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Clinical Seminar: The Future of atrial fibrillation management. Integrated care and stratified therapy

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Abstract

Atrial fibrillation is one of the major cardiovascular health problems: It is a common, chronic condition, affecting 2-3% of the populations in Europe and the USA and requiring 1-3% of health care expenditure due to stroke, sudden death, heart failure, unplanned hospitalizations, and other complications. Early diagnosis of AF, ideally before the first complication occurs, remains a challenge, illustrated by patients who are only diagnosed with AF when hospitalized for acute cardiac decompensation or stroke. Once diagnosed, AF requires chronic, multidimensional management in five domains (acute management, treatment of underlying and concomitant cardiovascular conditions, stroke prevention therapy, rate control, and rhythm control). Providing these treatment options consistently to all AF patients remains challenging, despite recent improvements. Integrated care models providing patient-centred care in or close to the community while maintaining access to all specialist treatment options emerge as the best approach to achieve consistent delivery of these chronic treatments to all AF patients in need of better management. Ongoing research efforts will determine when to initiate oral anticoagulation in patients with device-detected atrial high rate episodes, quantify the prognostic impact of early and comprehensive rhythm control therapy including AF ablation, and delineate optimal methods to reduce bleeding complications in anticoagulated AF patients. In addition, research efforts are needed to define different types of AF based on the main causes of AF in a given patient to pave the way for the clinical development of stratified AF therapy.

The atrial fibrillation epidemic. Atrial fibrillation (AF) affects 2-3% of the populations in Europe [1-3], and more than 1% of the entire health care expenditure is spent on AF management. [4,5] Less than one in 200 persons below 50 years of age, but more than one in ten in populations aged 80 or above suffer from AF. [1-3] Thirteen to 21 percent of the populations in Europe are aged 65 years or older today (http://data.org/search.aspx?q=age), and we enjoy ever longer lives. The projected population ageing, combined with an accumulation of chronic non-communicable cardiovascular diseases and risk factors [6], will lead to a dramatic increase of AF patients in the coming years. This AF epidemic and the severe complications associated with AF (Table 1A) render atrial fibrillation one of the major threats to cardiovascular health. [7]

Table 1A: ***Common symptoms and complications of atrial fibrillation.*** *Silent AF that does not cause symptoms but still leads to complications is not uncommon. Treatment can prevent many, but not all AF-related complications. Most symptoms and consequences of AF are interrelated and thus complications and symptoms can link across lines in this table.*

Symptoms of AF	Related complication of AF	Treatment to prevent symptoms and complications
-	Stroke	Treatment of underlying conditions, oral anticoagulation, possibly left atrial appendage occluders
Fatigue or tiredness	Depression, reduced quality of life	? (possibly rhythm control)
Shortness of Breath	Impaired autonomy, worsening of cardiac function, unplanned hospitalizations	ACE inhibitors, rate control, possibly rhythm control
Palpitations	Tachycardiomyopathy, reduced autonomy	Rate control, rhythm control, possibly anticoagulation
Chest pain	Acute coronary syndrome, unplanned hospitalizations	Treatment of underlying conditions, possibly anticoagulation
Depressed mood, anxiety	Frequent hospitalizations, Impaired cognitive function	Possibly rate control and rhythm control Possibly oral anticoagulation

Table 1B: ***The modified EHRA symptoms scale (mEHRA scale)*** *to describe severity of AF-related symptoms in a semi-quantitative fashion. Modified from Wynn et al[8] and recommended for use by the European Society of Cardiology.* [2]

mEHRA scale	Symptoms	Description
1	None	AF does not cause any symptoms (includes silent AF)
2a	Mild	Normal daily activity not affected by symptoms related to AF[a]
2b	Moderate	Normal daily activity not affected, but patient troubled by symptoms[a]
3	Severe	Normal daily activity affected by AF

4	Disabling	Normal daily activity discontinued due to AF

AF = atrial fibrillation; EHRA = European Heart Rhythm Association.

Clinical presentation and AF-related symptoms. AF is a common cause of ischemic stroke. [2] In AF patients on oral anticoagulation, stroke is relatively infrequent (1.5% per year in trials) [9,10], but worsening of heart failure and sudden death remain common even in adequately treated AF patients. [11,12] Common symptoms in AF patients are fatigue or shortness of breath, as well as palpitations [13-18], but also anxiety [19] and a depressed mood. [20-23] These symptoms may be especially pronounced during the initial presentation. Furthermore, stroke, heart failure, or even sudden death can constitute the initial presentation of AF patients. Sudden death can be a consequence of underlying cardiac diseases, e.g. inherited cardiomyopathies [24,25] or heart failure [26] , but may also be a consequence of the irregular ventricular activation pattern in AF. Every 4th to 5th AF patient is admitted to hospital in a year. [14,16,27,28] Hospitalizations are most commonly triggered by symptomatic AF, but also reflect that AF patients often suffer other cardiovascular conditions that require in-patient therapy.

Importantly, many patients do not experience any AF-related symptoms ("silent AF"), and a stroke may be the first presentation of AF. [29,30] Silent AF is common: When systematic ECG monitoring is applied to patients with symptomatic AF, around 70% of AF episodes are silent. [31] Patients with silent AF are still at risk of stroke, heart failure or sudden death, illustrating the public health importance of detecting silent AF. [32,33]

ECG screening in populations to diagnose silent AF. Unfortunately, AF is often not diagnosed before the first stroke: Approximately 5% of unselected patients admitted to stroke units present with overt (usually chronic) AF on admission. [29] Detecting AF prior to the first stroke should therefore be a public and individual health priority. "Opportunistic" screening for AF, i.e. pulse palpation followed by ECG in those with an irregular pulse [35], is recommended by AF guidelines in all patients aged 65 or more. [2,36] Initial experience with systematic ECG screening in elderly populations using patient-operated devices seems promising [32,37], but more research is needed before population-wide ECG screening can be recommended.

