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Outcome parameters for trials in atrial fibrillation

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

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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. New treatment modalities are therefore currently under evaluation in clinical trials. Given the multifold clinical consequences of AF, controlled 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 outcome parameters are described in each outcome domain. 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 several million people in the European Union. Its incidence and prevalence increases in an ageing population.[1] It is estimated that one in four 40-year-olds will develop AF during his or her life.[2,3] In subjects without overt heart failure, the lifetime risk for AF is still 16%, or one in seven persons. This epidemic of AF has important consequences, given the increased mortality and morbidity associated with this arrhythmia, particularly due

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to haemodynamic and thromboembolic complications.[4–7] The clinical syndrome 'AF' includes a broad spectrum of pathophysiological processes, probably ranging from a primary electrical myocardial disease[8,9] to a distant consequence of long-term systemic disease processes.[10] Likewise, the clinical consequences of the arrhythmia are multifold and often difficult to predict in an individual patient. Death, severe stroke, acute heart failure, or severe limitations of exercise capacity in some patients contrast with frequent asymptomatic episodes of the arrhythmia in others.[11–13] Treatment options are equally diverse and range from antithrombotic treatment,[14] control of ventricular rate by drugs or pacemakers,[15] antiarrhythmic drugs,[16] antiarrhythmic catheter interventions,[17] pacing interventions for rate or rhythm control, to operative compartimentalization of the atria.[18] These 'classical therapeutic options' have more recently been supplemented by so-called 'upstream therapies' targeted at the pathophysiological changes that are either believed to precede some forms of AF or attributable to the arrhythmia itself.[19]

The limited effectiveness and at times unfavourable side effect profile of available therapeutic options has resulted in an increasing number of controlled AF trials: a Medline search in February 2007 using the keywords 'atrial fibrillation', 'randomized', and 'trial' yielded over 1900 publications. The number of published trials has constantly increased in the past decades, with a large surge of published trials after 2002 (*Figure 1*). Because of the diverse therapeutic options and desired outcomes, trials that assess different treatment options for AF often use completely different outcome parameters. This renders a comparison of results very difficult, especially when the tested interventions aimed at different consequences of the arrhythmia. This situation is unfortunate, given the fact that physicians have to select the most appropriate treatment options for his or her AF patient. A uniform and comprehensive set of outcome parameters that are to be reported in every trial in AF would overcome this situation.

Throughout the text, outcome parameter is used instead of the more common, but potentially misleading term 'end point': many end points are reached without any 'ending'

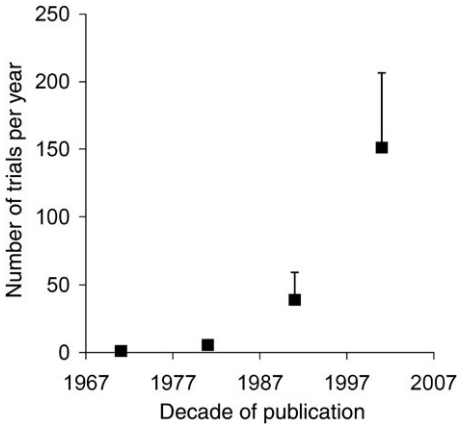

Figure 1 Number of randomized trials in AF as accessible by a Medline search (search terms: 'randomized'/'randomized', 'trial', and 'AF') in the decades from 1967 to 2006. Dots indicate the mean number of trials per year over a given decade, error bars the standard deviation.

(e.g. of participation in the study, or of study treatment), and some, e.g. AF burden, integrate measurements from the entire duration of the trial. Furthermore, the changing incidence of relevant outcome events, e.g. strokes, has resulted in the emergence of new or composite outcome parameters. This makes AF a difficult topic in the context of controlled trials and clinical day-to-day management.

To overcome this problem, the German Atrial Fibrillation Competence Network (AFNET, www.kompetenznetz-vorhofflimmern.de) and the European Heart Rhythm Association (EHRA, http://www.escardio.org/bodies/associations/EHRA/?hit=quick) 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 results of this conference. This document has been compiled based on the documents, statements, and presentations created during the conference during three plenary session and two half-day meetings of seven individual breakout groups. The members of the writing group and the chairmen of the breakout sessions are listed as authors of this document. The paper draft was circulated for critical comments among all participants of the conference and selected additional persons. These persons are listed as additional contributors.

The paper provides a list of patients' data that should be reported at entry in controlled trials in AF patients and discusses some general considerations relevant for outcome parameters in AF trials. The main body of the paper describes relevant outcome domains in a hierarchical structure, namely death, cerebro-vascular accidents (mainly stroke), changes in symptoms and quality of life, changes in rhythm, changes in left ventricular (LV) function and development of heart failure, health economics, and emerging outcome parameters. Every section ends with a list of required outcome parameters in the respective outcome domain for a well-designed trial in AF. The paper ends with a short discussion of specific, at times controversial, design aspects of controlled trials in AF patients.

