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Special article

Outcome parameters for trials in atrial fibrillation: executive summary

Recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA)

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Atrial fibrillation (AF), the most common atrial arrhythmia, has a complex aetiology and causes relevant morbidity and mortality due to different mechanisms, including but not limited to stroke, heart failure, and tachy- or bradyarrhythmia. Current therapeutic options (rate control, rhythm control, antithrombotic therapy, 'upstream therapy') only prevent a part of this burden of disease. Several new treatment modalities are therefore under evaluation in controlled trials. Given the multifold clinical consequences of AF, trials in AF patients should assess the effect of therapy in each of the main outcome domains. This paper describes an expert consensus of required outcome parameters in seven relevant outcome domains, namely death, stroke, symptoms and quality of life, rhythm, left ventricular function, cost, and emerging outcome parameters. In addition to these 'requirements' for outcome assessment in AF trials, further, more detailed outcome parameters are described. In addition to a careful selection of a relevant primary outcome parameter, coverage of outcomes in all major domains of AF-related morbidity and mortality is desirable for any clinical trial in AF.

Introduction

Atrial fibrillation (AF) affects a relevant, increasing part of the population of the European Union:[1] 25% of the currently 40-year-olds will develop AF.[2,3] AF causes relevant mortality and morbidity.[4–7] The clinical syndrome 'AF' includes a broad spectrum of pathophysiological processes, ranging from 'electrical accidents'[8,9] to long-term systemic processes.[10] Likewise, the clinical consequences of AF are difficult to predict in an individual patient. Death, stroke, or severe limitations of exercise capacity in some patients

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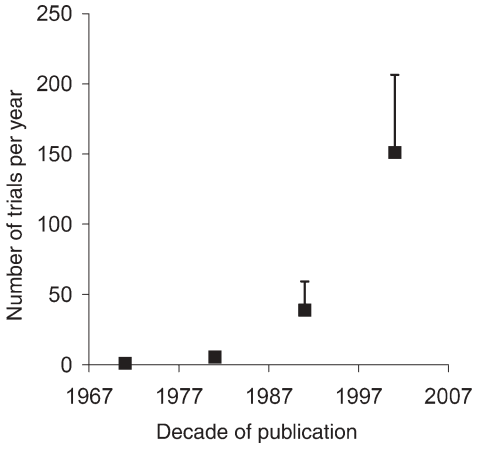

Figure 1 Number of randomized trials in atrial fibrillation published in Medline from 1967 to 2006. Dots indicate the mean number of trials per year over a given decade and error bars indicate the standard deviation.

contrast with frequent asymptomatic AF episodes in others.[11–13] Treatment includes antithrombotic medicines,[14] control of ventricular rate by drugs or pacemakers,[15] rhythm-control interventions,[16–18] and the so-called 'upstream therapy'.[19]

The limited effectiveness and at times unfavourable side-effect profile of available therapeutic options has resulted in a massive surge of randomized trials in AF in the past two decades (*Figure 1*). Due to the diverse therapeutic options and desired outcomes, trials that assess different treatment options for AF often use completely different outcome parameters. This makes AF a difficult topic in the context of controlled trials and clinical day-to-day management.

To tackle this problem, the German Atrial Fibrillation competence NETwork (AFNET, www.kompetenznetz-vorhofflimmern.de) and the European Heart Rhythm Association (EHRA www.escardio.org/ehra) convened 60 scientists and industry representatives at the European Heart House in Sophia Antipolis, France, for a consensus conference on 22–23 January 2007 to define minimal and reasonable outcome parameters for the assessment of AF in controlled clinical trials. This paper reports the summarized consensus reached during this conference. Seven relevant outcome domains are covered in a hierarchical structure: Death, stroke, symptoms and quality of life, changes in rhythm, left ventricular (LV) function and development of heart failure, health economics, and emerging outcome parameters.

Natural time course of AF, frequency, and timing of complications

AF is often a chronic, progressive arrhythmia. The first detected episode of AF is usually self-terminating or amenable to rhythm control interventions, mostly followed by intervals of sinus rhythm, interrupted by episodes of the arrhythmia ('paroxysmal AF'). The distribution and duration of AF episodes slowly increases over time, but is rather clustered[20,21] than random.[22] This biological pattern renders AF burden a cumbersome outcome parameter in terms of statistical power (*Figure 2*).[21,23] The recurrence of persistent AF, in contrast, is a single event and 'time to recurrence' is a reasonable outcome since this event often triggers a modification of therapy. After restoration of sinus rhythm, e.g. by cardioversion, persistent AF recurs in 25–50% of all patients

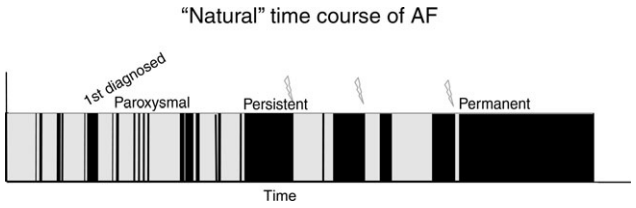

Figure 2 Time course of atrial fibrillation (AF). Shown is a typical chaotic pattern of time in AF (black) and time in sinus rhythm (grey) over time (X-axis). AF progresses from undiagnosed to first diagnosed, paroxysmal, persistent, and finally to permanent AF. Flashes indicate cardioversions as examples for therapeutic interventions that influence the 'natural' time course of the arrhythmia.

