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# Defining endpoints in clinical trials on atrial fibrillation

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The major factors influencing the choice of the primary endpoint in any clinical trial in patients with atrial fibrillation (AF) are the purpose of the trial, the specific characteristics of the study population in terms of the class and aetiology of AF concerned, co-morbidities, risk factors, symptom status, and whether the trial is designed for regulatory purposes. Clinically, symptom relief and improvement in quality of life are major therapeutic goals, but they are difficult to measure objectively and an effect of treatment on these parameters is currently insufficient to support drug registration. Hard endpoints such as mortality, stroke, and hospitalization are most relevant to patients with persistent AF and other concomitant morbidities resulting in a high risk of these outcomes; however, their inclusion in an appropriately weighted composite primary endpoint may be necessary in trials including less severely ill patient populations to demonstrate treatment efficacy in a regulatory context. A therapy that reduced AF and improved quality of life but increased mortality, heart failure, or other major morbid events would not be approved in the current era. Time to first AF recurrence has practical advantages as a primary endpoint, but does not accurately reflect clinically important parameters such as the frequency, type, and duration of AF recurrence and the overall AF burden. The clinical relevance of asymptomatic recurrence of AF with regard to prognosis, quality of life, and patient care, including the need for anticoagulation, is increasingly recognized. Improvement in devices enabling more continuous monitoring of cardiac rhythm now permits more accurate assessment of the effect of treatment on asymptomatic AF, representing the majority of episodes recorded in studies employing intensive monitoring procedures. An intention-to-treat analysis is always preferred, but this may not always be possible in clinical trials in patients with AF. Irrespective of the efficacy endpoint chosen, this should ideally be assessed starting from the time steady state is achieved, for drug therapy, or maturation of the lesions in the case of ablation. These time-points may be days to months after randomization. Events occurring during the period from randomization to the pre-defined start of endpoint assessment, known as the blanking period, are not taken into account in the primary efficacy analysis. The longer the blanking period, the further on-therapy analysis departs from true intention-to-treat analysis. However, on-therapy analysis is as essential as intention-to-treat analysis, especially when comparing drug vs. non-drug therapies, as it also takes into account both the frequently high crossover rates and the poor compliance with drug therapy commonly encountered in antiarrhythmic drug (AAD) trials.

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## Introduction

Before selecting the endpoints for any new clinical trial in patients with AF, several major issues must be addressed. The first concerns the definition of AF and the background to this arrhythmia with regard to co-morbidities such as hypertension, heart failure, or coronary artery disease (CAD). As pointed out in the European Heart Rhythm Association (EHRA)/Atrial Fibrillation Competence NETwork (AFNET) consensus report,[1] different diseases induce potentially distinct substrates for AF. These may differ in their evolution, may differently alter AF presentation and tolerance, and may require disparate therapies. Even though all the outcome parameters that may be influenced by any type of arrhythmia or therapy should be monitored, the relevant primary endpoints will vary greatly depending on the agent being tested, for example, an anticoagulant, an AAD, or a drug controlling heart rate. The choice of endpoints will also differ according to whether the trial is to be conducted in patients with persistent AF, and perhaps other risk factors, or patients with a normal heart presenting paroxysmal AF and in particular, lone AF. In the first case, thrombotic endpoints, particularly stroke and mortality might be appropriate, whereas in the second case, quality of life is likely to be more important, raising further issues of how this should be assessed and the relationship between symptoms and quality of life.

The choice of primary endpoint will also depend on whether the trial is designed primarily for regulatory purposes, i.e. to obtain approval for a particular therapeutic strategy by demonstrating its clinical benefit compared with a placebo (mandatory in the USA) or to other available treatments (mandatory in the European Union), or primarily to identify the optimal strategy to achieve specific clinical goals such as symptom relief and enhanced quality of life. It is currently impossible to obtain market authorization for an AAD solely on the strength of a demonstrated reduction in symptoms, yet this is often a crucial concern for patients and consequently an important clinical goal.

Up to now, regulatory agencies have been undecided about the question of how AF should be defined in the context of clinical trials. The results of studies on dofetilide, suggesting differing efficacy of this drug in patients with persistent AF and those with paroxysmal AF,[2,3] led to the recognition that efficacy of a drug might depend on the type of arrhythmia. With other drugs, however, efficacy was not so clearly correlated with the type of AF and at present, regulatory agencies do not insist on any distinction between AF associated with heart failure, AF associated with hypertension, AF associated with CAD, etc., along the lines of the 2006 ACC/AHA/ESC guidelines.[4] At least one clinical trial (SAFE-T) has suggested that the outcome of a particular AAD therapy might depend on the aetiology of the arrhythmia; the time to recurrence of AF in patients treated with sotalol was longer in the subgroup with AF associated with ischaemic heart disease than in other patients, whereas in patients treated with amiodarone, the reverse trend was seen.[5] It is likely that such distinctions will become important to both clinicians and regulators if the mechanisms, therapeutic options, and prognoses of AF in these various settings are shown to diverge.

Regulatory authorities demand 'hard' endpoints that can be objectively assessed, but have sometimes accepted the use of surrogate endpoints supposedly correlated with clinical benefit,[6] in place of endpoints such as mortality necessitating very large patient populations and very long follow-up periods. Although there is abundant evidence that patients with AF or other forms of atrial tachyarrhythmia are at increased risk for stroke and mortality,[7–10] no treatment for AF, apart from anticoagulation, has yet been conclusively shown to reduce either mortality or stroke incidence. Indeed, data from the AFFIRM study, including over 4000 patients, suggested that continuous anticoagulation is warranted in all patients with AF and risk factors for stroke even when sinus rhythm (SR) appears to be restored and maintained.[11]

To be useful and relevant, a surrogate endpoint should strongly predict the clinical outcome of interest, occur sooner and more often than this outcome, and be objectively measurable. The association between the surrogate endpoint and the clinical outcome of interest should be constant irrespective of treatment assignment.[12] For the last two or three decades, the surrogate primary endpoint used in clinical trials evaluating different AF therapies has predominantly been the recurrence of AF or other atrial tachyarrhythmia, often expressed as the time to first recurrence. It is nevertheless increasingly recognized that time to recurrence of AF may possibly have little impact on major health outcomes. Moreover, there is no consensus on the type of AF recurrence that should be considered (symptomatic/asymptomatic, paroxysmal/persistent) and the minimum duration of episodes, or the methods used to monitor and analyse recurrence.

The objective of this article is to review the important issues involved in the choice of endpoints for clinical trials evaluating treatments for AF, in the light of recent consensus conferences, clinical trial results, and debates at the second CREATE Annual Advisory Board Meeting held in Berlin on 5 October 2007.

## Consensus statements on the evaluation of atrial fibrillation therapies

Several expert consensus statements concerning the treatment of AF and the appropriate ways to evaluate different therapies were published in 2007: the Venice Chart international consensus document on AF ablation,[13] the Heart Rhythm Society (HRS)/EHRA/European Cardiac Arrhythmia Society (ECAS) expert consensus statement on catheter and surgical ablation of atrial fibrillation (AF),[14] the guidelines issued by the Workforce on Evidence-based Surgery,[15] and the report of a consensus conference organized jointly by the German Atrial Fibrillation Competence NETwork (AFNET) and EHRA.[1]

The Venice Chart,[13] focusing on the ablation of AF, notes that the success rate of any procedure can only be defined if there is a consistent approach to the technique, a

well-accepted method of follow-up, and a strict definition of success, and that currently available study reports differ with regard to all these points. It points out that most of the clinical studies consider the absence of AF as the gold standard in defining success, but some do not count very brief AF recurrences (<1–2 min) as failures, and the length of the blanking period post-ablation,* when recurrences are typically discounted, has varied from 2 to 6 months. Furthermore, there is no consensus with regard to the issue of whether success should be defined as freedom from AF recurrence in the presence of antiarrhythmic agents or without them.

The HRS/EHRA/ECAS consensus statement[14] advocates freedom from AF and atrial flutter/tachycardia of at least 30 s duration in the absence of AAD therapy as the primary endpoint in trials assessing the efficacy of AF ablation. However, this endpoint may be misleading in the absence of continuous ECG monitoring, e.g. by means of a sensitive and specific loop recorder, mobile cardiac outpatient telemetry (MCOT), or an implanted device, at present rarely feasible. When any kind of non-continuous monitoring is employed, the degree of underestimation of true events is uncertain, regardless of whether the therapy is pharmacological or non-pharmacological. Implicitly recognizing this problem, the consensus statement emphasizes the necessity of reporting the frequency of monitoring and patient compliance with this and recommends a minimum follow-up of 12 months with assessments at various points reported. It also suggests reporting of data based on a consistent post-ablation blanking period of 3 months, even if other blanking periods are chosen in the trial design.

In view of its clinical relevance, freedom from AF and atrial flutter or atrial tachycardia (AT) in the presence of previously ineffective antiarrhythmic therapy is recommended as a secondary endpoint, and the incorporation of standardized tools for assessing quality of life is advised, given that symptomatic AF is a primary indication for AF ablation. While the recommended primary endpoint is considered the gold standard, reporting all categories of outcome is encouraged, as each may be clinically relevant and provide insights into the role of AF ablation and the pathogenesis of AF.

The guidelines of the Workforce on Evidence-based Surgery of the Society of Thoracic Surgeons[15] call for greater consistency in reporting results from clinical trials in patients undergoing surgical procedures or catheter-based ablation to treat AF in order to facilitate comparison of the results obtained on different patient cohorts using different techniques. Recommendations for reporting cover a wide range of parameters, including the type and duration of AF, anticoagulant status, AF burden, and demographic and cardiovascular (CV) characteristics at baseline, post-procedure care, outcome rhythm, quality of life, and freedom from thromboembolic events at each follow-up time-point, and the time and cause of any deaths.

These guidelines emphasize the difficulty of analysing freedom from AF and freedom from AF symptoms, pointing out that although Kaplan–Meier analysis is widely used for this purpose, it is not an appropriate method, as these outcome parameters are conditions rather than events and occur intermittently. Patients may move over time between AF and SR and unless implantable recording devices are used, the time of recognition of AF rarely corresponds to the time of its initiation. Unlike events such as hospitalization, pacemaker insertion, stroke or repeat ablation, freedom from AF is therefore neither mathematically nor statistically suited to this type of analysis.

The AFNET/EHRA consensus conference[1] included trials on both pharmacological therapy and ablation for AF within its scope and specifically focused on the issue of outcome parameters. While noting that the primary outcome parameters will depend on the primary objective of the therapy assessed (rhythm-control, rate-control, or prevention of AF sequelae such as thrombo-embolism and heart failure), the consensus statement emphasized that a variety of parameters should be assessed in every trial to avoid losing important information. Even if time to first AF is the primary endpoint, patients should continue to be followed-up until the end of the study to determine the incidence of other outcomes such as stroke or death. Clinically one would also like to know the time to second and subsequent AF events, the proportion of the total time spent in SR, the total number of AF events, and/or the total AF burden (overall duration of AF as a percentage of the total time assessed). The specific outcome parameters debated in the conference were death, stroke, symptoms, and AF-related quality of life, rhythm, and other ECG-based parameters, left ventricular (LV) function and heart failure, and health economics.

