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**EHRA DOCUMENT**

EHRA European Heart Rhythm Association

# Atrial fibrillation burden in clinical practice, research, and technology development: a clinical consensus statement of the European Society of Cardiology Council on Stroke and the European Heart Rhythm Association

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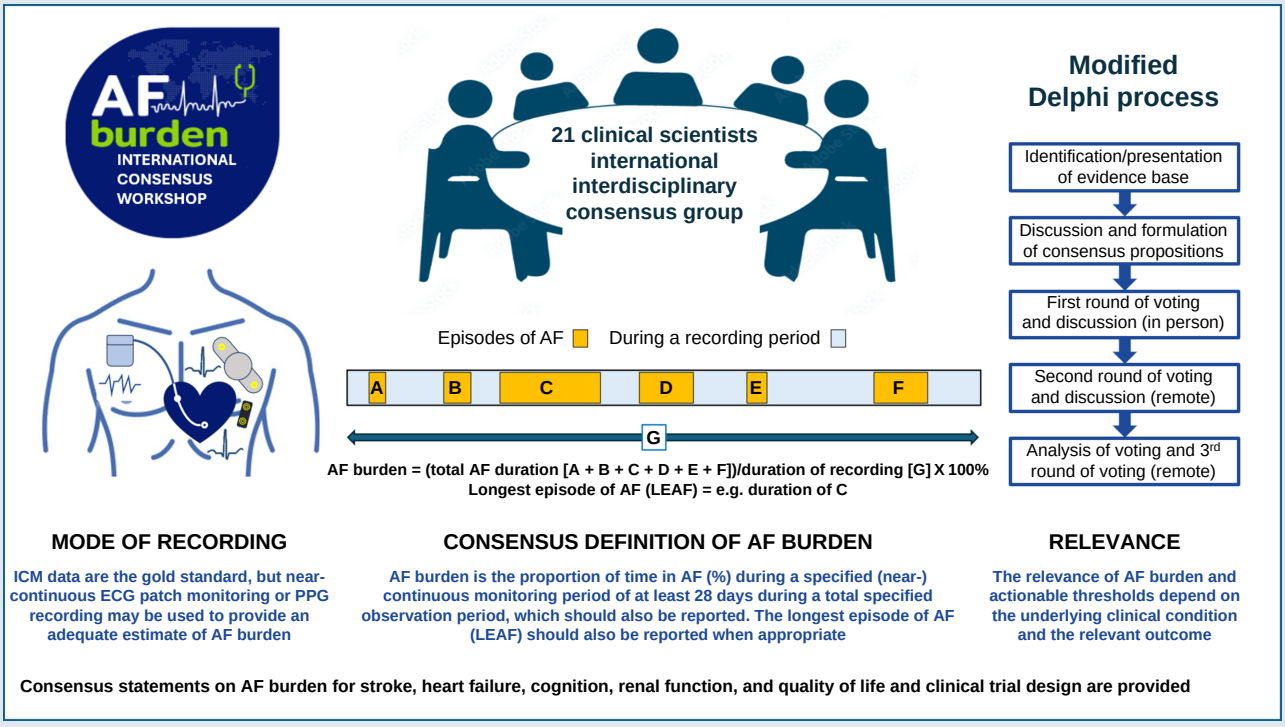
## Abstract

Atrial fibrillation (AF) is one of the most common cardiac diseases and a complicating comorbidity for multiple associated diseases. Many clinical decisions regarding AF are currently based on the binary recognition of AF being present or absent with the categorical appraisal of AF as continued or intermittent. Assessment of AF in clinical trials is largely limited to the time to (first) detection of an AF episode. Substantial evidence shows, however, that the quantitative characteristic of intermittent AF has a relevant impact on symptoms, onset, and progression of AF and AF-related outcomes, including mortality. Atrial fibrillation burden is increasingly recognized as a suitable quantitative measure of intermittent AF that provides an estimate of risk attributable to AF, the efficacy of antiarrhythmic treatment, and the need for oral anticoagulation. However, the diversity of assessment methods and the lack of a consistent definition of AF burden prevent a wider clinical applicability and validation of actionable thresholds of AF burden. To facilitate progress in this field, the AF burden Consensus Group, an international and multidisciplinary collaboration, proposes a unified definition of AF burden. Based on current evidence and using a modified Delphi technique, consensus statements were attained on the four main areas describing AF burden: Defining the characteristics of AF burden, the recording principles, the clinical relevance in major clinical conditions, and implementation as an outcome in the clinic and in clinical trials. According to this consensus, AF burden is defined as the proportion of time spent in AF expressed as a percentage of the recording time, undertaken during a specified monitoring duration. A pivotal requirement for validity and comparability of AF burden assessment is a continuous or near-continuous duration of monitoring that needs to be reported together with the AF burden assessment. This proposed unified definition of AF burden applies independent of comorbidities and outcomes. However, the disease-specific actionable thresholds of AF burden need to be defined according to the targeted clinical outcomes in specific populations. The duration of the longest episode of uninterrupted AF expressed as a time duration should also be reported when appropriate. A unified definition of AF burden will allow for comparability of clinical study data to expand evidence and to establish actionable thresholds of AF burden in various clinical conditions. This proposed definition of AF burden will support risk evaluation and clinical treatment decisions in AF-related disease. It will further promote the development of clinical trials studying the clinical relevance of intermittent AF. A unified approach on AF burden will finally inform the technology development of heart rhythm monitoring towards validated technology to meet clinical needs.


## Graphical Abstract




Clinical consensus statement to propose a unified definition of AF burden for clinical practice, research, and technology development. AF, atrial fibrillation; ECG, electrocardiogram; ICM, insertable cardiac monitor; LEAF, longest episode of atrial fibrillation; PPG, photoplethysmogram.

**Keywords** AF burden • Atrial fibrillation • ECG monitoring • Clinical outcome • Stroke • Heart failure • Quality of life • Mortality

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# Introduction

Atrial fibrillation (AF) is a major healthcare burden. The diagnosis of clinical AF is made if a complete 12-lead electrocardiogram (ECG; usually 10 s of recording), or a 30 s ECG rhythm strip shows a continuous rhythm with AF characteristics (irregular R–R intervals, absence of *P* waves, and irregular atrial activations).[1] Over half of the patients with AF have an intermittent form of the arrhythmia, ranging from short episodes (<24 h) to periods of AF extending to weeks, months, and longer. Intermittent forms of AF are categorized as 'paroxysmal', 'persistent', or 'long-standing persistent', according to the AF duration of up to 7 days, >7 days, or for >1 year without interruption, respectively. When physicians or the patient abandon any attempt to restore sinus rhythm 'permanent AF' is accepted. However, clinicians often fail to identify temporal patterns accurately, mixed forms often occur, and frequently, the arrhythmia progresses from paroxysmal through persistent to long-standing persistent and eventually to permanent AF.[2]

While the risk of intermittent AF for a wide range of adverse clinical outcomes is widely recognized, crucial aspects of the temporal character of intermittent AF are less well understood and a matter of ongoing studies. For instance, very short AF episodes are less likely to be associated with cardioembolic stroke and, therefore, may derive less therapeutic benefit from anticoagulant therapy than sustained AF.[3,4] However, there is little conclusive information about 'how much' AF is clinically relevant, prognostically significant, and therapeutically actionable. The answer to this question may vary substantially depending on the outcome that is being assessed. Moreover, risk categories and actionable thresholds of intermittent AF may depend on underlying diseases, other risk factors and the clinical outcome under consideration.

