Risk Assessment and Treatment for Stroke Prevention in Patients with Atrial Fibrillation

New Practice Guidelines and Recent Clinical Trials

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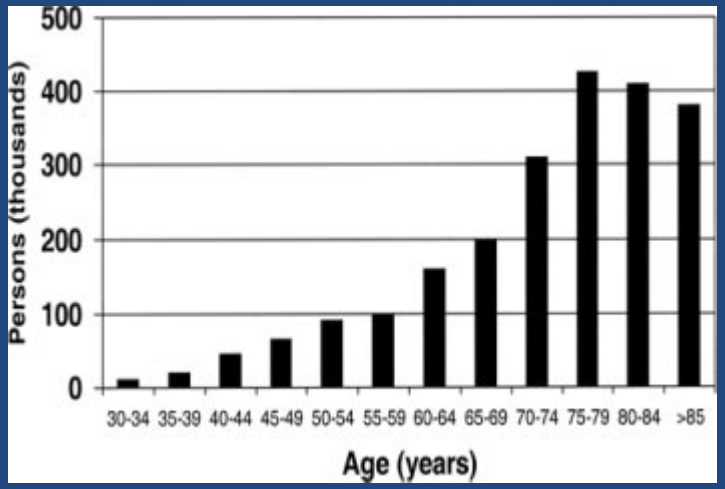
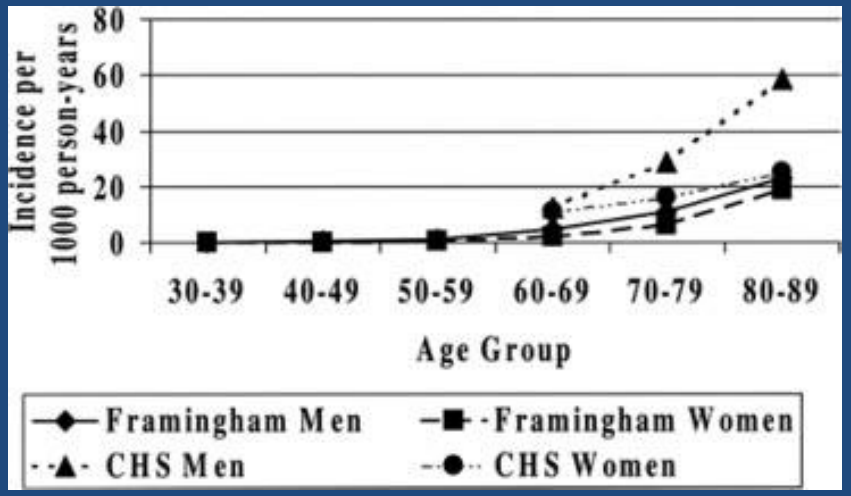
Atrial Fibrillation

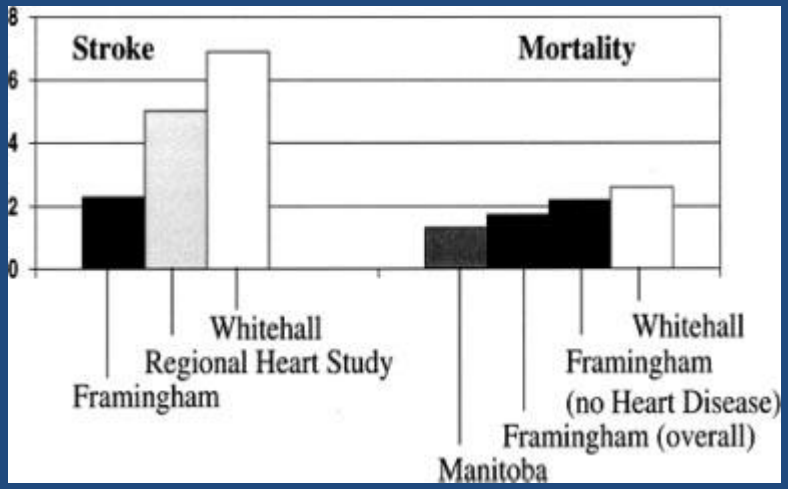
- 심방세동은 지속성 부정맥 중에서 가장 흔하다.
  - 서양 인구의 1-2%; silent AF가 1/3
  - 고령화로 50년 후 유병률은 최소 2배로 예상
  - 현재 40세 정상인; 향후 25%는 일생 중 AF를 경험
- 심방세동과 뇌졸중
  - 평균 5배의 위험성 증가
  - 다른 원인에 의한 것보다 치명적이거나 후유증이 큼
  - 1.5배의 진료비