## Endpoints commonly employed in clinical trials on atrial fibrillation: advantages, drawbacks and trial outcomes

Four endpoints and the controversies concerning their use are reviewed in the following sections: time to first recurrence of AF or AT, freedom from AF or AT recurrence during 1 year, mortality, and quality of life. Time to first recurrence of AF or AF/AT was the primary endpoint of the Canadian Trial of Atrial Fibrillation (CTAF),[16,17] the Sotalol-Amiodarone Fibrillation Efficacy Trial (SAFE-T),[5,18,19] and the EURIDIS and ADONIS trials,[20] and was part of the composite primary endpoint in the Prevention of Atrial Fibrillation After Cardioversion trial (PAFAC).[21]

Freedom from AF or AT during 1 year was the primary endpoint in several studies evaluating the efficacy of ablation in addition to, or vs. AAD therapy,[22–25] and was the original primary endpoint of the SAFE-T trial (redefined

*Discounting events occurring during the pre-defined blanking period has become customary in clinical trials evaluating ablation strategies, this period corresponding to the presumed time necessary for ablative lesions to become mature and stable, when their effect should be complete. This is analogous to not assessing the effect of a drug until its pharmacokinetics have reached the steady state.

after 1 year as the time to first recurrence of AF).[18] Mortality was the single primary endpoint in AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management).[11,26,27] It was also a component of the composite primary endpoint of RACE (RAte Control vs. Electrical cardioversion),[28,29] STAF (Strategies of Treatment of Atrial Fibrillation),[30] HOT CAFÉ (HOw to Treat Chronic Atrial Fibrillation),[31] ANDROMEDA (ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DecreAse),[32–34] the ADONIS and EURIDIS trials,[20] and ATHENA (A placebo-controlled, double-blind, parallel-arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of Hospitalization or death from any cause in patiENts with Atrial fibrillation).[34–37]

Symptom relief was the primary endpoint of the Pharmacological Intervention in Atrial Fibrillation Trial,[38] and the effect of treatment on quality of life was investigated in the sub-studies of several major trials (AFFIRM, CTAF, RACE, SAFE-T) as well as in the ablation study reported by Pürerfellner *et al*.[39] The main characteristics of the randomized clinical trials reviewed, including the procedure used to monitor AF recurrence are summarized in *Tables 1–3*.

## Time to first atrial fibrillation recurrence

### Advantages and drawbacks

Use of time to first event as the primary endpoint in clinical trials has the practical advantage that this outcome is easily analysed and can be displayed by life-table or survival techniques, survival analysis having the advantage that patients only need to be followed-up until occurrence of the first event. The drawback is that actual follow-up for some patients may then be very short, precluding thorough analysis of treatment safety and tolerability.[40] It is also strongly influenced by both symptom status and the method of monitoring technique employed. ECGs and transtelephonic monitoring (TTM) at specific intervals cannot provide the same accuracy as a continuous monitoring approach [auto-triggered memory loop recorder (MLR), MCOT, or implanted device]. The appropriateness of survival analysis in the context of AF recurrence has also been questioned.[15]

Time to first event is also a poor marker of the efficacy of a treatment to maintain SR, as it does not reliably reflect total AF events over time, the nature of the event, the frequency and pattern of recurrent AF episodes, or the overall AF burden. As shown in *Figure 1*, the same time to first event may be associated with widely differing levels of AF burden, i.e. the total time spent in AF, or inversely, the total time spent in SR. An endpoint defined in terms of AF burden might be of greater clinical relevance than time to first recurrence of arrhythmia, but presents a challenge in terms of measurement, ideally requiring continuous recording of the date, time of onset, and duration of each episode of arrhythmia.

One may also question whether it is any arrhythmia that is relevant and whether the time to arrhythmia onset is the sole parameter of interest. Clinically, the time to first recurrence of AF is less important than the frequency and duration of recurrences and the time between these. Is the rate of the arrhythmia important, or its irregularity? Should symptomatic arrhythmia be considered more clinically relevant than asymptomatic arrhythmia? What about anticoagulation management? What minimal duration should be set for episodes of symptomatic arrhythmia? Should brief episodes of paroxysmal AF be taken into account or only persistent arrhythmia? The impact of the choice between these various concepts on the 'time to first event' is schematically illustrated in *Figure 2*. Mehra,[41] discussing the justification for using time to first symptomatic event as a surrogate endpoint, emphasized that no clinical trial has yet demonstrated that a change in the frequency of symptomatic episodes of AF is a measure of the net effect of the treatment on the patient's quality of life.

The assumption that time to AF recurrence is correlated with the frequency of such episodes and is a valid representation of this only holds true if the episodes of arrhythmia arise randomly, independently of the time of the previous episode, i.e. fit an exponential Poisson distribution.[41] Early studies on small numbers of patients experiencing recurrent episodes of paroxysmal supraventricular tachycardia,[42] or paroxysmal AF,[43] suggested that this might be the case, the distribution of inter-episode intervals in the majority of the patients fitting an exponential distribution, corresponding to a Poisson process. However, the results of later studies, including more patients and monitoring arrhythmia episodes by implantable devices, suggested significant clustering of episodes in the majority of patients, better fitting a Weibull distribution,[44,45] or the mathematically related power law distribution,[46] than a Poisson distribution. Long-term follow-up of consecutive patients after the start of AAD treatment for AF, with no dose adjustment during the period analysed, also clearly indicated a pattern of AF recurrence not consistent with a Poisson distribution (Reiffel, previously unpublished data; *Figure 3*). This finding has major repercussions on clinical trial design as the error in using time to first recurrence to measure treatment efficacy increases dramatically if the pattern of recurrences deviates from the Poisson distribution, resulting in a significant loss of statistical power even with very large patient populations.[44]

### Symptomatic vs. asymptomatic recurrence

Both symptomatic and asymptomatic recurrence of AF are relevant to the assessment of net clinical benefit, particularly as several trials evaluating different types of therapeutic strategy have revealed that although treatment may achieve a reduction in the incidence of symptomatic episodes of AF, the frequency of asymptomatic episodes may actually increase compared with baseline. In a study of AF recurrence after radiofrequency catheter ablation,[47] a statistically significant increase in the prevalence of asymptomatic episodes was observed in an initially highly symptomatic patient population. Prior to ablation, only symptomatic episodes

**Table 1** Principal characteristics of reviewed comparative randomized clinical trials on antiarrhythmic drugs in atrial fibrillation

| References | Trial name | Treatments | No. of patients | Type of arrhythmia | Age (years, mean ± SD) | Primary endpoint | Secondary endpoints | Arrhythmia monitoring method |
|---|---|---|---|---|---|---|---|---|
| Fetsch *et al.*[21] | PAFAC | Quinidine+verapamil vs. sotalol vs. placebo | Q+V: 377; S: 383; P: 88 | Persistent AF (successfully cardioverted electrically) | Q+V: 63 ± 9; S: 62 ± 10; P: 62 ± 9 | Time to first recurrence of AF (any type) or death | Occurrence and time to persistent AF; no. of recurrences; AF-related symptom occurrence during recorded AF episodes | 1-min recording and transmission of ECGs at least once a day (independent of symptoms); additional Holter-ECG obtained if AF detected. Symptom occurrence determined at each transmission |
| Roy *et al.*[16,17], Paquette *et al.*[84] | CTAF | Low-dose amiodarone vs. sotalol or propafenone | AM: 201; S: 101; PF: 101 | AM: 49% paroxysmal AF; 51% persistent AF; S/PF: 43% paroxysmal AF; 57% persistent AF | AM: 65 ± 11; S/PF: 65 ± 11 | Time to first recurrence of AF lasting >10 min (BP = 21 days) | AAD-related adverse events; time to achieve SR; thrombo-embolic events; death; prevalence of SR at study end; cost benefit (hospital costs); quality of life at 3 and 12 months | Transtelephonic ECGs if symptoms occur+12-lead ECGs at 3 months, then every 6 months |
| Singh *et al.*[5,18,19], Atwood *et al.*[77] | SAFE-T | Amiodarone vs. sotalol vs. placebo | AM: 267; S: 261; P: 137 | Persistent AF | AM: 67 ± 9; S: 67 ± 9; P: 68 ± 10 | Time to first recurrence of AF after restoration of SR (BP = 28 days) | Quality of life (SF-36); exercise tolerance (treadmill) | Weekly transtelephonic ECGs+monthly 12-lead ECGs |
| Singh *et al.*[20] | EURIDIS | Dronedarone vs. placebo | DR: 411; P: 201 | At least one episode of ECG-confirmed AF; in SR at least 1 h before randomization | DR: 62 ± 10; P: 61 ± 11 | Time to first documented recurrence of AF lasting at least 10 min (BP = 0) | AF-related symptoms during ECG recordings; mean ventricular rate during first recurrence | Transtelephonic: ECGs recorded D2, D3, D5, at 3, 5, 7, 10 months and whenever symptoms were experienced |

*Continued*

**Table 1** *Continued*

| References | Trial name | Treatments | No. of patients | Type of arrhythmia | Age (years, mean ± SD) | Primary endpoint | Secondary endpoints | Arrhythmia monitoring method |
|---|---|---|---|---|---|---|---|---|
| Singh *et al.*[20] | ADONIS | Dronedarone vs. placebo | DR: 417; P: 208 | At least one episode of ECG-confirmed AF; in SR at least 1 h before randomization | DR: 65 ± 11; P: 63 ± 11 | Time to first documented recurrence of AF lasting at least 10 min (BP = 0) | AF-related symptoms during ECG recordings; mean ventricular rate during first recurrence | Transtelephonic: ECGs recorded D2, D3, D5, at 3, 5, 7, 10 months and whenever symptoms were experienced |
| Sablayrolles and Le Grand,[32] Dale and White,[33] Morrow and Reiffel[34] | ANDROMEDA | Dronedarone vs. placebo | 627 | LVEF < 35%; recent hospitalization for NYHA class III or IV CHF. Presence of AF/AFL not mandatory | 69 | Death or hospitalization for CHF | | Not applicable |
| Hohnloser *et al.*,[35] Morrow and Reiffel,[34] Sanofi-Aventis[37] | ATHENA | Dronedarone vs. placebo | 4628 | Paroxysmal or persistant AF. Age 70–75 years with ≥1 high-risk markers (HT, diabetes, prior CVA, LAD > 50 mm, LVEF < 40%) or >75 years | 72 | All-cause mortality or CV hospitalization | All-cause mortality; CV mortality; mortality due to arrhythmia; CV hospitalization; hospitalization for AF; hospitalization for ACS | Not applicable |

AAD, antiarrhythmic drug(s); AM, amiodarone; PP, propafenone; Q+V, quinidine+verapamil; S, sotalol; ACS, acute coronary syndrome; AF, atrial fibrillation; AFL, atrial flutter; CHF, congestive heart failure; CV, cardiovascular; CVA, cerebrovascular accident; DR, dronedarone; HT, hypertension; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; P, placebo; SR, sinus rhythm.

**Table 2** Principal characteristics of reviewed randomized clinical trials comparing antiarrhythmic drugs with ablation in atrial fibrillation

| Reference | Trial name | Treatments | No. of patients | Type of arrhythmia | Age (years, mean ± SD) | Primary endpoint | Secondary endpoints | Arrhythmia monitoring method |
|---|---|---|---|---|---|---|---|---|
| Wazni *et al.*[22] | | Ablation vs. AAD (chosen at the investigator's discretion; recommended initial therapy F, PP, or S at maximum tolerated doses) | AB: 33; AAD: 37 | AB: 32 patients (97%) paroxysmal AF; 1 patient persistent AF; AAD: 35 patients (95%) paroxysmal AF; 2 patients persistent AF | AB: 53 ± 8; AAD: 54 ± 8 | Any recurrence of symptomatic AF or asymptomatic AF lasting >15 s during 1 year (BP = 2 months) | Hospitalizations; quality of life (SF-36) at 6 months | Loop event-recorder worn for 1 month during first month, at 3 months, and later if symptoms. Recordings two to three times daily and if symptoms; 24-h Holter monitoring pre-discharge and 3, 6, 12 months post-enrolment |
| Oral *et al.*[23] | | Ablation+AM vs. AM alone (control) | AB+AM: 77; AM: 69 | Chronic AF | AB+AM: 55 ± 9; AM: 58 ± 8 | Absence of AF or AFL with no AAD during 1 year post-ablation (control: no AF/AFL during 1 year post-cardioversion (BP = 0) | Incidence of complications; change in LA diameter; change in LVEF; change in symptom severity | 5 days/week 3 min event monitor ECG recordings, plus additional ECGs if symptoms occur |
| Pappone *et al.*[24] | APAF | Ablation vs. AAD (AM, F, or S at maximum tolerated doses, singly or in combination) | AB: 99; AAD: 99 | Paroxysmal AF | AB: 5 ± 10; AAD: 57 ± 10 | Freedom from recurrent AT during 1 year (BP = 6 weeks) | Hospitalizations | 1-min event-monitor recordings one to three times daily and when symptoms suggestive of AT were experienced |
| Stabile *et al.*[25] | | Ablation+AAD vs. AAD alone (control); Preferred AAD AM, if history of intolerance to AM, class IC AAD | AB+AAD: 68; AAD: 69 | AB+AAD: 42 patients (62%) paroxysmal AF; 26 patients persistent AF; AAD: 50 pts (72%) paroxysmal AF; 19 pts persistent AF | AB+AAD: 62 ± 9; AAD: 62 ± 11 | Absence of any AA lasting >30 s during 1 year (BP = 1 month) | None | Daily transtelephonic 30 s ECG+ECG if palpitations for 3 months post-BP; standard ECG and Holter monitoring at 1, 4, 7, 10, 13 months |

AAD, antiarrhythmic drug(s); AM, amiodarone; AB, ablation; AFL, atrial flutter; BP, blanking period; LA, left atrial; LVEF, left ventricular ejection fraction.