'How much AF' has been conceptualized as 'AF burden', which is an estimate of the time spent in AF during a specified period of monitoring. In the literature, different definitions have been used which is confusing.[5–14] The term has been variably defined for specific clinical and research purposes and is very dependent on the ECG recording methodologies used. A sample of these multiple definitions of AF burden is illustrated in *Figure 1*. Very few studies have compared the different definitions, and there is little agreement between them.[15–17] Yet guidelines, therapeutic decisions, research study designs, regulators, and technology development of AF detection and monitoring devices increasingly rely on the concept of AF burden as a risk factor for adverse outcomes or as an outcome itself for the assessment of antiarrhythmic activity. Until recently, guidelines on the diagnosis and management of AF addressed the concept of AF burden but remained vague with regard to its exact meaning and simply acknowledged the diversity in the definition of the term.[18,19]

In contrast, the latest ESC guidelines on the management of AF include a description of AF burden[1] but do not provide the reasoning to support this as the appropriate definition and, in particular, do not consider a widely used alternative approach of measuring the longest episode of uninterrupted AF (LEAF), which has been frequently applied in clinical trials.

There is a declared need to develop a clinically applicable, unified and comprehensive concept of AF burden to improve clinical guidance, and to support research and technology development for the quantitative assessment of intermittent AF.[20]

The AF Burden Consensus group was assembled to develop a unified concept to assess AF burden by addressing the following key issues:

- What is AF burden?
- How should AF burden be measured?
- What is the clinical relevance of AF burden and what are meaningful actionable thresholds?
- How should AF burden be applied in clinical trials?
- What are the most significant current knowledge gaps on AF burden?

# Methods

An international, multidisciplinary expert panel convened at a 2 day International Consensus Workshop to address the topics discussed in this paper using a modified Delphi process.[21] The panel consisted of a 'Scientific Nucleus' of five experts with harmonizing function and a 'Faculty' of a further 16 experts, prominent in published literature related to AF burden. The panel consisted of members drawn from various fields and many countries. The key topics as listed in the previous section were addressed in a pre-defined structured workflow (*Figure 2*). Impulse presentations by selected panel members were followed by open discussions of the key question and preliminary consensus statements were presented for which the panel's consensus was gathered. A pre-defined consensus process (statement—vote—modifying debate—revote) included the entire panel and was applied to each preliminary statement. The voting for consensus was anonymous and was recorded according to pre-defined levels of consensus (*Table 1*). Following the single topics discussion and voting, the panel engaged in a final round of anonymous Delphi revoting, requiring at least an 85% engagement from the panel. Following the final round of voting only minor word changes were made to simplify and clarify statements. This process was designed so that the positions expressed by the entire panel are presented in this paper with the list of statements including the levels of agreement.

# What is atrial fibrillation burden?

The term AF burden is widely used in current literature and encompasses various interpretations. It can denote the symptoms experienced by a patient during episodes of AF compared with normal sinus rhythm. Alternatively, it may signify the consequences of AF, such as stroke, heart failure (HF), or cognitive impairment. It is also used to describe the socioeconomic impact of AF on healthcare systems and society. Increasingly, in a

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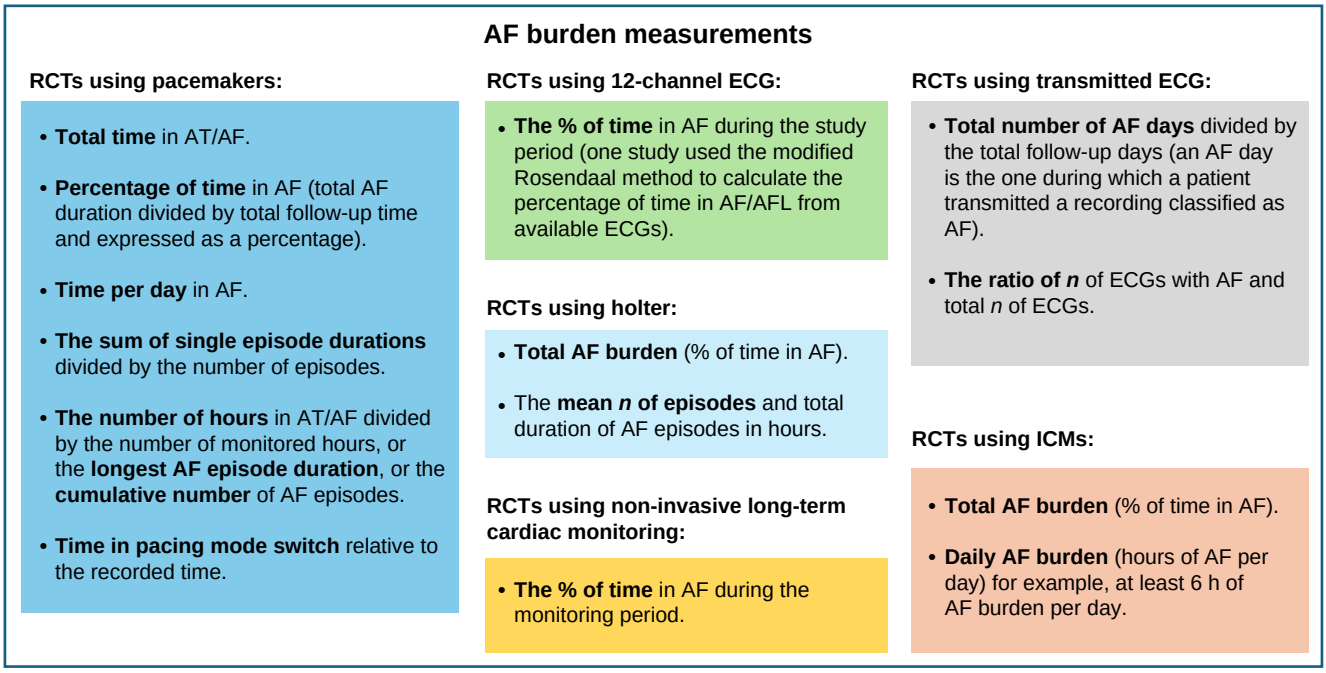


**Figure 1** Examples of the heterogeneity of AF burden measurements used in RCTs.[5–14] AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; ECG, electrocardiogram; ICM, insertable cardiac monitor; RCT, randomized controlled trial (for references, see Supplementary material).

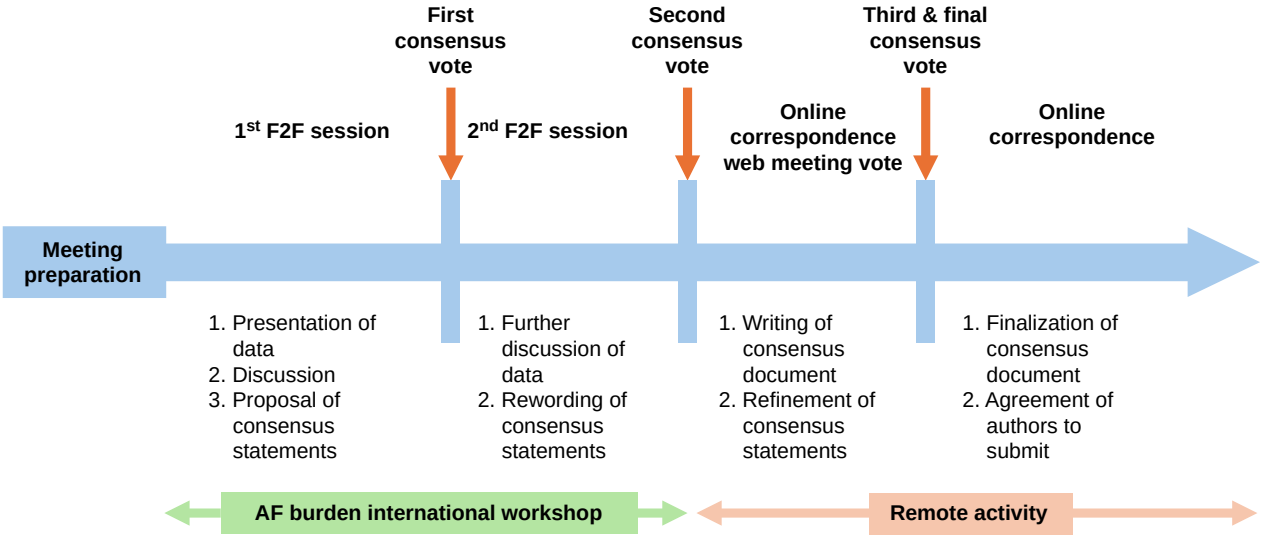


**Figure 2** Defined structure of consensus finding. AF, atrial fibrillation.

clinical context, the concept of AF burden is used as a measure of the extent of AF.

