Why does atrial fibrillation occur?

Electrical signals misfire

↓

Contractions of the atria (upper chambers of the heart) are irregular and the heart beats are often too fast or too slow

↓

Blood pools in the atria because there is stasis of blood; not all of the blood is pumped to the ventricles (lower chambers of the heart)

↓

The heart cannot pump effectively

1. Atrial Fibrillation Fact Sheet, National Heart Blood and Lung Institute Diseases and Conditions Index, October 2009. Last viewed June 2010 at http://www.nhlbi.nih.gov/health/dci/Diseases/af/af_what.html; **2.** Atrial Fibrillation Factsheet, Patient UK, March 2008. Last viewed June 2010 at http://www.patient.co.uk/health/Atrial-Fibrillation.htm

What causes atrial fibrillation?

- **Whilst some cases of atrial fibrillation have no known cause, conditions and lifestyle factors known to lead to atrial fibrillation include:[1,2]**
  - **Age**
  - **High blood pressure**
  - **Diabetes mellitus**
  - **Having an overactive thyroid gland**
  - **Heart failure**
  - **Drinking too much alcohol or binge drinking**
- **Atrial fibrillation is more common in people who have heart disease or heart-related conditions like heart failure[2,3]**

1. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, *et al*. *Circulation* 2004; 110:1042-6; **2.** http://www.nhlbi.nih.gov/health/dci/Diseases/af/af_what.html; **3.** http://www.patient.co.uk/health/Atrial-Fibrillation.htm.

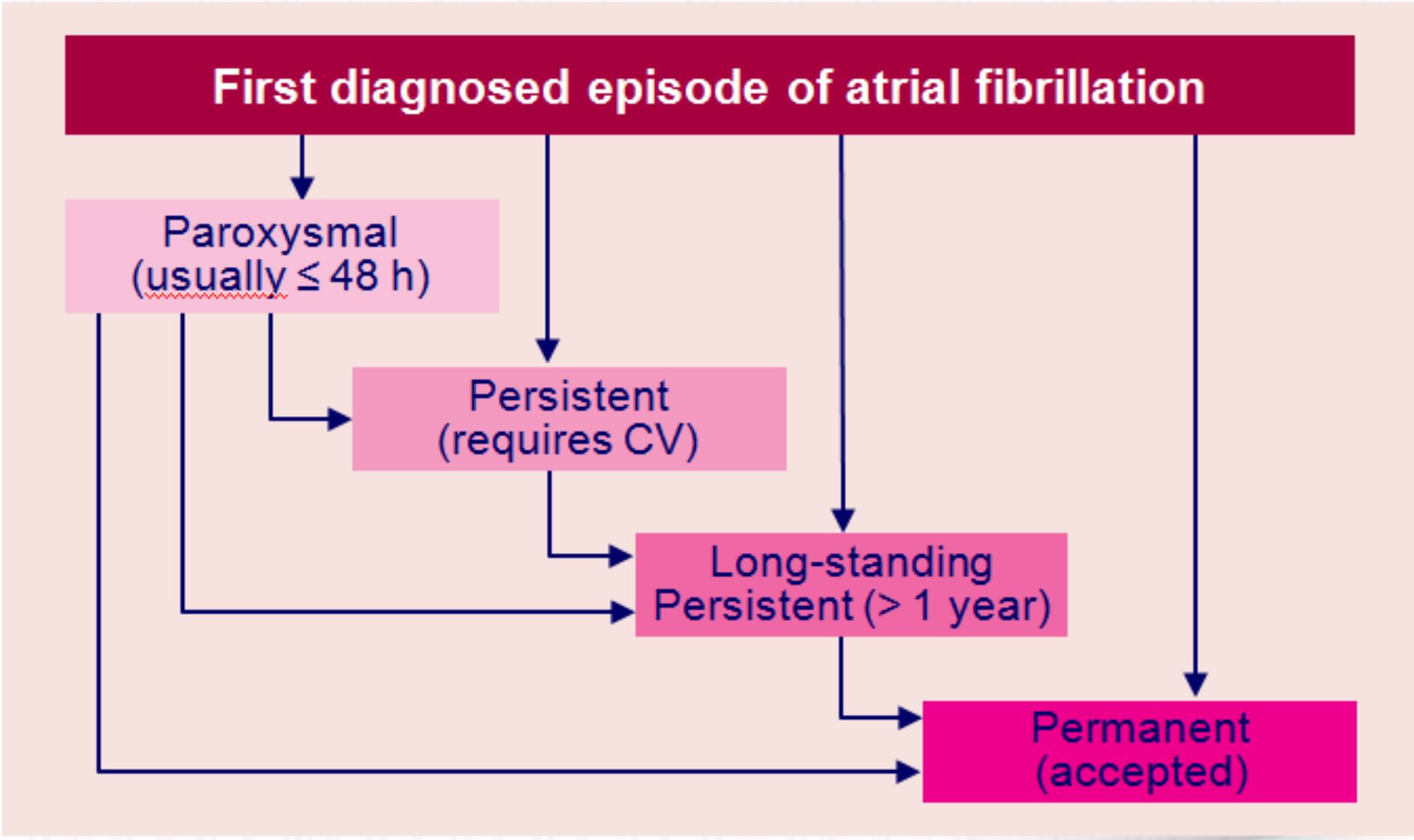
Conditions predisposing to, or encouraging progression of AF

- Hypertension
- Symptomatic heart failure (NYHA II - IV) including tachycardiomyopathy
- Valvular heart disease
- Cardiomyopathies including primary electrical cardiac disease
- Atrial septal defect and other congenital heart defects
- Coronary artery disease
- Thyroid dysfunction and possibly subclinical thyroid dysfunction
- Obesity
- Diabetes mellitus
- Chronic obstructive pulmonary disease (COPD) and sleep apnoea
- Chronic renal disease

Clinical Events (outcomes) affected by AF

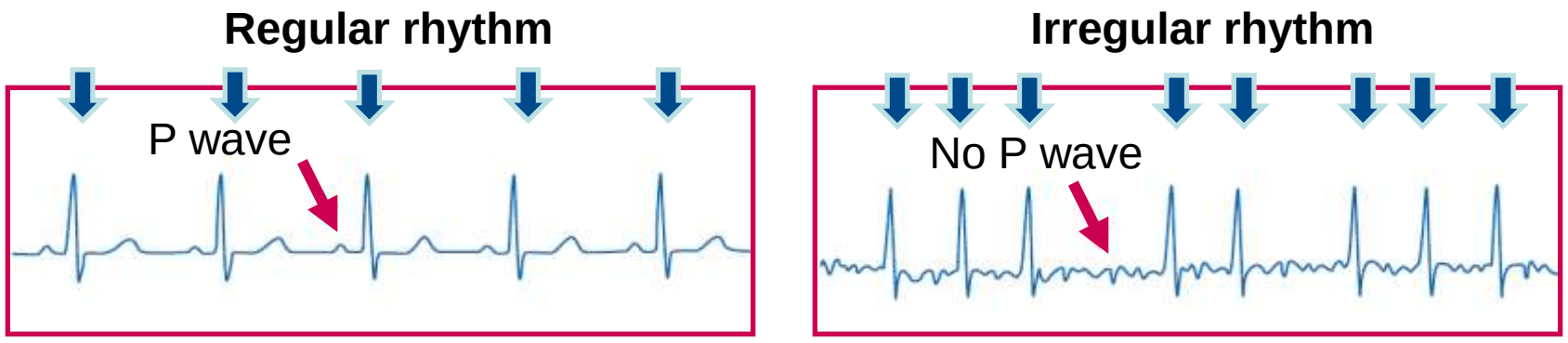
Outcome parameter	Relative change in AF patients
1. Death	Death rate doubled.
2. Stroke (includes haemorrhagic stroke and cerebral bleeds)	Stroke risk increased; AF is associated with more severe stroke
3. Hospitalisations	Hospitalisations are frequent in AF patients and may contribute to reduced quality of life.
4. Quality of life and exercice capacity	Wide variation from no effect to major reduction. AF can cause market distress trhough palpitations and other AF-related symptoms
5. Left ventricular function	Wide variation from no change to tachycardio-myopathy with acute heart failure.

