Le terapie anticoagulanti per la prevenzione dello Stroke nella Fibrillazione Atriale:

a chi e quale DOAC

Daniela Poli

Cremona 4 Marzo 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

Patients with stable coronary artery disease

First choice	Monotherapy with an NOAC is preferable for patients with AF and stable CAD. This suggestion is applicable to all NOACs
Second choice	In selected patients, addition of aspirin is still indicated in the long-term, based on individual risk assessment and coronary anatomy
Comment	In the absence of direct comparative studies, no particular NOAC can be favoured over another

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

Patients with stable peripheral artery disease

First choice	Until new evidence emerges, drug choice for antithrombotic therapy in patients with AF and PAD is the same as in those with AF and stable CAD

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

Patients undergoing percutaneous coronary intervention and stenting

First choice	In patients with percutaneous coronary intervention after stenting receiving triple therapy, well-controlled VKA (TTR >70%, preferred INR range 2.0–2.5) or an NOAC may be chosen When an NOAC is used in combination with dual antiplatelet therapy, the lower tested and licensed dose for stroke prevention in AF is preferred: dabigatran 110 mg twice daily, rivaroxaban 15 mg once daily, apixaban 2.5 mg twice daily, or edoxaban 30 mg once daily
Comment	There is no preference for one NOAC over another. Published evidence on the combination of dual antiplatelet therapy and an NOAC is currently available only for dabigatran from the RE-LY trial

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

Patients undergoing cardioversion

First choice	VKAs remain the standard of care in patients with AF undergoing cardioversion The available data suggest that the NOACs are safe and effective alternatives, with practical advantages such as shortening the time to cardioversion
Comment	*Post hoc* analyses suggest no apparent differences in safety and efficacy between apixaban, dabigatran, and rivaroxaban

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

Patients undergoing catheter ablation

First choice	In patients undergoing AF ablation, the OAC of choice is uninterrupted warfarin
Second choice	Uninterrupted dabigatran, apixaban, or rivaroxaban.
Third choice	Interrupted warfarin with bridging
Comment	Data on the efficacy and safety of edoxaban in patients undergoing AF ablation are not available

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

Patients with time in therapeutic range of >70% on warfarin

First choice	In patients with AF and TTR >70% on warfarin, it is reasonable to continue with VKA treatment, with careful monitoring to ensure that TTR remains >70%
Second choice	Substitution of VKA therapy with an NOAC may be considered in relation to the following: • previous complications (major bleeding event, ischaemic stroke) on VKA therapy • the SAMe-TT_2R_2 score (those with a score >2 are less likely to fare well on VKA therapy over the long term, and may be considered for NOAC therapy) • the patient's individual values and preferences
Comment	The selection of an NOAC agent and dose should be based on specific patient characteristics. There is no preference for one NOAC over another.

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1

Patients receiving rhythm- and rate-control therapy

Choice and dose of NOAC	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 dronaderone Edoxaban 30 mg should be used in patients on dronedrone

Diener HC. Eur Heart J 2016

Patients with renal impairment and on dialysis

Table I **Dose reduction of non-vitamin K oral anticoagulants for reduced creatinine clearance**

Drug	Dose reduction criteria	Reduced dose
Dabigatran	Creatinine clearance <50 mL/min	110 mg twice a day is recommended in ESC guidelines
Rivaroxaban	Creatinine clearance <50 mL/min	Use 15 mg once a day
Apixaban	2 of three criteria: age ≥80 years, weight ≤60 kg, creatinine ≥1.5 mg/dL	Use 2.5 mg twice a day
Edoxaban	Creatinine clearance ≤50 mL/min	Use 30 mg once a day

ESC, European Society of Cardiology.

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Patients with renal impairment and on dialysis

First choice	Patients with AF and stage III CKD (creatinine clearance 30–49 mL/min) may be treated with apixaban 5 mg twice daily (apixaban 2.5 mg twice a day if ≥1 additional criteria: age ≥80 years, body weight ≤60 kg, serum creatinine ≥ 1.5 mg/dL (133 μmol/L are present), rivaroxaban 15 mg daily, or edoxaban 30 mg once daily
Second choice	Dabigatran 110 mg twice daily
Not recommended	Dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Patients with renal impairment and on dialysis

First choice	For patients with AF on haemodialysis, no anticoagulation or VKA therapy is appropriate
Not recommended	Dabigatran, rivaroxaban, apixaban*, or edoxaban

First choice	Patients with AF and creatinine clearance of >95 mL/min may be treated with dabigatran 150 twice daily, rivaroxaban 20 mg once daily or apixaban 5 mg twice daily. No preference for NOACS over VKAs
Second choice	Edoxaban 60 mg once daily (not recommended in USA based on FDA indication approval)

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Patients with a high risk of gastrointestinal bleeding