Prevalence of AF





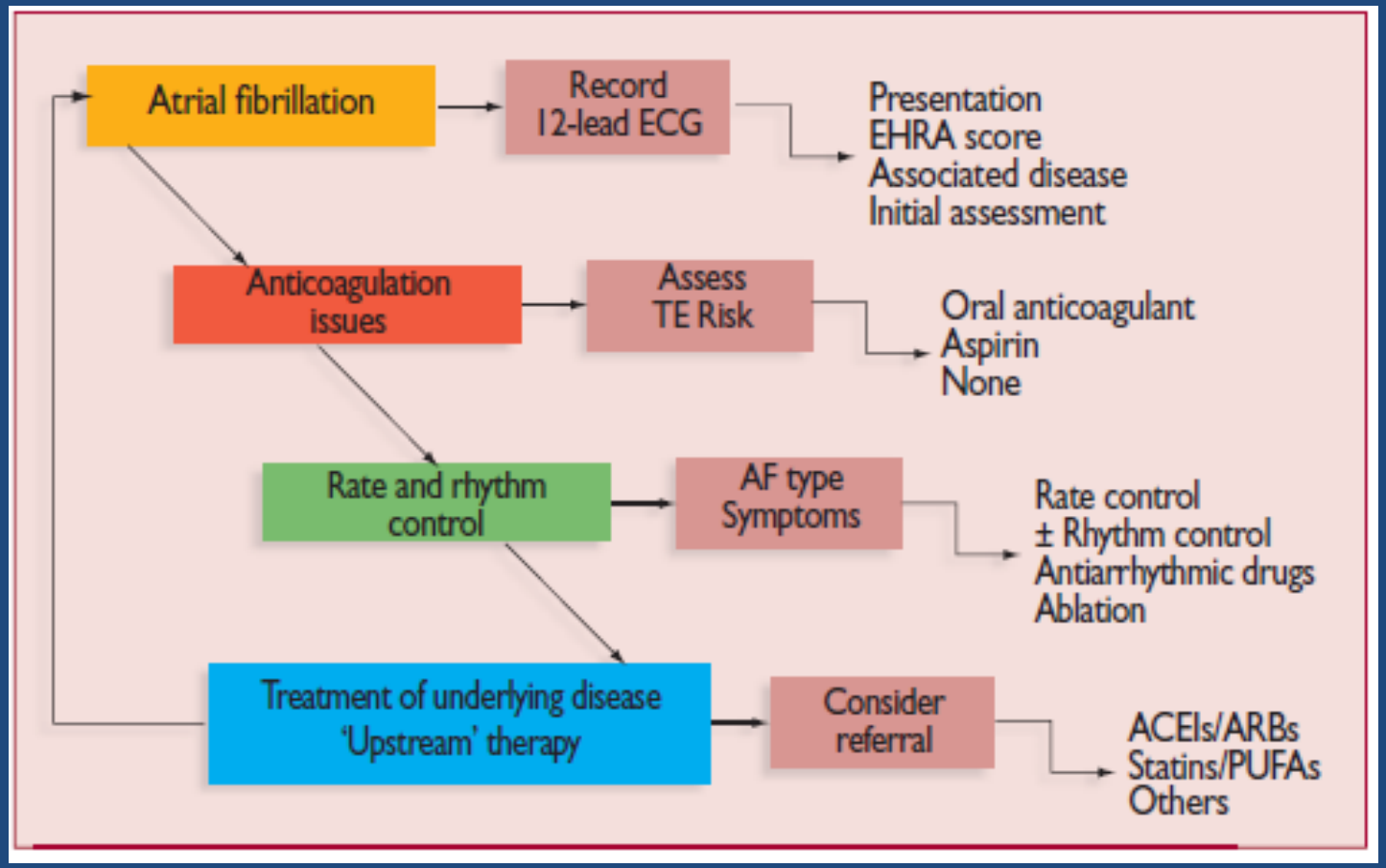
Relative risk of AF



Arch Intern Med 1995;155:469-73
Arch Intern Med 1987;147:1561-4
Circulation 1997;96:2455-61
Am Heart J 1983;106:389-96
Am J Med 1995;98:476-84

- Frustrations
  - Rate control vs. rhythm control
  - Strict vs. *laissez-faire* rate control
  - Early detection; silent or asymptomatic nature of AF
  - Ablation; Mortality?
- Hopes
  - Ablation; reduce symptomatic burden, cure in some patients?
  - New anticoagulants
  - New antiarrhythmic agent(s)

AFFIRM (the Atrial Fibrillation Follow-up Investigation of Rhythm Management) NEJM 2002;347:1825-33
RACE II (RAte Control Efficacy in permanent atrial fibrillation) NEJM 2010;362:1363-73


Atrial fibrillation
Record 12-lead ECG
Presentation
EHRA score
Associated disease
Initial assessment
Anticoagulation issues
Assess TE Risk
Oral anticoagulant
Aspirin
None
Rate and rhythm control
AF type
Symptoms
Rate control
± Rhythm control
Antiarrhythmic drugs
Ablation
Treatment of underlying disease
'Upstream' therapy
Consider referral
ACEIs/ARBs
Statins/PUFAs
Others

Guidelines for the Management of Patients with Atrial Fibrillation

- 2006 ACC/AHA/ESC guidelines
  Circulation 2006;114:e257-e354

- 2010 ESC guideline update
  Europace 2010 Oct;12(10):1360-420

- 2010 Canadian guideline update
  Canadian J Cardiol 2011 Jan-Feb;27(1):74-90

- 2011 ACCF/AHA/HRS focused update guidelines
  Circulation 2011 Mar;123(10):e269-e367

2006 ACC/AHA/ESC Guidelines

Risk Assessment for Antithrombotic Therapy

Risk Category		Recommended Therapy
No risk factors		Aspirin, 81 to 325 mg daily
One moderate-risk factor		Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or more than 1 moderate-risk factor		Warfarin (INR 2.0 to 3.0, target 2.5)*
Less Validated or Weaker Risk Factors	Moderate-Risk Factors	High-Risk Factors
Female gender	Age greater than or equal to 75 y	Previous stroke, TIA or embolism
Age 65 to 74 y	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve*
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

$CHADS_2$ score	Patients (n = 1733)	Adjusted stroke rate (%/year)[a] (95% confidence interval)
0	120	1.9 (1.2–3.0)
1	463	2.8 (2.0–3.8)
2	523	4.0 (3.1–5.1)
3	337	5.9 (4.6–7.3)
4	220	8.5 (6.3–11.1)
5	65	12.5 (8.2–17.5)
6	5	18.2 (10.5–27.4)

Antithrombotic Management

2011 ESC guideline

- Risk stratification — CHA_2DS_2-VASc score
- Antithrombotic treatment — New agents
- Bleeding risk stratification — HAS-BLED score
- Optimal INR
- Special situations

Paroxysmal AF, Perioperative anticoagulation, stable vascular disease, ACS±PCI, Elective PCI, NSTEMI, Acute STEMI with primary PCI, Acute stroke, Atrial flutter, Cardioversion, TEE-guided cardioversion, Non-pharmacological methods to prevent stroke

Risk Stratification for Stroke Prevention

2011 ESC Guidelines

Rationale; CHA_2DS_2-VASc score

- Age
  - Age > 65; ischemic stroke risk가 증가하기 시작
  - 75세 이후라고 갑자기 risk가 되는 것은 아니다.
  - 고령의 환자일수록 항응고제가 도움이 된다.
    - Antiplatelet agent는 고령에서 stroke 예방의 효과가 점차 감소
    - Anticoagulation의 stroke 예방효과는 나이와 무관
- HT
  - 이전의 정의; 혈압약을 복용하거나, 조절되지 않은 혈압이 > 160/95 mmHg
  - 잘 조절되는 고혈압은 risk가 되지 않는다.
- Heart failure
  - Heart failure with preserved ejection fraction; 연구(-)

- Atherosclerotic vascular diseases
  - Angina는 risk factor가 아니지만 prior myocardial infarction, peripheral artery disease, TEE 에서 발견된 aorta의 complex atheroma 등은 명백한 risk factor 이다.
- Female gender
  - RR 1.6 (95% CI 1.3-1.9)
- Proteinuria
  - RR 1.54 (95% CI 1.29-1.85)
- Other factors
  - GFR < 45 ml/min, hypertrophic cardiomyopathy, amyloidosis
- Original $CHADS_2$ score
  - 너무 많은 환자가 score 1-2 사이에 존재한다.