Table 1 Points to consider on the natural time course of atrial fibrillation

AF tends to progress to permanent AF:
~10% in the first year after symptomatic manifestation, 5% per annum thereafter.
Structural heart disease and age may promote this progression.
Paroxysmal AF recurrences follow chaotic patterns that are not random.
Recurrence of persistent AF can be classified as immediate, early, and late. Recurrent AF is most frequent in the first weeks after cardioversion.
Presence of AF approximately doubles mortality, with a likely even higher impact on cardiovascular mortality

AF, atrial fibrillation.

in the first month after cardioversion.[12,24] Thereafter, AF recurs in ~10% of patients per year (*Table 1*).

AF causes a variety of complications, most notably thromboembolic complications and reduced cardiac performance. The frequency of AF-related complications depends on the baseline patient characteristics.[25,26] Furthermore, complications vary over time: The risk of severe bleeding appears highest in the first months after initiation of antithrombotic treatment. Death is highest in the first year after the initial manifestation of AF,[5,27] and occurs steadily thereafter at 1.6–4.2% per annum in more recent controlled trials.[16,22,28] Moreover, complication rates have decreased over the years in AF trials.[14]

General considerations

Patient characterization

The inherent risk for recurrent AF and AF-related complications is heavily influenced by patient characteristics. There are published lists of such baseline data by ACC/AHA[29] and the society of Thoracic Surgeons.[30] The panel suggests to refer to them, especially to the more general ACC/AHA recommendations.[29] *Table 2* lists a set of required, minimal baseline characteristics for publication of an AF trial.

Choice of outcome parameters in AF trials

Different AF trials will require different primary outcome parameters, but the complex consequences of AF will require assessment of a variety of outcome domains in every trial (*Table 3*). Ideally, the primary outcome reflects the efficacy of treatment. Safety concerns about the study treatments should be reflected in the primary safety

Table 2 Minimal clinical parameters that should be given for baseline characterization of patients in an atrial fibrillation trial

Age, Gender
Type of AF (first detected, paroxysmal, persistent, permanent)
Duration of AF since first detection
Prior antiarrhythmic drug treatment
Number of antiarrhythmic drugs tested
Number of cardioversions
Number of catheter ablations or surgical interventions
$CHADS_2$ score
Prior antithrombotic treatment
Duration of anticoagulation (vitamin K antagonists, other anticoagulant)
Anti-platelet treatment (aspirin, clopidogrel, etc)
Symptoms due to AF
Arrhythmia-related symptoms (EHRA score)
Prior stroke/transitoric ischaemic attack
Heart failure indices
New York Heart Association class
Left ventricular ejection fraction
Treatment at enrolment
Antiarrhythmic drugs
Rhythm control drugs
Rate control drugs
Anticoagulation
Antihypertensive therapy (special report of angiotensin receptor inhibition is suggested)
Other cardiac medication
Concomitant cardiac disease

These data should be collected at study entry.
AF, atrial fibrillation.

Table 3 Examples for primary outcome parameters in prior and ongoing clinical trials in AF

Trial acronym/Name	Number of patients	Primary outcome parameter
Rate vs. Rhythm control trials		
AFFIRM[16]	4060	Mortality
RACE[97]	522	Composite
PIAF[13]	252	Symptom improvement defined as elimination of palpitations, dyspnoea, and shortness of breath
HOT-CAFÉ[98]	205	Composite (death and MACCE)
STAF[99]	200	Composite (death, embolic events, and others)
Rhythm control trials		
SAFE-T[24]	450	Time to persistent AF
PAFAC[12]	866	Time to persistent AF
CTAF[100]	403	Time to persistent AF
SOPAT[51]	1033	Time to symptomatic AF
ATHENA (NCT0017478)	4300	Death or cardiovascular Hospitalization
Flec-SL (NCT00215774,[55])	755	Time to persistent AF
ANTIPAF (NCT00098137)	422	Time in AF
Brignole[101]	137	Development of permanent AF
Madrid[102]	154	Time to persistent AF
Ueng[103]	145	Time to recurrent AF
Natale[104]	61	Atrial flutter, rehospitalization, quality of life
Wazni[105]	70	Time to recurrent AF, hospitalizations, and QoL
APAF[106]	198	Time to recurrent AF
Oral[107]	80	Recurrent AF (assessment not specified)
Karch[108]	100	Freedom from AF in 7-day Holter
Oral[109]	146	Freedom from AF at 1 year FU
Gaita[110]	105	Freedom from AF at 2 years FU
AF-CHF[111]	1450	Cardiovascular mortality
RAAFT NCT00392054	400	Time to recurrent AF (>30 s)
GAP-AF	196	Time to recurrent AF
AMICA	216	Change in LV function
CABANA	3000	Total mortality
Rate control trials		
AIRCRAFT[71]	99	Cardiac function, exercise capacity
FARFIC[70]	66	Quality of life, exercise capacity
OPSITE[112]	56	Quality of life, exercise capacity
RACE II[113]	500	Composite
Farshi[15]	12	Rate increase during exercise
Antithrombotic treatment trials		
AFASAK[114]	335	thromboembolic complication
BAATAF[115]	420	Stroke, death (not defined)
SPAF I[116]	1330	Stroke or peripheral embolism
SPINAF[117]	572	cerebral infarction
EAFT[38]	1007	Composite (death from vascular disease, any stroke, myocardial infarction, or systemic embolism)
CAFA[118]	187	Composite (non-lacunar stroke, non-central nervous systemic embolism, and fatal or intracranial haemorrhage)
AFASAK 2[119]	677	Stroke or a systemic thromboembolic event
SPAF II[120]	715	stroke or systemic embolism
SPAF III[121]	1044	Stroke or systemic embolism
SPORTIF III[28]	3410	Stroke or systemic embolism
SPORTIF V[122]	3922	Stroke or systemic embolism
NASPEAF[123]	1209	Composite (vascular death and non-fatal stroke or systemic embolism
TIARA (NCT00224757)	300	Composite (death, stroke, embolism, acute coronary syndrome, and major bleeding)
ACTIVE W[124]	6706	Composite (MACE)