Diener HC. Eur Heart J 2016

First choice	For patients with a high risk of gastrointestinal bleeding, apixaban 5 mg twice daily or dabigatran 110 mg twice daily may be used
Second choice	Dabigatran 150 mg twice daily, edoxaban 60 mg once daily, or rivaroxaban 20 mg once daily
Comments	Gastrointestinal bleeding, even in the setting of anticoagulation, does usually not cause death or permanent major disability. Thus, the choice of OAC should be driven mainly by stroke prevention considerations. The label 'high risk of gastrointestinal bleeding' is imprecise. For example, patients with *H. pylori*-related ulcer haemorrhage may no longer be at high risk of bleeding once the infection has been eradicated. The gastrointestinal bleeding risk associated with any anticoagulant is increased by concurrent use of antiplatelet agents, including aspirin.[41]

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Patients with a high risk of gastrointestinal bleeding

Diener HC. Eur Heart J 2016

- As with warfarin, NOAC agents should be restarted as soon as deemed safe to do so once gastrointestinal bleeding has been controlled.
- The gastrointestinal bleeding risk of dabigatran and edoxaban are dose-dependent.
- The increased gastrointestinal bleeding risk of dabigatran and rivaroxaban are most evident in patients ≥75 years old.
- Gastrointestinal tract cancer screening and surveillance strategies (e.g. colonoscopy) increase early detection of occult tumours and may thereby reduce the incidence of neoplasm-associated gastrointestinal bleeding in patients receiving OACs.[42] Age-appropriate colorectal cancer screening should be undertaken prior to initiation of OAC[43]

Table 2 **Major haemorrhage by age subgroups**

	No. of events (%/year)	No. of events (%/year)	Hazard ratio (95% CI)	*P*-value
ARISTOTLE	Apixaban 5 mg twice daily	Warfarin		
<65	56 (1.2)	72 (1.5)	0.78 (0.55–1.11)	0.63
65 to <75	120 (2.0)	166 (2.8)	0.71 (0.56–0.89)	
≥75	151 (3.3)	224 (5.2)	0.64 (0.52–0.79)	
RE-LY	Dabigatran 110 mg twice daily	Warfarin		
<75	138 (1.89)	215 (3.04)	0.62 (0.50–0.77)	0.0003
≥75	204 (4.43)	206 (4.37)	1.01 (0.83–1.23)	
	Dabigatran 150 mg	Warfarin		
<75	153 (2.12)	215 (3.04)	0.70 (0.57–0.86)	0.0001
≥75	246 (5.10)	206 (4.37)	1.18 (0.98–1.42)	
ROCKET AF	Rivaroxaban 20 mg once daily	Warfarin		
<65	59 (2.21)	59 (2.16)	1.02 (0.71–1.46)	0.59
65 to <75	113 (3.03)	123 (3.24)	0.94 (0.73–1.21)	
≥75	223 (4.86)	204 (4.40)	1.11 (0.92–1.34)	
ENGAGE AF-TIMI	Edoxaban 60 mg once daily	Warfarin		0.57
<75	(2.02)	(2.62)		
≥75	(4.01)	(4.83)		

The trials were different in the baseline risk for bleeding complications.

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Non-vitamin K oral anticoagulants and age

First choice	In patients older than 75 years, we suggest apixaban 5 mg twice daily [2.5 mg if ≥2 of the following: age ≥80 years, body weight ≤60 kg, or creatinine ≥1.5 mg/dL (133 μmol/L)]
Second choice	Dabigatran 110 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily

Diener HC. Eur Heart J 2016

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

Adherence

Table 5 Key points in counselling patients taking an oral anticoagulant to improve adherence

Explain how and when to take the drug and duration of treatment
Explain what to do if a dose is missed
Highlight importance of adherence and persistence
Check patients' understanding of this information
Explain what to do in the case of an overdose
Explain that OAC/NOAC treatment should not be stopped without consulting a doctor

Reducing the complexity of a medication regimen or frequency of dosing does not necessarily improve adherence.

Diener HC. Eur Heart J 2016

Interventions for improving modifiable risk factor control in the secondary prevention of stroke (Review)

Lager KE, Mistri AK, Khunti K, Haunton VJ, Sett AK, Wilson AD

THE COCHRANE COLLABORATION®

Main results

This review included 26 studies involving 8021 participants. There were no significant effects of organisational interventions medication adherence or recurrent cardiovascular events. Educational and behavioural interventions were not generally associated with clear differences in any of the review outcomes, with only two exceptions.

Authors' conclusions

Pooled results indicated that educational interventions were not associated with clear differences in any of the review outcomes. The estimated effects of organisational interventions were compatible with improvements and no differences in several modifiable risk factors. We identified a large number of ongoing studies, suggesting that research in this area is increasing.

The Cochrane Collaboration , 2014