**Table 3** Principal characteristics of the reviewed randomized rate- vs. rhythm-control trials in atrial fibrillation

| Reference | Trial name | Treatments | No. of patients | Type of arrhythmia | Age (years, mean ± SD) | Primary endpoint | Secondary endpoints | Arrhythmia monitoring method |
|---|---|---|---|---|---|---|---|---|
| The AFFIRM Investigators,[11,26] Cooper *et al.*[27] | AFFIRM | Rate-control vs. rhythm-control: AAD at investigator's discretion; predominantly AM and S, also PP, PC, Q, F, DP, M, DF | Rate-control: 2027; rhythm-control: 2033 | High probability of recurrent AF likely to cause illness or death (69% of patients had AF lasting at least 2 days at baseline) | Rate-control: 70 ± 9; rhythm-control: 70 ± 9 | All-cause mortality | Death, disabling stroke, disabling anoxic encephalopathy, major bleeding, cardiac arrest; secondary analyses according to pre-specified covariates (age, gender, rhythm at randomization, first vs. recurrent episode of AF, CAD, HT, CHF, LVEF, duration of AF | Not applicable |
| Van Gelder *et al.*,[28] Hagens *et al.*,[29,82] Rienstra *et al.*[65] | RACE | Rate-control vs. rhythm-control: EC then S; if recurrence within 6 months EC then F or PP; if recurrence within 6 months EC then AM | Rate-control: 256; rhythm-control: 266 | Recurrent, persistent AF (93%) or atrial flutter | Rate-control: 68 ± 9; rhythm-control: 68 ± 8 | Cardiovascular death, heart failure, thrombo-embolic complications, bleeding, need for pacemaker implantation, or severe adverse effects of AAD (BP = 0) | Individual components of composite primary endpoint; mean resting HR; quality of life | 12-lead ECG at 1, 3, 6, 12, 24 months post-randomization and at study end |
| Carlsson *et al.*[30] | STAF | Rate-control vs. rhythm-control: class I AAD or S if no CHD and normal LV function, otherwise beta-blocker ± AM | Rate-control: 100; rhythm-control: 100 | AF > 4 weeks (78%)* | Rate-control: 66 ± 8; rhythm-control: 65 ± 9 | Death, stroke or TIA, systemic embolism, cardiopulmonary resuscitation | Syncope; bleeding requiring hospitalization and/or transfusion; quality of life (SF-36); echographic parameters; resting HR; maintenance of SR at follow-up | Resting ECG at baseline and at 3, 6, 12, 18, 24, 36 months |
| Opolski *et al.*[31] | HOT CAFE | Rate-control vs. rhythm-control (AAD at investigator's discretion, initially PP, DS, or S) | Rate-control: 101; rhythm-control: 104 | Persistent AF | Rate-control: 61 ± 18; rhythm-control: 60 ± 8 | All-cause death, thrombo-embolic complications, intracranial, or other major haemorrhage | Rate-control; maintenance of SR; treatment discontinuation; hospitalization; new or worsening HF; changes in exercise tolerance | 24 h Holter monitoring at study entry, at 1 and 3 months post-randomization, then every 6 months |
| Hohnloser *et al.*[38] | PIAF | Rate-control (initially diltiazem) vs. rhythm-control (initially AM) | Rate-control: 125; rhythm-control: 127 | Symptomatic persistent AF | Rate-control: 61 ± 9; rhythm-control: 60 ± 10 | Improvement in AF-related symptoms (BP = 0) | Exercise tolerance (6 min walking); change in mean HR during AF; stabilization of SR; hospitalizations; quality of life (SF-36) | 24 h Holter monitoring at baseline and at 3, 6, 12 months |

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|---|---|---|---|---|---|---|---|
| The AF-CHF Trial Investigators,[67] Nainggolan and Barclay,[68] full study results not yet reported | AF-CHF | Rate-control vs. rhythm-control in patients with AF and CHF; preferred AAD: AM; S and DF if no response or intolerance to AM. Non-pharmacological strategies to maintain SR permitted for patients refractory to AAD | Rate-control: 694; rhythm-control: 682 | History of significant AF: ≥1 episode lasting >6 h in last 6 months or shorter episode but prior EC, with LVEF ≤ 35% and NYHA class II–IV symptoms of CHF or with no CHF symptoms but LVEF ≤35%. More than 66% of patients had persistent AF | Not stated in results summary | Cardiovascular mortality | Total mortality; worsening CHF; stroke; hospitalization; quality of life; cost of therapy | Not applicable |

AAD, antiarrhythmic drug; AM, amiodarone; DF, dofetilide; DP, disopyramide; EC, electrical cardioversion; F, flecainide; M, moricizine; PC, procainamide; PP, propafenone; Q, quinidine; S, sotalol; CHF, congestive heart failure; LVEF: left ventricular ejection fraction; NYHA, New York Heart Association; SR: sinus rhythm.

* Patients were also included in STAF if they had a left atrial diameter >45 mm, congestive heart failure, NYHA functional class II or greater, LVEF <45% or had undergone at least one prior cardioversion with arrhythmia recurrence.

of AF were recorded in 38% of the patients, both symptomatic and asymptomatic episodes in 57% and only asymptomatic episodes in 5%. After ablation, the percentage of patients experiencing only asymptomatic AF increased to 37% at six-month follow-up ($P < 0.05$). In this context, a follow-up assessment based solely on recurrence of symptomatic episodes of AF would have substantially overestimated the overall success rate of the procedure and provided an incomplete basis for subsequent therapeutic decisions, such as the need for continued oral anticoagulation. No specific patient characteristics or arrhythmia patterns were found to predict the development of asymptomatic AF post-ablation. Ventricular rate-slowing drugs may also convert symptomatic AF to minimally symptomatic or asymptomatic AF resulting in inaccurate assessment.

According to numerous studies, asymptomatic episodes comprise the great majority of AF/AT episodes,[48–50] and are often of clinically significant duration.[51] They clearly can have important clinical repercussions in terms of quality of life,[52] as well as prognosis and patient care, including the need for continuous anticoagulation.[53,54] The electrophysiological and mechanical effects of symptomatic and silent AF are the same and the risk of complications, including stroke and heart failure, is probably similar.[53]

However, assessment of asymptomatic recurrence requires more intensive monitoring, ideally using an implantable recorder, auto-triggered MLR, or MCOT. Ziegler *et al*.[55] retrospectively analysed data from 574 patients with an implanted pacemaker over 1 year and compared the amount of AT/AF detected each day with those indicated by simulated random Holter monitoring (annual, quarterly, and monthly 24-h recordings, and seven-day and 20-day annual long-term recordings) and symptom-based monitoring, approximated by analysing days when patients indicated symptoms with an external activator. Intermittent and symptom-based monitoring resulted in significantly lower sensitivity and negative predictive value for identification of patients with any AT/AF ($P < 0.001$) and underestimated AT/AF burden ($P < 0.001$) when compared with continuous monitoring.

Another retrospective study compared actual records obtained by Holter monitoring, standard MLRs, and auto-triggered (AT)-MLRs, analysing 600 patients per group.[56] At the time of each transtelephonic transmission, the patient was asked about the symptoms present during the recording and those present at the time of transmission, when additional recordings could be made and transmitted. The AT-MLR approach, associated with the highest number of transmissions, permitted better capture of symptomatic events and in particular, a much higher capture of clinically significant asymptomatic events, approaching the efficacy of continuously monitoring implanted devices.

A further problem is that symptoms associated with AF are often non-specific. In both a study using transtelephonic event recording and an ongoing study using auto-triggered memory loop recording, Reiffel *et al*.[57] found that in approximately one-half of the cases, symptoms suspected to reflect an arrhythmia did not in fact coincide

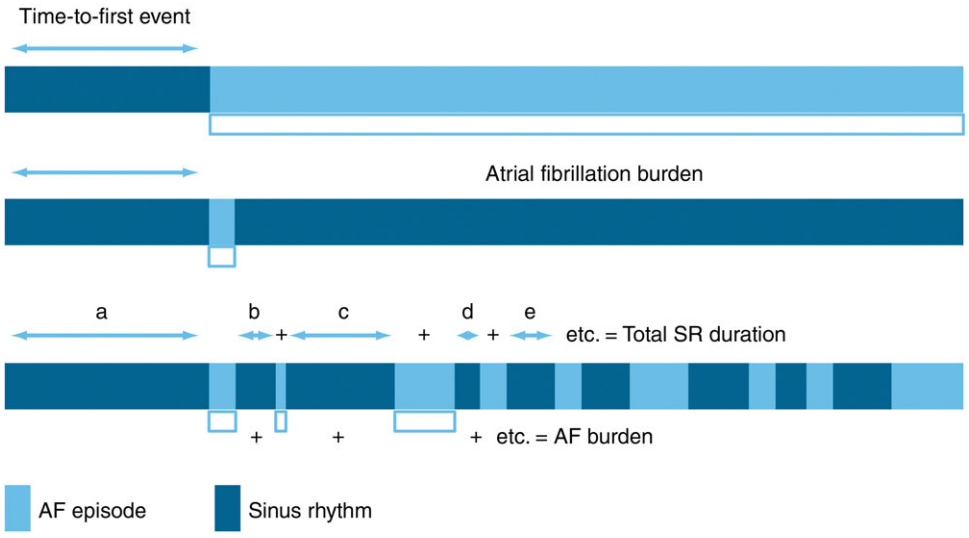


**Figure 1** Relationship between time to first event and atrial fibrillation burden.

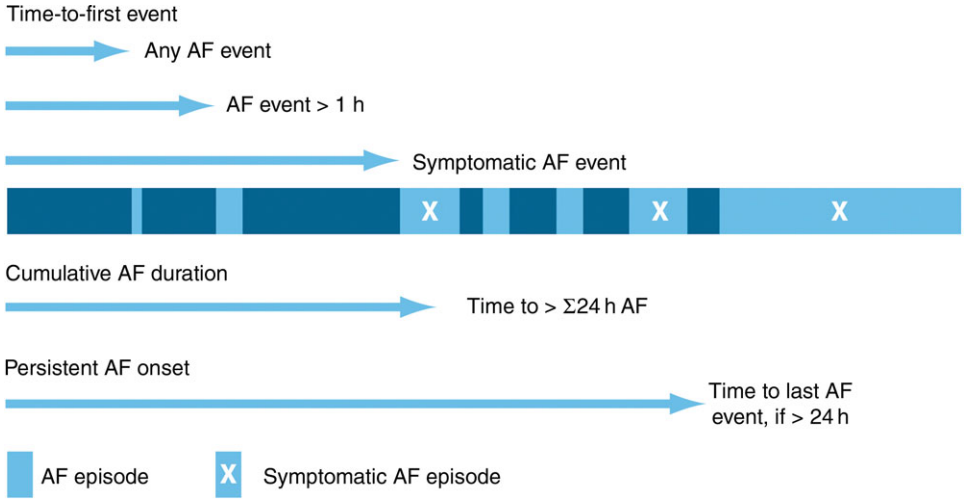


**Figure 2** Relationship between time to first event and type of event.

with any arrhythmia shown by ECG recordings. Thus, symptoms are not a reliable surrogate for a documented recurrence. Moreover, symptoms associated with AF are often attenuated when this arrhythmia becomes persistent or permanent, or when rate-control is attained. These phenomena can confound comparisons between different AADs, particularly amiodarone vs. other agents. Symptoms indistinguishable from those present in AF may also occur during SR as a consequence of therapy, e.g. fatigue may be the result of AF or the consequence of drug therapy, such as treatment with beta-blockers. Finally, the results of the recently completed AFFECTS registry (published only in abstract form so far)[58,59] demonstrated that the nature of symptoms differs in patients with paroxysmal and persistent AF. Persistent AF was more likely to be associated with non-specific dyspnoea (54 vs. 43%), fatigue (55 vs. 44%), and exercise intolerance (30 vs. 20%) than paroxysmal AF, whereas patients with paroxysmal AF were more likely to report palpitations (71 vs. 56%) and chest discomfort (21 vs. 13%) than those with persistent AF. These differences between the two populations may reflect adaptation to sensations and/or remodelling consequences of AF, but it should be borne in mind that accurate attribution of symptoms to AF is often difficult and that many symptoms can be non-specific.

