

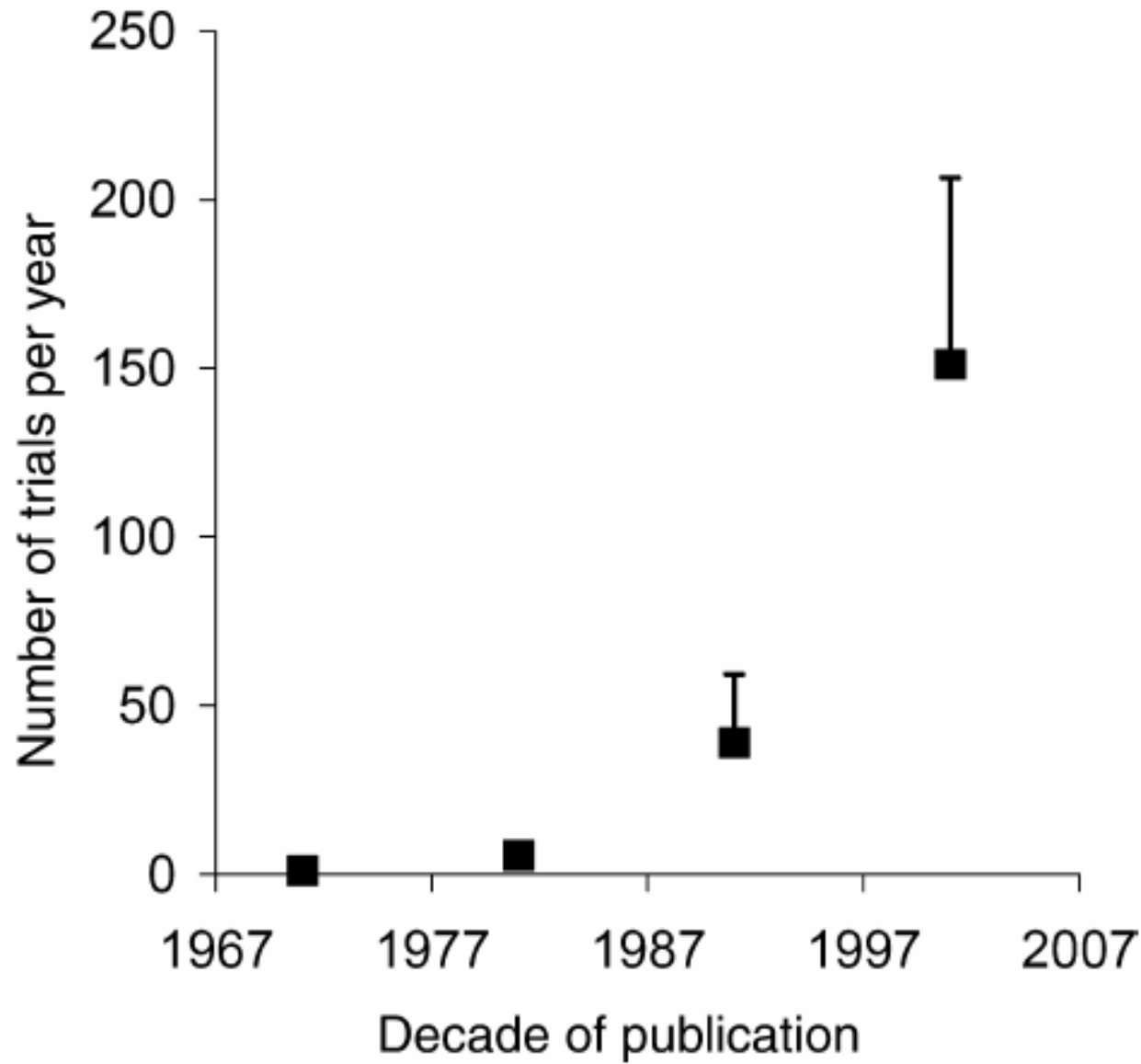
Outcome parameters for atrial fibrillation trials: A consensus statement

A Joint Initiative of the German Atrial Fibrillation
Network (AFNET) and the
European Heart Rhythm Association (EHRA)



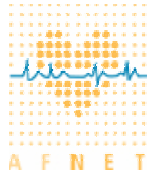
These slides summarize a consensus statement
reporting the results of a Consensus Conference
held at the European Heart House, Sophia
Antipolis, France
January 22 – 23, 2007

Number of published randomized trials in atrial fibrillation per decade (MedLine) from 1967 to 2006





Consensus Conference on Trials in AF



A Medline search in January 2007 using the key words “atrial fibrillation”, “randomized”, and “trial” yielded over 1900 publications, of which over 400 were published in 2005 and 2006

Major issues and problems

Due to the diverse therapeutic options and desired outcomes, trials have often used completely **different outcome parameters**

Furthermore, the changing incidence of relevant outcome events, e.g. strokes, has resulted in the emergence of new or composite outcome measures

This makes AF a difficult topic in the context of controlled trials and clinical day-to-day management



Consensus Conference on Trials in AF



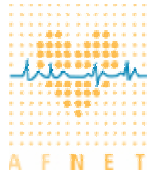
To overcome these problems,

- **the German Atrial Fibrillation competence NETwork (AFNET) and**
- **the European Heart Rhythm Association (EHRA)**

convened 60 scientists and industry representatives in the European Heart House in Sophia Antipolis, France, for a consensus conference on January 22 – 23, 2007, to define minimal and reasonable outcome parameters for the assessment of AF in controlled clinical trials.