Types of Atrial Fibrillation

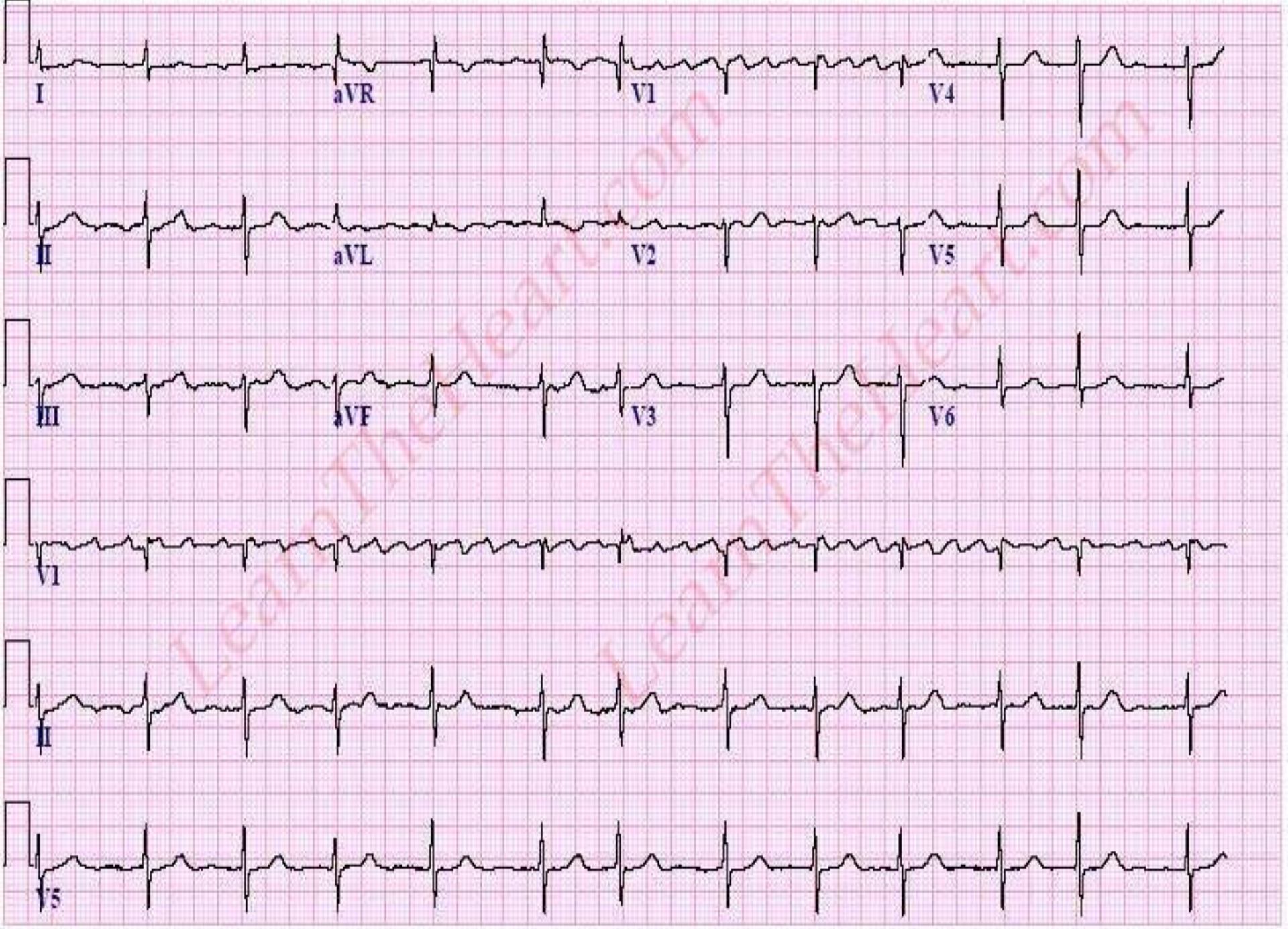


What are the symptoms of atrial fibrillation?