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

In order to define a reasonable set of outcome parameters for AF trials, it is necessary to recall the 'natural' time course of the arrhythmia and its consequences. Atrial fibrillation is a chronically progressing arrhythmia. The first detected episode of AF is often self-terminating or amenable to rhythm-control interventions. However, it is usually followed by intervals of sinus rhythm, interrupted by episodes of the arrhythmia ('paroxysmal AF', *Figure 2*). Although the frequency and duration of arrhythmia episodes increase over time, the distribution and duration of arrhythmia episodes is not random,[20] but clustered.[21,22] Time-based electrocardiogram (ECG) outcome parameters are inherently problematic since recurrences of paroxysmal AF are unpredictable. The natural variation in occurrence and duration of recurrent paroxysms of AF renders AF burden difficult in terms of statistical power, at least in pacemaker patients.[22,23] The recurrence of persistent AF, in contrast, is a single event that can be counted and its timing determined. After restoration of sinus rhythm, e.g. by cardioversion, persistent AF recurs in 25–50% of all patients in the

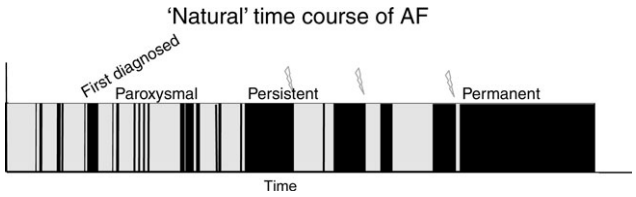

Figure 2 Time course of AF. Shown is a typical chaotic pattern of time in AF (black) and time in sinus rhythm (grey) over time (*x*-axis). Atrial fibrillation progresses from undiagnosed to first diagnosed, paroxysmal, persistent, to permanent. Flashes indicate cardioversions as examples for therapeutic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

Table 1 Points to consider on the natural time course of AF

Atrial fibrillation 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

first month after cardioversion.[12,24] Thereafter, AF recurs in 5–10% of patients per year (*Table 1*).

Atrial fibrillation causes a variety of complications, most notably thromboembolic complications and reduced cardiac performance. The risk for such complications heavily depends on the patient characteristics. Of note, the frequency of outcome events has decreased over time in AF trials,[14] possibly secondary to improved general management of cardiovascular risk. For example, adequate blood pressure control leads to less stroke and systemic embolic events in anticoagulated patients with AF.[25] The risk of severe or intracerebral bleeding associated with antithrombotic therapy may be highest immediately after the first initiation of anticoagulation in so-called 'antithrombotic-naïve patients'. Other complications also follow a certain time pattern: death is highest in the first year after the first manifestation of AF.[5,26] Thereafter, deaths occur at a steady rate[20] that is in the range of 1.6–4.2% per year in more recent controlled trials.[16,27] Rates of stroke are influenced by the standard risk factors for cerebrovascular accidents and depend on the type and quality of anticoagulation treatment.[28,29] Intracerebral bleeding, an adverse consequence of anticoagulation especially in hypertensive or accident-prone patients, occurs at a rate of $<1\%$ per year when the INR is maintained in the target range.[30,31]

General considerations

Patient characterization

Clinical outcome is heavily influenced by the inherent risk for adverse events in a study population. The best available method to estimate this inherent risk is to report baseline characteristics of the patients enrolled in a trial. The ACC/AHA[32] and the Society of Thoracic Surgeons[33] have agreed on key elements for the reporting of data in AF patients. These lists provide a good reference for the reporting of clinical characteristics of trial participants, and the panel suggests to use them, especially the more general ACC/AHA recommendations.[32] The panel agreed upon a set of required, minimal baseline characteristics, e.g. for publication of a controlled trial in AF. These characteristics are given in *Table 2*.

Table 2 Minimal clinical parameters that should be given for baseline characterization of patients in an AF 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/TIA
Heart failure indices
New York Heart Association (NYHA) class
Left ventricular ejection fraction (LVEF)
Treatment at enrolment
Antiarrhythmic drugs
Rhythm control drugs
Rate control drugs
Anticoagulation
Antihypertensive therapy (special report of angiotensin converting enzyme inhibition and angiotensin receptor blockade is suggested)
Other cardiac medication
Concomitant cardiac disease

These data should be collected at study entry.

Choice of outcome parameters in AF trials

Depending on the primary objective of the tested intervention, different AF trials will require different primary outcome parameters. On the other hand, the complex consequences of AF will require assessment of a variety of outcome domains in every trial. For example, a trial of a new antithrombotic agent may need less assessment of actual rhythm than a trial of a new rhythm-control intervention (e.g. catheter ablation). The detailed assessment of cognitive function and development of stroke during the study period will, in contrast, be more relevant for the antithrombotic trial. Both trials will, however, lose important—at times pivotal—information when rhythm, thromboembolism, and neurological outcome are not monitored at all. In the same line of thought, simple measures of LV function, quality of life, or exercise capacity may be needed in either of the aforementioned trials.