Consensus Conference on Trials in AF



The consensus statement provides a minimal set of patient data that should be reported at entry in controlled trials in AF patients and discusses some general considerations relevant for the design, conduct, and interpretation of trials in atrial fibrillation.

In principle, there are currently three major types 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)

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 AA treatment: Number of AA drugs tested, of cardioversions, of catheter ablations or surgical interventions

CHADS2 score

Prior antithrombotic treatment: Duration of anticoagulation; antithrombotic treatment (aspirin, clopidogrel, etc)

Symptoms due to AF: Arrhythmia-related symptoms (EHRA score); prior stroke / TIA

Heart failure indices: NYHA class; LVEF

Treatment at enrollment: AA drugs; anticoagulation; antihypertensive therapy (special report of ACE inhibition is suggested)

General Considerations

“outcome parameter” is more appropriate than the conventionally used “endpoints”, because such events often do not end study participation and should not

The **complex nature** of AF and the multifold consequences of the arrhythmia are reflected by a **wide variety of outcome parameters**

The **complex time** course requires **statistical methods** to integrate the time course of outcome parameters in a practical clinical design

Seven main outcome domains

Seven different relevant outcome domains:

- death
- cerebro-vascular accidents (mainly stroke)
- changes in symptoms and quality of life
- changes in rhythm as assessed by the ECG
- changes in left ventricular function and development of heart failure
- health economics, and
- emerging surrogate outcome parameters

Every section ends with a list of minimally required outcome parameters for a well-designed trial in AF

Choice of Outcome Parameters (I)

Depending on the primary objective of the tested intervention,
different AF trials will require different outcome parameters

On the other hand, the complex consequences of AF will
require assessment of a **variety of outcome parameters** 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)
- Detailed assessment of cognitive function and development of stroke during the study period will, in contrast, be more relevant for an **antithrombotic** trial

However, both trials will lose important – at times pivotal – information when rhythm, thromboembolism, and neurological outcome are not monitored at all

Choice of outcome parameters (II)

Quality of life may be more relevant in a trial that attempts **rhythm control in highly symptomatic AF patients** than in a large trial on different methods of **rate control** (e.g. pacemaker vs. AV-nodal slowing drugs), but an opportunity may be missed in both when quality of life is not assessed at all

In the same line of thought, simple measures of **LV function and exercise capacity** may be needed in either of the aforementioned trials

Symptoms and Quality of Life

Symptoms are the main reason for AF patients to seek medical attention

At present, **symptoms and QoL are recommended as secondary outcome parameters** because there are no reliable instruments to quantify AF-related symptoms

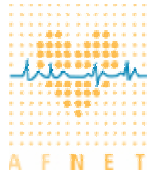
Symptoms and QoL should be assessed at entry and during follow-up in all AF trials

Outcome measures cannot be based on symptoms alone

In trials enrolling symptomatic patients, symptoms should be related to the underlying rhythm



The “EHRA score” for AF Symptoms



Proposal for a **new symptom classification scheme**

Having noticed that there is no simple, easily applicable, yet AF-specific score to measure symptoms in AF patients, the panel agreed on 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

The panel of experts suggests the following score to describe AF-related symptoms referred to as the **EHRA score**

EHRA Score for AF Symptoms

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, dyspnea, chest pain, anxiety***

In addition to this score, the ***frequency*** could be classified in three groups, namely ***occasionally*** (less than once per month); ***intermediate*** (1 / month to almost daily), and ***frequent*** (at least daily).