This amount, or 'load' of AF, has been measured in diverse ways, including the percentage of time during which AF has been present, the total duration of AF over time or the longest duration of uninterrupted AF. These parameters have been assessed and reported over a specified time frame, such as the percentage of AF over a 1 month period of monitoring or the longest daily duration of uninterrupted AF. However, these measurements can further be qualified as an average or a range, including the maximum value. With this heterogeneity of measurements, it is not surprising that there is considerable confusion regarding a preferred definition of AF burden. Since no commonly agreed definition of AF burden exists, the widely applied current practice has been to derive a bespoke definition of AF burden in the context of a given study.[19] Consequently, results from clinical or research studies using different measurement methods are challenging to compare or synthesize.

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**Table 1** Pre-specified criteria of consensus levels

| Levels of consensus | Percentage of agreement |
|---|---|
| Unanimous consensus | 100 |
| Strong consensus | 90–99 |
| Moderate consensus | 75–89 |
| Weak consensus, majority agreement | 50–74 |
| No consensus | <50 |

The complexity is compounded by the variety of monitoring methods available to estimate AF burden, ranging from a patient's clinical history with occasional ECG documentation of AF to continuous monitoring of the cardiac rhythm over extended periods using cardiac implantable electronic devices (CIEDs). The simplest approach involves categorizing the temporal pattern of AF into paroxysmal, persistent, or permanent, although this method is crude and often clinically imprecise.[2] Nevertheless, it has been shown in clinical studies using such semi-quantitative measures of AF burden that individuals with a higher category of AF burden tend to have a worse prognosis, including a higher stroke risk, than those with less AF.[22] This finding challenged the conventional belief that 'all AF is AF', regardless of its temporal classification and supports the concept that a quantitative assessment of AF burden may yield more useful information.

The concept of AF burden has become valuable and practical, although a precise and unified definition remains elusive. It is still uncertain whether an uninterrupted period of AF vs. an equally long cumulative duration of multiple AF episodes carries the same prognostic implications. To address this, the concept of 'AF density' was introduced, to further differentiate the characteristics of intermittent AF.[23] A density of 100% indicates that the total burden of AF within a monitoring period is not interrupted by sinus rhythm, whereas a density of 75% implies that the total AF burden is interspersed with sinus rhythm for 25% of the time. Accordingly, two patients may have identical burdens but variable densities. Further, terms like 'legato' (few longer AF episodes of uninterrupted AF) and 'staccato' (more short uninterrupted AF episodes) have been suggested to describe high-density AF vs. low-density AF which might total the same AF burden, but clinical data on the value and clinical meaning of AF density and its subtypes remain limited.[24]

Further electrocardiographic features related to AF may impact on the progression or deterioration in the patient's overall or cardiovascular health such as average or peak heart rates during the AF episode, frequency or length of pauses during AF or in the transition between sinus rhythm and AF, and other arrhythmia-dependent factors, such as the haemodynamic consequences, atrial and ventricular remodelling, atrial fibrosis, AV valve regurgitation, and others. For instance, the product of AF burden and the average heart rate during AF episodes may serve as a more informative risk factor for developing HF compared with AF burden alone.[25,26] Finally, the presence or absence of accompanying symptoms may be more relevant to clinicians and patients than the mere measurement of AF burden. While these aspects have been explored, their clinical significance in relation to AF burden remains to be determined.

The proportion of time in AF, expressed as a percentage, and the LEAF, expressed as a time duration, have been used as estimates of AF burden. However, these are different parameters which may engage different mechanisms leading to adverse clinical outcomes. This has not been well explored, but some valuable data are available, for example, AF burden, as a simple percentage of time in AF over a specified monitoring period, does associate with quality-of-life outcomes and mortality when studying antiarrhythmic drug (AAD) or ablation treatment for AF,[27] and on the other hand, LEAF has been associated with stroke risk in patients with underlying stroke risk factors.[3] The longest episode of uninterrupted AF, for example, measured on a daily basis, might precede an event such as a stroke or arterial embolus, whereas prolonged periods of intermittent or continuous AF and a high AF burden might lead to the progression of HF or dementia. When simply assessing an antiarrhythmic effect the proportion of time spent in AF together with a measure of its intermittency such as AF density might be best. These claims are speculative and there are few if any studies in specific clinical situations in which these different measures of AF burden have been compared regarding important and different clinical outcomes. Certainly, we do not have any comprehensive understanding of the value of these assessments in all clinical conditions concerning all AF-related outcomes. For this reason, it is difficult on the basis of clinical evidence alone to prefer one measure over another.

The proportion of time spent in AF is technically easier and more reliable to assess than it is to document the duration of LEAF (*Figure 3*), particularly, if continuous accurate monitoring cannot be achieved. Atrial fibrillation burden is most often used either to predict chronic disease outcomes or to document antiarrhythmic effects. Therefore, from a practical perspective, the AF Consensus Group prefers to primarily define AF burden as the proportion of time in AF, measured as a percentage of a specified monitoring period (within a specified overall observation period). However, the group also encourages, where appropriate, the assessment of LEAF within a specified time period, e.g. 24 h, measured over a similar total monitoring period. This will allow the consistent measurement of AF burden across trials, registries, and clinical databases, while also allowing further evaluation of secondary measures, such as the longest duration of uninterrupted AF in the same or more temporally defined pre-specified period, e.g. daily. In this way, the development of the AF burden concept will be systematically enriched.

**Clinical Consensus Statements (1): Proposing a unified definition of AF burden**

| No | Statements | % Agreement |
|---|---|---|
| **1.1** | **In patients with intermittent AF, AF burden is a measure of the amount of AF during a specified monitoring period.** | Unanimous |
| **1.2** | **Atrial fibrillation burden is defined as the proportion of time in AF, expressed as a percentage, during a specified and reported monitoring duration.** | Unanimous |
| **1.3** | **The LEAF within a specified monitoring period should also be reported, expressed as a time duration.** | Unanimous |

## How to measure atrial fibrillation burden?

Tools for monitoring cardiac rhythm evolved from those applied at the bedside to external devices that could be used outside of the hospital setting and further to those recording the rhythm continuously for up to weeks or at the time of symptoms for even longer periods. A variety of medical implantable devices now enable the monitoring and storage of very extended periods of cardiac rhythm data, suitable for real-time or deferred analysis, and clinical use. Additionally, a wide range