ECG screening in stroke survivors. ECG screening for silent AF has been extensively evaluated in survivors of a stroke or transient ischemic attack. ECG monitoring for a few days identifies silent AF in an additional 5% of unselected patients admitted to stroke units. [29,38] Longer ECG monitoring identifies even more patients with AF (5 – 25% additional yield) [29,30,39], especially in patients with "cryptogenic stroke" [38,40,41] or "embolic stroke of unknown source" (ESUS). [42] ECG monitoring for at least 72 hours is recommended in stroke survivors and in at-risk populations. [2] Recently, one of the first randomized studies confirmed that longer ECG monitoring results in a higher detection rate of AF in stroke survivors (13.5% vs. 4.5%). [43] Ongoing studies evaluate the effect of ECG screening in stroke survivors on uptake of anticoagulation and prevention of strokes. [44] Based on the high prevalence of silent AF, ongoing trials evaluate whether oral anticoagulation should be used in all patients with an embolic stroke of unknown etiology, irrespective of heart rhythm. [45,46]

Management of patients with AF detected by ECG screening. Detection of silent AF has immediate consequences for antithrombotic therapy: Most patients with incidentally diagnosed AF, or with AF detected by systematic ECG screening, will have stroke risk factors that render them eligible for oral anticoagulation. [2,32,35] Patients with silent AF should also be investigated for concomitant cardiovascular conditions that require therapy. [2] Rhythm control therapy is not required in patients

with silent AF, unless they develop AF symptoms. Periodic reassessment for symptoms and complications of AF is advisable.

Management of patients with atrial high episodes detected by implanted devices. Importantly, all AF therapies have been evaluated in patients with ECG-documented AF. Thus, atrial arrhythmias detected by other methods, e.g. an irregular pulse detected by blood pressure machines or by an optical device, or atrial high rate episodes (AHRE) detected by a pacemaker, require verification of AF by ECG before initiating AF therapy. [2] Importantly, not all atrial AHRE detected by implanted devices are AF. [47,48] Furthermore, there is good data to show that the stroke risk is lower in patients with AHRE, but without ECG-documented AF, than in patients with AF. Consequently, we cannot know whether patients with AHRE benefit from oral anticoagulation. Ongoing controlled trials such as ARTESiA (NCT01938248) and NOAH – AFNET 6 (NCT02618577) currently evaluate the benefit and risk of oral anticoagulation in patients with atrial high rate episodes.

The five domains of atrial fibrillation management.

Atrial fibrillation requires attention to five domains of management, where each treatment component targets different components of the heart (Figure 1). These five domains of AF management are: Acute stabilization of patients who present with AF complications or hemodynamic compromise, detection and treatment of underlying and accompanying cardiovascular conditions, stroke risk assessment and in most patients oral anticoagulation for stroke prevention, rate control, and rhythm control therapy in symptomatic patients (Figure 2). Acute stabilization, treatment of concomitant conditions, and stroke prevention carry prognostic benefits. Rate control and rhythm control therapy can help to maintain left ventricular function but are mainly used to improve AF-related symptoms. All domains have the potential to maintain functional integrity of the heart (Figure 1).

Detection and management of concomitant cardiovascular conditions: Hypertension, heart failure, valvular heart disease, diabetes, coronary and other arterial vascular disease, and others

The presence of atrial fibrillation should be taken as a strong suggestion that other cardiovascular conditions are present. To detect such conditions, a careful cardiovascular examination and an echocardiogram should be performed in all AF patients at the time of diagnosis. Comprehensive diagnosis and treatment of cardiovascular risk factors and concomitant diseases [51] should be an integral part of AF management.

Hypertension is common in AF patients. Adequate control of blood pressure reduces stroke risk, bleeding risk on anticoagulation, and probably recurrences of AF. ACE inhibitors and sartans appear to prevent AF slightly better than other hypertensive agents, especially in patients with left ventricular hypertrophy or heart failure, [52,53] but by and large antihypertensive agents can be used as recommended for hypertensive patients in general.

Heart failure and AF often coexist. [54] The management of patients with AF and heart failure requires simultaneous treatment of both AF [2] and heart failure [55], including acute control of rate and urgent cardioversion in hemodynamically compromised patients, diuretic therapy in patients with fluid overload, initiation of anticoagulation, and inhibition of the renin-angiotensin-aldosterone system. [56] Beta blockers can be safely used, but their prognostic benefit seems lost in patients with AF and heart failure. [57] It is often difficult to distinguish symptoms of heart failure from AF symptoms in the

acute setting, especially in patients with preserved or moderately impaired ejection fraction. A careful reconstruction of symptoms and disease signs over time often helps, and occasionally restoration of sinus rhythm is useful to distinguish AF-related symptoms from heart failure.

Valvular heart disease, especially mitral or aortic valve disease, can become more symptomatic when AF develops. New onset AF is regarded as a sign for progressive atrial damage, and is one of the factors that should be considered to determine the best time point for valve surgery. Patients with rheumatic heart disease [2] have not been tested in the NOAC trials programmes. Patients with mechanical heart valves [58] require vitamin K antagonists for oral anticoagulation.

Obesity contributes to recurrent AF, possibly via activation of adipocytes in the atria and/or by fatty infiltration of atrial myocardium. [59,60] Weight reduction and increased general fitness help to prevent AF in obese patients, and can even obviate the need for catheter ablation. [61-63]

Coronary artery disease can be managed with an anticoagulant without further antiplatelet therapy in stable patients. After stenting or an acute coronary syndrome, the added bleeding risk of combined antiplatelet and anticoagulant therapy needs to be balanced against the need to prevent recurrent thrombo-embolic events. Usually, this can be achieved by short-term combination therapy for 1-12 months, currently consisting of an anticoagulant, clopidogrel, and probably aspirin. [2,64-66] Ongoing studies will inform about the safety of other combination therapies with non-vitamin K antagonist oral anticoagulants and newer antiplatelet agents. [67] Most other treatments for coronary artery disease can readily be combined with AF therapy.