## Clinical trial designs and outcomes

In the CTAF trial, comparing low doses of amiodarone with sotalol or propafenone in patients with paroxysmal or persistent AF, the primary endpoint was the time to the first electrographically confirmed recurrence of symptomatic AF lasting at least 10 min[17] (*Table 2*). During a mean follow-up period of 468 $\pm$ 150 days, 35% of the patients receiving amiodarone had first occurrences of AF, compared with 63% of those receiving sotalol or propafenone ($P < 0.001$). The median time to recurrence was 98 days in the sotalol or propafenone group, and could not be calculated for the amiodarone group as over 50% of the

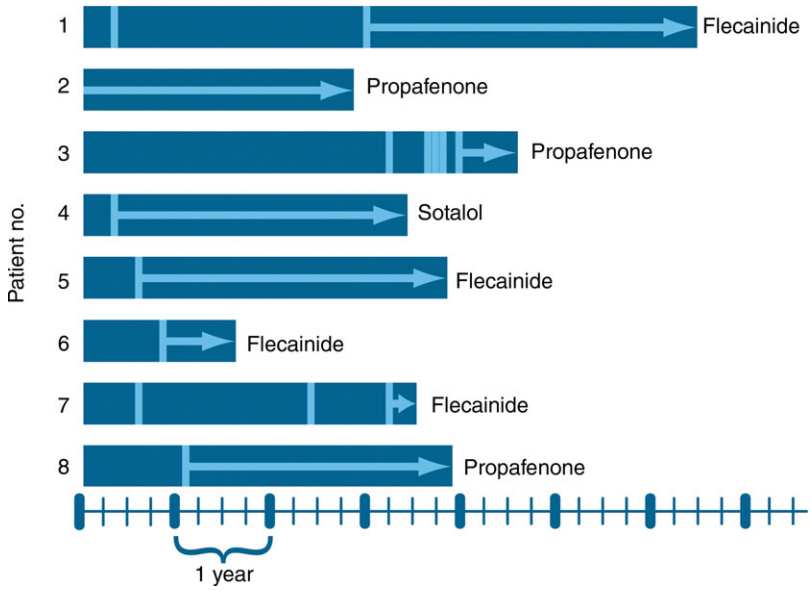


**Figure 3** Inter-atrial fibrillation (AF) intervals following the start of antiarrhythmic drugs (AADs). Eight consecutive patients with follow-up periods subsequent to the initiation of an AAD for AF during which no dose adjustment for that AAD was made. The pattern of recurrence does not fit a Poisson distribution. The bars represent the total duration of follow-up for each patient; the vertical bands represent episodes of AF; the arrows represent the duration for which no recurrence was recorded since the patient's last episode.

patients were in SR at the end of follow-up. The actuarial probability of remaining in SR for 1 year without recurrence of AF was significantly higher in the amiodarone group irrespective of whether the analysis was performed on the entire patient cohort [hazard ratio 0.43 (95% CI 0.32, 0.57)] or only on those who were in SR at the start of follow-up on day 21 post-randomization [$n = 350$; hazard ratio 0.45 (95% CI 0.32, 0.63)]. It must be recognized, however, that in CTAF, monitoring was based on ECGs at the follow-up visits (months 3, 6, 12, and every 6 months thereafter) plus TTM whenever the patients experienced symptoms. Thus, it is very likely that asymptomatic AF also occurred and would have been missed. The event rates reported should be interpreted in the light of this knowledge.

In the SAFE-T trial (*Table 1*), comparing the outcomes of patients with persistent AF randomized to treatment with amiodarone, sotalol, or placebo, the original primary endpoint was the percentage of patients remaining in SR at 1 year. With expected response rates of 60% for amiodarone, 50% for sotalol, and 35% for placebo, a power of 85% and an overall alpha level for the study of 0.05, the estimated target population was 1263. One year after the start of the study, the primary endpoint was redefined as time to first recurrence of AF following restoration of SR, based on the comparison of Kaplan–Meier time to event curves. This modification resulted in a revised target population of 706 patients, based on the same assumptions.[18] Use of time to recurrence of AF as the primary endpoint instead of the percentage of patients remaining in SR at 1 year reduced the required study population by 44% while maintaining the same statistical power. The median times to recurrence of AF were 487, 74, and 6 days, respectively, in the amiodarone, sotalol, and placebo groups, both active treatments being superior ($P < 0.001$) to placebo and amiodarone being superior to sotalol ($P < 0.001$). The percentage of patients experiencing spontaneous conversion to SR between randomization and day 28 was 70% with amiodarone, 59% with sotalol, and <1% with placebo.[5] In SAFE-T, too, monitoring methods might have affected the event rates, as this study used ECGs every 4 weeks plus TTM once a week to make its assessment.

In the identically designed EURIDIS and ADONIS trials, comparing dronedarone with placebo[20] (*Table 1*), the primary endpoint was the time from randomization to the first documented recurrence of AF lasting for at least 10 min, confirmed by two consecutive recordings (12-lead ECG or TTM). In both EURIDIS and ADONIS, median times-to-AF recurrence were increased more than two-fold in the dronedarone group compared with the placebo group (EURIDIS: 96 vs. 41 days; ADONIS: 158 vs. 59 days). The hazard ratio for recurrence of AF within 12 months (modified intention-to-treat analysis) was 0.78 (95% CI 0.64–0.96), $P = 0.01$ in EURIDIS, 0.73 (95% CI 0.59–0.89), $P = 0.002$ in ADONIS and 0.75 (95% CI 0.65–0.87), $P < 0.001$ in the two trials combined. On-treatment analysis of both the trials gave similar results, showing a significant benefit of dronedarone ($P = 0.01$ in EURIDIS, $P = 0.002$ in ADONIS). The benefit of dronedarone was consistent irrespective of the presence or absence of co-morbidities such as structural heart disease, hypertension, and heart failure.

The majority of first AF recurrences were symptomatic and the pattern of symptoms was similar in both the treatment groups. Analysis of the pooled data for both the trials showed that symptomatic recurrences occurred in 37.7% of patients receiving dronedarone and 46.0% of those receiving placebo ($P < 0.001$), compared with 64.1 vs. 75.2%, respectively, for overall AF recurrences

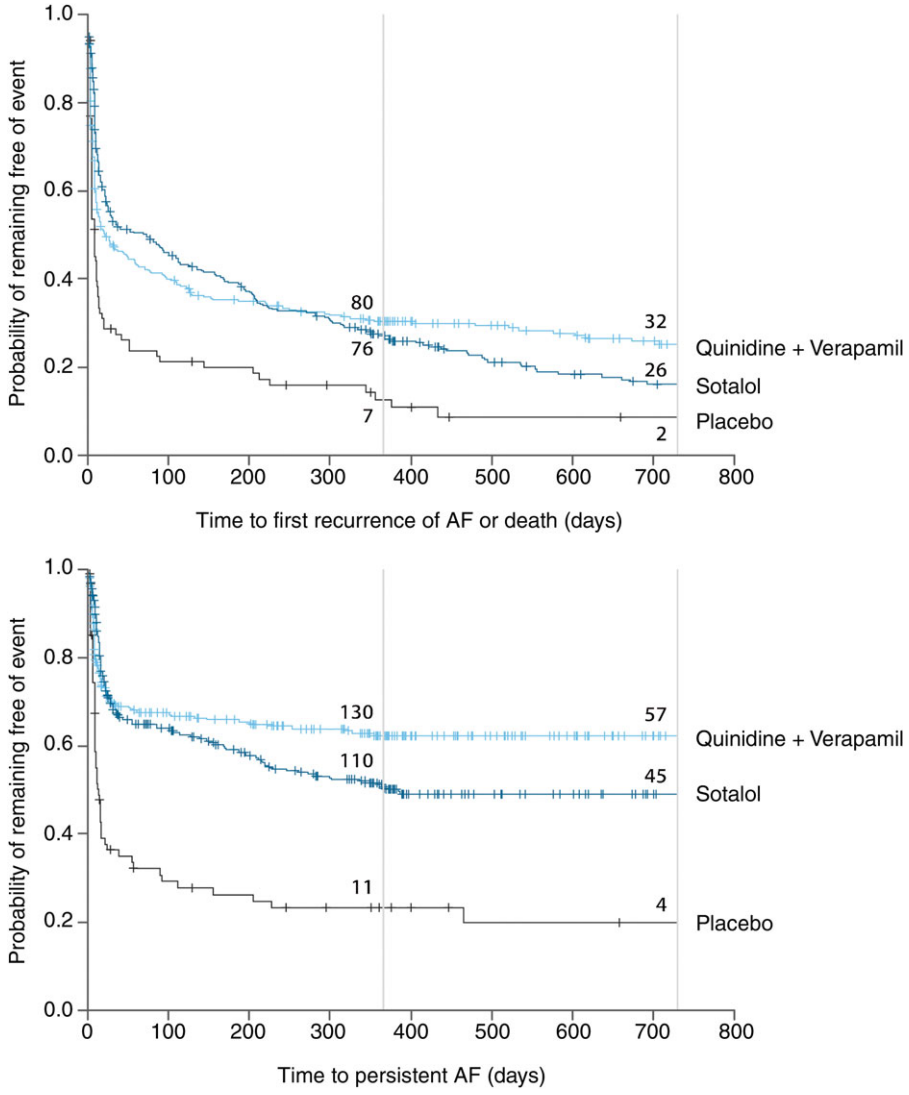


**Figure 4** Differentiation of treatment effects according to endpoint in the PAFAC trial (survival analysis): time to first recurrence of atrial fibrillation (AF) or death (primary endpoint) vs. time to persistent AF (secondary endpoint). The numbers of patients at risk are stated for 1 and 2 years of follow-up. Adapted from Fetsch *et al.*[21]

($P < 0.001$). The difference in recurrence rates between the active and placebo groups was therefore qualitatively quite similar for AF episodes as a whole, and symptomatic AF episodes. *Post hoc* analyses of EURIDIS and the pooled date of both the trials showed significantly lower rates of hospitalization or death at 12 months in the dronedarone group compared with the placebo group ($P = 0.02$ and $P = 0.01$, respectively), but the difference did not reach statistical significance in ADONIS.