The panel has had difficulties to identify the primary outcome parameter in some of the published trials. The panel strongly recommends that the primary outcome parameter should be specifically stated in the publication of a trial.
AF, atrial fibrillation.

outcome parameter. Outcome parameters reflecting net benefit should usually be presented as secondary outcome parameters. Generally, objectively measured parameters are preferred (but see section on Symptoms). If outcome measures do not cover all main outcome domains, at times pivotal information may be disguised.

Assessment of specific outcome parameters

Death

AF is associated with increased and premature mortality.[4,5] Furthermore, many available treatment modalities, e.g. but not limited to antithrombotic medicines, antiarrhythmic drugs, catheter interventions, or operations, will at times cause death as a serious adverse event (SAE). All deaths therefore need to be measured and reported in any trial of AF on an 'intention-to-treat' basis from the time of randomization. There are several causes of death (*Table 4*). Deaths should be classified according to the mode of death using all available methods, including autopsy, doctors' reports, read-out of ICDs/monitoring devices, or Holter ECG recordings. Death unrelated to AF (e.g. death due to cancer) will dilute the effect of any treatment aimed at reducing AF-related mortality in a controlled trial. This effect will be more prominent in elderly study participants who are prone to die. Mortality should only be part of the primary outcome parameter when the therapy or intervention tested is aimed at reducing mortality and the trial has sufficient statistical power and sufficient follow-up time to detect an effect on mortality. This will only be possible in large trials that enrol patients at relatively high risk for death who are followed for a sufficient time. In short-term studies, studies in patients at low risk of death, and in studies in which the intervention will not affect mortality to a relevant extent, death is not a reasonable primary outcome parameter. Death should always be assessed as a secondary outcome parameter in such trials. Generally, death from unrelated causes should not be included in the primary outcome parameter unless the study is adequately designed to detect an effect of therapy on total death. However, all deaths should be reported as a safety outcome parameter.

AF-related death is conceptually an attractive outcome parameter for AF trials, because it implies that the effect of the arrhythmia on mortality is directly measured. AF-related death should not substitute 'total death' as an outcome parameter, because AF-related death will be difficult to assess in a clinical trial, rendering AF-related death a potentially unreliable measurement, similar to and even more pronounced than cardiovascular death. Furthermore, there are no validated means to determine AF-related death. The panel acknowledges the potential relevance and the shortcomings of this outcome parameter and suggests a step-wise exclusion process to determine 'AF-related death': All deaths without a clearly determined non-cardiovascular cause should be classified as cardiovascular deaths. All cardiovascular deaths that do not have a clearly defined other cause (e.g. rupture of an aneurysm, pulmonary embolism, cardiac tamponade, myocardial infarction, among others) should be classified as AF-related death when AF was present during the 7 days prior to death. All deaths that are a consequence of AF-related treatment (SAE) should be reported in the primary safety outcome and counted as AF-related deaths. This process to determine AF-related death requires validation in prospective trials.

Table 4 Classification of deaths in atrial fibrillation trials

Non-cardiovascular, excluding sudden death
Cardiovascular death
Cardiac
Sudden (including arrhythmic, myocardial infarction, among others)
Non-sudden
Vascular (e.g. embolic, subarachnoidal bleeds, stroke, other)
Sudden
Non-sudden
AF-related
Treatment- or procedure-related (is also a serious adverse event)

All-cause death should be classified in the following groups.
AF, atrial fibrillation.

Requirements:

- Mortality is a valid outcome parameter in AF trials when trials are adequately powered and designed to detect differences in mortality between treatment groups.
- In the majority of trials, death is not a feasible primary outcome parameter, but may be part of a composite outcome parameter when the study treatment is aimed at reducing deaths.
- Death is a required secondary outcome parameter. All deaths should be reported on an intention-to-treat basis, and information on vital status needs to be assessed at regular intervals (minimum: at enrolment and at the end of the trial).
- All deaths must be reported in a safety outcome parameter.