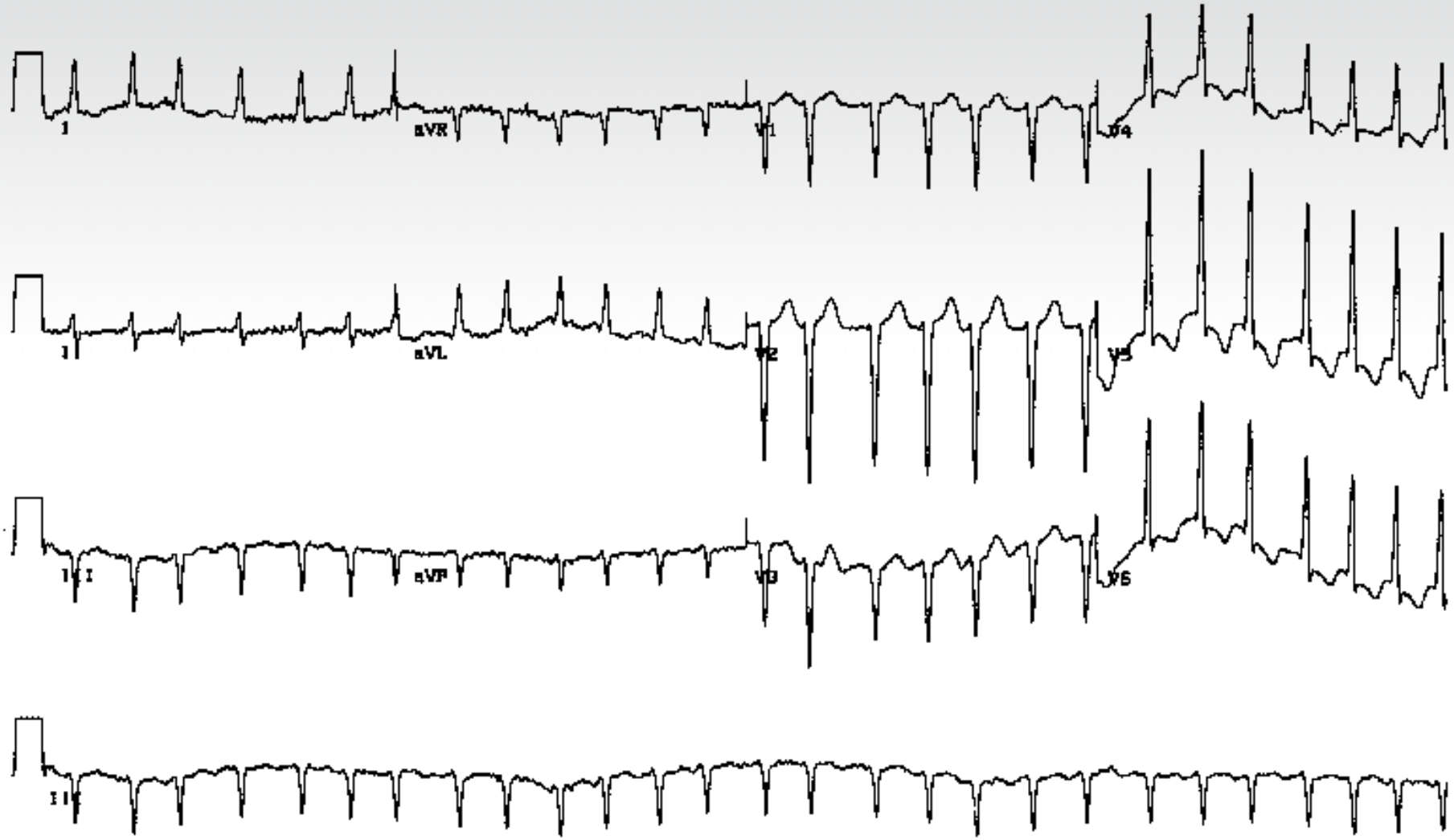
- **Symptoms may be experienced on a regular basis, intermittently or not at all:[1,2]**
  - **Fatigue, palpitations, dizziness, chest pains and breathlessness**
- **Many people with atrial fibrillation lack any symptoms:[1-3]**
  - **More than half of episodes of atrial fibrillation are not felt by the patient**
- **Atrial fibrillation if present can be diagnosed using an electrocardiogram[4]**



1. http://www.nhlbi.nih.gov/health/dci/Diseases/af/af_what.html; **2.** http://www.patient.co.uk/health/Atrial-Fibrillation.htm; **3.** PAFAC and SOPAT trials **4.**Ashley EA & Niebauer J. Cardiology explained. *Remedica*: London 2004.


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5
25mm/s 10mm/mV 150Hz 005C 12SL 250 CID: 1
EID:607 EDT: 14:06 17-NOV-2001 ORDER:

Atrial Fibrillation with Rapid Ventricular Response



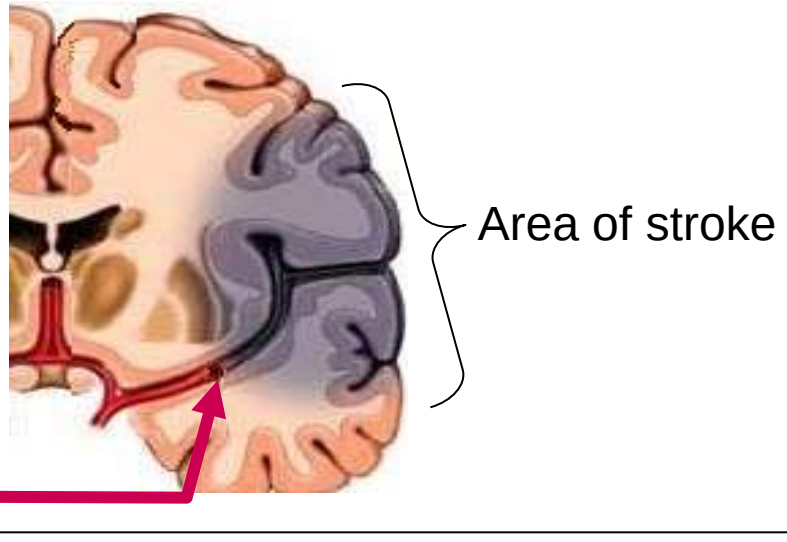
EHRA score of AF-related symptoms

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

AF = atrial fibrillation; EHRA = European Heart Rhythm Association

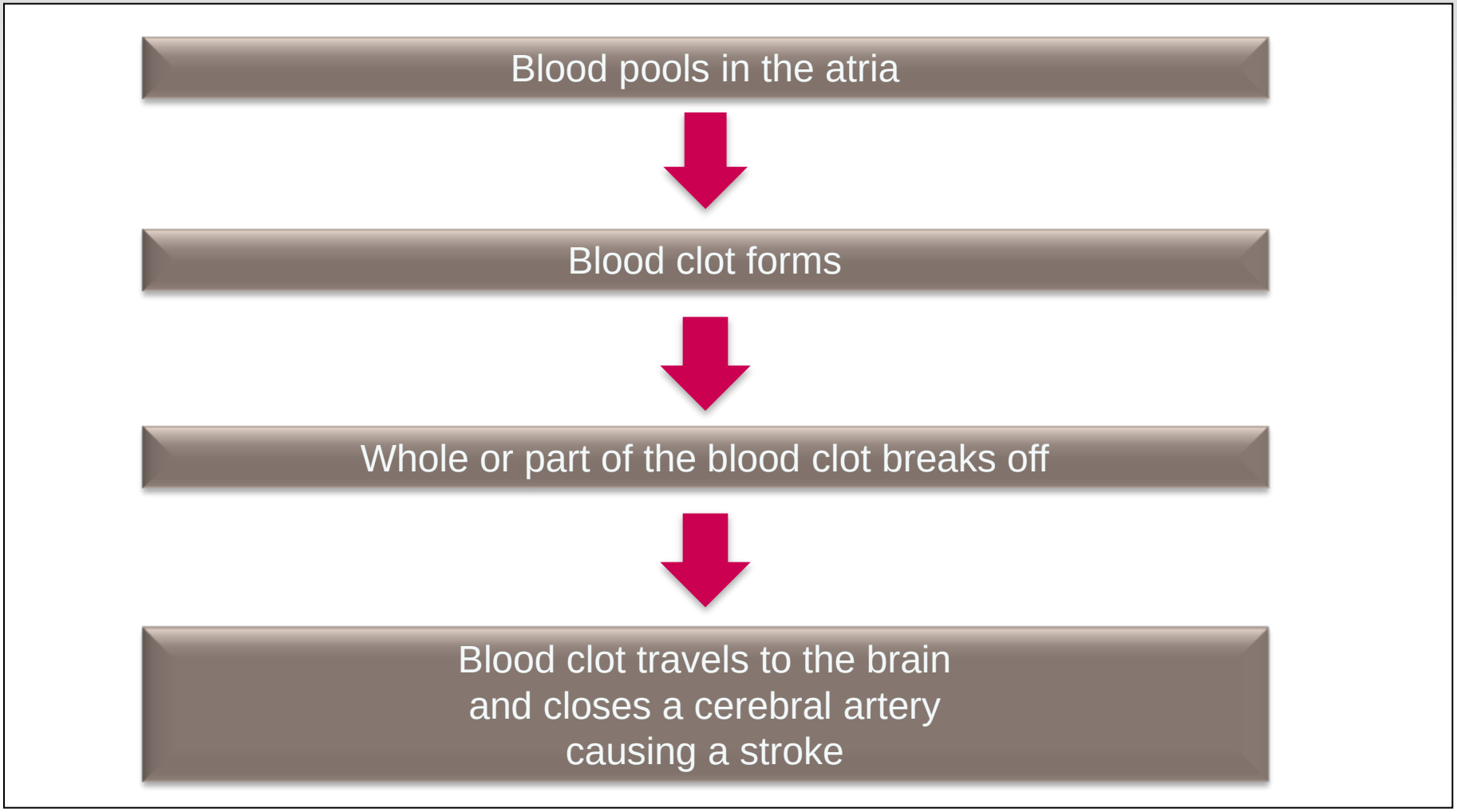
What is a stroke?