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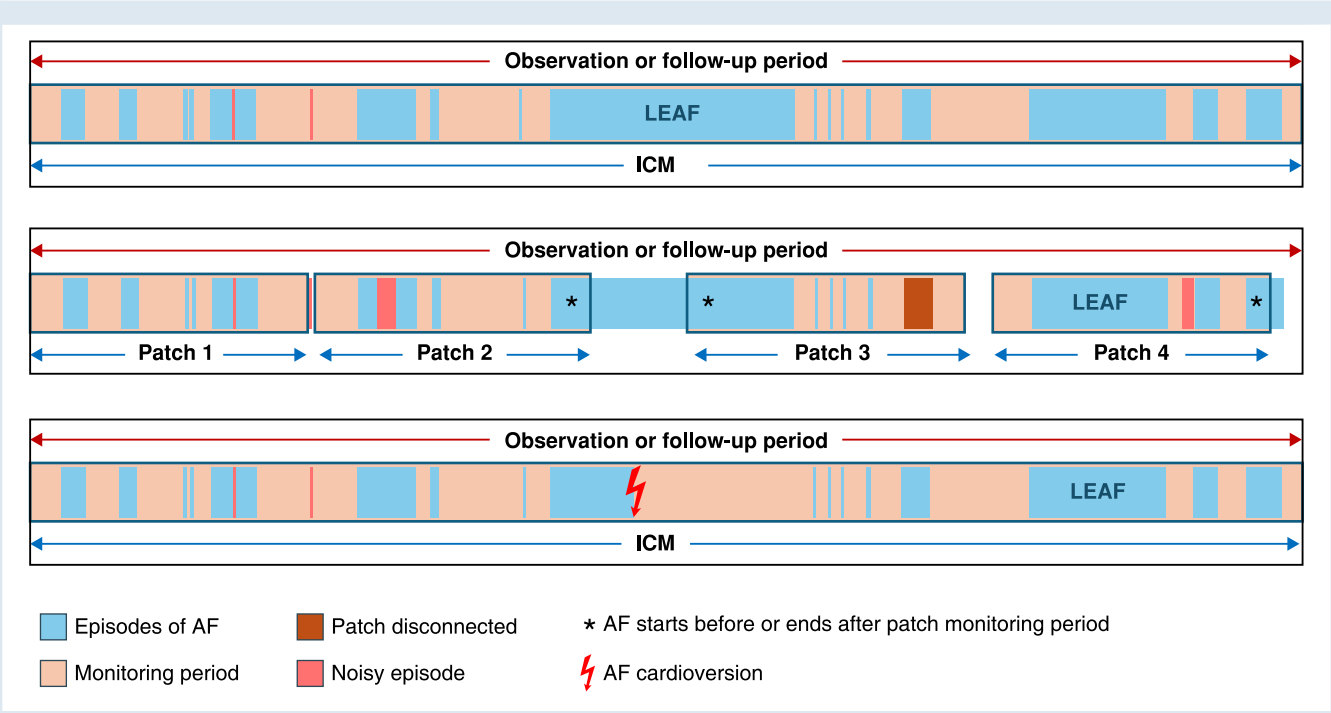


**Figure 3** Patch vs. ICM recordings. This diagram compares ICM and Patch monitoring of episodes of intermittent AF during the same observation or follow-up period. Inevitably, continuous monitoring documents the arrhythmia more fully and it is less vulnerable to contamination with noise. However, when AF is sufficiently prevalent to be clinically relevant, 28 days patch monitoring may be sufficient to provide a reasonably accurate estimate of AF burden. Because Patch monitoring periods may not be contiguous, the LEAF may not be accurately recorded if AF episodes start prior to monitoring, continue after monitoring, or occur when monitoring is not done or the Patch is disconnected. Atrial fibrillation episodes, particularly if prolonged, may be cardioverted. This may result in reduction of the LEAF duration and the AF burden. AF, atrial fibrillation; ICM, insertable cardiac monitor; LEAF, longest episode of atrial fibrillation.

of wearable devices, including both medical-grade and consumer-grade technology, has become available for rhythm monitoring.

The objective of this section is to discuss the fundamentals of rhythm monitoring for quantifying AF burden, to examine the clinical requirements and technological capabilities necessary for obtaining meaningful measurements of AF burden, and to address current limitations and emphasize the need for technological improvements.

## Role of symptoms

Atrial fibrillation may be symptomatic, partially or entirely asymptomatic, or symptoms due to AF may be mistakenly attributed to other medical conditions.[28] As a result, symptoms cannot be used as a surrogate for AF burden, i.e. they cannot be relied on to assess or trigger the assessment of AF burden.[2] Short episodes are often more symptomatic than longer sustained episodes and may give a false impression of the extent of AF burden and may not associate with other serious outcomes related to AF. However, the symptomatic AF burden may have clinical and regulatory importance and, for this purpose, 'on-demand' ECG monitoring using event recorders may be used, understanding that it will not provide an accurate assessment of the AF burden. Patient-initiated marking of symptoms during the continuous recording of the cardiac rhythm is preferable since the AF burden, its relationship to symptoms and an estimate of the so-called 'symptomatic AF burden' can all be derived.

## Electrocardiogram monitoring

Electrocardiogram monitoring to assess AF burden can take several forms: intermittent monitoring of various durations and with varying frequencies, ambulatory monitoring for a few days at a time, continuous long-term monitoring using external patch devices for up to 2 weeks at a time which can then be repeated, or very long-term monitoring via CIEDs or wearable technology, some of which is of medical grade.[29] The choice between intermittent, long-term and continuous monitoring is of paramount importance because it directly impacts the sensitivity of AF detection and the calculation of AF burden.

## Intermittent vs. continuous monitoring

Several studies have shown that brief intermittent rhythm monitoring results in unreliable estimates of AF burden[30] or AF recurrence,[31] particularly in patients with infrequent episodes of paroxysmal AF. In paroxysmal AF cases, even dense intermittent monitoring may lead to relative errors exceeding 80% of the true AF burden. This error diminishes with higher true AF burdens, lower AF densities, and more frequent intermittent or extended continuous recording.[30] However, even in patients with substantial AF burden and/or low AF densities, intermittent recording still results in significant deviations from the actual burden, leading to substantial measurement errors exceeding 20%.[32] Although continuous ECG monitoring is intrinsically more accurate for determining AF burden, automatic diagnosis of AF without manual over-read is not fool proof.

Gaps in the recording and short-duration, intermittent monitoring, generally result in an overestimation of the true AF burden when AF is captured, and in an underestimation of AF burden when no AF is captured during the monitoring period. Since extending monitoring duration yields improved accuracy of AF burden assessment, it seems evident that the gold standard for assessment of the true AF burden is continuous monitoring with an implantable device. If AF burden estimation must rely on intermittent ECG monitoring, serial longer term intermittent

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monitors (such as 14 day ECG monitors), used to achieve close to contiguous monitoring for a total of at least 4 weeks (28 days) was demonstrated to achieve comparable accuracy compared with measurements derived from implantable devices.[32] The duration of recording necessary to assess AF burden for risk prediction of certain outcomes, such as mortality, is not known, but risk assessment was possible with insertable cardiac monitor (ICM) recording in CASTLE-HF.

Importantly, in any case of intermittent and cumulated monitoring duration, the true duration of the monitoring period (not the prespecified or intended duration) must be reported together with the calculated AF burden. Any reported measurement of AF burden that is based on limited-duration monitoring can only be compared with measurements of the same monitoring duration.

## Devices for assessment of atrial fibrillation burden

The selection of the appropriate monitoring tool is of central importance for assessment of AF burden as shown by a comprehensive meta-regression analysis of paroxysmal AF ablation trials.[33] This analysis showed that thoroughness of AF monitoring and patient selection were more relevant to assess the absence of recurrent AF episodes, than the specific ablation technologies employed. The accuracy of available tools for measuring AF burden hinges on the technology itself and is subject to the pace of technical evolution. The characteristics of AF, including frequency of AF episodes, duration (particularly very short AF episodes), and density, determine the ability of a technology to sense AF and measure burden.