Original $CHADS_2$ score

$CHADS_2$ score	Patients (n = 1733)	Adjusted stroke rate (%/year)[a] (95% confidence interval)
0	120	1.9 (1.2–3.0)
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CHA_2DS_2-VASc score

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

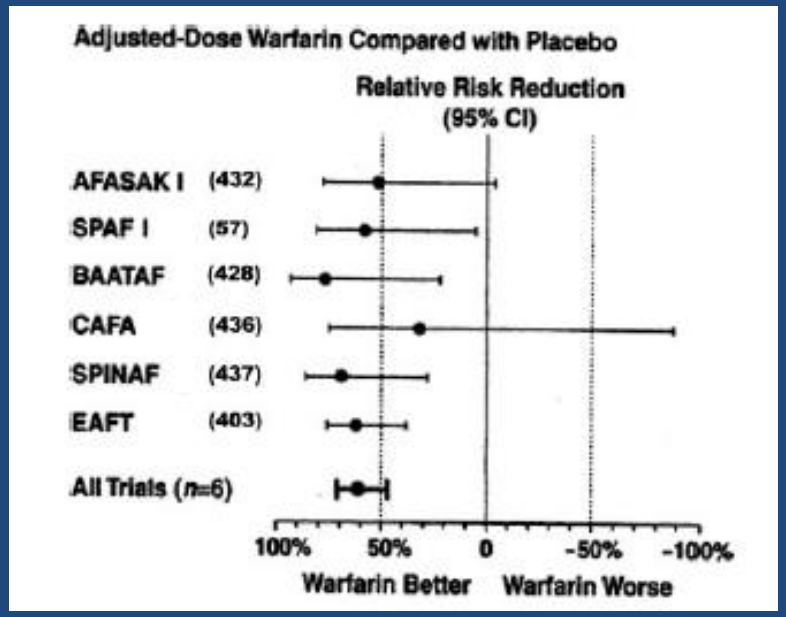
(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	**Patients (n=7329)**	**Adjusted stroke rate (%/year)[b]**
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Vascular disease; prior myocardial infarction, peripheral artery disease, aortic plaque

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' risk factors	≥ 2	OAC[a]
One 'clinically relevant non-major' risk factor	1	Either OAC[a] or aspirin 75–325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75–325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

Antithrombotic Therapy

2011 ESC Guidelines



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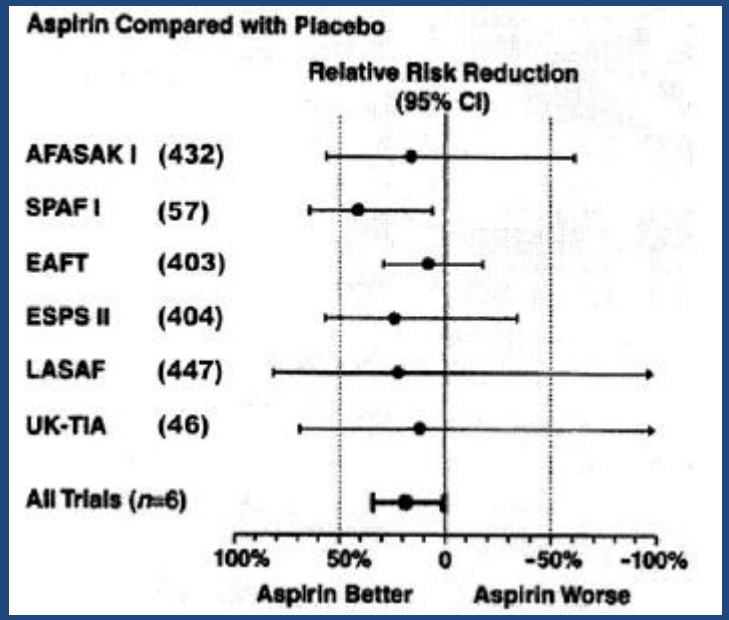

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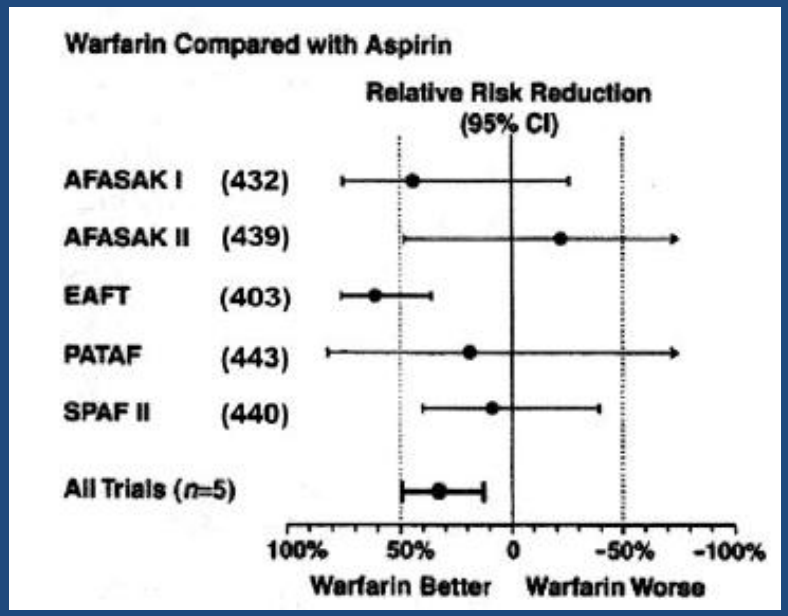