EHRA score for AF Symptoms

The **EHRA score** 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 score to describe AF-related symptoms

The panel is aware of the fact that this classification scheme requires prospective validation

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

Death as an Outcome Domain

Mortality is a valid outcome parameter when trials are adequately powered / designed to detect differences in mortality between treatment groups

In the majority of trials, death should not be part of the primary outcome parameter, but 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

Stroke as an Outcome Domain

AF is believed to cause a relevant portion of all strokes (**15 - 25%**)

The increased mortality associated with AF is in part attributable to stroke and its consequences

Not only does AF lead to an increase in stroke, such events are more severe in patients with AF, and more often result in permanent disability, with lower rates of discharge of patients to their own home

Stroke is identified by clinical examination and symptoms whereas “**silent stroke**” that is frequently associated with AF, can be seen only by cerebral imaging

Epidemiological data have associated stroke and silent cerebral ischemic events with **cognitive dysfunction and dementia**

Stroke as an Outcome Domain

Even in controlled trials, the **residual stroke rate** on optimal anticoagulation (INR 2-3) is relatively high (1.3% per year in individuals without prior stroke, 3% per year in individuals with prior stroke)

Therefore, stroke is **one of the most important primary outcome parameters** in long term AF trials

Strokes should be evaluated using best possible methods (including imaging with MRI/CT, assessing intensity of anticoagulation at time of event, severity of stroke acutely and during follow-up)

Intracerebral bleed is the natural counterpart of ischemic stroke in anticoagulated AF pts

TIA with matching lesion on imaging

Data on **transient ischemic 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

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 endpoint in future trials

- **Freedom from AF** (suitable for time-based assessment)
- **Change in AF pattern** (e.g. altered AF burden, altered AF type)
- **Proarrhythmia** (Torsades de pointes, bradycardia, atrial flutter)
- **Control of ventricular rate** at rest and during exercise

Available ECG recording Methods

- Non-continuous ECG recording
 - Symptom-activated (ECG, TTM)
 - Algorithm-activated (device monitors rhythm)
 - Scheduled
 - Resting ECG
 - Transtelephonic monitoring (TTM)
 - (24 – 168 hr) Holter recording
 - Loop recorders
- Continuous ECG monitoring
- Pacemakers / ICDs
- ECG garment equipped with radio data transmission

ECG Monitoring for asymptomatic AF

AF often recurs without clinical signs or symptoms, even in symptomatic patients

AF paroxysms are not randomly distributed, but clustered. This has important implications, e.g. for AF burden.

To detect both symptomatic and asymptomatic AF recurrences, **systematic ECG recordings** are 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 transmission) in the foreseeable future

ECG recordings triggered by symptoms will miss more than half of all AF episodes, even in symptomatic patients

ECG monitoring: Recommendations

At enrolment, AF should be documented by **ECG**

To demonstrate **persistent or permanent AF** at enrolment, a 24-hour Holter ECG is sufficient

AF recurrences are clustered and will be of unpredictable duration and frequency

Systematic data show that **7-day Holter ECG recordings and daily plus symptom-activated transtelephonic ECG monitoring** are equally powerful to detect paroxysmal AF episodes

Such scheduled ECG recordings will possibly detect 70% of all AF recurrences (educated guess)

ECG documentation of arrhythmia recurrences

Every arrhythmia that lasts longer than 30 seconds and has the ECG characteristics of AF should be counted as an AF recurrence

In rhythm control trials, recurrent arrhythmias on drug or after catheter ablation will not always be atrial fibrillation, 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 to reliably discern AF from such arrhythmias.

Blanking or “therapy stabilization” periods

These have been used in different trials, mainly of catheter ablation for AF

... 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

While there are aspects of trial design that strongly argue against such periods, there is 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

Blanking or “therapy stabilization” periods

In trials of such treatment strategies, such a blanking period may therefore be used

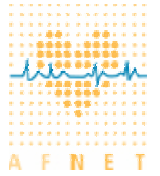
If used, however, there are several principles that need observation:

1. All events during the “stabilization period” need to be recorded and reported
2. All events not related to the ECG-based outcome, e.g., (performance measures and adverse events) have to be recorded and counted
3. For reasons of design (intention-to-treat, equal treatment in all study arms), such a “stabilization” or “blanking” period must be of equal duration in all study arms and begin at the time of randomization.

As the term “blanking period” can cause confusion among investigators and protocols, it is suggested to change the term to “early post-intervention interval”, or “stabilization period”



Consensus Conference on Trials in AF



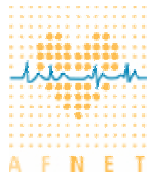
Summary

AF has a complex etiology 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 “minimal requirements” for outcome assessment in AF trials, more detailed outcome parameters are available in each outcome domain

A careful selection of relevant outcome parameters is mandatory for any AF trial



For more information, check the original consensus statements, available free for all on the Internet

Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, Goette A, Hindricks G, Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck G, Svernhage E, Tijssen J, Vincent A, Breithardt G. 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. *Europace* 2007:published on line Sept 25, 2007,

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17897925

Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener HC, Goette A, Hindricks G, Hohnloser S, Kappenberger L, Kuck KH, Lip GY, Olsson B, Meinertz T, Priori S, Ravens U, Steinbeck G, Svernhage E, Tijssen J, Vincent A, Breithardt G. 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). *Eur Heart J* 2007:published on line Sept 25, 2007,

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17897924

Kirchhof P, et al. *Europace* (full version) and *EurHJ* (summary).published on line Sept 25, 2007