Oral anticoagulation for stroke prevention.

The combination of a local prothrombotic milieu in the left atrium, systemic activation of coagulation, blood stasis in the atria, and expression of prothrombotic factors on the atrial endothelium all contribute to clot formation in patients with atrial fibrillation.[68-70] The annual stroke risk in non-anticoagulated AF patients is between <1% and >10%.[69,70] Oral anticoagulation therapy with vitamin K antagonists or non-vitamin K antagonist oral anticoagulants (NOACs) prevents most ischemic strokes in patients with atrial fibrillation at risk for stroke, translating into preserved independence and autonomy for patients, lower morbidity, and longer lives in AF patients at high stroke risk. [9,10] Antiplatelet therapy does not prevent strokes in AF patients. AF patients with two or more clinical stroke risk factors (Table 2A) benefit from oral anticoagulation, especially those at higher age (e.g. > 75 years) and survivors of a stroke, but also those with heart failure, hypertension, diabetes mellitus (especially when requiring insulin therapy), or vascular disease. Conversely, patients at low risk of stroke do not require antithrombotic therapy, i.e. those without clinical stroke risk factors, and some patients with one of the clinical stroke risk factors [2,71].

Oral anticoagulation is not without side effects: Approximately 2% of anticoagulated AF patients experience a major bleeding event per year of exposure to anticoagulants. [72,73] Modifiable bleeding risk factors should therefore be reduced in all anticoagulated AF patients (Table 2B) to minimise bleeding. Many bleedings have a treatable cause, e.g. bleeding due to gastric ulcers or cerebral aneurysms, and such causes should be identified and treated promptly in AF patients in need for anticoagulation. Importantly, most patients with a high bleeding risk are also at high risk of stroke and will benefit from anticoagulation. [2] Recent data suggest that selected biomarkers, e.g. troponin, BNP, or markers of kidney disease, can be used to refine stroke risk estimation in selected patients, although further data are needed to inform their use in routine care. [2,74,75]

Table 2A ***Clinical risk factors for stroke in patients with atrial fibrillation*** *as validated in the CHA_2DS_2-VASc score for stroke risk estimation in patients with atrial fibrillation.*

Clinical stroke risk factor	Definition and explanation
Congestive heart failure	Signs or symptoms of heart failure or evidence of reduced left ventricular ejection fraction
Hypertension	Resting blood pressure > 140/90 mmHg on at least two occasions or current antihypertensive treatment
Increasing age	Stroke risk continuously increases with age. Most stroke risk scores define age strata (e.g. ≥ 65 years or ≥ 75 years) to simplify stroke risk estimation
Diabetes mellitus	Fasting glucose > 125 mg/dL or treatment with hypoglycaemic agents, especially when patients require insulin for diabetes management
Previous stroke, transient ischemic attack, or thromboembolism	A prior stroke or transient ischemic attack, together with older age, is probably the strongest clinical stroke risk factor in patients with atrial fibrillation.
Vascular disease	Previous myocardial infarction, peripheral artery disease, or aortic plaque
Female sex	Female patients with AF appear to have a higher stroke risk than male patients when other risk factors are present. In patients with only one or two of the clinical stroke risk factors, female AF patients do not appear to have an increased stroke risk. [2,71]

CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female).

Table 2B: ***Modifiable bleeding risk factors in anticoagulated AF patients****, their definition, and interventions to minimize these bleeding risk factors. Modifiable bleeding risk factors have been extracted from several validated bleeding risk scores.* [2]

Modifiable bleeding risk factors	Definition, explanation	Proposed intervention
Concomitant therapy with antiplatelet agents or nonsteroidal anti-inflammatory medications	Including over the counter medication and paracetamol. Selected patients, e.g. those requiring stenting or those at risk of a recurrent acute coronary syndrome, require short term combination therapy.	Avoid co-medication, advise patients of risk
Uncontrolled hypertension	Blood pressure > 160/90 mmHg during office measurements, and uncontrolled blood pressure peaks	Treat hypertension adequately
Labile INR values in patients treated with vitamin K antagonists	Most often measured as a low time in therapeutic range	Control INR better (including self-measurement), change to a NOAC
Excess alcohol use	Daily alcohol consumption, consumption of more than 65g – 110g of alcohol per week (8 - 14 units)	Reduce alcohol consumption, provide access to behaviour changing programmes

Several oral anticoagulants are effective and approved for stroke prevention in AF. Four different vitamin K antagonists and four non-vitamin K antagonist oral anticoagulants (NOACs) are available and allow to select an appropriate oral anticoagulant in most patients with AF (Table 3). [2,76] Aspirin does not prevent ischemic stroke in AF patients. Of note, there is a tendency to prescribe lower doses of NOACs than those that were tested and approved in controlled trials, which seems associated with higher complication rates. [73] Oral anticoagulation can often be initiated by adequately trained general practitioners, especially when they form part of a larger network providing integrated AF care, and may be guided by IT tools to ensure appropriate selection of eligible patients for anticoagulation and for a specific dose of an anticoagulant. NOACs therapy is less likely to cause bleeding, especially intracranial hemorrhage, rendering them preferable over vitamin K antagonists in eligible patients. [10] In selected patients with true contraindications to any form of oral anticoagulation, interventional or surgical left atrial appendage occlusion can be considered as an alternative to oral anticoagulation. [77-81] Difficult anticoagulation decisions should be informed by a multidisciplinary AF Heart Team involving anticoagulation specialists, stroke neurologists, and experts in occluder therapy. [2]