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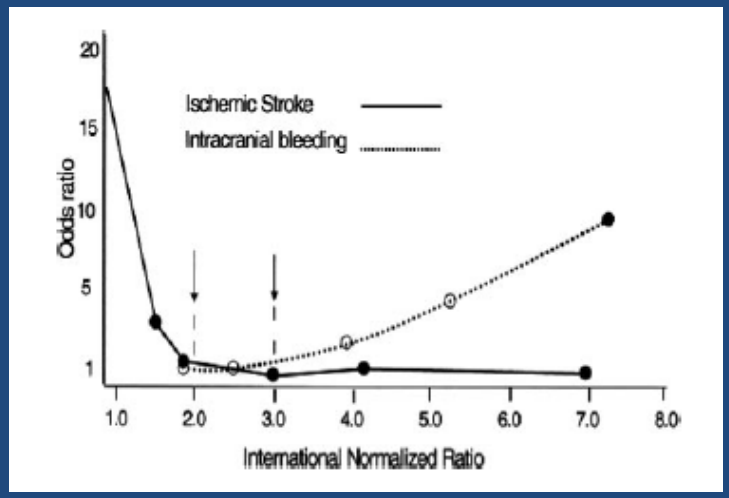
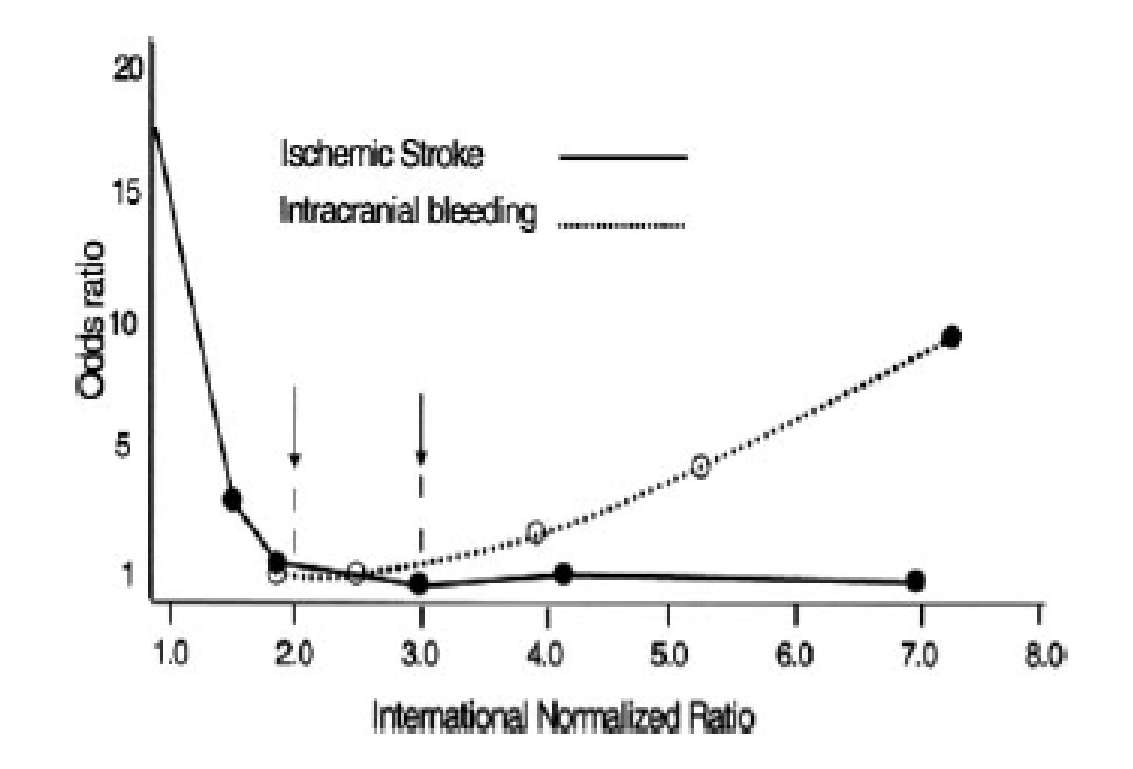


Ann Intern Med 1999;131:492-501
Ann Intern Med 1994;120:897-902


20
15
10
5
1
Odds ratio
Ischemic Stroke
Intracranial bleeding
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
International Normalized Ratio

Risk Stratification for Bleeding Complications

2011 ESC Guidelines

Risk of Bleeding

- 점차 더욱 고령의 환자에서 warfarin을 이용한 항응고치료를 하지만 intracerebral hemorrhage는 줄고 있다.
  - 낮은 INR을 유지 (2.0 ~ 3.0)
  - 보다 주의 깊은 dose adjustment
  - 보다 적절한 혈압의 조절

- 낮은 INR을 유지하는 것은 도움이 되지 않는다.
  - INR < 2.0에서는 ischemic stroke가 급격히 증가한다.
  - Bleeding complication은 INR 3.5-4.0 이상에서 높아지기 시작한다.

- 노령 환자의 낙상 사고로 인한 ICH를 두려워해서는 안된다.
  - Anticoagulation을 하는 사람에서 1년에 300 회 이상의 낙상사고가 발생하면 ICH의 risk가 높아진다.

- 고령의 환자에서는 실제로 aspirin에 의한 bleeding complication 과 warfarin에 의한 complication이 거의 비슷하다.

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

High risk of bleeding; HAS-BLED score ≥ 3

Chest 2010; Mar 18 [Epub ahead of print]

Special Situations

2011 ESC Guidelines

- Perioperative anticoagulation
  - High risk for thrombo-embolism ($CHADS_2$ score ≥ 2)
    - 'Bridging' anticoagulation with heparin (or LMWH)
  - Low to intermediate risk for thrombo-embolism
    - Stop anticoagulation ~ 5 half life; warfarin의 경우 5-7 일
    - INR < 1.5 에서 수술; 계속 INR > 1.5 이면 1-2 gm의 oral vitamin K 투여
    - 지혈이 잘 된 경우 수술일 저녁 혹은 다음날 아침부터 다시 warfarin 유지용량 투여; loading 하지 말 것

Br heart J 2010;31:967-75

- Warfarin 복용을 거절한 환자나 warfarin 복용에 대한 명백한 금기증이 있는 경우
  - Bleeding risk가 낮은 경우에는 aspirin+clopidogrel을 고려
- Stable vascular disease
  - Anticoagulation+antiplatelet agent는 ischemic stroke, systemic embolism의 risk는 줄이지 못하고 bleeding 만 증가시킨다.
- Paroxysmal atrial fibrillaiton; atrial flutter
  - Stroke risk는 다른 AF 과 비슷하다.

- Acute coronary syndrome &/or PCI
  - OAC는 angina의 secondary prevention에 있어서 아무리 못해도 aspirin 과 비슷하다.
  - 4주 이내의 triple therapy (OAC+Asp+Clopidogrel)의 bleeding risk는 크게 높지 않다.
  - Avoid DES (small vv, long lesion, restenosis, DM 등등을 제외하고는), 특히 '-olimuth'에 주의
  - OAC + clopidogrel; 대신 aspirin 사용시 PPI (H2-blocker or antacid)를 같이 사용한다.

- Acute stroke
  - 일단 혈압 조절이 급선무
  - Imaging study; hemorrhage 동반 여부 확인
  - Anticoagulation은 급성기 2주 이후부터 시작
  - 출혈이 있는 경우에는 OAC를 주지 않는다.
- Acute TIA
  - OAC as soon as possible
- Silent (old) stroke
  - AF 환자의 imaging study 에서 많이 발견된다.

