, 2) older-generation mechanical AVR, or 3) mechanical MVR	IIa-C-LD
Fresh frozen plasma or prothrombin complex concentrate in patients with mechanical valves receiving VKA therapy for emergency noncardiac surgery or invasive procedures.	IIa-C

AVR = aortic valve replacement; INR = international normalised ratio; MVR = mitral valve replacement; VKA = vitamin K antagonist. Source: Nishimura, et al., 2017.[79] Credit: American Heart Association, Inc

Table 7: EHRA 2015: Last Intake of Non-vitamin K Antagonist Oral Anticoagulant Before Elective Surgical Intervention

No Important Bleeding Risk and/or Adequate Local Haemostasis				
Possible: Perform 12–24 h After Last Intake				
	Dabigatran		**Apixaban/Rivaroxaban**	
	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24	≥48	≥24	≥48
CrCl 50–80 ml/min	≥36	≥72	≥24	≥48
CrCl 30–50 ml/min	≥48	≥96	≥24	≥48
CrCl 15–30 ml/min	not indicated		≥36	≥48

*Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants In patients with non-valvular atrial fibrillation. Europace. 2015;**17**:1467–507. Source: Katritsis, et al., 2016.Credit: p.589 Table 53.19, p.590 Table 53.20 & p.591 Table: 53.22 from Chapter 53 'Atrial Fibrillation' from Clinical Cardiology: Current Practice Guidelines, Updated Edition by Katritsis, D.G., Gersh, B.J. & Camm, A.J. (2016). Free permission Author's own material, appr. HPL. By permission of Oxford University Press.*

ACC 2017: Recommended Durations for Withholding Direct Oral Anticoagulants Based on Procedural Bleed Risk and Estimated CrCl When There Are No Increased Patient Bleed Risk Factors

	Dabigatran					**Apixaban, Edoxaban, Rivaroxaban**		
CrCl, mL/min	≥80	50–79	30–49	15–29	<15	≥30	15–29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	6–15	Apixaban: 17 Edoxaban: 17 Rivaroxaban: 9	Apixaban: 17 (off dialysis) Edoxaban 10–17 (off dialysis) Rivaroxaban: 13 (off dialysis)
Procedural bleed risk								
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h.	≥24 h	≥36 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT.	≥48 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥72 h.	

NOTE: The duration for withholding is based upon the estimated direct oral anticoagulants' half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 drug half-lives for uncertain, intermediate, or high procedural bleeding risk. CrCl = creatinine clearance; dTT = dilute thrombin time. Credit: Reprinted from Doherty, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69:871–98. With permission from the Journal of the American Society of Cardiology.

or LMWH that is discontinued ≥12 h before and restarted 24 h after the operation, has been recommended only in patients with certain mechanical heart valves and high risk of thrombosis (*Figure 5* and *Table 6*). In a recent meta-analysis, however, heparin bridging for invasive procedures and surgery in patients receiving vitamin K antagonists for AF, prosthetic heart valves, or VTE conferred a greater than five-fold increased risk for bleeding, whereas the risk of thromboembolic events was not significantly different between bridged and non-bridged patients.[65] The use of therapeutic dose LMWH was associated with an increased risk of bleeding compared with prophylactic or intermediate dose.[65] Thus, bridging is not required, especially in patients at low risk of thrombosis.[66–68] In the continued-warfarin group, the INR in the day of surgery should be ≤3, except for patients with one or more mechanical valves, for whom an INR ≤3.5 or less is permitted (Bridge or Continue Coumadin for Device Surgery Randomised Controlled Trial [BRUISECONTROL] trial).[67] In patients with AF, normal renal function and platelet count platelet count >100 × 10^9/L, even major surgery can be safely accomplished with warfarin

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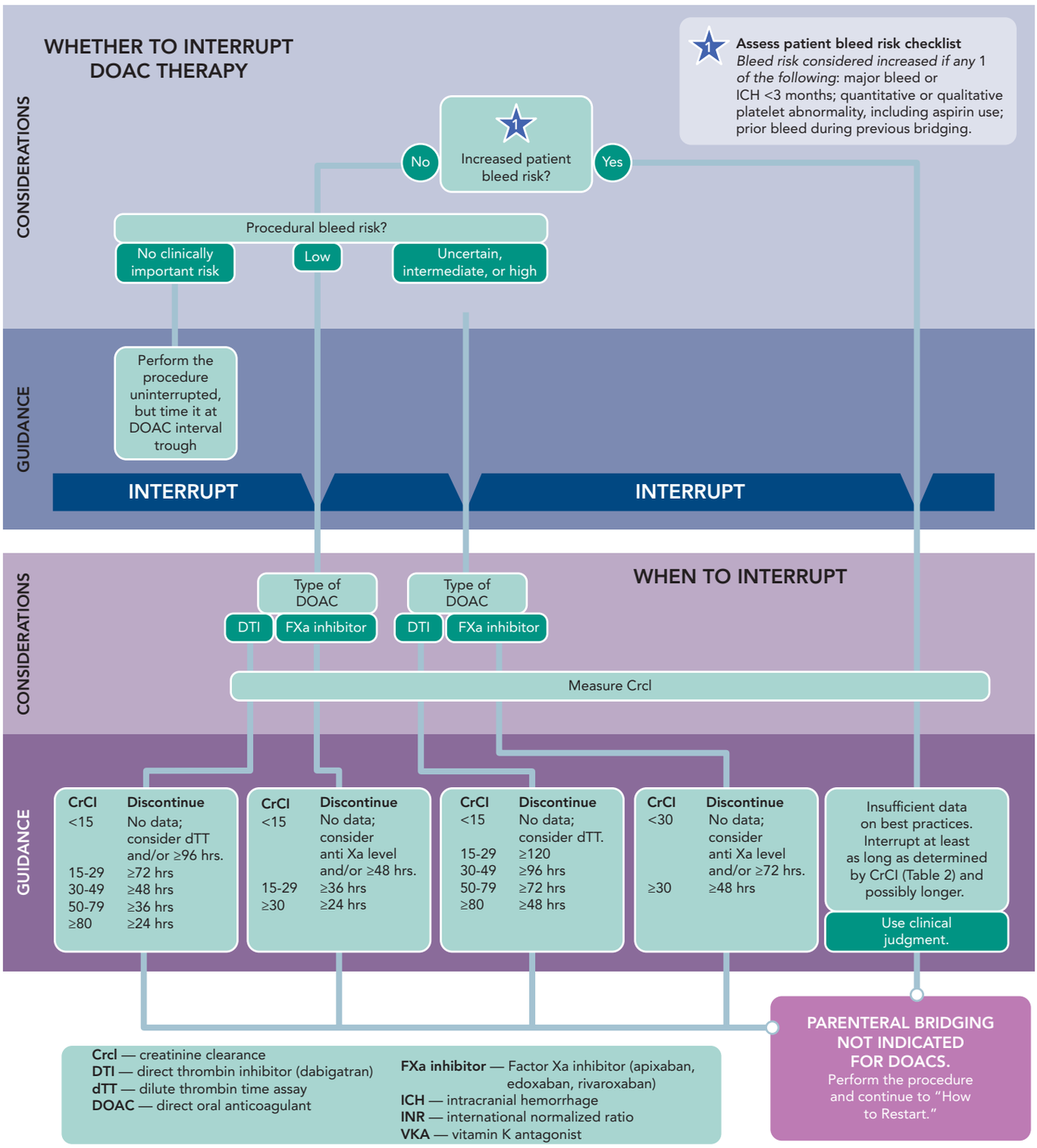
Figure 6: Whether to Interrupt, and How to Interrupt for Direct Oral Anticoagulants