Despite the proven benefits of oral anticoagulation in AF patients, many patients with AF at risk for stroke do not receive oral anticoagulation or discontinue oral anticoagulants soon after initiation. [82-88] Major bleeding events, e.g. gastro-intestinal, hypertensive or intracranial bleeds, are one of the major reasons to discontinue oral anticoagulation. [82,84,89-92] A short interruption of anticoagulation is usually required to manage acute bleeding events. [2,76] Once the cause of bleeding has been eliminated (e.g. treatment of a gastric ulcer, clipping or coiling of an arterial malformation, optimization of antihypertensive therapy, see also Table 2B), oral anticoagulation should probably be reinitiated in most AF patients at risk for stroke. [93,94] Information of AF patients about their therapy, leading to patients who “own” and participate in AF management, has the potential to improve this situation. [95-97] To improve continuation of chronic therapy, integrated AF management models should be developed (see below).

***Table 3:* Oral anticoagulants and interventional stroke prevention treatment in AF patients.**

	Dose	Dose reduction
Vitamin K antagonists		
Warfarin	typical dose 1 – 5 mg OD	Individual dose aiming at an international normalized ration (INR) of 2-3
Phenprocoumon	typical dose 0.5 – 3 mg OD	
Fluindione	typical dose 5 – 30 mg OD	
Acecoumarol	typical dose 2 – 4 mg OD	
Non-vitamin K antagonist oral anticoagulants		
Apixaban	5 mg BD	2.5 mg BD in patients fulfilling two of the following criteria: serum creatinine > 1.5 mg/dl, age 80 > 80 years, weight > 60 kg Apixaban has not been tested in patients with a baseline creatinine clearance < 25 ml/min.
Dabigatran	110 mg BD 150 mg BD	In Europe, a dose of 110 mg BD is suggested in patients > 75 years of age* Dabigatran has not been tested in patients with a baseline creatinine clearance < 30 ml/min.
Edoxaban	60 md OD	30 mg OD if creatinine clearance < 50 ml/min Edoxaban has not been tested in patients with a baseline creatinine clearance < 30 ml/min.
Rivaroxaban	20 mg OD	15 mg OD if creatinine clearance is < 50 ml /min Rivaroxaban has not been tested in patients with a baseline creatinine clearance < 30 ml/min.
Left atrial appendage occlusion		
Interventional left atrial appendage occlusion	The interventional procedure carries a risk of complications (tamponade, stroke, vascular access complications). Several post-interventional antithrombotic therapy regimes have been evaluated.	
Surgical occlusion of the left atrial appendage	Surgical atrial occlusion or exclusion does not add much to the risk of cardiac surgery when performed concomitant with open heart surgery. There is a small risk of bleeding and tamponade, and a risk of incomplete occlusion.	

*In the USA, dabigatran is not approved for stroke prevention in AF at the 110 mg BD dose. The FDA has also approved dabigatran 75 mg BD for stroke prevention in AF patients on dialysis.

Rate control therapy. During atrial fibrillation, each part of the atrial myocardium is stimulated at a rate of 300 – 400 activations per minute. The rapid reactivation of atrial myocardium leads to atrial contractile standstill in most patients and results in rapid and irregular ventricular rates. Most symptomatic AF patients therefore present with high ventricular rates, and control of ventricular rate is used to improve left ventricular function and AF-related symptoms. Rate control is achieved using beta blockers, digoxin or digitoxin, and verapamil or diltiazem. The initial heart rate target can be lenient (ventricular rate at rest < 110 bpm [98]). There is currently no evidence favouring stricter initial heart rate targets, and no clear evidence linking rate control therapy to better outcomes. [57,99] Rather, current recommendations for rate control therapy are based on small studies with composite outcomes [98,100] and on the therapies evaluated in the rate control arms of the AFFIRM, RACE, and PIAF trials. [101-103] Details of rate control therapy approaches can be found in the 2016 ESC guidelines on AF [2] and in a recent seminar published in the Lancet. [104] Even on adequate rate-control therapy, many AF patients remain symptomatic, thus requiring adaptation of rate control therapy and/or rhythm control therapy on top of rate control (see next section).

Rhythm control therapy. Restoring and maintaining sinus rhythm in AF patients can improve AF-related symptoms. There is no sign so far that rhythm control therapy improves outcomes in AF patients. Cardioversion, antiarrhythmic drugs, and catheter or surgical AF ablation are available for

this type of therapy. Ongoing controlled studies such as CABANA (NCT00911508) and EAST – AFNET 4 (www.easttrial.org [105]) will determine whether modern rhythm control therapy (early therapy including the use of catheter ablation) can improve prognosis in AF patients when added to evidence-based anticoagulation and rate control therapy. The current approach to rhythm control therapy is summarized in the 2016 ESC AF guidelines [2] and has recently been reviewed in a seminar in the Lancet. [106] Importantly, rhythm control therapy will benefit from integration into a "holistic", integrated approach to AF care that also provides treatment of underlying cardiovascular diseases and precipitating factors (e.g. obesity), continued stroke prevention and rate control therapy (see "integrated AF care" below). This will minimize AF recurrences and improve quality of life. Systematic symptom assessment, e.g. using the modified EHRA score (Table 1B), should guide the use of rhythm control therapy. Cardioversion, pharmacological or electrical [107-109], long-term [109,110] or targeted short-term [109,111] antiarrhythmic drug therapy, and catheter ablation are the main treatments to restore and maintain sinus rhythm. The choice of antiarrhythmic agent needs to consider concomitant cardiovascular conditions to minimize side effects. Abnormal prolongation of the QRS (by more than 25% of the baseline value [2,109]) and QT (by more than 60 ms [2,110,120]) intervals, during the initiation of antiarrhythmic drug therapy identifies patients at risk for proarrhythmia (Table 4). Amiodarone is more effective than other antiarrhythmic drugs (Table 4, [116,118]) and can be used in patients with AF and reduced left ventricular function [119], but commonly causes extracardiac side effects. Antiarrhythmic drugs can be combined with catheter ablation ("hybrid rhythm control therapy") to reduce AF recurrences. [122]