The PAFAC trial[21] (*Table 1*), using daily transtelephonic ECG monitoring, analysed the time to first recurrence of any type of AF or death (composite primary endpoint) and also, as secondary endpoints, the occurrence of and the time to persistent AF, and the occurrence of symptoms during recorded episodes of any type of AF (a secondary endpoint). The primary endpoint occurred within the 12 months of follow-up in 67% of the patients overall: 65% of patients in the quinidine+verapamil group, 67% in the sotalol group, and 83% of patients in the placebo group. Both active treatments were significantly more effective than placebo, but superiority of quinidine+verapamil to sotalol could not be shown. Incidence of the primary endpoint was predominantly due to recurrence of AF as in total only 11 patients died within the first 12 months, whereas the composite primary endpoint of death or AF of any kind occurred in 572 patients within the same time frame. The mortality rate (a safety endpoint) and the cause of death did not differ significantly between the sotalol and quinidine+verapamil groups (1.6 vs. 1.3%), no deaths occurring in the placebo group.

Analysis of time to persistent AF showed a greater separation between the treatment groups, 62% of patients on quinidine+verapamil, 51% on sotalol, and 23% on placebo being free of persistent AF at 12 months (*Figure 4*). The probability of experiencing persistent AF in the quinidine+verapamil group was reduced by 39% (95% CI: 28, 50) compared with placebo and by 12% (95% CI: 5, 18) compared with sotalol, indicating statistically

significant superiority of quinidine+verapamil over both placebo and sotalol. No significant difference in the percentage of either symptomatic or asymptomatic episodes of AF, considered separately, was seen between any of the treatment groups. Approximately 70% of all the documented episodes of AF were asymptomatic and only detected in the daily tele-ECG recording. On the basis of these findings, the authors questioned the role of symptoms as clinical surrogate parameters for detecting AF, particularly in trials evaluating AADs with beta-blocking properties, when a reduction in perceived symptomatic episodes of AF may reflect a slowing of ventricular rate rather than a decrease in arrhythmia. A similar concern would also apply to other antiarrhythmic drugs slowing the ventricular rate during AF recurrence, such as amiodarone, dronedarone, and several other drugs currently under investigation.

The frequency of rhythm monitoring in the above trials varied quite widely and the report on the EURIDIS and ADONIS trials noted that the predominance of symptomatic episodes among first recurrences of AF strongly suggested that not all episodes were detected with the monitoring protocol used in these studies.[20] The PAFAC study, employing a more intensive monitoring schedule (*Table 1*), showed a majority of asymptomatic episodes.[21]

## Freedom from atrial fibrillation/atrial tachycardia at 1 year follow-up

### Clinical trial designs and outcomes

Several recent clinical trials assessing the efficacy of catheter ablation for the control of AF defined their primary endpoint in terms of freedom from atrial tachyarrhythmias at 1 year[22–25] (*Table 2*). The blanking period from randomization to the start of therapy assessment, designed to exclude from analysis of the primary endpoint events occurring during the period of AAD loading or the period of recovery from the inflammatory effects of ablation, ranged from zero to two months in these trials (*Table 2*). Events occurring during the blanking period were generally recorded and analysed separately. Methods of arrhythmia detection were inconsistent (*Table 2*).

The primary endpoint of the study reported by Wazni *et al.*,[22] comparing the efficacy of ablation (pulmonary vein isolation) vs. AAD therapy in patients with symptomatic (predominantly paroxysmal) AF, was defined as any recurrence of symptomatic AF or asymptomatic AF lasting more than 15 s during the 12-month follow-up period (*Table 2*). After excluding the events occurring in the first two months post-enrolment, 63% of the patients randomized to AAD therapy experienced at least one recurrence of symptomatic AF during the 12-month follow-up, compared with 13% of those randomized to ablation ($P < 0.001$). Asymptomatic AF was documented in 16% of the AAD therapy group vs. 2% of the ablation group.

The trial reported by Oral *et al.*[23] was designed to determine the long-term efficacy of circumferential pulmonary vein ablation (CPVA) in patients with chronic AF, while controlling for the confounding variables of AAD therapy and electrical cardioversion. Patients with chronic AF were randomized to receive amiodarone and undergo a maximum of two cardioversions during the first three months alone (control group) or in combination with CPVA. The primary endpoint was freedom from AF and atrial flutter in the absence of AAD therapy 1 year after ablation or 1 year after cardioversion in the control group (*Table 2*).

At 12 months, 74% of patients in the ablation group were in SR and free of AF or atrial flutter in the absence of AAD therapy vs. 58% in the control group ($P = 0.05$; intention-to-treat analysis). Among the patients randomized to the ablation group, 26% underwent repeat ablation because of recurrent AF and 6% because of atrial flutter. In the control group, 77% of the patients crossed over to undergo ablation a mean of $128 \pm 57$ days after cardioversion. At 1 year, SR was present in 70% of these patients in the absence of AAD therapy. Only 4% of the patients in the control group were free of recurrent AF 1 year after the first cardioversion in the absence of AAD therapy or ablation ($P < 0.001$ vs. the group randomized to ablation).

The APAF study[24] (*Table 2*) compared the efficacy of CPVA and AAD therapy (amiodarone, flecainide, or sotalol at maximum tolerable dose) in patients with paroxysmal AF who had previously failed other AADs (mean duration of paroxysmal AF: $6 \pm 5$ years; mean frequency of AF episodes: 3.4 per month. The primary endpoint was freedom from documented recurrent atrial tachyarrhythmia lasting a minimum of 30 s at 1 year. Patients randomized to AAD therapy were considered for crossover to CPVA after a minimum of 3 months and failure of therapy with two different drugs.

Kaplan–Meier analysis (intention-to-treat) showed that 86% of patients randomized to CPVA were free of atrial tachyarrhythmia at the end of the 12-month follow-up after undergoing a single procedure compared with 22% of the patients randomized to AAD therapy who did not require the addition of a second AAD ($P < 0.001$). Among the patients randomized to AAD therapy, 42% crossed over to ablation after a mean of 5.8 months. At the end of the 12-month follow-up, 86% of these patients were free of recurrent AF in the absence of AAD therapy.

Stabile *et al.*[25] investigated the effect of ablation (CPVA plus an ablation line from the left pulmonary vein to the mitral annulus) in addition to AAD therapy vs. drug therapy alone (control group) in patients with paroxysmal or persistent AF in whom two or more previous AAD therapies had failed or were not tolerated (*Table 2*). The primary endpoint was the absence of any recurrence of atrial arrhythmia lasting more than 30 s in the 1-year follow-up period, after a 1-month blanking period (intention-to-treat analysis).

By the end of the follow-up, 91% of the patients in the control group had experienced at least one AF recurrence, compared with 44% randomized to drug therapy plus ablation ($P < 0.001$). All patients in the drug therapy plus ablation group underwent a single procedure. Among the patients in the control group experiencing AF relapses,

57% underwent catheter ablation while continuing the previous ineffective AAD regimen. After a median follow-up of 18 months, 61% of these patients remained free of further AF recurrence. Separate analysis of AF recurrence during the blanking period similarly showed a lower prevalence of recurrence in the drug therapy plus ablation group (35 vs. 71%; $P < 0.001$). The percentage of patients requiring electrical cardioversion during the blanking period in the two groups did not differ significantly (25 vs. 22%). Importantly, if one looks at the above trials not to see whether ablation works but rather to what extent, it must be recognized that the lack of continuous monitoring in some studies and the use of monitoring based only on symptoms in others inevitably resulted in overestimation of the true efficacy rates for freedom from AF.

### Survival benefit of conversion to sinus rhythm

Evidence that restoration and maintenance of SR is associated with improved survival was provided by a substudy of the DIAMOND trial,[60] and also by on-treatment analysis of the AFFIRM database exploring various baseline and time-dependent variables potentially associated with an increased risk of death.[26]

The two large, placebo-controlled DIAMOND trials investigated the survival benefit of the class III antiarrhythmic dofetilide in a total of 3028 patients with reduced LV function and congestive heart failure (CHF),[61] or recent myocardial infarction (MI),[62] with a primary endpoint of all-cause death. Among the patients enrolled in DIAMOND-CHF, and known to be in SR at baseline, AF developed significantly less often with dofetilide than with placebo (2 vs. 7%; $P < 0.001$), a benefit proposed as a possible explanation for the significantly lower rate of hospitalization for worsening heart failure in the dofetilide group [hazard ratio 0.75 (95% CI 0.63–0.89), $P < 0.001$].[61] AF or atrial flutter also occurred in fewer patients with SR at baseline randomized to dofetilide in the DIAMOND-MI study, but the difference between the groups was not statistically significant.[62]

A substudy focusing on the 506 patients with AF or atrial flutter at baseline in the two DIAMOND trials (17% of the total trial population) showed an overall rate of conversion to SR of 59% in the dofetilide group and 34% in the placebo group. Among patients converting to SR, the 1 year probability of maintaining SR was 79% in the dofetilide group compared with 42% in the placebo group ($P < 0.001$; intention-to-treat analysis). This advantage of dofetilide persisted beyond 1 year. Dofetilide was a predictor of successful maintenance of SR with a relative risk of relapse of 0.30 (95% CI 0.19–0.48); $P < 0.001$. Irrespective of the treatment group, or the mode of conversion to SR (spontaneous, electrical, or pharmacological), maintenance of SR was statistically significantly associated with a reduced risk of mortality [relative risk 0.44 (95% CI 0.30, 0.64); $P < 0.0001$].[60]

On-treatment analysis of the data obtained in the similarly large AFFIRM trial (*Table 1*), evaluating various time-dependent covariates by Cox proportional hazards regression showed a strongly reduced risk of death in patients with SR [hazard ratio = 0.53 (95% CI 0.39, 0.72); $P < 0.0001$].[26] However, the authors of this study emphasize that it remains unclear whether SR in itself is an important determinant of survival or rather a marker for other factors associated with survival.

## Mortality

The AFNET/EHRA consensus conference[1] considered death to be a mandatory outcome parameter in any trial on AF and recommended reporting this parameter on an intention-to-treat basis, from randomization onwards. Whether or not mortality is included in the primary outcome parameter will depend on the statistical power of the trial to detect a therapeutic effect on mortality, given the risk of death in the patient population included and the size and duration of the trial. The consensus conference recognized that although specifically AF-related death is an attractive outcome parameter, there are currently no validated means to determine this.

Lubsen and Kirwan,[63] reviewing the use of composite endpoints in clinical trials, ranked outcomes in four hierarchical levels, the highest level being all-cause mortality (level 1) followed by cause-specific mortality (level 2), non-fatal clinical events (level 3), and symptoms, signs, and paraclinical measures (level 4). They argue that distortion can occur when the analysis for an endpoint other than all-cause mortality ignores information from higher levels. For example, hospitalization and death cannot be considered as independent entities as death reduces the risk of subsequent hospitalization to zero, so freedom from hospitalization does not necessarily equal hospital-free survival. Use of a composite endpoint combining all-cause mortality with selected non-fatal clinical events addresses event-free survival, an important criterion in the evaluation of any therapy.

### Clinical trial designs and outcomes

To the best of our knowledge only one of the recent major trials in patients with AF, AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management; *Table 3*), defined mortality alone (in terms of all-cause death) as its primary endpoint, the secondary endpoint being a composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest. Consistent with the choice of mortality as its primary endpoint, AFFIRM was a very large trial, including 4060 patients with AF aged at least 65 years (mean $69.7 \pm 9.0$ years) and at high risk of stroke or death, with a mean follow-up of 3.5 years (maximum 6 years). Overall, 65% of the patients had an enlarged left atrium and 26% had depressed LV function.