- A stroke is the brain equivalent of a heart attack (i.e. a myocardial infarction). Blood must flow to and through the brain for it to work properly
- If this flow is blocked by a blood clot, the brain loses its energy and oxygen supply, causing brain damage that can lead to disability or death[1]



1. World Health Organization, Atlas of Heart Disease and Stroke, http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf.

How does atrial fibrillation lead to stroke?



1. Atlas of Heart Disease and Stroke, World Health Organization, September 2004. Last viewed June 2010 at http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf

What is the link between atrial fibrillation and stroke?

- **People with atrial fibrillation are five times more likely to have a stroke:[1]**
  - **20-30% of strokes are related to atrial fibrillation[2]**

Up to three million people worldwide have an atrial fibrillation-related stroke every year – that is one person every 12 seconds![3-5]

1. Fuster V, Rydén LE, Cannom DS, *et al*. *Circulation* 2006; 114:700-52; **2.** The Copenhagen Stroke Study. Jørgensen HS, Nakayama H, Reith J, et al. *Stroke.* 1996;27:1765-1769; **3.** Wolf PA, Abbott RD, Kannel WB. *Stroke* 1991; 22(8):983-8; **4.** Lin HJ, Wolf PA, Kelly-Hayes M, *et al. Stroke* 1996; 27:1760-4; **5**. Atlas of Heart Disease and Stroke, World Health Organization, September 2004. Viewed July 2009 at ttp://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf.

Risk factors for stroke and thrombo-embolism in non-valvular AF

Major risk factors
Previous stroke
TIA or systemic embolism
Age ≥ 75 years

Clinically relevant non-major risk factors
CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ≤ 40%]
Hypertension
Diabetes mellitus
Age 65-74 years
Female sex
Vascular disease

AF= atrial fibrillation; EF = ejection fraction (as documented by echocardiography, radionuclide ventriculography, card catheterization, cardiac magnetic resonance imaging, etc.); LV = left ventricular; TIA = transient ischaemic attack.

Asymptomatic atrial fibrillation

WWU Münster

- **Asymptomatic atrial fibrillation is a substantial problem for invidual health and for the health care system:**
  - **it may cause stroke**
  - **it is frequent despite antiarrhythmic drug therapy or catheter or surgical ablation**
  - **(it may cause cognitive dysfunction and dementia)**

How do you measure the risk of stroke?

- **$CHADS_2$-Score: a simple index that is widely used to assess the risk of stroke of a patient with atrial fibrillation. It can be used to guide antithrombotic therapy**
  - **Congestive heart failure history - 1 point**
  - **Hypertension history - 1 point**
  - **Age ≥ 75 years -1 point**
  - **Diabetes mellitus history -1 point**
  - **Stroke or TIA history - 2 points**
- **The higher your $CHADS_2$-Score, the higher your risk of having a stroke**
- **This score has been expanded in 2010 by additional factors: female gender, age between 65 and 74 years, presence of vascular disease: CHA2DS2VASc**

1. Fuster V, Rydén LE, Cannom DS, *et al*. *Circulation* 2006; 114:700-52.

Risk factor-based point-based scoring system - CHA_2DS_2-VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 ans	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65-74	1
Sex category [i.e. femal sex]	1
Maximum score	**9**

***Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.**

Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n = 7329)	Adjusted stroke rate (%/y)
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%

Predictors of Thromboembolic Risk in Atrial Fibrillation

- Previous Stroke or TIA - 2.5
- History of HTN - 1.6
- CHF - 1.4
- Advanced Age >65 yrs (cont. per decade) - 1.4
- DM - 1.7
- CAD - 1.5

Atrial Fibrillation Investigators. Arch Intern Med. 1994;154:1449-1457.

The HAS-BLED bleeding risk score

Letter	Clinical characteristic*	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

***Hypertension is defined as systolic blood pressure > 160 mmHg.**

INR = international normalized ratio.

General Management of the AF Patient

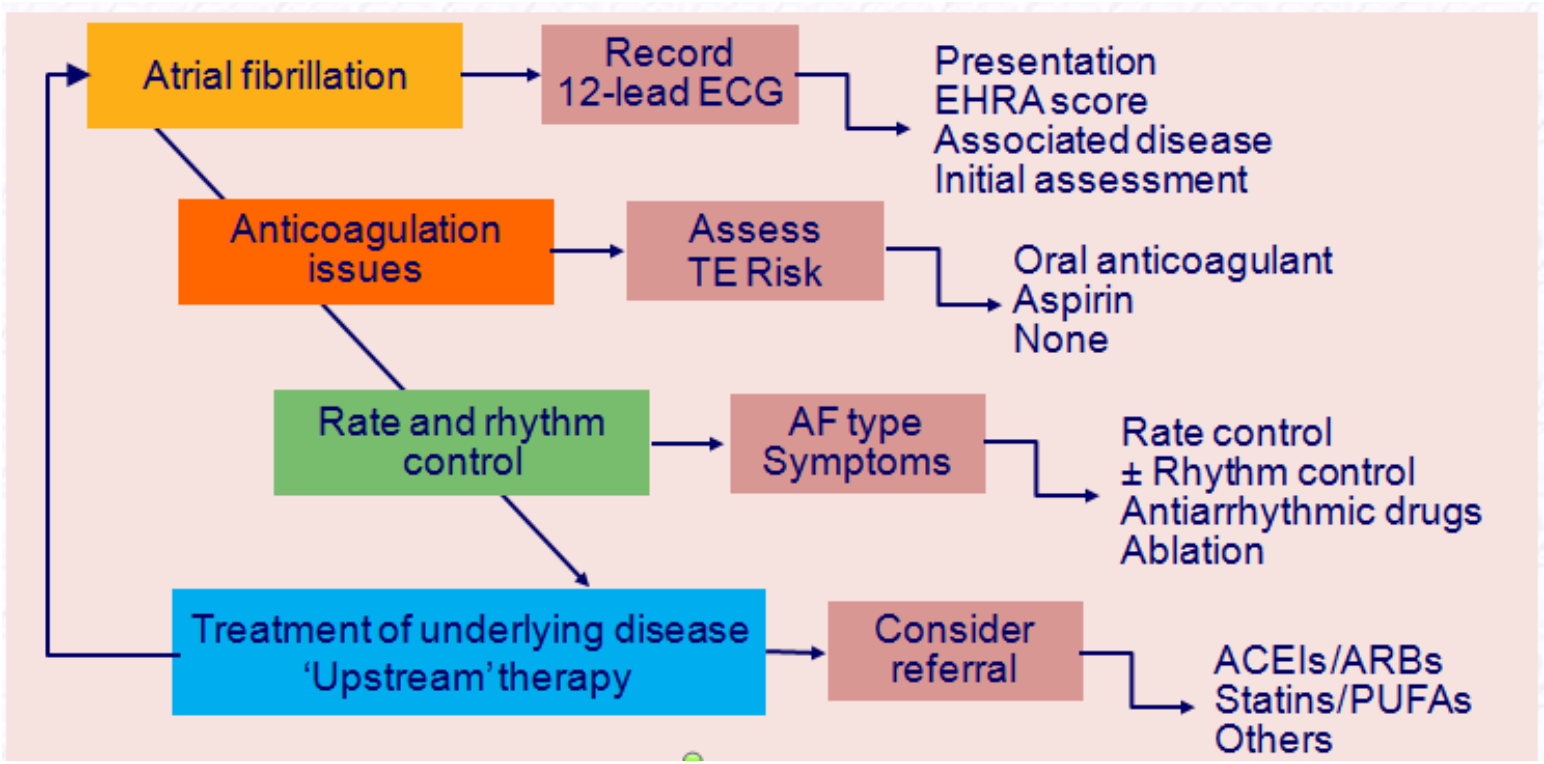
Clinical management of patients with AF involves the following five objectives:

1. Prevention of thromboembolism
2. Optimal management of concomitant cardiovascular disease
3. Symptom relief
4. Rate control
5. Correction of the rhythm disturbance

How is atrial fibrillation treated?

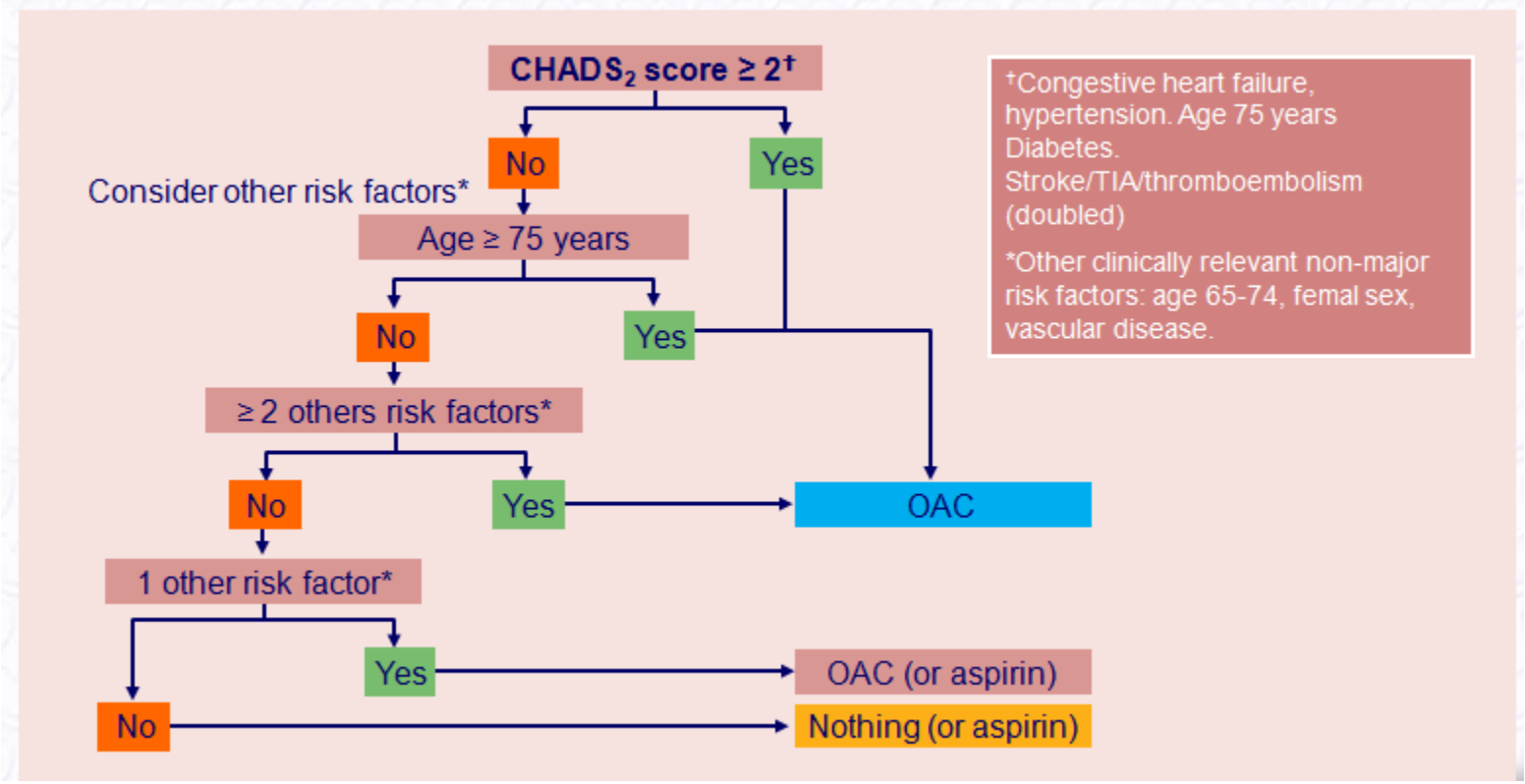
- **Antithrombotic therapy:**
  - Antiplatelet and anticoagulant medications (blood thinning therapies)
- **Rate control:**
  - Achieving ‘normal’ heart rates
- **Rhythm control may be attempted in selected patients:**
  - Cardioversion: using electricity
  - Cardioversion: using antiarrhythmic drugs
  - Catheter or surgical ablation(s)
- **Major issues at present:**
  - Early management by rhythm control therapy?
  - Antiarrhythmic drugs versus catheter ablation?
  - Better prevention of stroke by novel drugs: health care costs, benefits?

The management cascade for patients with AF



ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; PUFA = polyunsaturated fatty acid; TE = thrombo-embolism.

Use of oral anticoagulation for stroke prevention in AF



AF = atrial fibrillation; OAC = oral anticoagulant; TIA = transient ischaemic attack.

Approach to thromboprophylaxis in AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors	≥ 2	OAC
One 'clinically relevant non-major' risk factor	1	Either OAC 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.

AF = atrial fibrillation; CHA_2DS_2-VASc = cardiac failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female); INR = international normalized ratio; OAC = oral anticoagulation, such as a vitamin K antagonist (VKA) adjusted to an intensity range of INR 2.0–3.0 (target 2.5).