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[118]	522	Composite
PIAF[13]	252	Symptom improvement defined as elimination of palpitations, dyspnoea, and shortness of breath
HOT-CAFÉ[119]	205	Composite (death and MACCE)
STAF[120]	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[121]	403	Time to persistent AF
SOPAT[59]	1033	Time to symptomatic AF
ATHENA (NCT0017478)*	4300	Death or cardiovascular hospitalization
Flec-SL (NCT00215774)[63]*	755	Time to persistent AF
ANTIPAF (NCT00098137)*	422	Time in AF
Brignole[122]	137	Development of permanent AF
Madrid[123]	154	Time to persistent AF
Ueng[124]	145	Time to recurrent AF
Natale[125]	61	Atrial flutter, rehospitalization, quality of life
Wazni[126]	70	Time to recurrent AF, hospitalizations, and quality of life
APAF[127]	198	Time to recurrent AF
Oral[128]	80	Recurrent AF (assessment not specified)
Karch[129]	100	Freedom from AF in 7-day Holter
Oral[130]	146	Freedom from AF at 1 year FU
Gaita[131]	105	Freedom from AF at 2 years FU
AF-CHF[132]	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[81]	99	Cardiac function, exercise capacity
FARFIC[80]	66	Quality of life, exercise capacity
OPSITE[133]	56	Quality of life, exercise capacity
RACE II[75]	500	Composite
Farshi[15]	12	Rate increase during exercise
Antithrombotic treatment trials		
AFASAK[134]	335	Thromboembolic complication
BAATAF[135]	420	Stroke, death (not defined)
SPAF I[136]	1330	Stroke or peripheral embolism
SPINAF[137]	572	Cerebral infarction
EAFT[46]	1007	Composite (death from vascular disease, any stroke, myocardial infarction, or systemic embolism)
CAFA[138]	187	Composite (non-lacunar stroke, non-central nervous systemic embolism and fatal or intracranial haemorrhage)
AFASAK 2[139]	677	Stroke or a systemic thromboembolic event
SPAF II[140]	715	Stroke or systemic embolism
SPAF III[141]	1044	Stroke or systemic embolism
SPORTIF III[27]	3410	Stroke or systemic embolism
SPORTIF V[142]	3922	Stroke or systemic embolism
NASPEAF[143]	1209	Composite (vascular death and nonfatal stroke or systemic embolism
TIARA (NCT00224757)*	300	Composite (death, stroke, embolism, acute coronary syndrome, and major bleeding)
ACTIVE W[144]	6706	Composite (MACE)

Asterisks (*) indicate ongoing trials. In some trials, the panel has had difficulties to identify the primary outcome parameter. The panel strongly recommends that the primary outcome parameter should be specifically stated in the publication of a trial, and that secondary outcome parameters are reported following the recommendations given in this document.

In principle, there are currently three major categories of trials in AF patients, namely trials of interventions that attempt to restore sinus rhythm and/or prevent AF (rhythm-control trials), trials that test interventions aimed at optimizing ventricular rate in patients with AF (rate-control trials), and trials in patients with AF aimed at prevention of complications of the arrhythmia, mostly thromboembolic events (e.g. by anticoagulation) or heart failure. *Table 3* lists several of the published and ongoing larger clinical trials in AF patients, grouped in these three categories, and the respective primary outcome parameter.

Ideally, the primary outcome reflects the presumed efficacy of the treatment. Safety concerns about the study treatments should be reflected in the primary safety outcome parameter. Outcome parameters reflecting

net benefit should usually be presented as secondary outcome parameters. If treatments are given to prevent complications of AF, the time until first occurrence of a major complication or the number of such events at a given point in time should be the primary outcome of the study. If treatments are given to keep the patient in sinus rhythm, rhythm-based outcome parameters or symptoms should be the primary outcome. The choice between these parameters depends on the temporal pattern of the arrhythmia and its associated symptom profile. Generally, parameters that can be measured objectively are preferred (see section on symptoms and quality of life).

Assessment of specific outcome parameters

Death

Atrial fibrillation is associated with increased and premature mortality.[4,5] Furthermore, many available treatment modalities, e.g. but not limited to antithrombotic medicines, antiarrhythmic medicines, catheter interventions, or operations, will at times cause death as a serious adverse event. Death therefore obviously needs to be measured and reported in any trial of AF, and the 'intention-to-treat' principle of reporting is crucial for reporting of death in AF trials. In contrast to time-based rhythm outcome parameters which may at times require a post-intervention 'stabilization period', all deaths need to be recorded and reported from the time of randomization on. There are several causes of death (*Table 4*): death can be due to the arrhythmia, but AF can also be a 'marker' rather than a cause of death, treatment can cause death, and last but not least death will at times be unrelated to AF. Therefore, the mode of death needs special attention in AF trials. 'Unknown' causes of death should be evaluated using best possible methods, including e.g. autopsy, doctor's reports, read-out of ICDs/monitoring devices, or Holter ECG recordings. Death is often a distant consequence of the arrhythmia. 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. 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 a therapeutic effect on mortality. This will only be possibly 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. Mortality may be an important secondary outcome parameter or part of a secondary composite outcome parameter, depending on the expected effect of the tested intervention on mortality in the study population. 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. A new treatment method aimed at improving treatment in AF patients should not impact negatively life expectancy. Therefore, all deaths should be assessed and reported as part of the safety outcome parameter in any clinical trial.

'Atrial fibrillation-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. Atrial fibrillation-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 death events 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 in the 7 days prior to death. All deaths that are a consequence of AF-related treatment (serious adverse event) should be reported in the primary safety outcome and counted as AF-related deaths. This process to determine AF-related deaths requires validation in prospective trials.

Table 4 Classification of deaths in AF trials

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

All-cause death should be classified in the groups given above.

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

Atrial fibrillation causes a relevant portion of all strokes (15–25%).[34] The increased mortality associated with AF is in part attributable to stroke and its consequences.[35] Not only does AF lead to stroke, strokes are also more severe in patients with AF.[36] Compared with patients with other aetiologies of ischaemic stroke, stroke in the presence of AF more often result in permanent disability.[37] While stroke is identified by clinical examination and symptoms, 'silent stroke' is frequently associated with AF and can be seen by cerebral imaging. Epidemiological data have associated stroke and silent cerebral ischaemic events with cognitive dysfunction and dementia.[38]

Ischaemic strokes among patients with AF are often caused by cardioembolism, most frequently from within the left atrial (LA) appendage.[39] Atrial fibrillation fulfils Virchow's triad for thrombogenesis, with abnormal blood flow (e.g. stasis within the LA appendage, diminished LV function), abnormalities of vessel wall (e.g. endothelial/endocardial damage, other structural heart disease, etc.), and abnormalities of blood constituents (with abnormalities of coagulation, fibrinolysis, and activation of platelets),[40,41] thus resulting in a prothrombotic state in the fibrillating atria.[42,43] Even in controlled trials, the residual stroke rate on optimal anticoagulation (vitamin K antagonists, most often warfarin or phenprocoumon, at an INR 2–3) is relatively high (1.3% per year in individuals without prior stroke, 3% per year in individuals with prior stroke).[44–47] Therefore, stroke is one of the most important outcome parameters in AF trials. Stroke should be evaluated using the best possible methods [including imaging with magnetic resonance imaging (MRI)/computed tomography (CT), assessing intensity of anticoagulation at time of event, neurological outcome acutely and during follow-up].