### Technical limitations

The technical limitations of devices (including CIEDs) render them inaccurate for the reliable detection of AF episodes as short as 30 s, the current threshold definition for AF. A minimum duration of AF that can be accurately diagnosed is dependent on the particular technology. Episodes shorter than 2 min on a CIED may be frequently misdiagnosed as AF, while episodes exceeding 6 min more accurately represent true AF. In general, losing AF episodes <6 min, unless very frequent, does not significantly impair the overall calculation of AF burden.[34] Devices that record from extracardiac sites are intrinsically less accurate than devices linked to intracardiac lead(s), and need longer sampling periods to reach an accurate measurement of AF burden. Both internal and external devices may erroneously divide longer episodes of AF into several shorter episodes if there are periods of ventricular regularity. Most wearables using photoplethysmogram (PPG) technology are not designed to alert the user of pulse irregularities lasting <30–60 min in order to reduce the rate of false positives.

Lastly, the sampling frequency in wearable devices is manufacturer dependent, with some devices providing opportunistic surveillance for rhythm irregularities every 2 hours and assessment every 15 min if an AF burden algorithm is activated. As a result, shorter episodes of AF may be missed entirely due to technical limitations, patient compliance (in the case of wearables), and AF density.

### External cardiac monitors

External cardiac monitors are commonly used to assess the presence and extent of AF, offering advantages for patient comfort and compliance. However, their diagnostic accuracy is limited due to the length and frequency of monitoring. Studies examining the sensitivity of routine external monitoring for AF detection in screening populations and in patients with embolic stroke of undetermined source have demonstrated that all forms of routine external monitoring have <50% sensitivity.[35,36] Repeated short-term monitoring spanning 1–30 days shows improved technology-dependent results but may encounter logistical challenges associated with multiple ambulatory visits and declining long-term patient compliance. Patients with high-density AF, where most episodes occur within a narrow time frame, require more frequent or extended monitoring to avoid under-detection.[23] Short-term monitoring has the significant limitation that only frequent paroxysmal AF episodes are reliably detected, while rare occurrences of AF episodes may be entirely missed. Since the modality of continuous (implanted) ECG monitoring is not universally applicable, there is a need for non-invasive technology improvements to provide suitable solutions for AF burden assessment for patients in diverse clinical contexts.

### Implantable cardiac monitors

Atrial fibrillation detection from implantable devices was initially diagnosed from dual-chamber pacemakers where atrial high-rate events triggered a mode switch to avoid atrial tracking and the frequency and duration of mode switching gave an approximate estimate of AF burden. However, the high false-positive rates of AF, which were noted particularly for brief episodes, were attributed to factors such as ectopic beats and background biological or electromagnetic noise.[37] Frequent atrial premature contractions (APCs) or other atrial tachyarrhythmias, and non-arrhythmia factors, such as far-field ventricular sensing, may also be misinterpreted as AF. Conversely, atrial undersensing may lead to underestimations of AF burden.

Originally, ICMs relied solely on irregularities in the R–R interval for AF detection. The incorporation of advanced diagnostic features, including the integration of artificial intelligence, has substantially enhanced AF detection algorithms, resulting in a reduced rate of false positives generated by these devices, while still capturing genuine AF events.[38] Insertable cardiac monitors with this improved technology may be considered the reference method for assessing AF burden, given that they record the cardiac rhythm continuously and are highly accurate. However, the invasive nature and associated costs[39] related to device implantation and follow-up pose significant challenges to the routine use of ICMs for evaluating AF burden in many clinical scenarios, such as post-ablation. Further, the patient's perspective and preference need to be considered when selecting the appropriate rhythm monitoring method.

### Digital health devices

The widespread availability of consumer-grade digital health devices, capable of performing 'on-demand' ECG or PPG, and passive surveillance of irregular rhythms using PPG in wearable devices have brought increased attention to AF detection within both the medical and lay communities. These standalone 'on demand' devices offer a brief, usually 30 s, assessment of cardiac rhythm. However, it is important to note that the automated diagnosis from these devices varies significantly in terms of sensitivity and specificity and cannot be relied upon in isolation for clinical decision-making.[40] Photoplethysmogram technology has limited accuracy in patients with high melanin content in their skin, making their accuracy biased to a white population.[41] Further, potential false positives may apply, especially for short AF episodes, due to susceptibility to movement artefacts, background noise, and ectopic beats. In turn, the restricted recording duration may result in false negatives. Even a once-daily recording over 365 consecutive days has a sensitivity of only 50% when compared with continuous monitoring with a cardiac implantable electronic device.[42] The combination of PPG/ECG sensing has been successfully applied, as in the Apple Watch to allow efficient monitoring with PPG and diagnostic accuracy/validation with ECG. Furthermore, the algorithms and thresholds for detecting abnormalities in tachograms and defining AF differ substantially among device manufacturers and is often not transparent to users or the medical community.[43,44] This lack of standardized analysis criteria hinders the comparability of AF burden measurements between devices.

The limitations outlined make most consumer-grade technology unsuitable for diagnosing and confirming AF burden, a task best suited for medical-grade technology that relies on electrocardiographic signal

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assessment reviewed by a physician. However, in patients with a confirmed diagnosis of AF and known AF burden, monitoring of trend development with intra-individual comparisons may be feasible using electrocardiographic, plethysmographic, or potentially other signal assessment methods.[45] Despite their limitations, consumer-grade digital health devices offer a cost-effective approach to intra-individual, long-term AF burden monitoring for a range of indications, thanks to their relative affordability, user-friendliness, and widespread availability, which will further increase in the future. One manufacturer (Apple Inc., Cupertino CA, USA) has received Food and Drug Administration (FDA) clearance of their PPG-based AF history algorithm which provides a retrospective estimate of AF burden (defined as % of time in AF during watch wear). The same device has also received FDA clearance as a Medical Device Development Tool to estimate AF burden in the context of a clinical study, though it is not intended to replace traditional methods of AF monitoring for clinical purposes.

**Clinical Consensus Statements (2): How to measure AF burden**

| No | Statements | % Agreement |
|---|---|---|
| 2.1 | **Accurate measurement of AF burden requires extended continuous ECG monitoring with longer monitoring duration resulting in higher precision.** | Unanimous |
| 2.2 | **The optimal assessment of AF burden requires long-term, uninterrupted ECG monitoring (e.g. by ICM or CIED).** | Strong |
| 2.3 | **Near-continuous monitoring using medical grade wearable patch technology for a period of 28 days or more may provide a reasonable and feasible assessment of AF burden, depending on the outcome to be evaluated.** | Unanimous |
| 2.4 | **The measurement of AF burden depends on the monitoring duration; only measurements using the same monitoring duration are comparable.** | Unanimous |
| 2.5 | **In patients with known AF, validated wearable devices utilizing ECG- or PPG/ECG-based signals may provide a suitable method for the assessment of AF burden.** | Strong |

# The clinical relevance of atrial fibrillation burden and actionable thresholds

## General considerations

It is the understanding of this consensus group that a proposed unified definition of AF burden may be applied as a quantitative measure of intermittent AF that is independent of the clinical disease or conditions. The clinical relevance of AF burden, however, should be assessed in relation to a specific underlying disease or AF-related outcome. Accordingly, different disease-specific actionable thresholds of AF burden may be validated, and risk categories may be applied to define diagnostic and therapeutic targets of a given disease or outcome at risk. In the scientific literature, clinically relevant limits of AF burden range from 1 to 24 h or more, to identify actionable thresholds of an increased risk in different medical conditions. This section will explore the relationship between AF burden and a range of conditions including: stroke, HF, renal disease, and cognition. In addition, the impact of AF on quality of life (QoL) will be discussed.