Targeting triggers in, or close to, the pulmonary vein ostia has revolutionised AF ablation, [126] and isolation of the pulmonary veins is the accepted target of contemporary AF ablation procedures. [127,128] When used in experienced centres, first-line ablation therapy is as safe and effective as antiarrhythmic drug therapy in selected patients [129,130]. Catheter ablation is often the treatment of choice in AF patients who had recurrences on antiarrhythmic drug therapy. Catheter ablation is more effective than antiarrhythmic drug therapy in patients with paroxysmal [127] and chronic (persistent or long-standing persistent) AF. [128,132,133] Thus, the AF pattern is not considered a major factor in the decision for AF ablation. [2,128,134] Patients with recurrent AF despite initial ablation therapy should be discussed in a Rhythm Control AF Heart Team. More research is needed to guide the best method of catheter ablation beyond isolation of the pulmonary veins.

***Table 4:* Rhythm control therapy options in AF patients.** *All rhythm control interventions are clinically indicated to improve AF-related symptoms. Available data suggest an improvement in quality of life by rhythm control therapy.*

Rhythm control treatment	Antiarrhythmic effect	Unwanted effects	ECG signs of unwanted effects
Antiarrhythmic drugs			
Dronedarone 400 mg BD	Doubling of sinus rhythm compared to placebo	worsening of severe heart failure, torsades de points and/or heart block (rare)	QT prolongation by > 60 ms on therapy, QT > 0.5 s, higher degree heart block
Flecainide 100 – 150 mg BD		ventricular tachycardia in patients with prior myocardial infarction or heart failure, torsades de pointes (rare)	Increase of QRS duration by >25% on therapy
Propafenone 150 – 300 mg TD		ventricular tachycardia in patients with prior myocardial infarction or heart failure, torsades de pointes (rare)	Increase of QRS duration by >25% on therapy
Sotalol 160 mg BD		torsades de pointes, heart block, accumulation in acute kidney failure, increased proarrhythmia risk in left ventricular hypertrophy and heart failure	QT prolongation by > 60 ms on therapy, QT > 0.5 s, higher degree heart block
Amiodarone 200mg OD (loading required over several weeks)	More effective than other antiarrhythmic drugs in maintaining sinus rhythm	High rate of extra-cardiac side effects (thyroid and liver dysfunction, light sensitivity, peripheral neuropathy), torsades de points and/or heart block (rare)	QT > 0.5 s, higher degree heart block
Interventional therapy			
Pulmonary vein isolation using cryoballoon or radio frequency energy	Slightly more effective than antiarrhythmic drugs as first-line therapy, often requiring 2 or 3 procedures, clearly more effective in patients who had recurrent AF on antiarrhythmic drugs	periprocedural stroke, cardiac tamponade, oesophageal fistula, phrenic nerve palsy, brain white matter lesions, vascular damage, radiation exposure	n.a.
Additional ablation, e.g. linear lesions, ablation of specific electrogram patterns, etc.	Effective for post-ablation tachycardias, effectiveness for AF unclear	Same as pulmonary vein isolation, probably higher complication risk due to longer and less standardized procedures	n.a.
Surgical AF ablation	Slightly more effective than catheter ablation	Sinus node dysfunction, pneumothorax, cardiac tamponade, stroke	n.a.

Integrated AF management, access to all therapy options, and the need to develop stratified AF therapy.

The need for integration and differentiation of AF management. Implementation of the recent advances in AF management, e.g. access to medications that require specialist initiation or interventional and surgical therapy options, is not universal, as illustrated by the variable use of evidence-based treatments in recent observational data sets. [12,15,16,73,137] Furthermore, AF requires chronic management in a large population of patients, including provision of specialist treatment options when needed. Integrated, patient centred approaches to AF care are thus being developed to provide access to all forms of treatment and to ensure continuous management for all AF patients [2,95,96], transferring concepts tested in other areas of medicine. [138-140] The size of the AF population calls for a staged approach to provide access to AF management for all patients. In fact, the first "nurse-led" models of integrated AF care were at least partially designed to cope with the sheer number of AF patients in need for advice and monitoring. [97]

Integrated AF care. Integrated AF care can be described as a care model that is open to all AF patients while providing an efficient infrastructure delivering care in all required treatment domains (Figure 3). Integrated AF care seems more timely now than ever, as more and more patients are in need for AF care (see section on AF screening above, and [1-3]), while on the other hand subspecialist treatment options including stratified approaches to treatment are entering clinical practice. The best patterns of integrated AF care models will vary regionally, and there may be opportunities to merge integrated AF care services with other programmes, e.g. integrated heart failure and/or stroke care programmes. Even though the details of such integrated AF management programmes will vary locally and await optimisation by research [2,95,96], there is already a strong case underpinning integrated AF care programmes. Figure 3 outlines aspects of the current structure of AF care and the general structure of integrated AF care. A few key features of integrated AF care can be defined:

1. The diagnosis of atrial fibrillation needs to be established by ECG before treatment can start.
2. Integrated AF care provides easy access to AF care for all AF patients, close to where they live (Figure 3). Processes and infrastructures ensure that all patients in need for treatment in each of the five domains of AF care receive the care they need.
3. Most initial management decisions can be made on the spot or after a few simple tests by general or acute physicians or experienced, specially trained nurses, including anticoagulation, antihypertensive therapy, life style advice, and initiation of rate control therapy. Regular follow-up visits that can also be performed locally, e.g. by nurses, pharmacists, general practitioners, and other health care professionals working within an integrated AF care framework.
4. Integrated AF care requires good communication between all stake holders. Such communication will benefit from a common IT infrastructure, e.g. tools used by patients and health care professionals. The European Society of Cardiology, supported by the CATCH ME consortium (www.catch-me.eu), has provided two exemplary IT tools supporting integrated AF care for smartphones. They provide the essential knowledge to highlight AF management domains and to propose common solutions in line with evidence-based care.
5. Specialist cardiology input and cardiac imaging (usually by transthoracic echocardiography) will be beneficial during the initiation of AF management in most patients. This can be provided remotely in collaborative teams.
6. Shared decision making, putting the patient at the centre of the care process and involving families and carers, has the potential to increase adherence to chronic therapy. [141] Hence, shared decision making should be part of integrated care. Documenting this process will

benefit from a validated capture of patient-reported outcomes. [142,143] Adequately informed patients will be able to "own" the day-to-day management of AF, thereby ensuring adherence to chronic therapy.

7. Patients who develop problems or complications on therapy and those who remain symptomatic should be managed with adequate specialist input, culminating in hospital care and multidisciplinary AF Heart Teams to guide and inform difficult management decisions in selected AF patients (Figure 3). Teamwork across disciplines and care boundaries can replace the current emphasis on triaging of patients.
8. Integrated AF care programmes provide all AF patients access to research projects in AF, thus providing patients the choice to participate in such research projects and contributing to the further development of AF care.
9. Integrated AF care structures allow to measure and improve quality of care [144] with a denominator that is reflecting the AF population.

Stratified therapy of AF patients considering drivers of AF. Integrated AF care has the aim to render the best current AF therapy accessible for all AF patients in an efficient way. Even the best AF therapy, e.g. delivered in controlled clinical trials or in specialized centres, is only partially effective in preventing AF-related complications.[2,11,12,72] Applying potentially effective therapies to large, unselected AF patient cohorts can completely avert expected treatment effects. [145-148] We currently do not have reliable methods to determine which AF patient will respond well to which therapy. This is particularly challenging for rate and rhythm control therapy. Hence, we are beginning to develop stratified or personalized approaches to AF therapy, and the tools to underpin such therapies are not available in full. [149] AF clinicians and researchers recognise that AF is caused by different disease drivers in different patients , and that these differences can be used to develop stratified approaches to AF management. [150] Unfortunately, different drivers for AF will overlap in individual patients [144,150], and AF-inflicted damage will contribute common elements to cardiac dysfunction. [47,151-153] Still, a few examples exist where mechanism-based stratification of AF therapy has been successfully translated into clinical management:

- Obese patients with AF benefit from structured weight reduction and fitness programmes, at times even obviating the need for scheduled AF ablation procedures. [61-63] It is not unlikely that fatty infiltration of the atria and activation of atrial adipocytes [59,60] mediate the "proarrhythmic" effect of obesity, and the antiarrhythmic effects of weight loss.
- Sodium channel gene variants or mutations are not infrequent in patients with early-onset AF [154-158], and inherited arrhythmogenic diseases conveyed by sodium channel mutations include early-onset AF in their phenotype. [159-161] Sodium channel modulating ion channel blockers could be a promising treatment for such patients to prevent AF [162,163], similar to the effect of similar substances to prevent ventricular arrhythmias. The ESC AF guidelines suggest to actively assess the ECG and echocardiogram for such inherited conditions leading to AF, especially in young patients presenting with AF. Recent data furthermore suggest that common gene variants associated with AF can also modify the response to sodium channel blockers. [164]
- ACE inhibitors can prevent incident AF in patients with left ventricular hypertrophy [52] and those with markedly reduced left ventricular function [165], while the same treatment does not prevent recurrent AF in other patients. [147,148] This suggests that inhibition of the renin-angiotensin system can prevent some forms of atrial cardiomyopathy [166], while the therapy seems without effect in patients without atrial damage mediated by activation of the renin-angiotensin system.

Clearly, these examples can only illustrate how different types of AF, differentiated by the major pathophysiological drivers of the arrhythmia in individual patients, could potentially be used to develop personalised treatment concepts for atrial fibrillation in the future. [149] Ongoing research programmes will need to translate mechanistic insights into AF and its complications into clinical management concepts to unleash the full potential of personalized AF management. Integration of specialist knowledge and AF Heart Teams into clinical care will be the key to support these developments and to adjust them to clinical needs.

In summary,

I. Screening for silent AF emerges as an important opportunity to prevent AF-related complications.

II. All AF patients should receive long-term treatment in five domains (Figure 2):

1. Acute hemodynamic stabilization
2. Detection and treatment of concomitant cardiovascular diseases
3. Assessment of stroke risk and (in most patients) oral anticoagulation
4. Assessment of ventricular rate and (in most patients) rate control therapy
5. Assessment of symptoms related to AF and rhythm control therapy in those with AF-related symptoms.

III. Successful AF management relies on integration of the following components (Figure 3)

1. timely detection of AF (ideally prior to the first complication)
2. provision of chronic support for the care of all AF patients,
3. active patients who “own” their management,
4. measurable quality of care,
5. access to all treatment options for all AF patients,
6. early identification and fast-track triaging of patients in need for specialist interventions,
7. multidisciplinary AF Heart Teams informing difficult management decisions, and
8. integration of clinical research projects into AF care programmes, e.g. developing stratified approaches to management.

This can best be provided by integrated care provided by interdisciplinary and cross-sector health care teams including pharmacists, nurses, general physicians, and AF specialists (Figure 3). Difficult decisions will arise in some patients and should be guided by advice from AF Heart teams comprising specialists in stroke prevention, stroke therapy, rate and rhythm control therapy, interventional and surgical treatment of AF.

IV. Future improvements will require a new taxonomy of AF identifying the major causes of AF in individual patients and the development and systematic evaluation of stratified AF therapy.