Intracerebral bleed is the natural counterpart of ischaemic stroke in anticoagulated AF patients. All bleeding events need to be reported. Bleeds become more prevalent during supratherapeutic anticoagulation (INR > 3.5).[48] Risk factors for bleeds include age and typical cardiovascular risk factors. In addition, small vessel disease increases the risk of bleeding in anticoagulated patients. Age over 65 years plus two out of the following three criteria, namely gait apraxia, mild cognitive impairment, and urinary incontinence, may indicate patients with small vessel disease. Brain imaging (MRI) could potentially help to identify patients with small vessel disease who are at high risk for bleeding. Bleeds should be classified as major when one of the following criteria is met: fatal outcome; clinically overt bleeding causing a fall in haemoglobin concentration of 2 g/dL or more or leading to transfusion of one or more units of whole blood cells; bleeding in areas of concern, e.g. retroperitoneal, intracranial, intraspinal, or intraocular; or bleeding leading to treatment cessation and/or surgical intervention. Other bleeding events should be reported as minor bleeds. Extracerebral but intracranial bleeds (subdural or epidural haemorrhage) are not strokes, but should be reported as serious adverse events, together with a statement whether they appear attributable to treatment. The primary outcome parameter should only include stroke and systemic embolic events. Intracranial bleeds may be included in a secondary composite stroke outcome because the combination of strokes and intracerebral bleeds can reflect the clinical benefit of a treatment. Data on transient ischaemic attacks (TIA) 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. They may become part of a composite secondary outcome parameter in future trials. If TIA with structural lesion is part of the primary outcome, cranial imaging is mandatory. Transient ischaemic attacks should always be adjudicated for the presence of stroke, and the clinical characteristics and the clinical estimation of the adjudicating neurologist may determine the ultimate classification. Cause of stroke should be classified according to TOAST criteria (*Table 5*).[49] Stroke consequences should be evaluated 90 days after the event using the Rankin score.[50]

Patients who enter an AF trial involving antithrombotic therapy, including trials in which antithrombotic therapy is part of concomitant therapy, who have a prior cerebrovascular accident should be considered for brain imaging to exclude bleeding prior to inclusion in the trial. Anyone with a new neurologic event fulfilling the definition of stroke needs repeat imaging. The preferred method of imaging is MRI because of its sensitivity and the avoidance of ionizing radiation. Computed tomography may substitute MRI in specific situations (e.g. metallic implants such as pacemakers which currently preclude MRI imaging, or where local facilitates dictate so). In a subgroup of patients (high risk, e.g. $CHADS_2$ score >2, clinical symptoms of small vessel disease) that did not have cerebrovascular event at study entry, MRI is suggested at baseline and at the end of follow-up to detect silent stroke, small vessel disease, and 'asymptomatic' white matter lesions. To measure cognitive function, we recommend the mini-mental state examination at baseline and during follow-up. Additional neuro-psychological tests may be reasonable when cognitive dysfunction is part of the

Table 5 TOAST criteria for classification of strokes (modified from Adams *et al.*),[49] and Rankin score for stroke severity (modified from Rankin)[50]

TOAST criteria: Aetiology of ischaemic strokes can be classified in five categories by clinical and imaging criteria. These are
Large-artery atherosclerosis
Cardioembolism
Small-vessel occlusion
Stroke of other determined aetiology (e.g. large vessel dissection)
Stroke of undetermined aetiology
Rankin score of stroke severity as described in Rankin[50]
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 AF.

targeted outcome. These need to be assessed at baseline and during follow-up. Usually, cerebral vascular events and other major cardiovascular events (e.g. myocardial infarction, pulmonary embolism) should be assessed as separate outcome parameters.

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.
- Transient ischaemic attacks are not counted as a stroke and should not be used as part of the outcome parameter.
- 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 the primary outcome parameter, additional psychometric tests are recommended.