All-cause mortality (the primary endpoint) did not differ significantly between the two groups ($P = 0.08$), but a trend towards a difference in mortality in favour of rate-control began to emerge at around 1.5–2 years of follow-up. This trend persisted after adjustment for age, CAD, CHF, LV ejection fraction, and hypertension

($P = 0.07$). Subgroup analyses showed a higher risk of death in the rhythm-control group with respect to older patients, those without CHF, and those with coronary disease. The rates of the composite secondary endpoint were similar in the rate-control and rhythm-control groups ($P = 0.33$).[11]

A sub-study of AFFIRM re-analysed the primary trial results to determine the cause-specific modes of death according to treatment strategy. Rates of cardiac-related mortality were similar in the rhythm-control and rate-control groups (9 vs. 10%; $P = 0.95$), but there were significantly more non-CV deaths in the rhythm-control group (169 vs. 113 deaths; $P = 0.0008$), potential causes of this discrepancy including the less frequent use of anti-coagulation in this group and adverse effects of the AADs used (predominantly amiodarone).[64] Another sub-study showed that the presence of SR was associated with a 47% lower risk of death, but that AAD use, after adjusting for the presence of SR, increased the risk of death by 49%, negating the potential beneficial effects of SR and resulting in no net difference in mortality between the rate- and rhythm-control groups.[26]

Three smaller trials comparing rate-control and rhythm-control in patients with AF (*Table 3*) included mortality (either CV or all-cause death) in a composite primary endpoint, namely RACE (RAte Control vs. Electrical cardioversion), STAF (Strategies of Treatment of Atrial Fibrillation), and HOT CAFÉ (HOw to Treat Chronic Atrial Fibrillation).

RACE enrolled 522 patients with persistent AF, 90% of whom had at least one risk factor for stroke. The composite primary endpoint comprised CV death, hospitalization for CHF, thrombo-embolic complication, bleeding, pacemaker implantation, and severe adverse effects of AADs with a maximum of 3 years follow-up (intention-to-treat analysis). The primary endpoint occurred in 17.2% patients in the rate-control group vs. 22.6% of those in the rhythm-control group, representing a non-significant trend in favour of rate-control. The hazard ratio for the risk of the primary endpoint in the rate-control group, compared with the rhythm-control group was 0.73 (95% CI 0.53–1.01), $P = 0.11$.[29] The rate of death from CV causes was similar in the rate-control and rhythm-control groups (7.0 vs. 6.8%), but thrombo-embolic complications were more frequent in the rhythm-control group (7.9 vs. 5.5%).[28] A separate predefined analysis of the 261 patients with mild to moderate heart failure at enrolment (New York Heart Association class II or III), randomized evenly between rate- and rhythm-control, similarly showed no difference in the rate of occurrence of the primary endpoint between the two groups (22.3 vs. 24.4%).[29]

Several other subgroup analyses were performed in the context of this study. One of these indicated higher rates of primary endpoint events in the rhythm-control group in women [32.0 vs. 10.5%; absolute difference −21.5 (95% CI −30.8 to −12.1)] and in patients with hypertension [30.8 vs. 17.3%; absolute difference −13.5 (95% CI −22.2 to −4.9)].[28] A later analysis of gender-related differences in outcome similarly showed a significantly worse event-free survival with rhythm-control treatment in female patients [adjusted HR 3.1 (95% CI 1.5–6.3)]; $P = 0.002$], mainly due to the higher occurrence of heart failure, thrombo-embolic complications, and severe adverse effects of AADs.[65] Another subgroup analysis showed that in the rhythm-control group, the incidence of the components of the primary endpoint did not differ significantly according to whether the patient had SR or AF at the end of follow-up. However, the rates of occurrence of certain components of the primary endpoint varied markedly in patients in SR compared with those in AF at the end of the study, including CV deaths (0 vs. 9.5%) and progression of CHF (2.1 vs. 4.8%).[29]

The primary endpoint of the STAF pilot trial, including patients over 60 years old with persistent AF and a moderate- to high-risk arrhythmia recurrence, comprised a composite of all-cause death, cardiopulmonary resuscitation, cerebrovascular event, and systemic embolism. No difference in occurrence of this endpoint was seen between the rate-control and rhythm-control groups up to a mean follow-up of $19.6 \pm 8.9$ months. Eight patients (4.9%) died in the rate-control group, all of CV causes, four patients (2.5%) dying in the rhythm-control group (three of CV causes). In contrast, the rate of cerebrovascular events was higher in the rhythm-control group (3.1 vs. 0.6% per year). Notably, 18 of the 19 composite primary endpoints recorded occurred while the patient was in AF.[30]

The HOT CAFÉ study enrolled 205 patients with persistent AF (mean age $61.4 \pm 17.6$ years in the rate-control group and $60.4 \pm 7.9$ years in the rhythm-control group), the maximum follow-up being 2.5 years (mean $1.7 \pm 0.4$ years). The primary endpoint was a composite of all-cause death, thrombo-embolic complications (especially disabling ischaemic stroke), and intracranial or other major haemorrhage. No difference was seen between the two groups with respect to the rate of occurrence of this endpoint or any of its components analysed separately.[31]

The results obtained in these trials were therefore qualitatively quite similar irrespective of whether the primary endpoint was mortality alone or a composite of mortality and other adverse events, particularly thrombo-embolic complications.

Anticoagulation trials commonly include major haemorrhage as well as mortality and stroke rates in their primary endpoint, to assess the net clinical benefit. This approach has been adopted in the ongoing Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM),[66] which also incorporates in its primary endpoint the novel component of patients' will to switch from the assigned therapeutic strategy to the alternative strategy. The primary endpoint is defined as a composite of total mortality, symptomatic cerebral infarction, systemic embolism, major bleeding, hospitalization for heart failure requiring intravenous administration of diuretics, or physical/psychological disability requiring discontinuation of the assigned therapeutic strategy. The J-RHYTHM trial is designed to compare rate-control and rhythm-control strategies, both combined with antithrombotic therapy for a 3-year period, the target population being 2600

patients. In contrast to AFFIRM, anticoagulation therapy will be continued in patients with one or more risk factors for stroke, even if the patient appears to be in SR. The study population will include both patients with paroxysmal AF (spontaneous conversion to SR expected within <48 h of onset) and those with persistent AF (AF that persists for at least 48 h but less than 1 year after onset).

The randomized, multicentre AF-CHF trial was the first trial to compare rhythm- vs. rate-control strategies, specifically in patients presenting both AF and CHF. It was designed to show the potential benefits of maintaining SR on CV mortality (the primary endpoint), the rationale being that AF appears to be an independent predictor of mortality in patients with CHF.[67] In the rhythm-control group, amiodarone was the initial drug of choice, sotalol and dofetilide being used in selected cases. Electrical cardioversion was performed within 6 weeks of randomization in patients who did not convert to SR after AAD therapy and again, if necessary, within 3 months of enrolment. Pacemakers were recommended to control bradycardia and allow continued AAD administration. Patients refractory to AAD therapy could be referred for additional non-pharmacological therapies such as catheter ablation. Patients in the rate-control group received titrated doses of beta-blockers and digitalis, or both, and could undergo AV-node ablation and pacemaker insertion if necessary to achieve target heart rate. All patients received optimal treatment for heart failure, including angiotensin-converting enzyme-inhibitors, beta-blockers, and anticoagulant therapy. The percentage of patients receiving a pacemaker or implantable cardioverter defibrillator, or undergoing catheter ablation, was similar in both the groups.

The results of the AF-CHF trial were reported by Roy at the American Heart Association (AHA) Scientific Sessions (Late-breaking session) in Orlando on 7 November 2007.[68] The trial included 1376 patients with a LV function 35% or less and New York Heart Association class II–IV symptoms of CHF. More than two-thirds of the patients had persistent AF on enrolment and over 50% had been previously hospitalized for AF or CHF. Intention-to-treat analysis showed no difference in CV mortality between the rhythm- and rate-control groups, the respective rates of CV deaths being 27 vs. 25%, respectively (hazard ratio 1.058, $P = 0.59$).

The secondary endpoints of total mortality, worsening CHF, and stroke, as well as the composite endpoint of CV death, worsening CHF, and stroke, were similar between the two groups. The hospitalization rate was higher in the rhythm-control group [46 vs. 39% at 1 year ($P = 0.0063$)], mainly due to hospitalization for AF and bradyarrhythmias (8.5 vs. 4.9%, $P = 0.0074$). The rate of cardioversions was also higher in the rhythm-control group (39 vs. 8%). During the study, 21% of patients crossed over from rhythm- to rate-control, principally because of the inability to maintain SR, whereas 10% crossed over from rate- to rhythm-control, mainly because of worsening heart failure. On the basis of these results, the trial investigators concluded that a routine strategy of rhythm-control could not be advocated in patients presenting AF in the context of heart failure, rate-control representing a simpler strategy involving fewer cardioversions and fewer hospitalizations.[68]

ANDROMEDA (Antiarrhythmic trial with Dronedarone in Moderate to severe CHF Evaluating morbidity Decrease) was designed primarily to assess the safety of dronedarone in patients without AF who had moderate or severe heart failure (HF; recent episode of NYHA class III or IV and LVEF < 35%), a group with a high baseline mortality rate and a high risk of torsade de pointes (TdP). The primary endpoint was death or hospitalization for HF.[32–34]

A total of 627 patients were enrolled, with a mean age of 69 years. Most had NYHA class II or III symptoms of CHF at the time of enrolment. It was hoped that this study would confirm the absence of adverse events in a high-risk group of patients and perhaps, demonstrate a benefit in reducing the morbidity and mortality of HF in these patients. However, the preliminary results showed a trend towards a higher rate of hospitalization/mortality (RR 1.38, 95% CI 0.918–2.088, $P = 0.118$) among dronedarone-treated patients compared with the placebo group, although no TdP was observed. Retrospective analysis revealed a possible explanation for the results: like amiodarone, dronedarone decreases renal creatinine secretion without affecting the actual renal function. The dronedarone-treated patients enrolled in ANDROMEDA showed a mean increase in plasma creatinine concentration of 10–15%, leading to more frequent discontinuation of angiotensin-converting enzyme-inhibitors (ACE-I) or angiotensin-receptor blockers (ARBs) in these patients, apparently because investigators assumed that the rise in creatinine levels reflected renal dysfunction caused by these heart failure medications. A more detailed analysis of this interaction is beyond the scope of this review. In patients in whom ACE-I or ARB treatment was never started or never interrupted, there was no increase in mortality or hospitalization in dronedarone-treated patients vs. those receiving placebo.

The recently completed, multinational, double-blind, randomized study ATHENA (A placebo-controlled, double-blind, parallel-arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of Hospitalization or death from any cause in patiENts with Atrial fibrillation) had a composite primary endpoint comprising all-cause mortality and hospitalization for CV reasons. This trial, designed to provide further data on the efficacy and safety of dronedarone in a high-risk population, enrolled a total of 4628 patients with paroxysmal or persistent AF randomized to dronedarone or placebo. Enrolment was limited to patients aged 70–75 years (after an initial period allowing recruitment of younger patients as well) with one or more high-risk markers (hypertension, diabetes, prior CVA, left atrium size >50 mm, or LVEF < 40%) or to patients aged over 75 years with or without additional risk markers. Patients with NYHA class IV HF were excluded.[35]

The results of this trial were presented by Hohnloser at the Annual Scientific Sessions of the Heart Rhythm Society in San Francisco on 15 May 2008.[36,37] The enrolled patients had a mean age of 72 years (19% <65 years, 42% >75 years), 53% were male, 6% presented lone AF, and

60% had structural heart disease (86% hypertension, 30% CAD, 16% valvular disease, 6% non-ischaemic cardiomyopathy). LVEF was <45% in 12% of patients and <35% in 4% of patients, and 29% of the patients had a history of HF (mostly NYHA class II).