## Atrial fibrillation burden and risk of stroke

### Risk of incident stroke

Individuals with persistent and permanent AF have higher risk of stroke compared with those with paroxysmal AF.[46,47] Varying AF burden stratification categories have been used to evaluate the association between AF duration and future stroke risk in studies of prolonged cardiac monitoring (*Table 2*). These studies are heterogeneous in terms of population characteristics, duration of follow-up, proportion of participants with a remote cerebrovascular event or prior AF, use of oral anticoagulants, and study endpoints. Only AF lasting >24 h was associated with increased risk of ischaemic stroke or systemic embolism in the ASSERT trial.[48] In contrast, the >24 h threshold did not show higher ischaemic stroke rates in the SOS-AF collaborative project[49] or the NOAH-AFNET 6 trial.[50] Thresholds of ≥5.5 or 6 h have failed to show a significant association with embolic risk in several studies, including ASSERT[48] and the SOS-AF project,[49] but stroke was temporally associated with AF episodes durations of >5.5 h in a large retrospective study of CIED patients.[51] Lower thresholds such as >5 min or ≥1 h were associated with significantly increased stroke risk in the larger SOS-AF project.[49]

These inconsistencies across studies, mainly based on differences in baseline vascular risk profiles, likely explain discrepancies in stroke risk estimates for similar AF burden categories. Indeed, AF burden-associated stroke risk is significantly modified by baseline $CHA_2DS_2$-VASc or $CHADS_2$ scores.[3,52] Hence, combining AF burden with individual risk factors, such as the $CHA_2DS_2$-VASc score, may offer superior prognostic precision compared with each aspect in isolation (*Figure 4*).

Analyses in CIED patients, based on AF burden quartiles[52] or tertiles,[53] have shown stronger associations between AF burden and stroke risk than rigid dichotomized thresholds. This further supports an association between AF duration as continuous rather than dichotomized variable, and the risk of stroke. A harmonization of the measurement of AF burden is therefore highly needed for future research.

Two recent RCTs have compared anticoagulation with DOACs vs. aspirin or placebo in patients with short episode of device-detected AF (DDAF). The NOAH-AFNET 6 trial could not demonstrate a benefit of oral anticoagulation to prevent stroke and cardiovascular death.[54] In contrast, the ARTESIA trial showed a reduction in stroke or systemic embolism by 37% relative to antiplatelet treatment [hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.45–0.88].[55] Among patients with a higher predicted risk of stroke (i.e. CHADS-VASc>4), the use of DOAC appears particularly favourable, as it reduces absolute stroke risk by 1.28% per year, while increasing major bleeding by only 0.68% per year.[56] A study-level meta-analysis combining both trials concluded that DOACs reduce stroke risk in patients with short episodes of DDAF at the expense of major bleeding.[57] In subanalyses of baseline data from both trials, an association of temporal pattern of AF with the risk of stroke could not be demonstrated.[50,58] However, the risk of stroke associated with subclinical AF is lower when compared with clinical AF, and this gives rise to the discussion that patients with brief DDAF requires individualized decision-making with regard to the best suitable threshold and the appropriate timing for initiation of anticoagulation.

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**Table 2** Studies assessing stroke risk in relation to longest episode of AF

| Study | Device | *n* | Follow-up | Endpoint | AF burden thresholds |
|---|---|---|---|---|---|
| RATE Registry | PPM/ICD | 5379 | 23 months (median) | Stroke/TIA | <1 min vs. no AF: HR 0.30 (0.03-3.2); $P = 0.3$ |
| ASSERT | PPM/ICD | 2580 | 30 months (mean) | Stroke/SE | >6 min–6 h vs. no AHRE: HR 0.75 (0.29–1.96); $P = 0.56$<br>>6 h–24 h vs. no AHRE: HR 1.32 (0.40–4.37); $P = 0.65$<br>>24 h vs. no AHRE: HR 3.24 (1.51–6.95); $P = 0.003$ |
| MOST | PPM | 312 | 27 months (median) | Death or non-fatal stroke | >5 min vs. no AHRE: HR 2.79 (1.51–5.15); $P = 0.001$ |
| TRENDs | PPM/ICD | 2486 | 17 months (mean) | Stroke/TIA/SE | <5.5 h vs. no AF: HR 0.98 (0.34, 2.82); $P = 0.97$<br>>5.5 h vs. no AF: HR 2.2; $P = 0.06$ |
| SOS-AF Project | CIEDs | 10 016 | 24 months (median) | Ischaemic stroke | >5 min vs. no AHRE: aHR 2.79 (1.51–5.15); $P = 0.001$<br>≥1 h vs. no AHRE: aHR 2.11 (1.22–3.64); $P = 0.008$<br>≥6 h vs. no AHRE: aHR 1.74 (0.96–3.41); $P = 0.07$<br>≥12 h vs. no AHRE: aHR 1.72 (0.92–3.22); $P = 0.09$<br>≥23 h vs. no AHRE: aHR 1.44 (0.69–3.01); $P = 0.33$ |
| KP rhythm | 14 day patch | 1965 | 1915 person-years | | 3rd tertile vs. 1st tertile: aHR 3.13 (1.50–6.56)<br>3rd tertile vs. 2nd tertile: aHR 3.16 (1.51–6.62) |
| REVEAL AF | ILR | 385 | 23 months (mean) | | Adj. analyses for AF burden categories not reported |
| SCREEN-AF | 14 day patch ×2 | 822 | 6 months | | No analysed stroke events in any group |
| ASSERT II | CIED | 256 | 16 months (mean) | | Adj. analyses for AF burden categories not reported |
| NOAH-AFNET | CIED | 2389 | 22 months (median) | Stroke/syst. embolism/CV death | ≥24 h vs. >6 min–24 h: aHR 0.86 (95% CI 0.62–1.19) |
| ARTESiA | CIED | 3986 | 420 months (mean) | Stroke/syst. embolism | <6 min vs. ≥6 min AHRE: aHR 0.48 (0.27–0.85)<br>1–6 h vs. <1 h: aHR 1.27 (0.85–1.90)<br>>6 h vs. <1 h: aHR 1.02 (0.63–1.66) |

AF, atrial fibrillation; aHR, adjusted hazard ratio; AHRE, atrial high-rate events; CIED, cardiac implanted electronic device; HR, hazard ratio; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; PPM, pacemaker; SE, systemic embolus; TIA, transient ischaemic attack.

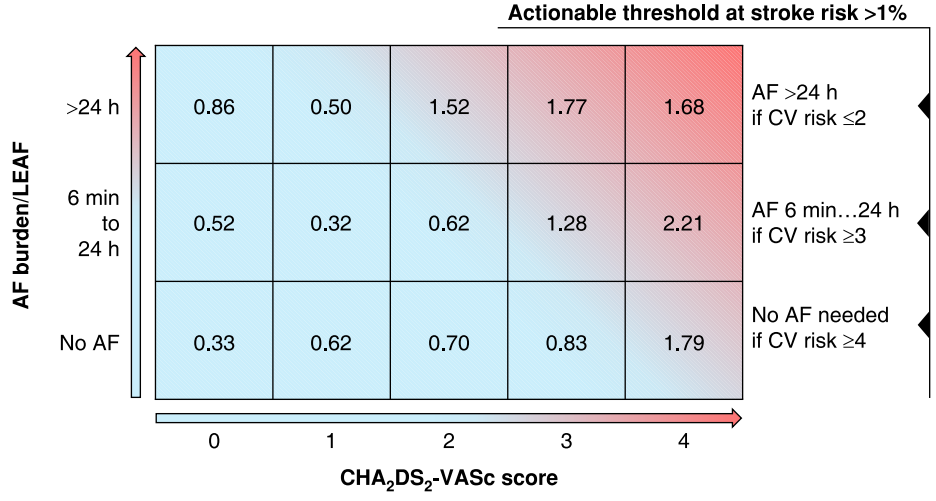


**Figure 4** Interaction between AF burden and stroke risk score. AF, atrial fibrillation; CV, $CHA_2DS_2$-VASc score; LEAF, longest episode of atrial fibrillation (modified from Kaplan *et al.*[3]). Actionable threshold refers to the treatment with oral anticoagulation.