Symptoms and AF-related quality of life

Most available data suggest that patients with AF have a poorer quality of life than comparable healthy volunteers, samples from the general population, or patients with coronary artery disease.[51] Furthermore, symptoms and perceived suffering from the arrhythmia are the main motivation for AF patients to seek medical attention, and the main indication for rate- or rhythm-control therapy at present.[39,52] They should, therefore, be measured in any trial in AF. Quality of life, disease-related impairment, and suffering or 'illness intrusiveness'[53,54] are difficult to measure objectively. Nonetheless, improved quality of life has been found in several studies assessing rate- or rhythm-control interventions in AF patients.[13,55,56] Haemodynamic deterioration in AF is an apparent cause of acute symptoms, but does not sufficiently explain the individual symptom perception in patients with chronic AF. The elusive relation between symptoms and arrhythmia recurrences, and specifically the high incidence of asymptomatic AF recurrences in patients with symptomatic AF, furthermore 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. Most often, the following self-administered questionnaires have been applied in controlled trials: short form (SF) 36, symptoms check list (SCL), AF symptoms scale (AFSS, Toronto), and the living with heart failure questionnaire (LWHF, Minnesota). These instruments are validated for global illness intrusiveness, but are—with the exception of the AFSS—not specific for AF-related symptoms. With the exception of SF36, these instruments are not validated for most languages. Such standard instruments are recommended in AF trials, but the authors acknowledge both their shortcomings in assessing AF-related symptoms and the relevant resources that such scales require for data collection and analysis. Given the elusive relation between symptoms and actual rhythm, it is recommended to establish a relation between rhythm and symptoms. In selected studies in low-risk patients, robust, validated measurements of quality of life may in the future become a primary outcome parameter, especially in small, hypothesis-generating trials. 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.

Proposal of a new 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 simple instrument to assess AF-related symptoms, the panel agreed to suggest an AF symptoms score. This classification relates not to the type of AF (to be determined by the physician), but exclusively to the patient-reported symptoms. An initiative to suggest such a score had been taken in 2004 by Douglas Zipes at the occasion of a symposium (see discussion in ref[57]). The panel of experts present in Sophia Antipolis took on this initiative and suggests the following score to describe AF-related symptoms (which is to be referred to as the EHRA classification, *Table 6*). The EHRA classification relates specifically to the time when the patient feels to be in the arrhythmia. The purpose of this new classification is to provide a specific yet simple quantification of the symptoms that are attributable to the functional consequences of AF. 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

Table 6 EHRA AF 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

This symptom classification is suggested by the panel present in Sophia Antipolis following a published suggestion by D. Zipes (see discussion in ref[57]). Similar classifications have been suggested before on several occasions, although to the knowledge of the panel never in an officially published form, and may be in the process of validation in ongoing trials. The following items 'during presumed arrhythmia episodes' are checked to determine the score: palpitations, fatigue, dizziness, dyspnoea, chest pain, and anxiety. In addition to this score, the frequency could be classified in three groups, namely occasional (less than once per month), intermediate (once per month—almost daily), and frequent (at least daily).

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 may potentially serve as 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 score may be helpful to compare AF-related symptoms across trials and in clinical practice.

Assessment of rhythm and other ECG-based outcome parameters

Electrocardiogram-based outcome measures have been used in almost all trials that assessed interventions for rhythm or rate control (*Table 3*). A relevant outcome parameter for any trial that attempts 'rhythm control', i.e. restoration and maintenance of sinus rhythm, is valid detection of recurrent AF. In the past, we have learned that AF often recurs without clinical signs or symptoms, even in symptomatic patients. Electrocardiogram recordings triggered by symptoms will miss more than half of all AF episodes, even in symptomatic patients.[12,46,58,59] To detect both symptomatic and asymptomatic AF recurrences, systematic (scheduled) ECG recordings are therefore needed. To assess freedom from AF, continuous ECG recording is the gold standard. This gold standard is not available at present, and will be available only using advanced technology (implanted devices or special garments with ECG-recording capabilities and satellite- or GSM-based data transmission) in the foreseeable future (*Table 7*). The work load for manual analysis of continuous ECG recordings is considerable. Automated analysis of stored electrograms may provide an at times reasonable, faster, but less specific alternative for AF detection.

Table 7 ECG-based outcome parameters for AF 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 (TTM)
(24–168 h) Holter recording
Loop recorders
Continuous ECG monitoring
Pacemakers/implanted defibrillators
ECG garment equipped with radio data transmission (e.g. GSM-based)

At enrolment, AF should be documented by ECG. To demonstrate persistent or permanent AF at enrolment, a 24-h Holter ECG is sufficient. The available data suggest that AF recurrences are clustered and will be of unpredictable duration and frequency.[21–23] There are systematic data to show that 7-day Holter ECG recording and daily plus symptom-activated transtelephonic ECG monitoring are equally powerful to detect paroxysmal AF episodes.[59–61] Atrial fibrillation burden in pacemakers correlates well with AF time in 7-day Holter ECG recordings.[62] Such scheduled ECG recordings will probably detect ~70% of all AF recurrences. At present, reaching 100% detection rate of paroxysmal AF will be extremely resource-intensive for the sponsor and cumbersome for the patient. One has to accept that the negative predictive value for 'freedom from AF' is 25–40% in paroxysmal AF patients with the above-mentioned 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.[23,61]

Considering a desirable intensity of ECG monitoring and the available technology, we suggest the following ECG monitoring scheme for a rhythm-control trial: all ECG recordings should be analysed blind to treatment. We recommend the establishment of a core ECG analysis laboratory. Every perceived (symptomatic) episode of AF should trigger an ECG. Any type of (e.g. single-lead) ECG recording that allows assessment of rhythm is adequate for this purpose. To measure the frequently asymptomatic episodes, additional scheduled regular ECG recordings are necessary. This can be done by regular Holter ECG recordings (e.g. 24 h/month). On the basis of the data from pacemaker databases and post-ablation surveillance with two methods, at least 72 h of Holter monitoring per 3 months will be necessary.[22,23,60,61] An alternative, acceptable option are repetitive transtelephonic short-time ECG recordings.[59,61] The available data suggest that 1 min daily transtelephonic monitoring yields similar detection rates as regular 24 h/month Holter ECG monitoring.[60,61] Daily transtelephonic monitoring may be more feasible, especially as this technique 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.[12,24,63]

Rhythm analyses need to be pre-specified and at defined intervals. Any arrhythmia that has the ECG characteristics of AF and lasts longer than 30 s should be reported as recurrent AF. In addition, we recommend grading paroxysmal AF episodes by their duration: a reasonable distinction may be to differentiate between short paroxysms of AF (30 s–24 h duration) and long paroxysms of AF (>24 h duration). Persistent or permanent AF is assumed to be present when the episode does not terminate spontaneously or is terminated by an intervention. This distinction is based on the assumption that longer AF episodes constitute a

greater risk of stroke, although some data suggest that every arrhythmia longer than 5 min may pose a risk for thromboembolic complications.[64]

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 always be described, and in almost all trials be included in the arrhythmia recurrence outcome parameter. Often, only a 12-lead ECG will allow AF to be reliably discerned from such arrhythmias.