Search strategy. We searched the Cochrane Library (date range), MEDLINE (date range), and EMBASE (date range), supplemented by publications known to the author were necessary. We used the search terms “atrial fibrillation” combined with “stroke prevention”, “risk factor”, “rate control”, “rhythm control”, “anticoagulation”, “combination therapy”, “stroke”, “occluder”, “ablation”, or “surgery” where required. We largely selected publications in the past 6 years based on novelty, citations, and relevance for this clinical seminar, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers.

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Legends to Figures

Figure 1: Main treatment options in the different domains of AF management and their cardiac targets. Shown is a CT image of a heart in an oblique and rotated view showing all four heart chambers, the pulmonary veins, the left atrial appendage, and the atrio-ventricular node. Boxes depict commonly used therapies and interventions in patients with atrial fibrillation. Arrows point to the main target of those therapies. Solid lines point to established treatment targets, dashed lines indicate potential additional treatment targets. AVN Atrio ventricular node, LA left atrium, LAA left atrial appendage, LV left ventricle. PV pulmonary veins, RA right atrium, RV right ventricle. CT image provided by Dr Dipak Kotecha, Birmingham.

Figure 2: The five domains of AF management. AF patients require acute hemodynamic stabilization (depending on clinical presentation), detection treatment of concomitant cardiovascular conditions, stroke risk assessment and decision on oral anticoagulation therapy. These treatment domains have the potential to improve prognosis. Most AF patients also require rate control therapy, and those who are symptomatic will need rhythm control therapy to improve symptoms. Reproduced from [2], adapted from [167].

Figure 3: Structure of Integrated AF Care (bottom panel) compared to current AF care (top panel). Current care models provide different access points for care, including no access, general practice / internists, office based cardiologists / cardiology outpatients, TIA and stroke services, emergency and acute medicine departments, and hospital-based cardiology and electrophysiology departments. Patients are often not put in contact with the team that can provide the best care for them, and follow-up is not structured across disciplines or sectors. Recently, many examples of better integration of AF care have been described. Integrated AF care (bottom panel) provides a common access point for all patients with AF, where initial assessment and therapy is delivered. The process of engaging and empowering patients is started here. Patients are then fast-tracked to receive appropriate further input into their treatment which may be continued in the community or supported by general practitioners, outpatient cardiologists, hospital-based specialties, or even AF Heart Teams providing input into difficult decisions and access to subspecialist interventions. Bringing health care professionals closer to the patient, ideally in the communities where they live, and working as a team supported by an IT infrastructure across disciplines and health care sectors are key components of integrated AF care. Such a service fulfils the quality criteria for a good AF service: Provision of all therapy options for all patients, measurable quality of care, multidisciplinary decision making when needed, and a service that is accessible to all AF patients. At the same time, reorganisation has the potential to manage more patients in the community, thus taking pressure off hospitals and specialist services. Integrated care will also allow to measure and improve quality of care across entire catchment areas.[144] Furthermore, integrated AF care is conducive to innovation and research, e.g stratified therapy of AF patients. C counsellor, N nurse, O other health care professional, P physician, S specialist doctor.

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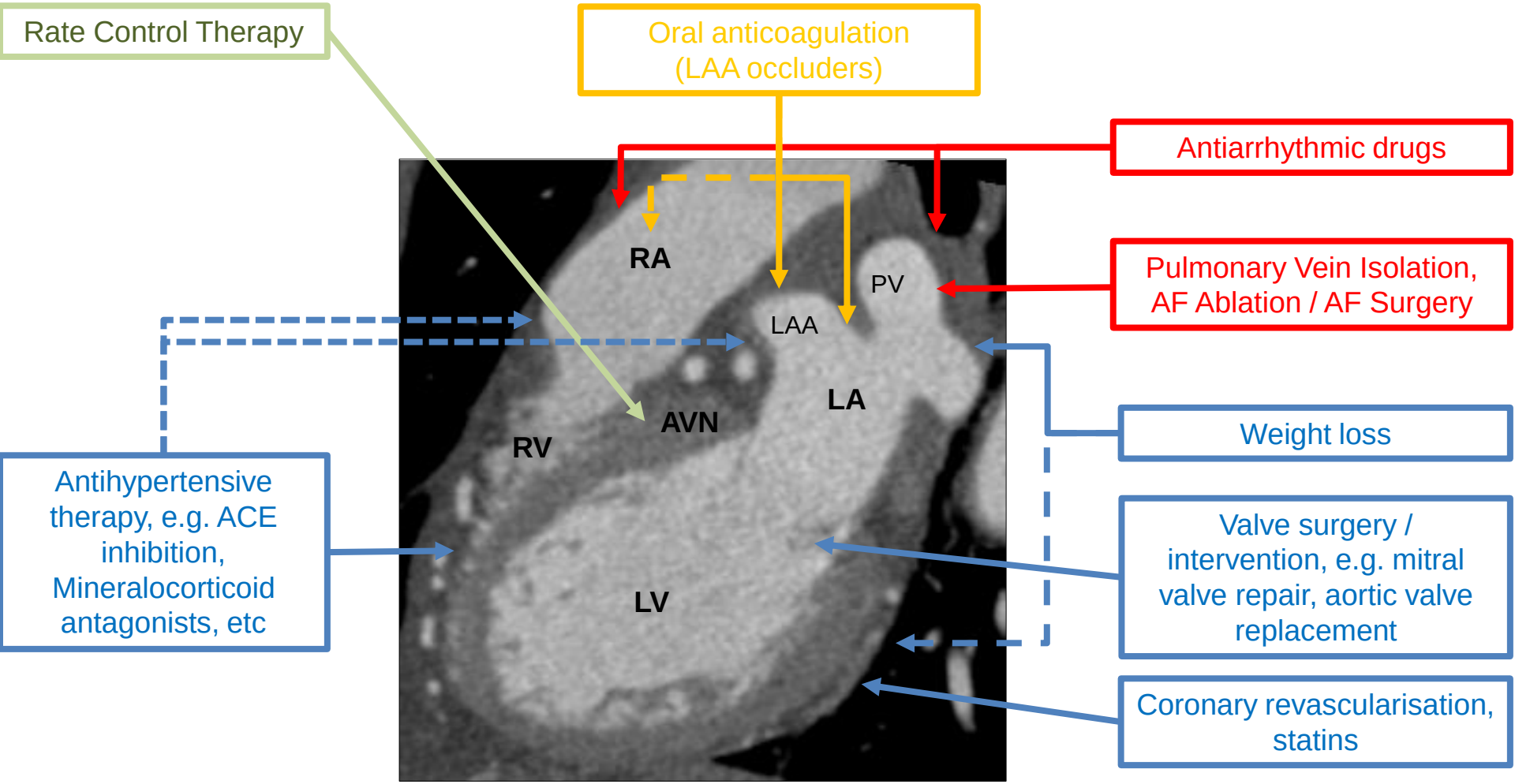
Rate Control Therapy
Oral anticoagulation (LAA occluders)
Antiarrhythmic drugs
Pulmonary Vein Isolation, AF Ablation / AF Surgery
Weight loss
Valve surgery / intervention, e.g. mitral valve repair, aortic valve replacement
Coronary revascularisation, statins
Antihypertensive therapy, e.g. ACE inhibition, Mineralocorticoid antagonists, etc
RA
PV
LAA
LA
AVN
RV
LV