Credit: Reprinted from Doherty, et al. 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69:871–98. With permission from the Journal of the American Society of Cardiology.

cessation without bridging when the INR is <1.8 (Effectiveness of Bridging Anticoagulation for Surgery [BRIDGE] trial). Warfarin is then resumed the evening after the procedure.[68] There are limited data on safety of cardiac surgery or other major surgery with a very high risk of thromboembolism and bleeding, in patients who are on warfarin. Currently, these patients are bridged with heparin prior to surgery. In the need of emergent coronary artery bypass grafting (CABG), fresh frozen plasma and vitamin K may be used to reduce the risk of bleeding.

Non-vitamin K Anticoagulants

Preoperative interruption of DOAC depends on the risk of bleeding and renal function (*Table 7* and *Figure 6*)[52,63,69] In low-risk patients with normal renal function 24–48 h interruption of dabigatran and

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24 h interruption of Xa inhibitors is sufficient. In patients at high bleeding risk dabigatran is interrupted 120 h (CrCl <30 ml/min) to 48 h (CrCl >80 ml/min), and Xa inhibitors 72 h (CrCl <30 ml/min) to 48 (CrCl >30 ml/min).[63] There has been recent evidence that continuation or short-interruption of DOAC are safe strategies for most invasive procedures.[70] Bridging with heparin is, on most occasions, not necessary and may increase the risk of bleeding.[70] In an analysis of data from the Randomised Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, interruption of dabigatran (2 days) or warfarin (5 days) for allowance of surgery was not associated by a significant occurrence of stroke and systemic embolism although heparin bridging was used in <80 % of patients on dabigatran, and major bleeding was not different in the two treatment groups.[71] However, discontinuation of rivaroxaban in the ROCKET AF trial for at least 3 days was associated with a higher incidence of stroke compared to discontinuation of warfarin.[72] Thus, in patients with a $CHADS_2DS_2VASC$ score >4, i.e. >5 % annual risk of stroke, bridging therapy with LMWH should be considered. Procedures with low haemorrhagic risk (dental extraction, skin biopsy, cataract surgery) can be safely performed without interruption of NOACs, especially if carried out 12 h after last dosing. For pacemaker and ICD implantation a 24-h discontinuation with re-initiation 48 h after implantation (24 h in patients with a $CHADS_2DS_2VASC$ score >4) is recommended.[73,52]

If urgent surgery or intervention is required, the risk of bleeding must be weighed against the clinical need for the procedure. Dilute TT for dabigatran and anti-Xa assays for rivaroxaban and apixaban are used to assess anticoagulant activity. aPTT and PT may also be used as rough estimates of the anticoagulant activity of dabigatran and rivaroxaban, respectively.[28] Sensitive PT may be used as a rough estimate of the antocoagulation intensity of all FXa inhibitors. Specific coagulation test (dTT for dabigatran; chromogenic assays for FXa inhibitors) can also be considered, but no clinical experience exists.[52] Surgery or intervention should be deferred, if possible, until at least 12 h and ideally 24 h after the last dose. Non-specific antihaemorrhagic agents, such as recombinant human activated factor VIIa or prothrombin complex concentrates should not be given for prophylactic reversal due to their uncertain benefit-risk.[74] Re-initiation of these agents should be delayed for 24–48 h and once complete haemostasis is assured, since within 1–2 h of re-initiation the patient will be anticoagulated. For procedures with immediate and complete haemostasis NOACs can be resumed 6–8 h after the intervention.[52] ■

Clinical Perspective

- Patients on anticoagulation for atrial fibrillation are still at risk of ischaemic stroke, and may also develop haemorrhagic complications.
- Prompt diagnosis and therapy is necessary for these conditions.
- Specific antidotes are now available for the new, direct oral anticoagulants.

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