Studies attempting to improve the technique of electrical cardioversion have used different definitions of successful cardioversion.[65–71] The panel suggests to use the following definitions: cardioversion is successful when AF has been terminated and at least one beat of an atrial rhythm has been recorded. Any recurrence of AF thereafter is recurrent AF. The timing of AF recurrence after cardioversion may be an indication for different pathophysiological processes.[72–74] Depending on the primary outcome parameter, a distinction between these 'different forms' of recurrent AF after cardioversion may be reasonable. The panel suggests the following classification: When AF recurs in the first 5 min after cardioversion, this event should be described as immediate recurrence of AF. Atrial fibrillation 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'.

'Safety' issues may require additional ECG recordings, e.g. in antiarrhythmic drug trials. This may be required for the detection of ventricular tachyarrhythmias (proarrhythmic effects), but also to identify asymptomatic yet potentially relevant bradycardia signals early during the course of a trial. 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.

Values for optimal rate control during AF are still unsettled, but the recent guidelines on AF recommend a heart rate between 60 and 80 bpm at rest and between 90 and 115 bpm during moderate exercise.[39,75] 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, possibly maximal heart rate on Holter ECG) at entry and during follow-up. Studies that compare rate- and rhythm-control strategies require detailed ECG monitoring like rhythm control studies (see above). In trials that do not target rate or rhythm (e.g. an anticoagulation trial), regular 12-lead ECGs should be performed, e.g. in 6-month 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

Atrial fibrillation can impair LV function due to different mechanisms, and depressed LV function can also pre-dispose to AF. Prior studies have shown that rate-control (either by medicines or by AV nodal ablation and pacemaker implantation)[76–81] or rhythm-control[82,83] interventions can ameliorate LV function.

Left ventricular size and function

At study entry, every patient should undergo LV assessment by echocardiography.[39] Long axis M mode measurements can be used to assess LV size (LVEDD, LVESD) and to 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 abnormal LV function is expected, two-dimensional echocardiography using a (modified) Simpson's approach is preferred.[84] Left ventricular function should be measured at a normal heart rate (60–100 bpm). In patients with irregular ventricular rhythm, averaging of LV measurements over five beats is recommended. For clinical studies, an independent Core lab is strongly recommended. Preferably, function should be compared under the same rhythm and at comparable ventricular rate. When a Core lab is used, measurements can also be done at the same time for the same patient (parallel approach, in a random order). There are no data on the incremental value of transesophageal or intracardiac ultrasound over standard echocardiography for assessment of LV size and function. Doppler techniques may provide useful information on stroke volume and cardiac output. Currently, data in AF patients are not available. Three-dimensional echocardiography may provide more reliable assessment of LV function,[85,86] but is not yet available at sufficient sites to be recommended for AF trials. Tissue Doppler and strain (rate) imaging may provide adequate reflections of global and regional systolic LV function. These techniques are currently being validated.

Diastolic LV function

At present, there is no systematic evaluation on the role of AF and of AF treatment on diastolic function. However, there is epidemiological evidence of co-existence of diastolic dysfunction and AF.[5] In sinus rhythm, pulsed Doppler assessment of mitral inflow (*E*/*A* ratio) is used to evaluate diastolic LV function. In addition to the mitral inflow pattern, isovolumetric relaxation time and pulmonary vein flow can be used. Tissue Doppler imaging techniques may supplement this information, and particularly the *E*/*E*'

ratio has been shown to correlate well with the pulmonary capillary wedge pressure (even in AF). It is uncertain whether diastolic function is relevant for therapeutic decisions in AF patients (see emerging surrogates).

Left atrial size and function

Various animal and clinical studies have shown that AF causes electrical, contractile, and structural remodelling of the atria. Conversely, restoration of sinus rhythm (by cardioversion, medication, or ablation) can lead to reverse remodelling with decrease in LA size and improvement of LA function.[87] However, even despite adequate rate control, progressive LA enlargement is observed, suggesting a progression of underlying disease processes and the continuation of arrhythmia.[83] 'Upstream therapy' by ACE-inhibitors/angiotensin-receptor antagonists and potentially by diuretics may prevent this progressive remodelling.[88] M-mode imaging from the parasternal long-axis view gives a unidimensional measurement (antero-posterior direction) and first impression of LA size. It should be used as routine LA measurement before patients are included in an AF trial. Better LA size information can be obtained from 2D-echo measurements with tracing of endocardial contours (planimetry of the two- and four-chamber views), and volumetric assessment using either the area–length method or the prolate ellipse method. These methods should be considered when LA size is used as an outcome parameter in AF trials. The American Society of Echocardiography recently emphasized the importance of volumetric assessment of the LA, since asymmetric LA remodelling will not be noticed on linear evaluations. Computed tomography is a valid alternative to echocardiography for LA size measurements,[89] but requires ionizing radiation and potentially nephrotoxic contrast media.