Figure 1

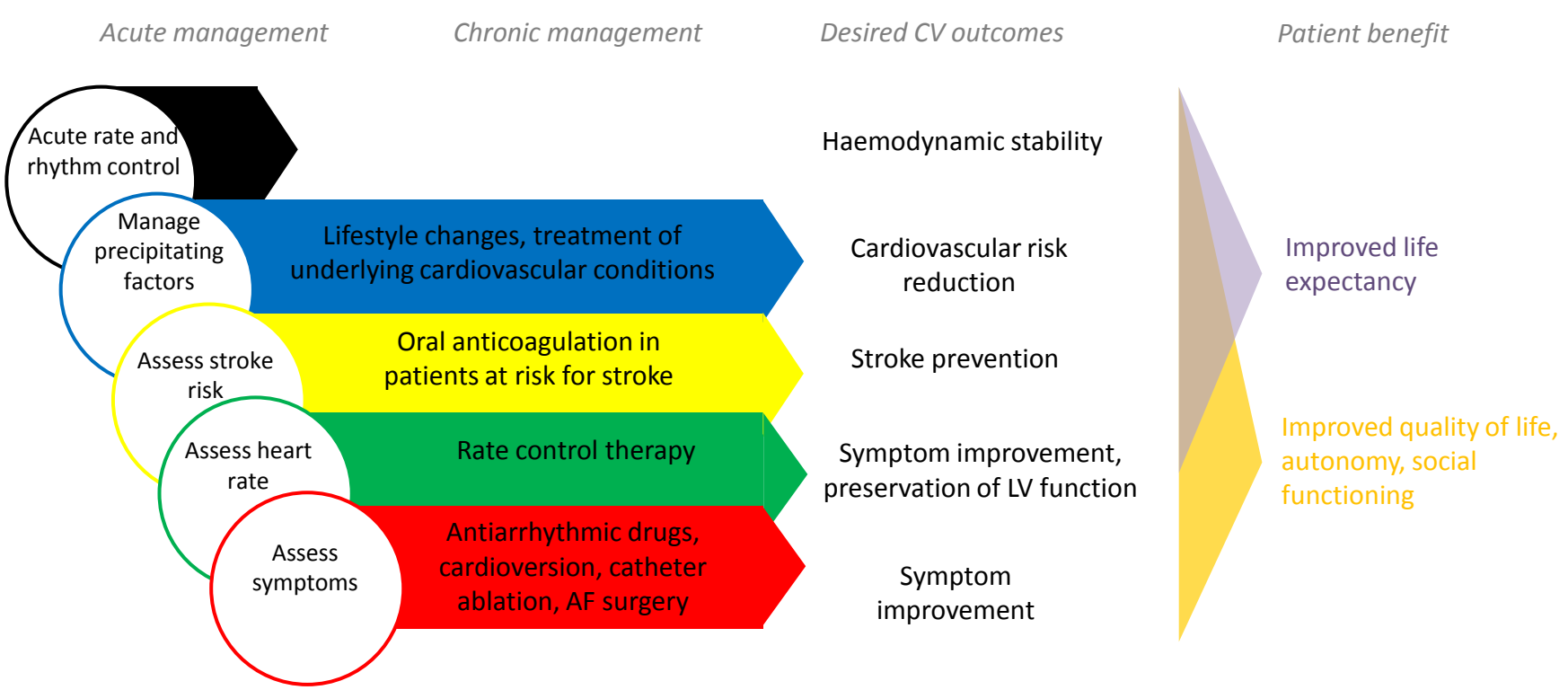
Acute management
Chronic management
Desired CV outcomes
Patient benefit
Acute rate and rhythm control
Manage precipitating factors
Assess stroke risk
Assess heart rate
Assess symptoms
Lifestyle changes, treatment of underlying cardiovascular conditions
Oral anticoagulation in patients at risk for stroke
Rate control therapy
Antiarrhythmic drugs, cardioversion, catheter ablation, AF surgery
Haemodynamic stability
Cardiovascular risk reduction
Stroke prevention
Symptom improvement, preservation of LV function
Symptom improvement
Improved life expectancy
Improved quality of life, autonomy, social functioning

Figure 2

Figure 3 as illustrator file