The primary endpoint, all-cause mortality combined with CV hospitalization, was reduced by 24% in the dronedarone group compared with the placebo group ($P < 0.001$). With respect to the secondary endpoints, dronedarone-treated patients showed a trend towards a reduction in total mortality (16%; $P = 0.176$ vs. placebo), the rate of initial CV hospitalization was reduced by 25% ($P < 0.001$), and CV mortality decreased by 29% ($P = 0.034$). The incidence of death owing to arrhythmia was also reduced in the dronedarone group. The decrease in hospitalization rate was mainly because of lower rates of hospitalization for AF ($P < 0.001$) and for acute coronary syndrome ($P = 0.030$). Discontinuation rates were approximately 30% in both the dronedarone and placebo arms. In the dronedarone group, 12.7% of patients discontinued the study prematurely because of adverse events (mainly GI symptoms) compared with 8.2% of those in the placebo group in which the principal reason for discontinuation was AF recurrence. In contrast to ANDROMEDA, ATHENA showed no excess withdrawal of ACE-Is or ARBs among dronedarone-treated patients in comparison with those receiving placebo. These striking results, demonstrating that an AAD shown to be effective in reducing AF recurrence was also effective in decreasing CV mortality and CV hospitalization (as well as arrhythmic death), are exciting and so far novel in the antiarrhythmic world.

### Cardiovascular hospitalization as a surrogate for mortality

Analysis of data on 4060 patients enrolled in the AFFIRM trial to ascertain the relative frequency of events that could potentially be considered as surrogate endpoints for mortality (stroke, MI, major bleeding, and hospitalization for CV reasons) revealed that only CV hospitalization occurred more often than death.[12] To take into account the fact that hospitalization to cardiovert AF or to change AADs was also classified as CV hospitalization in the AFFIRM trial, two cohorts were analysed. The inclusive cohort comprised all CV hospitalizations; in the censored cohort, all CV hospitalizations that occurred in the same follow-up period as a cardioversion or drug change were excluded.

Cox proportional hazards analyses including CV hospitalization as a time-dependent covariate showed that this event was significantly associated with death in both rhythm- and rate-control arms, regardless of cohort ($P < 0.0001$). In the inclusive cohort, the hazard ratio was 2.15 (95% CI 1.69–2.74) in the rate-control group and 1.71 (95% CI 1.37–2.13) in the rhythm-control group, and in the censored cohort the hazard ratios were 2.39 (1.86–3.07) and 1.98 (95% CI 1.52–2.57), respectively. There was no evidence of an interaction between CV hospitalization and treatment assignment as a predictor of death, regardless of the cohort considered. The time to death after CV hospitalization did not differ between the two treatment groups. The sensitivity and specificity for CV hospitalization as a predictor of death were 100% and 60%, respectively, in the inclusive cohort and 87% and 74%, respectively, in the censored cohort.

A retrospective estimation of the power of the AFFIRM trial to detect differences in hazard ratio using the composite endpoint of death or CV hospitalization showed that detection of a 20% difference would be virtually assured, with a power of at least 99% irrespective of the cohort considered. In contrast, acceptable power for an endpoint of mortality alone would be achieved only with a relative difference in hazard ratio of at least 30%. Comparison of the sample sizes needed to detect a 30% relative difference in event rates indicated that with the composite endpoint, the same power could be achieved with one-third of the patients required for an endpoint of mortality alone.

On the basis of this study, CV hospitalization appears to meet the criteria for an acceptable surrogate endpoint for mortality, occurring sooner and more often than death, and being highly predictive of this outcome irrespective of treatment assignment. Its applicability to other patient populations and other treatment strategies remains to be confirmed. Notably, both CV hospitalization combined with all-cause mortality (the primary efficacy endpoint) and CV hospitalization alone were significantly reduced in ATHENA.

## Quality of life

In its discussion of quality of life as a clinical endpoint, the report of the AFNET/EHRA consensus conference[1] notes that 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 CAD, citing the comprehensive review by Thrall *et al*.[69] However, the report emphasizes that while symptoms are the main motivation for patients with AF to seek medical attention and the main indication for rate- or rhythm-control therapy at present, the relationship between symptoms and arrhythmia recurrences is elusive. In conjunction with the high incidence of asymptomatic recurrences in patients with symptomatic AF, this suggests that symptoms may sometimes be unrelated to AF, but rather expressions of other disease-causing processes.[1]

The consensus conference therefore concluded that symptoms and disease-related quality of life are unreliable outcome parameters in clinical trials on AF and, while emphasizing that they should be measured in all such trials, recommends them only as secondary endpoints. Because quality of life and symptoms are qualitative endpoints, whereas death, hospitalization and stroke can be quantified, it is hard to combine them in a single endpoint, although they are all important in the clinical assessment of the therapy being employed. Noting that up to now, trials assessing AF-related quality of life have generally used self-administered questionnaires such as the Medical Outcomes Study short-form health survey (SF-36),[70,71] the symptoms check list (SCL),[72] the AF

symptoms scale (AFSS),[73] and the heart failure questionnaire (LWHF), it points out that these instruments have been validated for global illness intrusiveness but, except for AFSS, are not specific for AF-related symptoms.

Compared with many other cardiac disorders, AF is associated with a particularly great individual variation in symptoms; some patients remain completely asymptomatic during AF episodes, whereas others may suffer from a wide range of disabling symptoms including palpitations, dyspnoea, dizziness, diaphoresis, general fatigue, chest discomfort, mental disturbance, exercise intolerance, or acute or chronic heart failure.[74] The symptoms reported most frequently in a study of consecutive patients with AF admitted to a general hospital[75] were dyspnoea (52%), chest pain (34%), palpitations (26%), and dizziness or syncope (16%). In a French general practice study, the complaint most frequently voiced by patients with paroxysmal AF was palpitations (reported by 79% of the patients), whereas dyspnoea was the symptom most commonly reported by patients with chronic AF.[76]

However, symptoms and quality of life are not necessarily correlated, as patients with highly symptomatic AF sometimes report only mildly reduced quality of life, while totally asymptomatic patients may complain of impaired wellbeing. Savelieva *et al.*[52] compared quality of life (SF-36 scores) in patients with asymptomatic or very mild symptomatic AF ('asymptomatic' group), patients with symptomatic AF (those in the upper three quartiles with regard to symptom scores), and a control group without any documented CV or serious systemic disease. Compared with the control group, patients in the 'asymptomatic' group had a significantly poorer perception of their general health ($P < 0.003$) and their global life satisfaction was significantly reduced ($P < 0.003$). This finding is of particular interest as both pharmacological treatment and ablation may lead to a decreased incidence of symptomatic AF, but an increase in asymptomatic AF. Furthermore, co-morbidities are common in patients with AF and individual perception of health will inevitably reflect symptoms associated with these co-morbidities as well as those related to AF. ECG-documented presence of AF, symptoms, and quality of life therefore only partially overlap (*Figure 5*).[74]

Improving exercise tolerance is an important therapeutic objective in AF, as this condition is typically associated with a 15–20% reduction in exercise capacity.[77] In some patients, reduced exercise tolerance may even be the major presenting symptom of AF. However, clinical trial results emphasize that exercise capacity in AF varies widely between individuals and is probably influenced by many factors, including the specific underlying disease but also factors that are as yet unknown. In a substudy of SAFE-T specifically focusing on exercise tolerance, advanced age, obesity, and presence of symptoms were found to be significant predictors of exercise capacity, but these factors accounted for only 10% of the inter-individual variance.[77]

It has been proposed, originally by Zipes in 2004,[78] then by Dorian *et al.*,[79] and most recently in the AFNET/EHRA Consensus Statement of Endpoints in Atrial Fibrillation Trials[1] that the functional status of patients with AF should be classified in a similar way to that of patients with angina (NYHA classification) or dyspnoea (Canadian Cardiovascular Society). The EHRA classification grades the functional status of AF into four classes, ranging from I (mild) to IV (severe), according to the absence or presence of symptoms and the effect of these on everyday activity (*Table 4*). As in the case of the other classifications cited above, routine use of the EHRA classification would bring a degree of uniformity to the reporting of the functional status of AF patients and the effect of various treatments on this parameter.

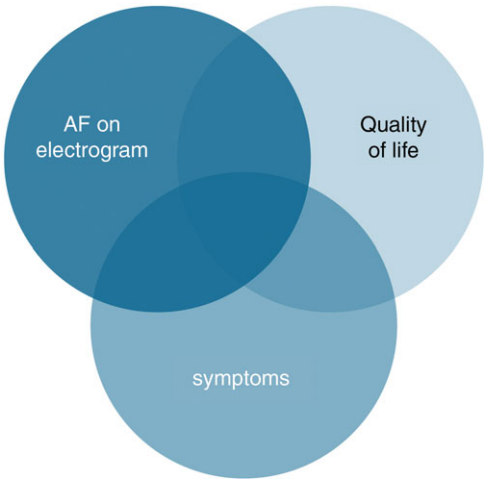


**Figure 5** Potential overlap between ECG-documented presence of atrial fibrillation (AF), symptoms, and quality of life. Quality of life may be impaired in the absence of symptoms or by symptoms related to concomitant disorders rather than AF. Adapted from: Grönefeld and Hohnloser.[74]

**Table 4** Proposed European Heart Rhythm Association (EHRA) atrial fibrillation symptom classification (Kirchhof *et al.*[1])

| Class | 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, and anxiety.

## Clinical trial designs and outcomes

The open, randomized, multicentre PIAF (Pharmacological Intervention in Atrial Fibrillation) trial, comparing rate-control (diltiazem) vs. rhythm-control (amiodarone) in 252 patients with symptomatic AF (persistent AF between 7 and 360 days' duration), selected improvement in AF-related symptoms as its primary endpoint.[38] Symptom improvement was assessed by interview at each follow-up visit by the changes compared with

baseline in the three symptoms most frequently reported by patients with AF, namely palpitations, dyspnoea, and dizziness. Improvement was defined in hierarchical order as elimination (or continued absence) of palpitations, reduction in the frequency of episodes of dyspnoea, or reduction in the frequency of dizzy spells. Another common AF-related symptom 'easy fatigability' was separately addressed as a secondary endpoint by assessment of 6-min walking tests. Quality of life was evaluated using the SF-36 questionnaire at baseline and after 12 months.

Symptomatic improvement (primary endpoint) was reported in the majority of patients in both the rate-control and the rhythm-control groups at all time points, with no statistically significant differences between the two groups. No baseline factors were predictive of response in either group. Most items on the SF-36 quality-of-life questionnaire improved compared with baseline in both the groups, with no statistically significant difference between the groups. In contrast, exercise tolerance (6-min walk test) was significantly greater in the rhythm-control group at all three follow-up study visits, possibly as a result of improved haemodynamics after restoration of SR. By the end of the study period, 56% of the patients in the rhythm-control group were in SR compared with only 10% in the rate-control group ($P < 0.001$). Restoration of SR occurred during amiodarone loading in 23% of patients, the percentage of patients in SR increasing to 40% at 3 weeks and reaching a plateau at 12 weeks.

The absence of any significant difference between the groups in terms of symptom improvement (primary endpoint) or quality of life (secondary endpoint) despite restoration of SR in the majority of patients on amiodarone, is consistent with the results of other trials showing rather a correlation between slowing of ventricular rate and symptom reduction.[80,81] In the PIAF study, mean 24-h heart rate declined continuously over the study period in the rate-control group and more rapidly (during amiodarone loading) in the rhythm-control group. By the end of the study, heart rate was similar in the two groups.[38]

The SAFE-T trial, randomizing 665 patients with persistent AF to receive amiodarone, sotalol, or placebo, with a primary endpoint of time to recurrence of AF, compared changes in quality of life and exercise tolerance in patients with sustained SR and persistent AF, respectively. Follow-up lasted for a minimum of 12 months and a maximum of 54 months.[5] Compared with the group of patients with persistent AF, the group exhibiting continued SR showed significantly better improvement in quality of life (SF-36 scores) between randomization and 1 year with regard to physical functioning ($P = 0.05$), general health (0.003), and social functioning (0.01), with a trend to improvement in vitality ($P = 0.08$). Resting and peak heart rates recorded in the treadmill exercise test decreased between randomization and 1 year to a greater extent in patients who maintained SR ($P < 0.001$) and the increase in duration of exercise was also superior ($P = 0.02$).