Haemorrhagic risk	Clinical setting	Stent implanted	Anticoagulation regimen
Low or intermediate (e.g. HAS-BLED score 0–2)	Elective	Bare-metal	1 month: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Lifelong: VKA (INR 2.0–3.0) alone
	Elective	Drug-eluting	3 (-olimus[a] group) to 6 (paclitaxel) months: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b] (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
	ACS	Bare-metal/ drug-eluting	6 months: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b] (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
High (e.g. HAS-BLED score ≥3)	Elective	Bare-metal[c]	2–4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Lifelong: VKA (INR 2.0–3.0) alone
	ACS	Bare-metal[c]	4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b] (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone

감사합니다

ACTIVE Trial

In the **A**trial fibrillation **C**lopidogrel **T**rial with **I**rbesartan for prevention of **V**ascular Events

- ACTIVE-W (ACTIVE warfarin arm)
  - Anticoagulation is superior to the combination of aspirin and clopidogrel
    - RR reduction 40% (95% CI 18-56)
- ACTIVE-A (ACTIVE aspirin arm)
  - Combination therapy is superior to aspirin monotherapy
    - RR reduction 11% (95% CI 0.81-0.98); 28% RR reduction in ischemic stroke
    - Major bleeding; 57% increased (95% CI 1.29-1.92): 2.0%/yr *vs.* 1.3%/yr
    - Major bleeding rate was similar to anticoagulation

Lancet 2006;367:1903-1912

Other Trials

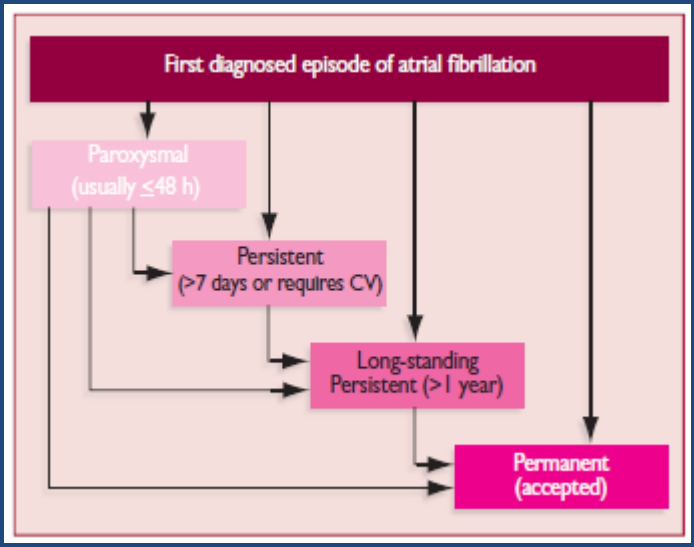
- Other antiplatelet agents
  - Some benefits with Indobufen and Triflusal
  - More data are required
- Anticoagulation (INR 2.0-3.0) + antiplatelet agent
  - No beneficial effect on ischemic stroke or vascular events
  - More bleeding was evident
  - INR 2.0-3.0 에서도 재발하는 ischemic stroke 환자에서는 antiplatelet agent를 추가하지 말고, INR을 3.0-3.5로 조절하는 것이 낫다.

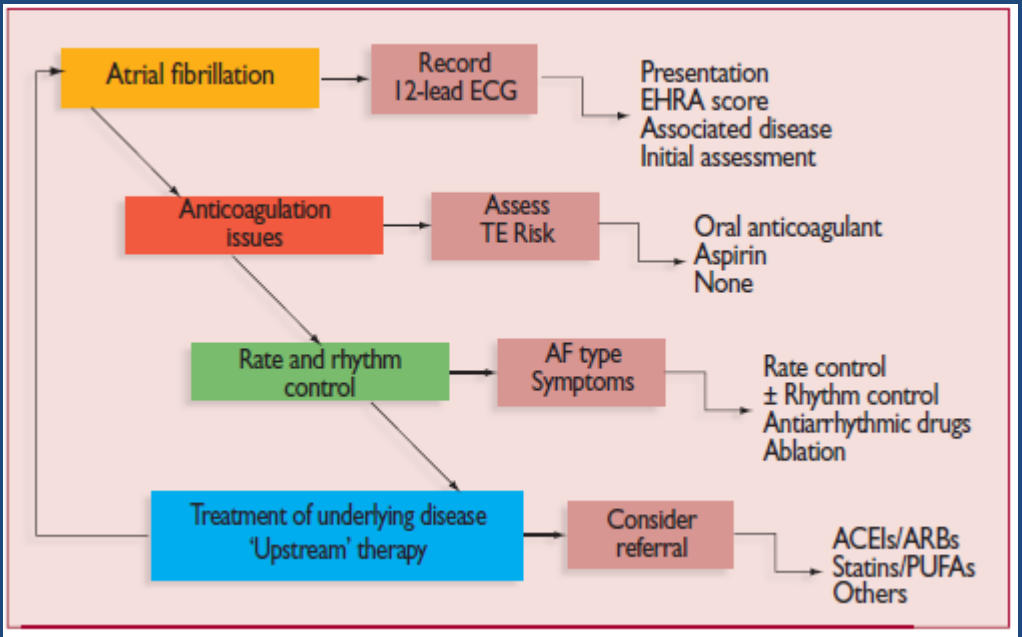
Rate vs. Rhythm Control

Trial	Ref	Patients (*n*)	Mean age (years)	Mean follow-up (years)	Inclusion criteria	Primary outcome parameter	Patients reaching primary outcome (*n*)		
							Rate control	Rhythm control	*P*
PIAF (2000)	92	252	61.0	1.0	Persistent AF (7–360 days)	Symptomatic improvement	76/125 (60.8%)	70/127 (55.1%)	0.32
AFFIRM (2002)	86	4060	69.7	3.5	Paroxysmal AF or persistent AF, age ≥65 years, or risk of stroke or death	All-cause mortality	310/2027 (25.9%)	356/2033 (26.7%)	0.08
RACE (2002)	87	522	68.0	2.3	Persistent AF or flutter for <1 years and 1–2 cardioversions over 2 years and oral anticoagulation	Composite: cardiovascular death, CHF, severe bleeding, pacemaker implantation, thrombo-embolic events, severe adverse effects of antiarrhythmic drugs	44/256 (17.2%)	60/266 (22.6%)	0.11
STAF (2003)	88	200	66.0	1.6	Persistent AF (>4 weeks and <2 years), LA size >45 mm, CHF NYHA II–IV, LVEF <45%	Composite: overall mortality, cerebrovascular complications, CPR, embolic events	10/100 (10.0%)	9/100 (9.0%)	0.99
HOT CAFÉ (2004)	89	205	60.8	1.7	First clinically overt persistent AF (≥7 days and <2 years), age 50–75 years	Composite: death, thrombo-embolic events; intracranial/major haemorrhage	1/101 (1.0%)	4/104 (3.9%)	>0.71
AF-CHF (2008)	90	1376	66	3.1	LVEF ≤35%, symptoms of CHF, history of AF (≥6 h or DCC <last 6 months)	Cardiovascular death	175/1376 (25%)	182/1376 (27%)	0.59
J-RHYTHM (2009)	91	823	64.7	1.6	Paroxysmal AF	Composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure, or physical/ psychological disability	89/405 (22.0%)	64/418 (15.3%)	0.012