### Risk of recurrent ischaemic stroke

Current evidence on AF-related stroke risk is largely based on symptomatic, ECG-detected AF observed in patients with permanent or persistent AF. This evidence underlies the common practice to initiate anticoagulation in patients with a history of ischaemic stroke, regardless of stroke aetiology, temporal association with stroke, mode of monitoring, and AF burden. The temporal association of paroxysmal AF episodes with stroke onset remains less well established and a matter of ongoing

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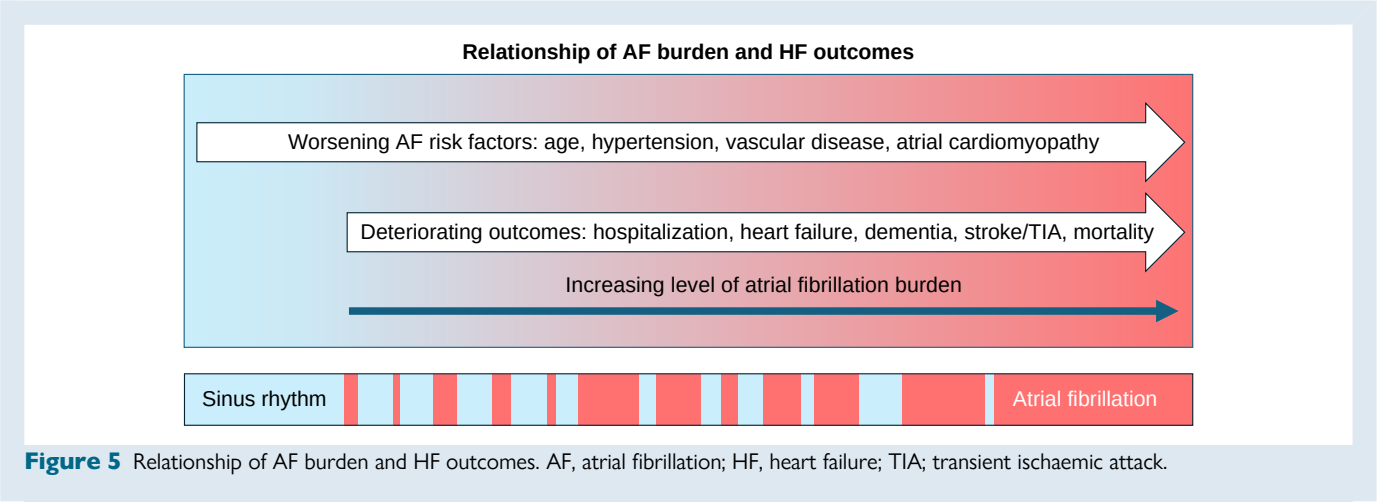


**Figure 5** Relationship of AF burden and HF outcomes. AF, atrial fibrillation; HF, heart failure; TIA; transient ischaemic attack.

research. Notably, specific attributes of DDAF identified post-stroke have led to the term 'AF detected after ischaemic stroke' (AFDAS).[59] Population-based studies[60] and meta-analyses[61] suggest that AFDAS initially identified in patients through prolonged cardiac monitoring has a considerably less ominous risk profile compared with AF detected prior to a stroke.[62] AF detected after ischaemic stroke is typically low burden, in patients with a relatively low prevalence of cardiovascular comorbidities, vascular risk factors, and atrial cardiomyopathy, and carries a 26% lower risk of recurrent ischaemic stroke than AF identified prior to stroke onset.[62] Currently, it remains unclear whether the observed lower stroke risk in patients with AFDAS justifies different actionable thresholds for anticoagulation therapy compared with current primary prevention strategies in stroke patients with newly detected AF.

Despite numerous publications on cardiac monitoring post-stroke, data on AF burden stratification in stroke patients are limited and are further restricted by heterogeneity in the method of AF burden measurement across studies. These measures encompass the median or mean duration of the longest episode or the first event, mean or median cumulative duration within 24 h, stratification into duration categories, or the proportion of time spent in AF. The mean duration of the longest AF paroxysm in studies involving stroke patients with an ICM ranges from 77 to 120 min.[63,64] The DELIMIT-AF STROKE study quantified AF burden in stroke patients undergoing 14 day monitoring.[65] The median AF duration was 5.2 h (0.3–33.0 h), and the median AF density was 2.23% (interquartile range, 0.13–12.25). The categorization of AF burden according to the TRENDS study thresholds (19% 30 s–<6 min, 33% 6 min–5.5 h, 19% >5.5–24 h, 29% >24 h) did result in significant differences due to the large proportion of use of anticoagulants (>82%) and the resulting low numbers of recurrent stroke events (2 of 178 patients with newly detected AF at a median follow-up of 17 months).[66] Find AF reported similar results: 32% of patients with AF 30 s–<6 min, 20% 6 min–5.5 h, 12% 6–24 h, 36% >24 h.[67]

## Atrial fibrillation burden and risk of heart failure

A well-established bi-directional association exists between AF and HF, with AF contributing to the onset and deterioration of HF, and HF, in turn, is facilitating the development and progression of an AF-promoting substrate[68] (*Figure 5*). While much attention has historically been directed towards HF with reduced ejection fraction (HFrEF), the connection of AF and HF with preserved (HFpEF) or mildly reduced ejection fraction (HFmrEF) has recently been increasingly examined.[69,70] Epidemiological studies reveal an overall prevalence of 50% of AF among HFpEF patients. An important limitation of all the studies is that detection of asymptomatic AF is dependent on the methods used and the extent of monitoring. Asymptomatic AF is frequent in all the subtypes of HF.[71] Notably, prevalence of AF is higher in HFpEF than in HFmrEF and HFrEF. Factors that explain the association of AF and HFpEF include older age, associated comorbidities, diastolic dysfunction, atrial cardiomyopathy, and links with inflammatory processes.[72–74]

Despite extensive observational studies and registries in HF, precise assessment of AF burden through cardiac rhythm monitoring is limited.[75] However, some insight into the impact of AF burden can be derived from quantitative categories of AF (i.e. paroxysmal, persistent, or permanent) linked with HF. Permanent AF is associated with a higher prevalence of HFpEF than paroxysmal AF, suggesting an impact of AF burden on HF development.[76,77] In patients with HFpEF left atrial compliance and mechanics progressively decline with increased AF burden.[78] Among patients with pre-existing HF, a higher AF burden was associated with an increased risk of HF-related hospitalization and all-cause mortality.[75] In turn, reduced AF burden secondary to AF ablation therapy was predictive of reduced mortality and decreased hospitalization for HF.[79,80] The binary endpoint of '30 s AF recurrence' had the same prognostic significance as no AF recurrences.[15]

Moreover, a large Medicare data set also showed that in patients without pre-existing HF a higher AF burden significantly correlates with new-onset of HF.[75]

Notably, the assessment of the clinical implications of AF burden must consider the dynamic nature of AF progression from paroxysmal to permanent AF,[81] and within paroxysmal AF, the shift from minutes to hours of subclinical AF to over 24 h or even clinical AF. It has been shown that a CIED-detected increase in AF burden over time is associated with an elevated risk of HF-related hospitalization[82] and, in some clinical conditions, also with an increased mortality.[70,75,83]

Despite our understanding of the temporal relationship between AF burden and the onset and progression of HF, there is currently a lack of data to define clinically relevant thresholds of AF burden in relation to risk evaluation of onset, progression, or outcomes of HF. Additionally, there was no consensus in the literature on how to measure and report AF burden, with published data mainly related to assessment of AF burden in terms of LEAF. There is actually an unmet need in order to propose actionable AF burden thresholds for preventing the onset or progression of HF and to define categories of increased risk of hospitalization of death.