In a sub-study of this trial, focusing specifically on the quality of life and exercise performance,[19] patients were classified into the SR or AF groups according to their rhythm status at 8 weeks and 1 year regardless of the intermittent rhythm changes during follow-up. Changes from baseline to 8 weeks in SF-36 scores were significantly greater in the SR group with respect to physical functioning ($P < 0.001$), physical role limitations ($P = 0.03$), general health ($P = 0.002$), and vitality ($P = 0.001$), improvements in symptom severity, functional capacity (specific activity scale, SAS), and AF symptom burden score also being significantly superior in this group ($P = 0.01$, $P = 0.003$, and $P < 0.001$, respectively). Improvements from baseline to 1 year were significantly greater in the SR group with respect to the SF-36 items of general health ($P < 0.007$) and social functioning ($P = 0.02$), as well as symptom frequency (SAS; $P = 0.05$), symptom severity (SAS; $P < 0.001$), and AF symptom burden ($P < 0.001$). Overall, the improvement in exercise tolerance was significantly higher in the SR group at 8 weeks ($P = 0.01$) and 1 year ($P = 0.02$). Patients who were symptomatic at baseline were more likely to experience improvement in quality of life than those who were asymptomatic. Increase in exercise tolerance compared with baseline was significantly higher in the SR group both at 8 weeks ($P = 0.01$) and at 1 year ($P = 0.02$). Improvement in exercise tolerance correlated well with improvement in quality of life scores in both SR and AF groups at 8 weeks and in the SR group at 1 year.

In another sub-study of SAFE-T, focusing specifically on exercise tolerance, patients in SR at the time of the exercise test were further divided into those with sustained SR and those who had experienced intermittent AF, i.e. paroxysmal AF during follow-up.[77] Regardless of whether they had experienced recurrent episodes of AF during follow-up, patients in SR at the time of the test exhibited significantly greater baseline-to-1 year improvements in resting heart rate ($P < 0.001$), peak heart rate ($P < 0.001$), and duration of exercise (sustained SR: $P < 0.015$; SR with recurrent AF: $P < 0.008$), compared to those with AF at the time of the test (including patients who had never converted to SR and those who had reverted to AF or atrial flutter). The differences between patients with sustained SR and those with recurrent AF but in SR at the time of the test were not statistically significant. The changes in exercise capacity were poorly related to changes in left atrial diameter or ejection fraction.

A sub-study of the AFFIRM trial investigated whether achievement of lower resting or peak exercise heart rates was associated with improved prognosis, quality of life, functional status, and exercise tolerance in 680 patients randomized to the rate-control arm.[27] Survival free of CV hospitalization and overall survival did not differ significantly between quartiles of achieved resting heart rate or achieved exercise heart rate. After controlling for covariates, there was no significant relationship between achieved resting or exercise heart rate and event-free survival. Neither was there any significant association between achieved heart rate and quality of life (SF-36 physical and mental summary scores, SCL symptom frequency and severity scores, and QoL Index Health and Functioning Subscale), NYHA functional class, or 6-min walking distance at 1 year.

Analysis of the 352 patients included in the RACE trial who had completed the SF-36 quality-of-life questionnaire

at baseline, after 1 year, and at the end of follow-up (24 months for 134 patients and 36 months for 218 patients) showed significant ($P < 0.05$) improvement from baseline at both 1 year and end of the study in the rate-control group, and from baseline to 1 year in the rhythm-control group.[82] In the rate-control group, the items improved were general health (at 1 year only), physical role limitations, mental health, and social functioning. In the rhythm-control group, the items improved were general health and physical role limitations. Regression analysis indicated that younger age (<69 years), shorter duration of AF (<32 days), SR at the end of the study, and complaints of AF symptoms (particularly dyspnoea and fatigue) at baseline, were significantly correlated with improvement in quality-of-life, but therapeutic strategy was not a determinant. A total of 35 patients (10%) showed a major improvement in quality of life, defined as relevant improvements on five or more subscales of the SF-36, the parameters associated with such improvement being the same as those revealed by the regression analysis: younger age ($P = 0.020$), shorter duration of AF ($P = 0.005$), presence of dyspnoea ($P = 0.048$), or fatigue ($P = 0.005$) at inclusion and SR at the end of the study ($P = 0.003$). In the rate-control group, five of 17 patients (29%) with SR at the end of the study showed a relevant improvement on five or more SF-36 subscales, and in the rhythm-control group 11 of 65 patients (17%).

A substudy of the RACE trial explored gender-related differences in outcomes following rate- or rhythm-control treatment.[65] Analysis of baseline parameters showed that, compared with male patients, female patients had more AF-related complaints (especially palpitations and fatigue) and a significantly lower quality of life measured on six of the eight SF-36 subscales (general health, physical functioning, physical role impairment, bodily pain, mental health, and vitality). At 12 months, female patients had lower scores on five of the eight scales than men and at the end of the study, on seven scales. No significant differences in the effect of treatment on the quality of life of female patients were seen between the rate- and rhythm-control groups.

Change in quality of life with treatment was also assessed in a prospective sub-study of the CTAF trial, including patients with a history of paroxysmal (42%) and persistent (58%) AF.[83] Summary measures of physical and mental health on the SF-36 scale improved significantly from baseline to the 3-month visit ($P = 0.001$ and $P = 0.023$, respectively). With respect to the eight SF-36 subscales, the greatest improvement was seen in physical role (39%), vitality improving by 8%. A small, but significant, improvement was also observed on the general health subscale ($P < 0.05$). Both symptom frequency and symptom severity, evaluated using the SCL scale, decreased markedly from baseline to 3 months ($P < 0.001$). These improvements were similar in the amiodarone and sotalol groups.

In contrast, AF burden, evaluated using the AFSS scale, decreased significantly between baseline and 3 months in the amiodarone group, but not in the sotalol or propafenone groups in which it actually increased slightly, reflecting the differences in AF recurrence in the three treatment groups. There was a significant interaction between time and treatment ($P = 0.001$). These differing results in terms of treatment effect highlight the need to use multiple measures of quality of life. Global well-being, assessed using a visual analogue scale from 1 to 10, was significantly worse in patients experiencing recurrent AF compared with those who did not ($P = 0.04$). Variables such as gender, age, NYHA class, beta-blocker use, and ejection fraction had little effect on quality-of-life outcomes. A previous sub-study showed significantly greater quality-of-life impairment in women than in men at baseline ($P < 0.01$ for SF-36 physical health summary, symptom frequency, and severity (SCL) and Duke Activity Status Index), despite comparable disease severity. Importantly, effects of a therapy, such as an AAD or a rate-control agent can itself confound or obscure the effects of quality of life assessment with recurrent AF.[84] Beta-blockers, digitalis, and sotalol, to name but a few treatments can produce in some patients fatigue as profound as that associated with their AF. Thus, just as a monitoring method might confound assessment of AF recurrence, so, too, can the therapy employed confound the assessment of quality of life and symptoms.

The effect of ablation on quality of life was the focus of a study in 75 patients with paroxysmal AF undergoing pulmonary vein ostial isolation.[39] After a mean follow-up of 191 $\pm$ 109 days, scores for symptom frequency and severity (SCL) and SF-36 physical and mental summary measures showed significant improvement ($P < 0.0001$). The SF-36 scores achieved by patients who had undergone ablation were similar to those determined in an age-matched healthy population. Neither baseline quality of life scores, nor demographic or clinical variables were predictive of improvement in quality of life after ablation. In contrast, response to the procedure in terms of arrhythmia recurrence markedly affected the results of quality of life assessment. Patients classified as full responders (free of arrhythmias without the use of AADs; $n = 41$, 55%) showed significant improvement in all quality of life measures, whereas partial responders (without recurrences while taking AADs; $n = 26$; 35%) improved to a clearly lesser extent, the change in the SF-36 physical summary measure being non-significant). No improvement in quality of life was seen in patients classified as non-responders.

Quality of life was a secondary endpoint in the trial reported by Wazni *et al.*[22] comparing ablation (pulmonary vein isolation) vs. AADs as first-line treatment in 67 patients with symptomatic AF. At six-month follow-up, the improvement in quality of life of patients in the ablation group, compared with baseline, was significantly better than that in the drug therapy group with respect to five subscales of the SF-36: general health ($P < 0.001$), physical functioning ($P = 0.001$), role physical ($P = 0.047$), bodily pain ($P = 0.004$), and social functioning ($P = 0.004$). These results are consistent with the rates of symptomatic or asymptomatic AF recurrence (defined as episodes lasting more than 15 s) during the 1 year follow-up in the ablation and drug-therapy groups (13 vs. 63%, $P < 0.001$).

For trials not designed primarily for drug registration, endpoints defined in terms of major clinical goals, such

as symptom relief or improved quality of life, are highly relevant. In view of the importance of symptom relief to many patients with AF, symptoms should be logged in any trial investigating treatments for this condition, but whether they should be selected as an endpoint or incorporated into a composite endpoint is still a matter of debate. Like symptom relief, improvement in quality of life is a major clinical goal, but it is also a subjective endpoint and its assessment presents many problems in terms of the specificity and selectivity of available evaluation techniques and confounding factors such as co-morbidities, age, and gender. Quality of life is notoriously difficult to assess in clinical trials in patients with AF and the reported effect of restoring SR on this parameter is not consistent from one clinical trial to another. A composite primary endpoint including measures of quality of life, symptoms, or AF burden may be most relevant as these outcomes reflect the principal aim in treating patients with AF. Assessment of quality of life should include the use of multiple scales, including scales specifically developed for trials in patients with cardiac arrhythmias.

## Conclusion

The selection of primary and secondary endpoints in clinical trials in patients with AF will depend on the principal purpose of the trial, as well as the demographic and clinical characteristics of the patient population targeted. Hard endpoints such as mortality, stroke, and hospitalization are most relevant to patients with persistent AF and other concomitant morbidities resulting in a high risk of these outcomes. However, their inclusion in an appropriately weighted composite primary endpoint may be necessary for trials in other, less severely ill patient populations if these are intended to support drug registration. The challenge is to select for each specific clinical trial the surrogate endpoint that enables the most accurate prediction of the effect of the therapies tested on crucial health outcomes, such as mortality, hospitalization, or quality of life.

Combined endpoints of clinical benefit plus safety concerns, expressing 'net clinical benefit' are of interest, corresponding to the clinical goal of improving the patient's life with the lowest risk, using the treatments available for the population concerned and the type of AF being treated. This concept takes into account, besides attainment of the primary goal, any other positive outcomes achieved and any harm caused. However, endpoints defined in terms of net clinical benefit may be treatment-specific. In general, although the treatment goal will differ according to the particular patient subset considered, all outcomes that may be influenced by arrhythmia should be monitored in any clinical trial.

Irrespective of the efficacy endpoint chosen, this should ideally be assessed starting from the time steady state is achieved, in the case of drug therapy, or maturation of the lesions in the case of ablation. On-therapy analysis is a useful complement to intention-to-treat analysis, especially for trials comparing drug treatments to non-drug therapies, as it takes into account the often high crossover rates as well as the issue of compliance with drug therapy. Biases are also inherent in trials comparing two pharmacological treatments if both are not dose-ranging.

Time to first event, now increasingly criticized as a primary endpoint, has practical advantages but does not accurately reflect clinically important parameters such as the frequency, type, and duration of AF recurrence and the overall AF burden. In general, the main clinical goal in treating AF is to enhance patient well-being by reducing symptoms and increasing quality of life, but these highly subjective, and not necessarily related, outcomes are difficult to assess accurately with the evaluation techniques currently available. Several studies involving the use of pharmacological and non-pharmacological therapies indicate a correlation between improved quality of life and maintenance of SR. In contrast, although symptoms may be associated with reduced quality of life, there is increasing evidence that quality of life may be impaired even in patients experiencing predominantly asymptomatic episodes of AF. In addition, the assignment of symptoms to AF events, in the absence of simultaneous monitoring, is hazardous as the symptoms reported are often non-specific and can even be the result of the therapy used rather than recurrent AF. The development of better means of continuously monitoring AF should further clarify the potential impact of such episodes on crucial clinical outcomes.

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