Why is stroke prevention in atrial fibrillation sub-optimally managed?

- **Only half of diagnosed patients with atrial fibrillation at risk of stroke receive anticoagulation therapy:[1-4*]**
  - **Vitamin K antagonists (VKAs) are highly effective when a patient's blood clotting value is maintained within the narrow therapeutic INR range of 2.0-3.0**
  - **Fewer than half of patients on VKAs are controlled within this narrow therapeutic range**
  - **Patients with a very high risk of stroke (e.g. elderly patients with co-morbidities) are withheld oral anticoagulation due to fear of the risk of bleeding**

* e.g. warfarin, a vitamine K antagonist

1. Dulli DA et al. *Neuroepidemiology* 2003;22:118–23; **2.** Hylek EM, DAntonio J, Evans-Molina C, *et al*. *Stroke* 2006; 37:1075-80; **3.** Hart GR, *et al. Ann Intern Med.* 2007; 146:857-867; **4.** Samsa GP, Matchar DB, Goldstein LB, *et al. Arch Intern Med 2000;160:967-7.*

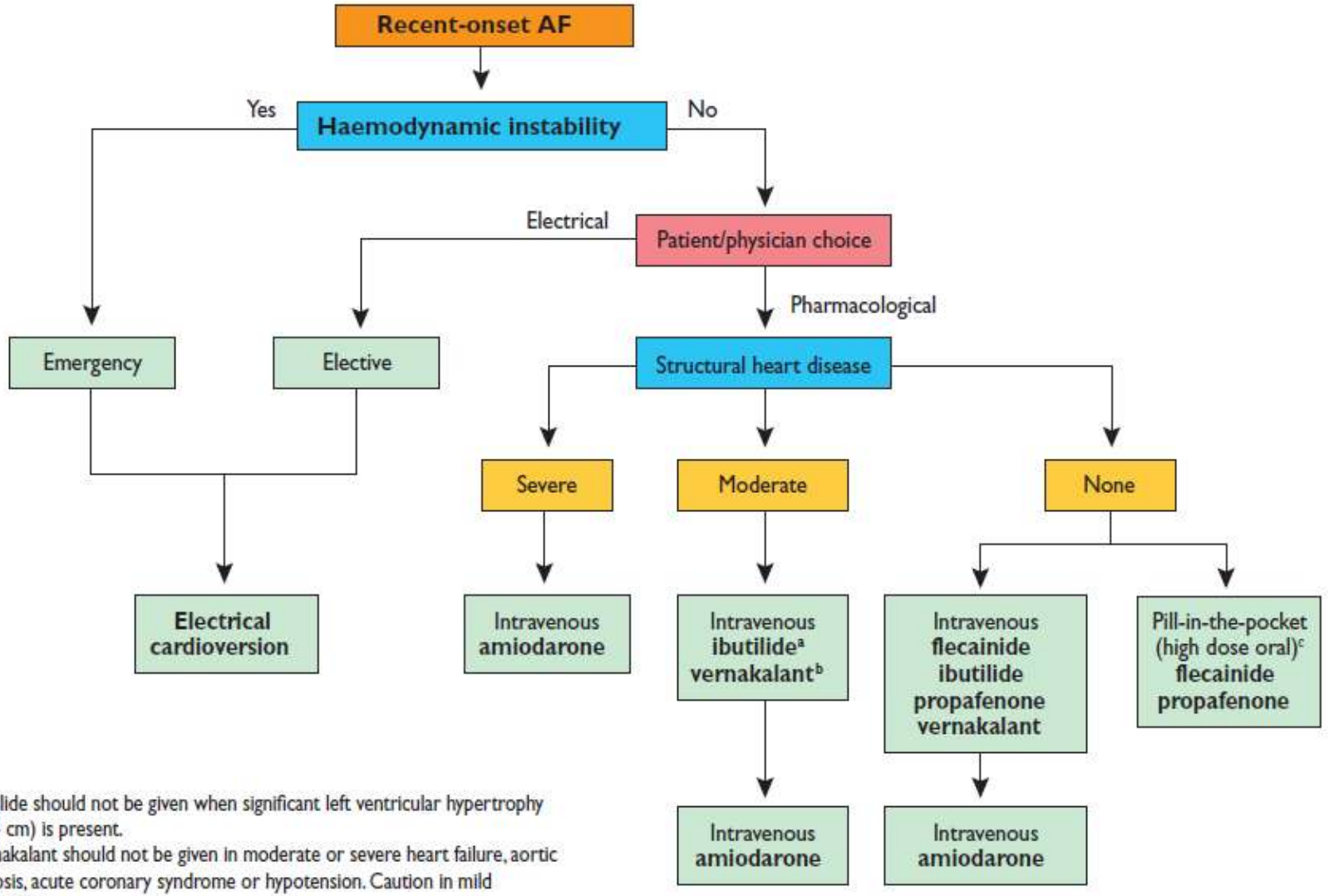
Acute rate control in AF

Recommendations	Class[a]	Level[b]
In the acute setting in the absence of pre-excitation, i.v. administration of β-blockers or non-dihydropyridine calcium channel antagonists is recommended to slow the ventricular response to AF, exercising caution in patients with hypotension or heart failure.	I	A
In the acute setting, i.v. administration of digitalis or amiodarone is recommended to control the heart rate in patients with AF and concomitant heart failure, or in the setting of hypotension.	I	B
In pre-excitation, preferred drugs are class 1 antiarrhythmic drugs or amiodarone	I	C
When pre-excited AF is present, β-blockers, non-dihydropyridine calcium channel antagonists, digoxin and adenosine are contraindicated.	III	C

Recommendations	Class[a]	Level[b]	Ref[c]
Recommendations for prevention of thromboembolism in non-valvular AF—general			
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications.	I	A	21, 63, 104, 105, 106
The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.	I	A	21, 63, 105
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A	25, 36 ,39
In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B	21, 36, 82
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended, unless contraindicated.	I	A	3, 4, 70, 82
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] …. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A	33, 44
Female patients who are aged <65 and have lone AF (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered.	IIa	B	33, 44
When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily.	IIa	B	21, 26, 51, 109