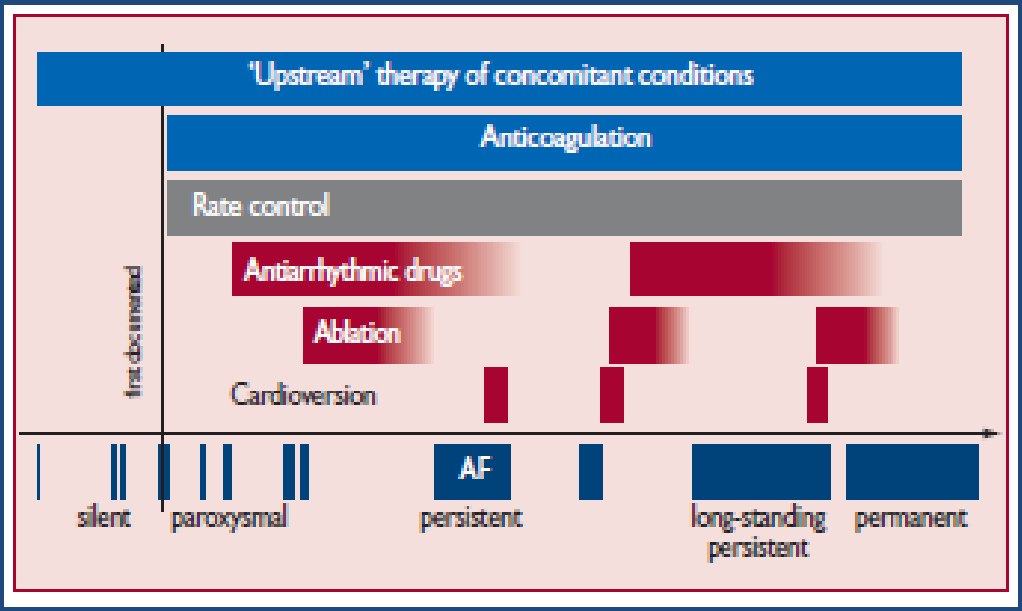
Rate vs. Rhythm Control

Trial	Ref	Deaths from all causes (in rate/rhythm)	Deaths from cardiovascular causes	Deaths from non-cardiovascular causes	Stroke	Thrombo-embolic events	Bleeding
PIAF (2000)	92	4	1/1	1[a]	ND	ND	ND
AFFIRM (2002)	86	666 (310/356)	167/164	113/165	77/80	ND	107/96
RACE (2002)	87	36	18/18	ND	ND	14/21	12/9
STAF (2003)	88	12 (8/4)	8/3	0/1	1/5	ND	8/11
HOT CAFÉ (2004)	89	4 (1/3)	0/2	1/1	0/3	ND	5/8
AF-CHF (2008)	90	228/217	175/182	53/35	11/9	ND	ND





Classification of AF-related symptoms (EHRA score)	
EHRA class	**Explanation**
EHRA I	'No symptoms'
EHRA II	'Mild symptoms'; normal daily activity not affected
EHRA III	'Severe symptoms'; normal daily activity affected
EHRA IV	'Disabling symptoms'; normal daily activity discontinued



Europace 2010 Oct;12(10):1360-420

Patient Features	Antithrombotic Therapy	Class of Recommendation
Age less than 60 y, no heart disease (lone AF)	Aspirin (81 to 325 mg per day) or no therapy	I
Age less than 60 y, heart disease but no risk factors*	Aspirin (81 to 325 mg per day)	I
Age 60 to 74 y, no risk factors*	Aspirin (81 to 325 mg per day)	I
Age 65 to 74 y with diabetes mellitus or CAD	Oral anticoagulation (INR 2.0 to 3.0)	I
Age 75 y or older, women	Oral anticoagulation (INR 2.0 to 3.0)	I
Age 75 y or older, men, no other risk factors	Oral anticoagulation (INR 2.0 to 3.0) or aspirin (81 to 325 mg per day)	I
Age 65 or older, heart failure	Oral anticoagulation (INR 2.0 to 3.0)	I
LV ejection fraction less than 35% or fractional shortening less than 25%, and hypertension	Oral anticoagulation (INR 2.0 to 3.0)	I
Rheumatic heart disease (mitral stenosis)	Oral anticoagulation (INR 2.0 to 3.0)	I
Prosthetic heart valves	Oral anticoagulation (INR 2.0 to 3.0 or higher)	I
Prior thromboembolism	Oral anticoagulation (INR 2.0 to 3.0 or higher)	I
Persistent atrial thrombus on TEE	Oral anticoagulation (INR 2.0 to 3.0 or higher)	IIa

Recommendations for prevention of thromboembolism

Recommendations	Class[a]	Level[b]	Ref.[c]
Antithrombotic therapy to prevent thrombo-embolism is recommended for all patients with AF, except in those at low risk (lone AF, aged <65 years, or with contraindications).	I	A	47, 48, 63
It is recommended that the selection of the antithrombotic therapy should be based upon the absolute risks of stroke/thrombo-embolism and bleeding, and the relative risk and benefit for a given patient.	I	A	47, 48, 50
The $CHADS_2$ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] score is recommended as a simple initial (easily remembered) means of assessing stroke risk in non-valvular AF.	I	A	50
• For the patients with a $CHADS_2$ score of ≥2, chronic OAC therapy with a VKA is recommended in a dose-adjusted regimen to achieve an INR range of 2.0–3.0 (target 2.5), unless contraindicated.	I	A	47, 48, 54
For a more detailed or comprehensive stroke risk assessment in AF (e.g. with $CHADS_2$ scores 0–1), a risk factor-based approach is recommended, considering 'major' and 'clinically relevant non-major' stroke risk factors[a].	I	A	52
• Patients with 1 'major' or ≥ 2 'clinically relevant non-major' risk factors are high risk, and OAC therapy (e.g. with a VKA, dose adjusted to achieve the target intensity INR of 2.0–3.0) is recommended, unless contraindicated.	I	A	52
• Patients with one 'clinically relevant non-major' risk factor are at intermediate risk and antithrombotic therapy is recommended, either as:	I	A B	52
i. OAC therapy (e.g. VKA), or	I	A	52
ii. aspirin 75–325 mg daily	I	B	48
• Patients with no risk factors are at low risk (essentially patients aged <65 years with lone AF, with none of the risk factors) and the use of either aspirin 75–325 mg daily or no antithrombotic therapy is recommended.	I	B	52
For patients with AF who have mechanical heart valves, it is recommended that the target intensity of anticoagulation with a VKA should be based on the type and position of the prosthesis, maintaining an INR of at least 2.5 in the mitral position and at least 2.0 for an aortic valve.	I	B	63, 64
Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF.	I	C	