Stroke

AF causes a relevant portion of all strokes (15–25%)[31], and AF-associated mortality is in part attributable to stroke and its consequences.[32] Strokes in patients with AF are more severe than other forms of stroke.[33] 'Silent stroke' is associated with AF and can be seen by cerebral imaging. Epidemiological data have associated silent cerebral ischaemic events with dementia.[34] Stroke is often caused by cardioembolism in AF patients, most frequently from the left atrial (LA) appendage.[35] Even in controlled trials, the residual stroke rate on optimal antithrombotic treatment (vitamin K antagonists, target INR range 2–3) is relatively high (1.3% per year in individuals without prior stroke, 3% per year in individuals with prior stroke)[36–39]. Therefore, stroke is one of the most important outcome parameters in AF trials. Stroke should be evaluated using the best possible methods (including MRI/CT brain imaging, assessing intensity of anticoagulation, severity of stroke, and neurological end result). All stroke events should be adjudicated by a committee that is usually blind to treatment/study arm.

Intracerebral bleed is the natural counterpart of ischaemic stroke in anticoagulated patients. All bleeding events need to be reported. Bleeds become more prevalent during supratherapeutic anticoagulation (INR$>$3.5[40]). Risk factors for bleeds include age, typical cardiovascular risk

factors, and presence of cerebral small vessel disease. A bleeding event is major when it is fatal; haemoglobin concentration falls by more than 2 g/dL; requires transfusion of whole blood cells or operation; affects areas of concern, e.g. retroperitoneal, intracranial, intraspinal, or intraocular; or results in treatment cessation. Other bleeding events are minor. Intracranial bleeds may be included in a composite stroke outcome because the combination of strokes and intracerebral bleeds can reflect the clinical benefit of antithrombotic treatment. Subdural or epidural haemorrhages are not strokes, but should be reported as SAEs, together with a statement whether they appear attributable to treatment. Data on transient ischaemic attacks (TIAs) with acute lesion matching the symptoms on imaging should be collected and reported, as there is discussion on the classification of such outcome events, and a new definition that might classify such events as 'stroke' is under consideration at the World Health Organization. TIAs should always be adjudicated for the presence of stroke, and the clinical adjudication may determine the ultimate classification as stroke or TIA. Cause of stroke should be classified according to TOAST criteria, stroke end results by the Rankin score (*Table 5*, [41,42]). Usually, cerebral vascular events and other major cardiovascular events (e.g. myocardial infarction, pulmonary embolism) should be assessed as separate outcome parameters.

Cerebral imaging should be used to identify baseline cerebral defects in patients who suffered a cerebrovascular accident prior to trial inclusion. The preferred method of imaging is magnetic resonance imaging (MRI). Computed tomography may substitute MRI in specific situations. To measure cognitive function in trials, we recommend the Mini-Mental State Examination at baseline and during follow-up. Additional psychometric tests may be reasonable when cognitive function is part of the outcome. A minimal requirement is assessment of mini-mental state at enrolment and at the end of trial.

Table 5 TOAST criteria for classification of strokes (modified from Adams *et al.*[41]), and Rankin score for stroke severity (modified from Rankin[42])

TOAST criteria: etiology of ischaemic strokes can be classified into five categories by clinical and imaging criteria
Large-artery atherosclerosis
Cardioembolism
Small-vessel occlusion
Stroke of other determined etiology (e.g. large vessel dissection)
Stroke of undetermined etiology.
Rankin score of stroke severity as described in Rankin[42]
Grade I. No significant disability: able to carry out all usual duties.
Grade II. Slight disability: unable to carry out some of previous activities but able to look after own affairs without assistance.
Grade III. Moderate disability: requiring some help but able to walk without assistance.
Grade IV. Moderate severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance.
Grade V. Severe disability: bedridden, incontinent, and requiring constant nursing care and attention.

In larger studies, each TOAST category comprises ~20% of all strokes. Cardioembolic strokes are often due to atrial fibrillation.

Requirements:

- All strokes (ischaemic and haemorrhagic) and systemic embolic events should be recorded and reported separately.
- All clinical events fulfilling the criteria of stroke should be verified by brain imaging, ideally by MRI.
- TIAs are not counted as a stroke and should not be used as part of the stroke outcome.
- Major bleeding should be reported separately, usually as a safety outcome parameter.
- To assess cognitive function in trials, the Mini-Mental State examination should be recorded at baseline and at least also at the end of follow-up. If cognitive function is an outcome parameter, additional psychometric tests are recommended.

Symptoms and AF-related quality of life

AF is associated with poor quality of life.[43] Rate- or rhythm control interventions can improve quality of life in AF patients.[13,44,45] Symptoms and perceived suffering from the arrhythmia are the most common reason for AF patients to seek medical attention, and the main indication for rate- or rhythm-control therapy at present.[35,46] Quality of life, and suffering or 'illness intrusiveness'[47,48] are difficult to measure objectively. The elusive relation between symptoms and arrhythmia recurrences, and specifically the high incidence of asymptomatic AF recurrences in patients with symptomatic AF, suggest that symptoms may at times not be related to AF, but rather an expression of other disease-causing processes. This renders symptoms and disease-related quality of life a potentially unreliable outcome parameter in AF trials. Therefore, symptoms and quality of life are only recommended as secondary outcome parameters.