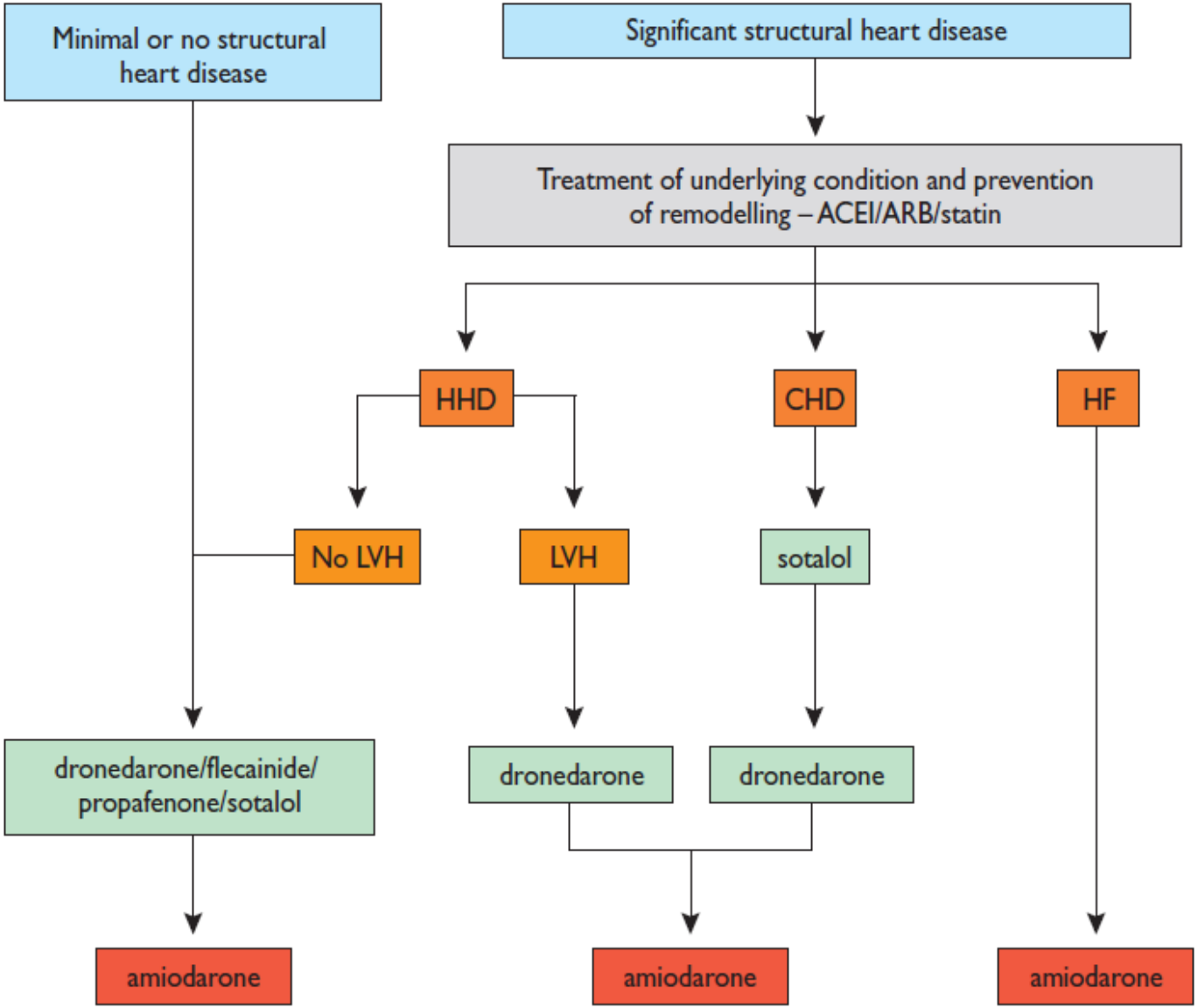
Recommendations for prevention of thromboembolism in non-valvular AF—NOACs			
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended.	I	B	2, 28, 65, 107
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A	3, 4, 70, 82
Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in: • elderly patients, age ≥ 80 • concomitant use of interacting drugs (e.g. verapamil) • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	B	85, 96
Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in: • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	C	3, 108
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.	IIa	B	85
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III	A	3, 24, 70

Recommendations	Class[a]	Level[b]	Ref[c]
Recommendations for prevention of thromboembolism in non-valvular AF—bleeding			
Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin).	I	A	25, 54, 59, 60
The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A). Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B). Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not be used on its own to exclude patients from OAC therapy (LoE = B).	IIa	A B	25, 54, 60
The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC.	IIa	B	18, 21, 23, 24, 26, 35
Recommendations for prevention of thromboembolism in non-valvular AF—peri-cardioversion			
For patients with AF of ≥48 h duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2-3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological).	I	B	93
In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.	I	B	110



[a]Ibutilide should not be given when significant left ventricular hypertrophy (≥1.4 cm) is present.
[b]Vernakalant should not be given in moderate or severe heart failure, aortic stenosis, acute coronary syndrome or hypotension. Caution in mild heart failure.
[c]'Pill-in-the-pocket' technique – preliminary assessment in a medically safe environment and then used by the patient in the ambulatory setting.

Figure 3 Indications for electrical and pharmacological cardioversion, and choice of antiarrhythmic drugs for pharmacological cardioversion in patients with recent-onset AF.



ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; HHD = hypertensive heart disease; CHD = coronary heart disease; HF = heart failure; LVH = left ventricular hypertrophy, NYHA = New York Heart Association. Antiarrhythmic agents are listed in alphabetical order within each treatment box.

Figure 4 Choice of antiarrhythmic drug according to underlying pathology.

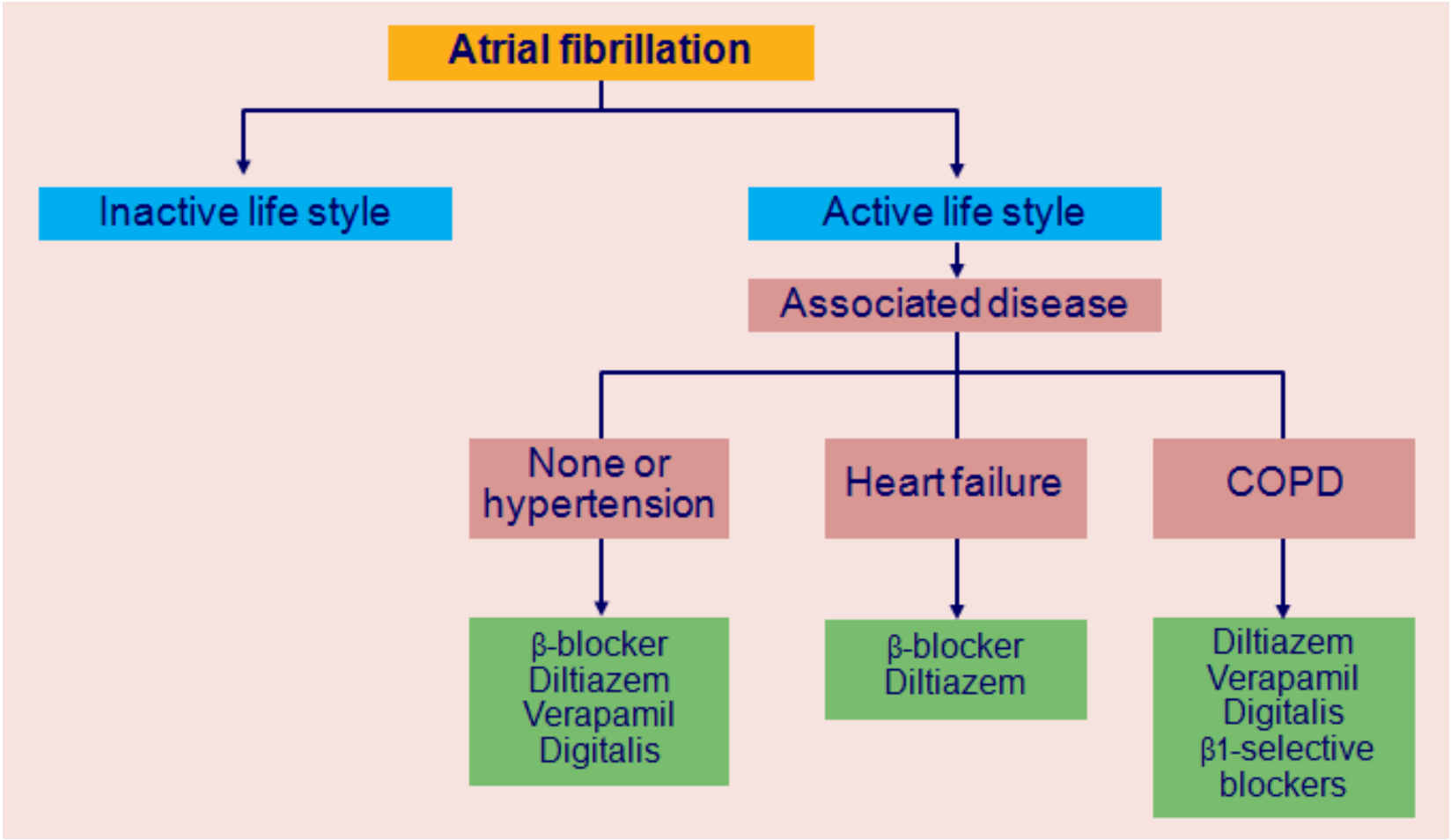
Drugs and doses for pharmacological conversion of (recent-onset) AF