Left atrial function may be a reasonable secondary outcome and safety parameter when LA scars are deployed to prevent AF. In patients with sinus rhythm, the A-wave on pulsed Doppler echocardiography reflects atrial contraction and thus provides information on LA function. Both the maximal A-wave velocity and the time–velocity-integral correlate with the LA contractility. Flow velocities (pulsed Doppler imaging) in the LA appendage provide adequate information on LA contractile function, even in AF, but this measurement requires transesophageal echocardiography. The maximal velocity during atrial contraction correlates to the force of LA appendage emptying. Recent preliminary reports used LA strain analysis,[90] but this approach needs validation.

Other imaging techniques

Highly reliable information on LV volumes and function can be obtained using CT,[89] MRI, or gated nuclear imaging.[91] 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. Furthermore, nuclear imaging techniques and CT require exposure to ionizing radiation.

'Heart failure' should be a secondary outcome parameter because it is difficult to quantify. Definitions of clinical signs of heart failure should closely follow heart failure guidelines. New York Heart Association 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. Evaluation of functional parameters (such as 6 min walk test, anaerobic threshold, and VO_2max)[13] that measure clinical signs of LV (dys)function may be important in addition to echocardiographic data in patients with depressed LV function, irrespective of the underlying aetiology.[92,93] In addition, neurohormones like nt-proBNP and ANP may be helpful as a general measure of cardiac strain,[94] although elevated levels of these peptides may reflect atrial as well as ventricular strain.

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), and LV function (M Mode, preferably two-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 is 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.

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 pathophysiologic mechanisms underlying AF in a given patient. Different diseases induce different 'substrates' for AF with different evolution, and therefore, different forms of AF may require different therapies.[40,41,95–102] In better defined patient populations (inclusion criteria), it might be easier to demonstrate a therapeutic effect. As unproven working hypothesis, we propose that the therapy of the cause will be more efficient than the therapy of a symptom. Surrogates are useful for small (e.g. phase II) interventional studies to prove novel concepts or to examine the underlying pathophysiological mechanisms (*Table 8*). These may include use of advanced ECG signal analysis to identify electrophysiological mechanisms and intervention effects;[103,104] use of advanced mapping technologies and/or signal analyses to identify pathophysiological mechanisms to guide AF ablation;[105] prothrombotic indices to test antithrombotic regimes (e.g. warfarin plus antiplatelet agent) or new antithrombotic medicines (e.g. oral thrombin inhibitors, oral factor Xa inhibitors). Given the extensive list of potential surrogate markers, it is the educated guess of the panel that some of them may develop into novel diagnostic techniques for tiered therapy of AF.[10,106–109]

Table 8 Emerging surrogate outcome parameters in AF trials

Surface ECG
Frequency analysis of fibrillatory activity
Signal-averaged ECG of the P-wave
Amplitude of the QRS-complex/markers for LV 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)

Health economics

Society cost of management of AF and its consequences is currently increasing for several reasons. The number of affected patients increases by ageing of the population, but also from increased AF occurrence in age-standardized populations. Complications of AF by stroke cause large cost, often not visible within traditional healthcare budgets. Limited adherence to guidelines probably adds further, presumably unnecessary expenses to this part of the total AF-related cost. Use of new treatment options may reduce this economic burden, but causes additional cost for treatment.

Although cost–benefit analyses of individual treatment options in the care of AF patients have been reported, few attempts have been made to estimate total society cost, genuinely linked to AF and its management. The cost related to care of concomitant and/or underlying diseases further obscures the true society cost of AF. In parallel with increasing AF cost, healthcare cost limitations appear increasingly obvious in a global perspective.

Therefore, 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 healthcare related cost is difficult between different healthcare 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 healthcare provision.

Specific design issues in AF trials

Composite outcome parameter in AF

Treatment of AF aims at prevention of clinically important outcome events. This is reflected in 'composite' outcome parameters that sum e.g. up death, stroke, heart failure, and major bleeding. These 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. Relative importance of the components in the composite outcome parameter should be accounted for upfront. Analysis of composite outcome parameters should account for imbalances at baseline and during study conduct. Composite outcome parameters are not recommended, but are at times necessary to reduce sample size. 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' have been used as primary outcome parameter or as the main component of a composite primary outcome parameter for AF trials (*Table 3*). This outcome parameter attempts to assess the global change in 'cardiovascular health'. Cardiovascular hospitalizations can be easily and reliably measured in multicentre trials. This has been appreciated by trialists and regulatory bodies. Cardiovascular hospitalizations integrate, however, information from several outcome domains which at least comprise rhythm and further interventions (e.g. hospitalization for cardioversion or further AF ablation after AF recurrence), heart failure (e.g. hospitalization for acute heart failure), thromboembolic complications (e.g. hospitalization for acute stroke), adverse events (e.g. hospitalization due to symptomatic bradycardia), and health economics. Furthermore, local or national treatment routines will at times determine whether a given medical condition is treated on an outpatient 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). These considerations suggest that cardiovascular hospitalizations may actually blur or dilute the net clinical effect of a given treatment, especially in trials assessing a rhythm-control treatment. Under those circumstances, 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 therapies. Any procedure or change in therapy with potential influence on the primary outcome has to be documented as 'further intervention', e.g. change in medical therapy (dosage or drug), non-pharmacological procedures, and pill out of the pocket.