The selection of antithrombotic therapy should be considered using the same criteria irrespective of the pattern of AF (i.e. paroxysmal, persistent, or permanent).	IIa	A	47, 48
Most patients with one 'clinically relevant non-major' risk factor should be considered for OAC therapy (e.g. with a VKA) rather than aspirin, based upon an assessment of the risk of bleeding complications, the ability to safely sustain adjusted chronic anticoagulation, and patient preferences.	IIa	A	47, 48
In patients with no risk factors who are at low risk (essentially patients aged <65 years with lone AF, with none of the risk factors), no antithrombotic therapy should be considered, rather than aspirin.	IIa	B	47, 48
Combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g. inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding.	IIa	B	58
Assessment of the risk of bleeding should be considered when prescribing antithrombotic therapy (whether with VKA or aspirin), and the bleeding risk with aspirin should be considered as being similar to VKA, especially in the elderly.	IIa	A	56, 60, 65
The HAS-BLED score [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly] should be considered as a calculation to assess bleeding risk, whereby a score of ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or aspirin.	IIa	B	60
In patients with AF who do not have mechanical prosthetic heart valves or those who are not at high risk for thrombo-embolism who are undergoing surgical or diagnostic procedures that carry a risk of bleeding, the interruption of OAC (with subtherapeutic anticoagulation for up to 48 h) should be considered, without substituting heparin as 'bridging' anticoagulation therapy.	IIa	C	
In patients with a mechanical prosthetic heart valve or AF at high risk for thrombo-embolism who are undergoing surgical or diagnostic procedures, 'bridging' anticoagulation with therapeutic doses of either LMWH or unfractionated heparin during the temporary interruption of OAC therapy should be considered.	IIa	C	
Following surgical procedures, resumption of OAC therapy should be considered at the 'usual' maintenance dose (without a loading dose) on the evening of (or the next morning after) surgery, assuming there is adequate haemostasis.	IIa	B	
Re-evaluation at regular intervals of the benefits, risks, and need for antithrombotic therapy should be considered.	IIa	C	
In patients with AF presenting with acute stroke or TIA, management of uncontrolled hypertension should be considered before antithrombotic treatment is started, and cerebral imaging (computed tomography or magnetic resonance imaging) performed to exclude haemorrhage.	IIa	C	
In the absence of haemorrhage, OAC therapy should be considered ~2 weeks after stroke, but, in the presence of haemorrhage, anticoagulation should not be given.	IIa	C	
In the presence of a large cerebral infarction, delaying the initiation of anticoagulation should be considered, given the risk of haemorrhagic transformation.	IIa	C	

In some patients with one 'clinically relevant non-major' risk factor, e.g., female patients aged <65 years with no other risk factors, aspirin may be considered rather than OAC therapy.	IIb	C	
When surgical procedures require interruption of OAC therapy for longer than 48 h in high-risk patients, unfractionated heparin or subcutaneous LMWH may be considered.	IIb	C	
In patients with AF who sustain ischaemic stroke or systemic embolism during treatment with usual intensity anticoagulation with VKA (INR 2.0–3.0), raising the intensity of the anticoagulation to a maximum target INR of 3.0–3.5 may be considered, rather than adding an antiplatelet agent.	IIb	C	

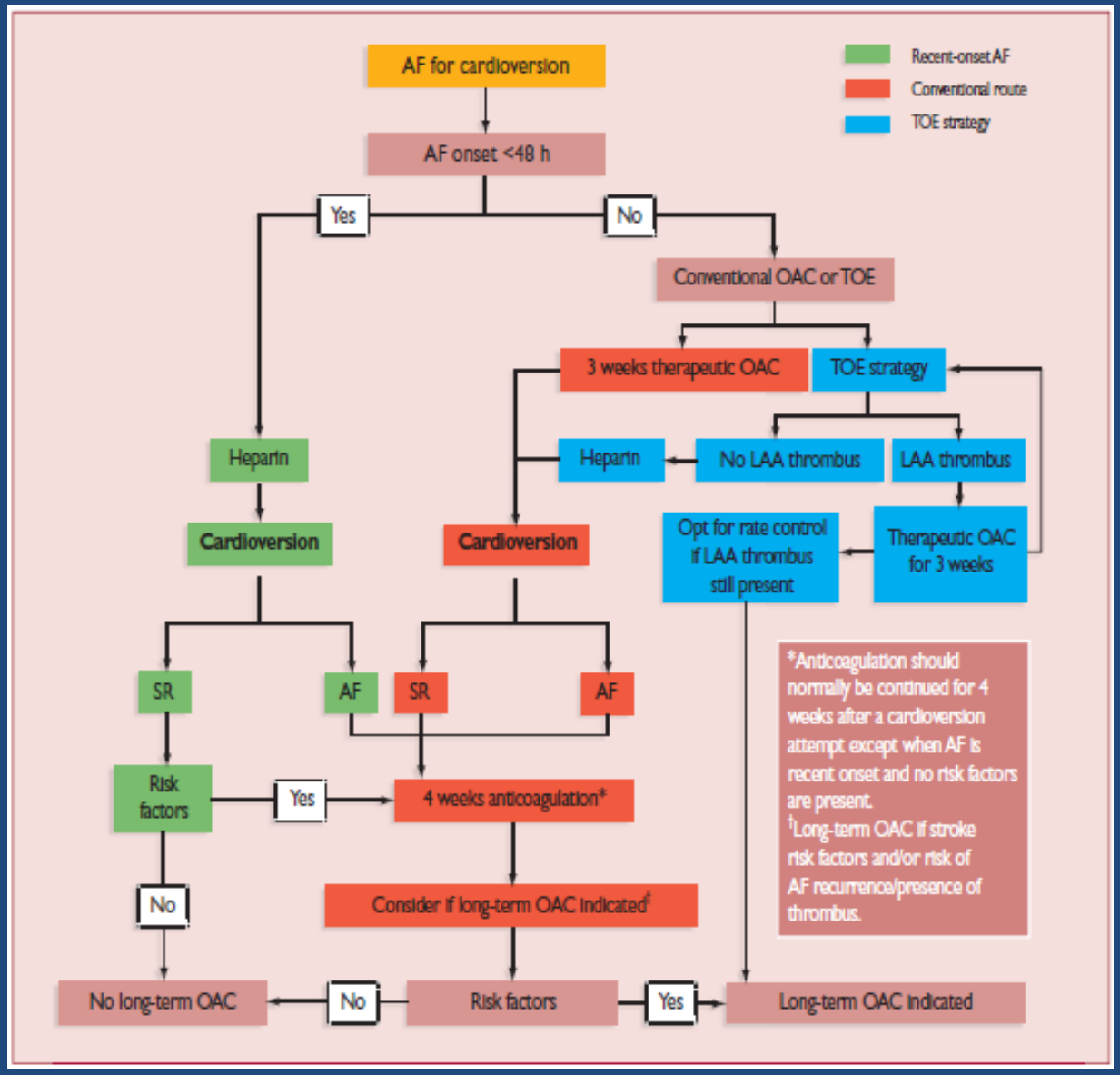
Recommendations for anti-thrombotic therapy in AF with ACS/PCI