Several instruments have been used to measure AF-related quality of life, usually as self-administered questionnaires [e.g. SF 36, symptoms check list, atrial fibrillation symptoms scale (AFSS), and the living with heart failure questionnaire (LWHF)]. These instruments are validated for global illness intrusiveness, but are—with the exception of the AFSS—not specific for AF-related symptoms. Furthermore, they are not available in many languages. Such standard instruments are recommended in AF trials, but the authors acknowledge their shortcomings in assessing AF-related symptoms. The panel recommends to design, validate, and use further, AF-specific instruments to assess AF-related quality of life, especially when improvement of symptoms and quality of life are the intended primary outcome of a trial. In selected studies in low-risk patients, robust, validated measures of quality of life may in the future become a primary outcome parameter, especially in small, hypothesis-generating trials.

Proposal of a symptom classification for AF

Having noticed the apparent discrepancy between the clinical relevance of AF-related symptoms for treatment decisions in AF and the lack of a practicable instrument to

Table 6 EHRA atrial fibrillation symptoms classification

	Symptom severity	Definition
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

The following items *during presumed arrhythmia episodes* are checked to determine the score: palpitations, fatigue, dizziness, dyspnoea, chest pain, anxiety. In addition to this score, the frequency could be classified into three groups, namely occasionally (less than once per month), intermediate (once per month—almost daily), and frequent (at least daily).

assess AF-related symptoms, the panel agreed to suggest a score to assess symptoms related to AF (see discussion in[49]). The panel suggests the so-called EHRA classification to describe AF-related symptoms (*Table 6*). The EHRA classification relates specifically to the time when the patient feels to be in the arrhythmia. The panel is aware of the fact that this classification requires prospective validation.

Requirements:

- Symptoms are the main reason for AF patients to seek medical attention. At present, symptoms and quality of life are recommended as secondary outcome parameters because there are no reliable instruments to quantify AF-related symptoms.
- Symptoms and quality of life should be assessed at entry and during follow-up in all AF trials.
- In trials enrolling symptomatic patients, symptoms should be related to the underlying rhythm.
- When the tested intervention is expected to primarily affect symptoms and quality of life, measures of quality of life and symptoms are potentially the primary outcome parameter. In such studies, the design, validation, and use of 'specific' instruments for AF-related symptoms in addition to standard instruments is recommended.

Once validated, the suggested EHRA AF symptoms classification may be helpful to compare AF-related symptoms across trials and in clinical practice.

Assessment of rhythm and other ECG-based outcome parameters

ECG-based outcome measures have been used in almost all trials that assessed interventions for rhythm or rate control (*Table 7*). In the past, we have learned that AF often recurs without clinical signs or symptoms: ECG recordings triggered by symptoms will miss more than half of all AF episodes, even in symptomatic patients.[12,38,50,51] To detect both symptomatic and asymptomatic AF recurrences, systematic (scheduled) ECG recordings are therefore needed. Continuous ECG monitoring, the gold standard for detection of recurrent AF, is not available at present, and will be available only using advanced technology in the foreseeable future.

Table 7 ECG-based outcome parameters for atrial fibrillation trials and available methods to assess them

- ECG-based outcome parameters
  - Freedom from AF (suitable for time-based assessment)
  - Change in AF pattern (e.g. altered AF burden, altered AF type, among many others)
  - Proarrhythmia (e.g. sudden death, ventricular tachycardia, torsades de pointes, atrial flutter, bradycardia, AV nodal block)
  - Ventricular rate during AF at rest and during exercise
- Available ECG methods
  - Non-continuous standard ECG recording
    - Symptom-activated ECG (e.g. during triggered visits, patient-activated devices)
    - Algorithm-activated (device monitors rhythm)
    - Scheduled
      - Resting ECG
      - Transtelephonic monitoring
      - (24–168 h) Holter recording
      - Loop recorders
  - Continuous ECG monitoring
    - Pacemakers/implanted defibrillators
    - ECG garment equipped with radio data transmission (e.g. GSM-based)

AF, atrial fibrillation.

In all patients, AF should be documented by ECG at enrolment, persistent, or permanent AF by Holter ECG. Seven day Holter ECG recording and daily plus symptom-activated transtelephonic ECG monitoring are equally powerful to detect recurrent paroxysmal AF[51–54] and detect ~70% of AF recurrences. One has to accept that the negative predictive value for 'freedom from AF' is 25–40% in paroxysmal AF patients with the aforementioned monitoring intensity, indicating that only one in three patients without any detected AF in all monthly Holter ECGs or daily transtelephonic monitoring during a 1-year follow-up period will really be free of AF.[23,53]

On the basis of this knowledge, we suggest the following: All ECG recordings should be analysed blind-to-treatment in a core laboratory. Every perceived (symptomatic) episode of AF should trigger an ECG. Single-lead ECGs are sufficient for this monitoring. Additional scheduled regular ECG recordings are mandatory, either by scheduled 24 h/month Holter ECG, or by daily 30–60 s short-term (e.g. transtelephonic) ECG recordings.[21,23,51–53] Daily transtelephonic monitoring may be more feasible because it allows recordings of additional ECGs during times of perceived symptoms. Holter ECG recordings, in contrast, have the advantage that the duration of AF episodes can be assessed.