Drug	Dose	Follow-up dose	Risks
Amiodarone	5 mg/kg i.v. over 1 h	50 mg/h	Phlebitis, hypotention. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm.
Flecainide	2 mg/kg i.v. over 10 min, or 200-300 mg p.o.	N/A	Not suitable for patients with market structural heart disease; may prolong QRS duration, and hence the QT interval; and may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.
Ibutilide	1 mg i.v. over 10 min	1 mg i.v. over 10 min after waiting for 10 min	Can cause prolongation of the QT interval and torsades de pointes; watch for abnormal T-U waves or QT prolongation. Will slow the ventricular rate.
Propafenone	2 mg/kg i.v. over 10 min, or 450-600 mg p.o.		Not suitable for patients with market structural heart disease; may prolong QRS duration; will slightly slow the ventricular rate, but may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1;1 conduction to the ventricules.
Vernakalant	3 mg/kg i.v. over 10 min	Second infusion of 2 mg/kg i.v. over 10 min after 15 min rest	So far only evaluated in clinical trials; recently approved.

Pharmacological cardioversion of AF

Recommendations	Class[a]	Level[b]
When pharmacological cardioversion is preferred and there is no structural heart disease, i.v. fleainide or propafenone is recommended for cardioversion of recent-onset AF.	I	A
In patients with recent-onset AF and structural heart disease, i.v. amiodarone is recommended.	I	A
In selected patients with recent-onset AF and no significant structural heart disease, a single high oral dose of flecainide or propafenone (the 'pill-in-the-pocket' approach) should be considered, provided this treatment has proven safe during previous testing in a medically secure environment.	IIa	B
In patients with recent-onset AF, structural heart disease, but without hypotension or manifest congestive heart failure, ibutilide may be considered. Serum electrolytes and the QTc interval must be within the normal range, and the patients must be closely monitored during and for 4 h after the infusion because of risk of proarrhythmia.	IIb	A
Digoxin (LoE A), verapamil, sotalol, metoprolol (LoE B), ajmaline and other β-blocking agents (LoE C) are ineffective in converting recent-onset AF to sinus rhythm and are not recommended.	III	A B C

Rate control of atrial fibrillation



	Intravenous administration	Usual oral maintenance dose
β-Blockers		
Metoprolol CR/XL	2.5–5 mg iv bolus over 2 min; up to 3 doses	100–200 mg o.d. (ER)
Bisoprolol	N/A	2.5–10 mg o.d.
Atenolol	N/A	25–100 mg o.d.
Esmolol	50–200 μg/kg/min iv	N/A
Propranolol	0.15 mg/kg iv over 1 min	10–40 mg t.i.d.
Carvedilol	N/A	3.125–25 mg b.i.d.
Non-dihydropyridine calcium channel antagonists		
Verapamil	0.0375–0.15 mg/kg iv over 2 min	40 mg b.i.d. to 360 mg (ER) o.d.
Diltiazem	N/A	60 mg t.i.d. to 360 mg (ER) o.d.
Digitalis glycosides		
Digoxin	0.5–1 mg	0.125 mg–0.5 mg o.d.
Digitoxin	0.4–0.6 mg	0.05 mg–0.1 mg o.d.
Others		
Amiodarone	5 mg/kg in 1 h, and 50 mg/h maintenance	100 mg–200 mg o.d.
Dronedarone[a]	N/A	400 mg b.i.d.

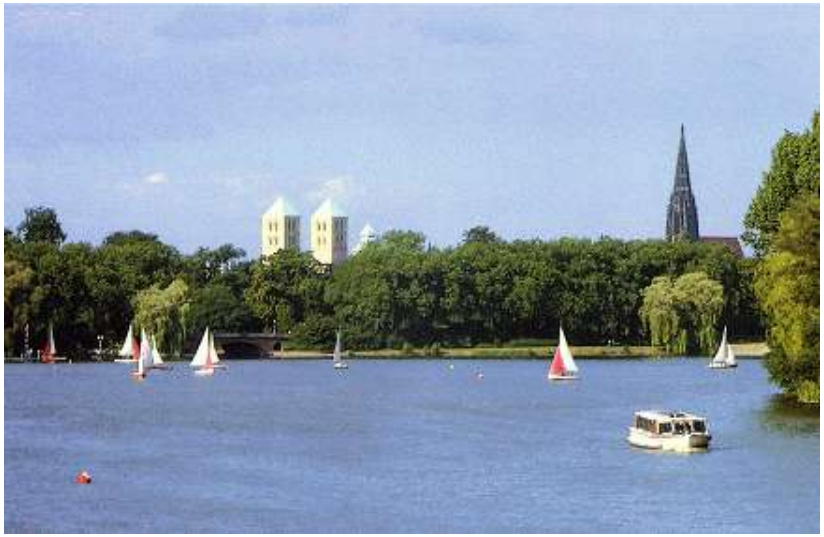
Drugs for rate control

Why is awareness of atrial fibrillation low?

- **Many people are unaware of the increased risk and potential life changing consequences of having an atrial fibrillation-related stroke, many of which can be prevented:[1]**
  - **In the AF AWARE international survey, 46% of physicians agreed that their patients would not be able to explain atrial fibrillation**
  - **A quarter of physicians thought atrial fibrillation was too complex to explain during a clinic visit or that they did not have enough time**

There is a need for increased awareness and understanding

1. http://www.world-heart-federation.org/fileadmin/user_upload/images/AF-Aware/AF%20AWARE%20booklet%20v11.pdf.



Thank you very much for your attention

Thank you