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 outcome parameter' event is reached, the patient often ends his/her participation in an AF trial. This has been a particular problem in AF trials. For example, when time to first recurrence of AF is the primary outcome parameter, the patient should still be followed for other outcome events (e.g. death or stroke) until the end of the trial. It is recommended that follow-up continues after reaching a time-based rhythm outcome in trials investigating interventions for AF in order to fully assess the effect of the intervention on the recurrence and consequences of the arrhythmia. It is difficult to combine outcome parameters that are time based with those that are not. Different statistical models are required to compensate for missing data in these different situations.

'Blanking' or 'therapy stabilization' periods

These have been used in different trials, mainly of catheter ablation for AF or in antiarrhythmic drug trials when it is expected that several weeks of therapy are necessary to reach a stable therapeutic state. 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. Although there are aspects of trial design that strongly argue against such periods, there is sometimes a relevant biological rationale for such a 'stabilization' period: antiarrhythmic drugs need adjustment of dose, and catheter-based or surgical interventions may require some time for wound healing or repeated interventions. In trials of such treatment strategies, such a blanking period may therefore be used. 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' or 'blanking' period must be pre-specified in the protocol, begin at the time of randomization, and comprise an equal duration 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.

As the term 'blanking period' can cause confusion among investigators and protocols, it is suggested to use the term 'stabilization period'. As all events should be recorded during such a period, and adverse events and events not related to ECG-based outcome will be counted, the concept of 'blanking', e.g. used in pacemaker algorithms, does not apply to such periods.

Assessment of radiation exposure

Catheter ablation procedures and radiation-based imaging (e.g. CT of brain and heart) cause considerable exposure to ionizing radiation for patients[110,111] and operators.[112] Although non-fluoroscopic catheter guidance systems and experienced operators are capable of reducing procedure-related fluoroscopy,[113,114] there is a relevant population-wide excess risk for cancer induced by ionizing radiation.[110,112,115] 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 to guide therapy.

Radiation dose is determined by multiple factors (equipment-based, patient-based, and operator-based). All modern fluoroscopy systems have dose–area product meters (DAP). Cumulative DAP (expressed in Gy $\times$ cm^2) is a useful surrogate measurement for the total amount of radiation energy delivered to the patient and of the scatter-dose to the operator. Cumulative DAP should be reported instead of fluoroscopy time in any AF trial that uses fluoroscopy-based interventions (e.g. catheter ablation) or radiation-based imaging (e.g. CT). For more detailed assessment of radiation dose, DAP values can be converted to effective patient dose by simulating the biological absorption in computer models (Monte Carlo simulation) based on the above-mentioned variables.[116,117] Separate DAP measurements should be made for both planes of biplane fluoroscopy systems with registration of the used angles. Although useful, these approximations remain imprecise to some extent. Effective dose calculations must include any radiation resulting from pre- or post-procedural cardiac or brain imaging (e.g. cardiac CT scans for image fusion).

Summary

Atrial fibrillation 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 categories of outcome parameters. In addition to these 'requirements' for outcome assessment in AF trials, which are listed above, further, more detailed outcome parameters are available in each outcome domain. A careful selection of relevant outcome parameters is mandatory for any AF trial. This paper describes an expert consensus of required outcome parameters and gives information on additional, more intensive monitoring of outcome in different domains.

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Gerd Hindricks	Bard St. Jude Medical	Biosense Biotronik Philips Stereotaxis St. Jude Medical	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
Lukas Kappenberger	Medtronic	None	None	Medtronic Schiller	None	None
Karl-Heinz Kuck	Biosense-Webster St. Jude Medical Cryocath Edwards	None	None	BMBF Stereotaxis St. Jude Medical Cryocath Medtronic	AMICA GAP-AF VTACH SMS PPT	None
Gregory Y.H. Lip	AstraZeneca Bayer Astellas Daiichi Sankyo Sanofi-Aventis Takeda	AstraZeneca Bayer	None	AstraZeneca Pfizer Sanofi-Aventis Medical Research Council	Trials sponsored by AstraZeneca Astellas Daiichi	None
Bertil Olsson	AstraZeneca Boehringer-Ingelheim Daiishi-Sankyo	None	AstraZeneca Pfizer	AstraZeneca NordForsk Swedish Heart Lung Foundation Lund University/Hospital Local foundations	Stroke prevention studies with AZ	None
Thomas Meinertz	3M Medica Sanofi-Aventis Servier	None	None	Daiishi-Sankyo Medtronic German Federal Ministry for Education and Research (BMBF)	ANITPAF AFNET	None
Silvia Priori	Pfizer Procter & Gamble Reliant Pharmaceuticals Medifacts Corp.	None	None	Medtronic	None	None
Ursula Ravens	Cardiome Pharma Corporation Aventis	None	None	German Federal Ministry for Education and Research (BMBF) Fondation Leducq German Research Foundation (DFG)	None	None
Gerhard Steinbeck	Medtronic St. Jude Medical AstraZeneca Sanofi-Aventis	None	None	Medtronic St. Jude Medical Guidant	IRIS	None
Elisabeth Svernhage	None	None	Employee of AstraZeneca	None	None	Yes
Jan Tijssen	None	None	None	None	None	None
Alphons Vincent	None	None	Employee of Medtronic	None	None	Yes
Günter Breithardt	Boston Scientific Johnson & Johnson Bayer Sanofi-Aventis	None	None	3M Medica/MEDAPharma Medtronic	Flec-SL AFNET E-SIRIUS RECORD AF ROCKET CAD-Ref Registry	None

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Appendix

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