When the outcome parameter is freedom from *persistent or permanent* AF, daily or twice-weekly short-term (e.g. transtelephonic) ECG recording followed by rapidly scheduled confirmatory Holter recording in case of a documented AF recurrence are sufficient.[12,24,55]

Any arrhythmia that has the ECG characteristics of AF and lasts longer than 30 s should be reported as recurrent AF. Persistent or permanent AF is assumed to be present when the episode does not terminate spontaneously or is terminated by an intervention. In rhythm control trials, recurrent arrhythmias on drug or after catheter ablation will not always be AF, but at times constitute atrial

tachycardias or atrial flutter. These should be included in the arrhythmia recurrence outcome parameter. Often, only a 12-lead ECG will distinguish these arrhythmias from AF.

Recurrent AF after cardioversion is time-dependent.[56–62] We suggest the following definitions: Cardioversion is successful when AF has been terminated. When AF recurs in the first 5 min after cardioversion, this event should be described as immediate recurrence of AF. AF recurrences within 6 min and 28 days after cardioversion should be called early recurrence of AF. Recurrent AF more than 4 weeks after cardioversion is 'late'.[63–65]

Safety

Safety issues may require additional ECG recordings to detect tachycardia and bradycardia signals. Bradycardia detection may require night-time ECG monitoring. Any arrhythmia that might constitute a proarrhythmic event (e.g. torsades de pointes, atypical or typical atrial flutter, or symptomatic bradycardia) must be reported as an adverse event.

Control of **ventricular rate** should be assessed by a resting ECG and a standardized submaximal exercise test (e.g. treadmill ECG, two-flights-of-stairs test, or a 6 min walk test). Maximal heart rate and potentially mean heart rate on Holter ECG may be used instead of an exercise test. Studies that compare rate- and rhythm-control strategies require detailed ECG monitoring like rhythm control studies (discussed earlier). In trials that do not target rate or rhythm, regular 12-lead ECGs should be performed, e.g. in 6 months intervals, to document the presence or absence of AF.

Requirements:

- Every arrhythmia with the ECG characteristics of AF and a duration >30 s should be reported as an AF recurrence.
- Every symptomatic event should trigger an ECG recording.
- Regular scheduled additional ECG recordings are needed to detect asymptomatic episodes.
  - For detection of persistent or permanent AF, daily or twice-weekly short-term ECG recordings with rapidly ensuing confirmatory Holter in case of an arrhythmia recurrence are sufficient.
  - For detection of paroxysmal AF, regular Holter ECGs (24 h/month) or regular transtelephonic short-term ECGs (30–60 s once daily) are recommended. Even this intensity of ECG monitoring will not detect all patients with recurrent AF.
- Ventricular rate should be assessed by resting ECG and a standardized exercise test. Alternatively, heart rate on Holter ECG may be used.
- Safety measures may require additional ECG recordings, e.g. to detect proarrhythmia.

Left ventricular function and heart failure

AF may impair LV function. On the other hand, AF and its complications may also occur in the presence of LV dysfunction. Rate- or rhythm-control therapy can improve LV function.[66–73]

LV size and function

LV function should be measured at baseline in every AF study patient.[35] Echocardiography is widely available and provides real-time imaging. Long axis M-mode measurements assess LV size (LVEDD, LVESD) and estimate global LV function. M mode echocardiography will be sufficient in many trials in AF patients to give a global estimate of LV systolic function. When regionally or severely abnormal LV function is expected, apical 2-dimensional LV planimetry using a (modified) Simpson's approach is preferred.[74] LV function should be measured at a normal heart rate (60–100 b.p.m.). In patients with irregular ventricular rhythm, averaging of LV measurements (five consecutive beats) is recommended. Analysis should be done by a core lab. There is epidemiological evidence of co-existence of diastolic dysfunction and AF.[5] When the diagnostic or therapeutic value of diastolic function is evaluated, transmitral pulsed wave Doppler measurements can be used. M-mode imaging from the parasternal long-axis view gives a unidimensional measurement (antero-posterior direction) and first impression of LA size. Better LA size information can be obtained from 2D or volumetric LA measurements. In patients with sinus rhythm, the maximal A-wave amplitude or its velocity–time integral on pulsed Doppler echocardiography provides information on LA function. Flow velocities (pulsed Doppler imaging) in the LA appendage provide adequate information on LA contractile function, even in AF, but this measurement requires transoesophageal echocardiography.

Highly reliable information on LV volumes and function can be obtained using computed tomography,[75] MRI, or gated nuclear imaging.[76] In contrast to the real-time imaging obtained by echocardiography, these modalities rely on ECG-based signal averaging. This technical requirement has prevented the use of these techniques in trials of AF patients so far. Furthermore, nuclear imaging techniques and computed tomography require exposure to ionizing radiation.

Heart failure should be a secondary outcome parameter because it is difficult to quantify. NYHA class is widely accepted but not very sensitive to change. Hospitalization for heart failure is a reasonable way to measure the consequences of heart failure in a clinical trial. In addition, VO_2(max), 6 min walking distance, and nt-proBNP may be helpful as general measures of cardiac strain and performance.