Recommendations	Class[a]	Level[b]	Ref.[c]
Following elective PCI in patients with AF with stable coronary artery disease, BMS should be considered, and drug-eluting stents avoided or strictly limited to those clinical and/or anatomical situations (e.g. long lesions, small vessels, diabetes, etc.), where a significant benefit is expected when compared with BMS.	IIa	C	
Following elective PCI, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short term, followed by more long-term therapy (up to 1 year) with VKA plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection with PPIs, H_2 antagonists, or antacids).	IIa	C	
Following elective PCI, clopidogrel should be considered in combination with VKA plus aspirin for a minimum of 1 month after implantation of a BMS, but longer with a drug-eluting stent (at least 3 months for a sirolimus-eluting stent and at least 6 months for a paclitaxel-eluting stent); following which VKA and clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection with either PPIs, H_2 antagonists, or antacids) should be considered, if required.	IIa	C	
Following an ACS with or without PCI in patients with AF, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short term (3–6 months), or longer in selected patients at low bleeding risk, followed by long-term therapy with VKA plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection with PPIs, H_2 antagonists, or antacids).	IIa	C	
In anticoagulated patients at very high risk of thrombo-embolism, uninterrupted therapy with VKA as the preferred strategy and radial access used as the first choice even during therapeutic anticoagulation (INR 2–3).	IIa	C	
When VKA is given in combination with clopidogrel or low-dose aspirin, careful regulation of the anticoagulation dose intensity may be considered, with an INR range of 2.0–2.5.	IIb	C	
Following revascularization surgery in patients with AF, VKA plus a single antiplatelet drug may be considered in the initial 12 months, but this strategy has not been evaluated thoroughly and is associated with an increased risk of bleeding.	IIb	C	
In patients with stable vascular disease (e.g. >1 year, with no acute events), VKA monotherapy may be considered, and concomitant antiplatelet therapy should not be prescribed in the absence of a subsequent cardiovascular event.	IIb	C	

Recommendation for anticoagulation pericardioversion

Recommendations	Class[a]	Level[b]	Ref.[c]
For patients with AF of 48 h duration or longer, or when the duration of AF is unknown, OAC therapy (INR 2.0–3.0) is recommended for at least 3 weeks prior to and for 4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological).	I	B	63
For patients with AF requiring immediate/emergency cardioversion because of haemodynamic instability, heparin (i.v. UFH bolus followed by infusion, or weight-adjusted therapeutic dose LMWH) is recommended.	I	C	
After immediate/emergency cardioversion in patients with AF of 48 h duration or longer, or when the duration of AF is unknown, OAC therapy is recommended for at least 4 weeks, similar to patients undergoing elective cardioversion.	I	B	63
For patients with AF <48 h and at high risk of stroke, i.v. heparin or weight-adjusted therapeutic dose LMWH is recommended peri-cardioversion, followed by OAC therapy with a VKA (INR 2.0–3.0) long term.	I	B	47, 54, 63
If AF is of ≥48 h, OAC therapy is recommended for at least 4 weeks after immediate/emergency cardioversion, similar to patients undergoing elective cardioversion.	I	B	63
In patients at high risk of stroke, OAC therapy with a VKA (INR 2.0–3.0) is recommended to be continued long-term.	I	B	47, 54, 63
As an alternative to anticoagulation prior to cardioversion, TOE-guided cardioversion is recommended to exclude thrombus in the left atrium or left atrial appendage.	I	B	42
For patients undergoing TOE-guided cardioversion who have no identifiable thrombus, cardioversion is recommended immediately after anticoagulation with heparin, and heparin should be continued until OAC therapy has been established, which should be maintained for at least 4 weeks after cardioversion.	I	B	42
For patients undergoing a TOE-guided strategy in whom thrombus is identified, VKA (INR 2.0–3.0) is recommended for at least 3 weeks, followed by a repeat TOE to ensure thrombus resolution.	I	C	
For patients with atrial flutter undergoing cardioversion, anticoagulation is recommended as for patients with AF.	I	C	

In patients with risk factors for stroke or AF recurrence, OAC therapy should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.	IIa	B	63
If thrombus resolution is evident on repeat TOE, cardioversion should be performed, and OAC should be considered for 4 weeks or lifelong (if risk factors are present).	IIa	C	
If thrombus remains on repeat TOE, an alternative strategy (e.g. rate control) may be considered.	IIb	C	
For patients with AF duration that is clearly <48 h and no thrombo-embolic risk factors, i.v. heparin or weight-adjusted therapeutic dose LMWH may be considered peri-cardioversion, without the need for post-cardioversion oral anticoagulation.	IIb	C	


Recent-onset AF
Conventional route
TOE strategy
AF for cardioversion
AF onset <48 h
Yes
No
Conventional OAC or TOE
3 weeks therapeutic OAC
TOE strategy
Heparin
Heparin
No LAA thrombus
LAA thrombus
Cardioversion
Cardioversion
Opt for rate control if LAA thrombus still present
Therapeutic OAC for 3 weeks
SR
AF
SR
AF
Risk factors
Yes
4 weeks anticoagulation*
No
Consider if long-term OAC indicated†
No long-term OAC
No
Risk factors
Yes
Long-term OAC indicated
*Anticoagulation should normally be continued for 4 weeks after a cardioversion attempt except when AF is recent onset and no risk factors are present.
†Long-term OAC if stroke risk factors and/or risk of AF recurrence/presence of thrombus.