Requirements:

- All trials of rate- or rhythm-control interventions should report standard transthoracic echocardiographic data at entry and during follow-up. The assessment should include LA size (M Mode), LV size (M Mode), LV function (M Mode, preferably 2-dimensional echocardiography, modified Simpson technique).
- For trials assessing other (e.g. antithrombotic) interventions, echocardiography assessment is required at entry and strongly recommended during follow-up.
- When LV function or heart failure are part of the main outcome parameter set, it is reasonable to supplement echocardiography with a test for exercise capacity (6 min walk test, standardized exercise test) and potentially with a serologic marker (e.g. nt-proBNP).
- Hospitalizations may serve as an intermediary outcome parameter for heart failure that is easily quantified.

Table 8 Emerging surrogate outcome parameters in atrial fibrillation trials

Surface ECG
Frequency analysis of fibrillatory activity
Signal-averaged ECG of the P-wave
Amplitude of the QRS-complex/markers for left ventricular hypertrophy
Markers of the autonomic tone (heart rate variability)
P-on-T ectopic beats
Intracardiac atrial electrograms
Morphology of atrial electrograms
Amplitude of atrial electrograms
Frequency analysis of fibrillatory activity
Blood levels
Collagen/collagen metabolism (e.g. procollagens, matrix metalloproteinases)
Inflammatory mediators (e.g. TNF-alpha, interleukins, high-sensitivity C-reactive protein, adhesion molecules)
Thrombotic markers (e.g. clotting factors, von Willebrandt factor, platelet markers, fibrolytic indices)
Neurohumoral factors (e.g. angiotensin II, aldosterone, atrial natriuretic peptide, brain-type natriuretic peptide)
Proteomic profiles
Histological and molecular markers
Atrial cell size/hypertrophy
Interstitial fibrosis
Ultrastructural changes in atrial myocytes
Components of signalling pathways (e.g. phosphatases, kinases, proteases)

Emerging surrogates as outcome parameters

A limitation of current trials is that AF is considered as one entity. Emerging surrogates will allow to better identify pathophysiological mechanisms underlying AF in a given patient. Different diseases induce different 'substrates' for AF. Hence, different forms of AF may require different therapies.[77–86] In better defined patient populations, it might be easier to demonstrate a therapeutic effect of a given intervention. As an unproven working hypothesis, we propose that the therapy of the cause will be more efficient than the therapy of a symptom. Given the extensive list of potential surrogate markers (*Table 8*), it is the educated guess of the panel that some of them may develop into novel diagnostic techniques for tiered therapy of AF.[10,87–90]

Health economics

The mere number of AF patients and the frequency of complications of the arrhythmia cause large cost, often not visible within traditional health care budgets. Use of new treatment options may reduce this economic burden, but causes additional cost for treatment. It is important that any large-scale controlled AF trial includes a detailed analysis of cost. The result of such exploration should be extended beyond the actual study, projecting the application of the study results on a more general basis. This recommendation is issued with the notice that comparison of health-care related cost is difficult between different health-care systems. Important information related to cost may include hospitalizations including total duration of time spent in a hospital and number and timing of interventions, but also type and duration of medication, time spent on sick-leave, and cost of ambulatory health-care provision.

Specific design issues in atrial fibrillation trials

Composite outcome parameters in atrial fibrillation

Composite outcome parameters should usually be spared for secondary analyses. In any case, the relative contribution of each of these parameters for the composite outcome should be reported and accounted for upfront. At times, a larger or longer trial with less frequent follow-up may yield more important clinical information (e.g. on death or stroke) than a smaller trial with more intensive follow-up details (e.g. on the composite of death, hospitalization, myocardial infarction, and stroke).

Cardiovascular hospitalizations

Cardiovascular hospitalizations have been used as primary outcome parameter or as the main component of a composite primary outcome parameter for AF trials (*Table 3*). Cardiovascular hospitalizations can be easily and reliably measured in multi-centre trials, but integrate information from several outcome domains, depending on the primary reason for admission, including rhythm, further interventions, heart failure, thromboembolic complications, adverse events, and health economics. Local treatment routines will influence whether a given medical condition is treated on an out-patient basis or in hospital (e.g. cardioversion, initiation of antiarrhythmic drug treatment). Last but not least, a potentially relevant portion of cardiovascular hospitalizations may be unrelated to AF (e.g. myocardial infarctions, see section on AF-related deaths). Hence, number of hospitalizations will measure AF-related *and* unrelated effects. At times, the time spent in hospital may be more relevant than the number of hospitalizations. The panel recommends to use cardiovascular hospitalizations as a secondary outcome parameter, to report the time (e.g. days) spent in hospital, and to report the contribution of the different causes of cardiovascular hospitalization to this composite outcome parameter.

Further interventions

The necessity for repeated treatment has been used as an outcome parameter in AF trials, especially in trials investigating rhythm-control interventions. Ideally, such 'further interventions' are pre-specified parts of the study protocol, rendering them part of the tested (e.g. rhythm control) strategy. The underlying arrhythmia, not the repeated intervention *per se*, should be defined as outcome parameter.

Time-based assessment of outcome parameters

When a rhythm-based primary outcome event is reached, the patient often ends his/her trial participation. This has been a problem in AF trials. After reaching a time-based (e.g rhythm) primary outcome event, all patients should be followed until the end of the trial to assess death, stroke, and potentially other outcome domains.

'Blanking' or 'therapy stabilization' periods

Such a period is defined as the time interval during which episodes of recurrent AF should be documented but not counted as components of the ECG-based outcome parameter. As the term 'blanking period' can cause confusion among investigators and protocols, it is suggested to use the term 'stabilization period'. While there are aspects of trial design that strongly argue against such periods, there is sometimes a relevant biological rationale for such a 'stabilization' period. If used, however, there are several principles that should be observed: (i) All events during the 'stabilization period' need to be recorded and reported. (ii) For reasons of design (intention-to-treat, equal treatment in all study arms), such a 'stabilization period' must be pre-specified in the protocol, begin at the time of randomization, and comprise an equal period for all study arms. (iii) All events not related to the ECG-based outcome, e.g. performance measures and adverse events, have to be recorded and counted from the time of randomization.

Assessment of radiation exposure

Catheter ablation procedures and radiation-based imaging (e.g. computed tomography of brain and heart) cause considerable exposure to ionizing radiation for patients[91,92] and operators.[91,93,94] Assessment of radiation dose is therefore a required part of the safety outcome in every trial that includes fluoroscopy-based interventions or radiation-based imaging, e.g. to guide therapy. Fluoroscopy time is not adequate to measure radiation exposure. Dose–area products (expressed in $Gy \times cm^2$) are readily available and recommended to measure radiation energy delivered to the patient and to the operator. They can be used to estimate effective patient-doses.[95,96] Radiation exposure must include all exposure including those resulting from pre- or post-procedural imaging (e.g. cardiac CT scans for image fusion).

Conclusion

AF has a complex aetiology and causes morbidity and mortality due to many different mechanisms. A controlled trial in AF patients requires assessment of the effect of therapy in each of the main outcome categories. A careful selection of relevant outcome parameters is mandatory for any AF trial. This paper describes an expert consensus of required outcome parameters in seven relevant outcome domains and gives information on additional, more intensive monitoring of outcome. Although this exceeds current practice in some trials, the panel recommends basal assessment of all major outcome domains in AF trials. Only such a comprehensive set of outcome parameters will allow to compare the effects of different treatments across trials.

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AFNET and EHRA support a policy of transparency towards such involvements as required by the ESC journals. Therefore, the following table lists potential conflicts of interest of the authors. Furthermore, corporate affiliations of the other contributors to this document, who are listed in the *Appendix* section are indicated after the respective names.

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Paulus Kirchhof	3M Medica AstraZeneca Medtronic Sanofi-Aventis Servier Siemens Takeda	None	None	Cardiovascular Therapeutics 3M Medica/MEDAPharma Medtronic OMRON German Federal Ministry for Education and Research (BMBF) Fondation LeDucq German Resarch Foundation (DFG)	APAL MOBIPAPA MOBIPAPA II Flec-SL AFNET	None
Angelo Auricchio	Medtronic Boston Scientific Sorin Biotronic Takeda	None	None	Medtronic Boston Scientific	None	None
Jeroen Bax	None	None	None	Boston/Guidant GE Medical Medtronic St. Jude Medical	None	None

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Harry Crijns	Sanofi-Aventis AstraZeneca Cardiome Meda	Sanofi-Aventis AstraZeneca St. Jude Medical Meda	None	Medtronic St. Jude Medical Sanofi-Aventis	TIARA RACE II ATHENA ICARIOS CardioFit Cardiome CORYFEE MAIA	None
John Camm	Sanofi-Aventis Medtronic Cryocor Servier Xention Prism GlaxoSmithKline Novartis Lundbeck Guidant Sorin	Sanofi-Aventis Bristol Myer Squibb	None	Pfizer Sanofi-Aventis Bristol Myer Squibb Guidant		
Hans-Christoph Diener	Abbott AstraZeneca Bayer Vital BMS Boehringer Ingelheim D-Pharm Fresenius GlaxoSmithKline Janssen Cilag MSD Novartis NovoNordisk Paion Parke-Davis Pfizer Sanofi-Aventis Sankyo Servier Solvay Thrombogenics Wyeth Yamaguchi	None	None	AstraZeneca GlaxoSmithKline Boehringer Ingelheim Novartis Janssen-Cilag Sanofi-Aventis Bertelsmann Foundation Heinz-Nixdorf Foundation European Union German Federal Ministry for Education and Research German Resarch Foundation (DFG)	None	None
Andreas Goette	Daiichi-Sankyo Sanofi-Aventis 3M Medica Boehringer Servier BMS AstraZeneca	None	None	German Federal Ministry for Education and Research (AFNET; NBL3) Sanofi-Aventis Daiichi-Sankyo 3M Medica/MEDAPharma OMRON	ANTIPAF CREATIVE AF AFNET	None
Gerd Hindricks	Bard St. Jude Medical	Biosense Biotronik Philips Stereotaxis St. Jude	None	St. Jude Medical Biotronik Biosense Stereotaxis	None	None
Stefan Hohnloser	St. Jude Medical Sanofi-Aventis BMS P&G Boehringer Ingelheim	Sanofi-Aventis	None	St. Jude Medical Sanofi-Aventis Boehringer Ingelheim	Numerous trials in the past and present (sponsors to the right)	None
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Continued

Continued

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Appendix

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