## Atrial fibrillation burden and risk of impaired renal function

Renal impairment is a prevalent concern in patients with AF, affecting ~50% of patients with AF. Chronic kidney disease (CKD) and AF share common risk factors, such as obesity, diabetes, older age, and hypertension. It was demonstrated that AF burden increased with advancing age,

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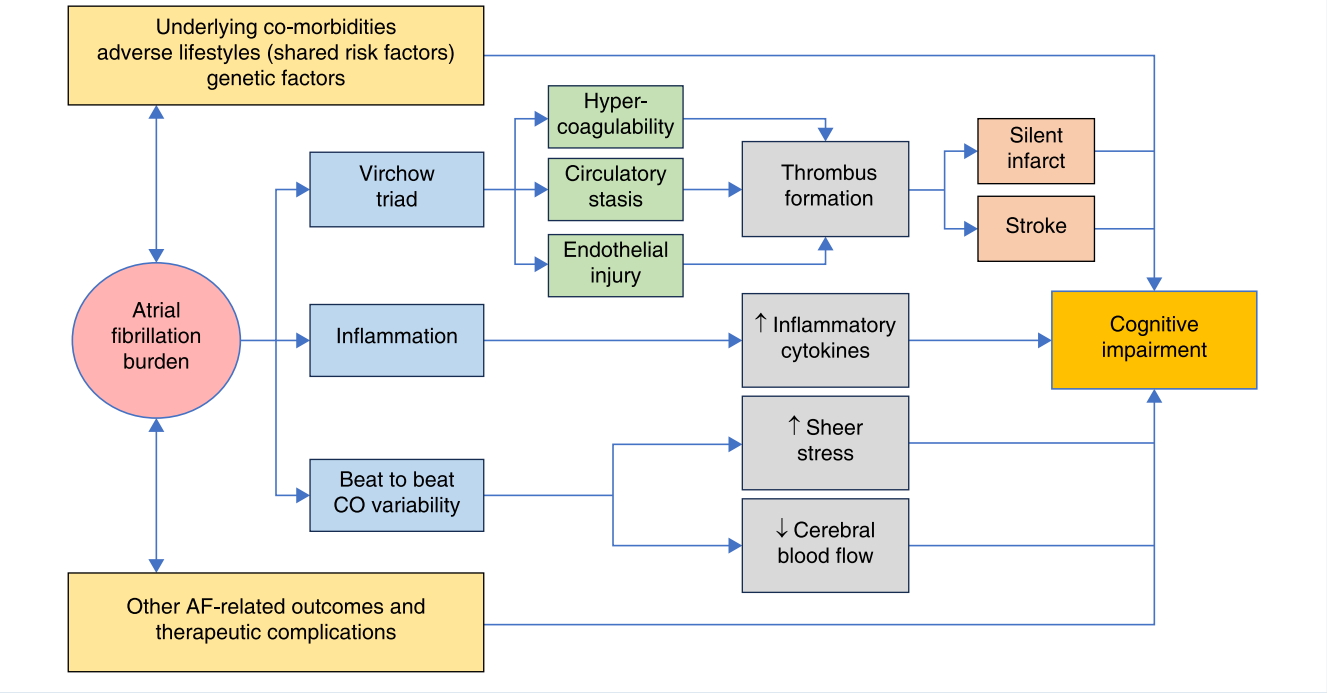


**Figure 6** Pathophysiology of AF and cognitive decline (adapted from Dagres et al.[94]). AF, atrial fibrillation; CO, cardiac output.

systolic blood pressure, blood urea nitrogen, and serum creatinine levels.[84] Conversely, CKD elevates the risk of developing AF, creating a bidirectional relationship.[84]

Furthermore, AF itself heightens the risk of CKD progression.[85] Among patients with CKD, the presence of AF was associated with a threefold higher risk of progression to end-stage kidney disease when compared with patients without AF (HR 3.2; 95% CI 1.9–5.2).[86] The restoration of sinus rhythm following ablation was associated with an improved estimated glomerular filtration rate and urine albumin-to-creatinine ratio, but this improvement was not observed in patients with paroxysmal AF.[87]

Despite this well-established temporal relationship between AF burden and progression of kidney injury, no actionable thresholds have been validated to date to inform clinical decision-making on risk categories, diagnostic workup or treatment options.

## Atrial fibrillation burden and risk of impaired cognition

Atrial fibrillation is an independent risk factor for cognitive impairment and dementia, despite the numerous shared risk factors, such as hypertension and HF, and a similar prevalence among the elderly.[88,89] Candidate mechanisms for this interaction include AF-related stroke (both clinically overt or 'silent'/unapparent stroke), chronic cerebral hypoperfusion, abnormal endothelial shear stress through beat-to-beat-variability, and systemic inflammation. Other contributing factors may include genetic risk factors, side effects of AF-related medications (such as beta-blockers or anticoagulants[90] or cerebral injury due to AF-related interventions such as catheter ablation,[91] cardioversion,[92] or left atrial appendage occlusion[93] (*Figure 6*). A large variety of features of cognitive dysfunction, definitions of dementia as well as neuropsychological test batteries have been used in studies combined with varying definitions of AF, which limits the interpretation and comparability of the data.[88]

Only a few studies have focused on the association of AF burden and declining cognitive function mostly limited by small size[95,96] and by using only screening tests for cognitive function.[96,97] A small randomized controlled study using ICM for ECG monitoring showed that a reduced AF burden (assessed as % of monitoring duration) following AF ablation was associated with improved cognitive functions in verbal learning 6 months after left atrial ablation compared with baseline.[95] A prospective observational study using a 14-day patch-based rhythm monitoring showed an association of higher AF burden with lower cognitive function assessed by MoCA test.[96] In contrast, a subanalysis of the randomized controlled LOOP study observed no association between AF burden and the cognitive function assessed by MoCA testing during a 3-year follow-up in 1194 participants free of AF at baseline of whom 339 developed AF during follow-up.[97]

The importance of AF burden in the onset and progression of AF-related cognitive decline is not well established.[98] A unified approach for assessment of AF burden will be crucial in future studies to obtain comparable and clinical data on the association of AF burden and progression of cognitive dysfunction and dementia.

## Atrial fibrillation burden and quality of life

When AF is symptomatic, it has a major impact on QoL. In turn, improved QoL is a major goal of treatment for rhythm control in the AF population. To date, the majority of clinical trials assessing efficacy of rhythm control use a documented single episode of 30 s AF recurrence as the primary endpoint. It seems intuitively unlikely that this outcome measure will correlate closely with an improvement of QoL. However, almost all, 16/18 (89%) randomized clinical trials comparing the efficacy of AF ablation vs. AADs in a general AF population have used this endpoint of rhythm control as the primary endpoint, even though improved QoL was the main goal of treatment.[13,99–113] Among these trials, AF burden was only used in one.[101] Only 2 of the 18 recent randomized clinical trials on AF ablation in general AF populations used major clinically relevant primary outcomes: QoL in the CAPTAF trial[31] and a composite of death, disabling stroke, serious bleeding, or cardiac arrest in the CABANA trial.[114]

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**Clinical Consensus Statements (3): Clinical value of measuring AF burden**

| No | Statements | % Agreement |
|---|---|---|
| 3.1 | **AF burden is a standard quantitative measurement of intermittent forms of AF independent of the underlying disease or specific targeted outcome.** | Strong |
| 3.2 | **Actionable thresholds of AF burden are specific to the clinical background and the relevant outcome.** | Unanimous |
| 3.3 | **Current prognostic and therapeutic implications of AF burden have been mainly based on clinically detected AF.** | Strong |
| 3.4 | **Stroke risk increases in proportion to the duration of uninterrupted AF; at present, >24 h of uninterrupted AF is regarded as a threshold for increased stroke risk, although shorter durations may also increase stroke risk.** | Strong |
| 3.5 | **AF burden contributes to the risk of stroke, together with clinical risk factors. The combination of AF burden with clinical factors may define actionable thresholds.** | Strong |
| 3.6 | **High AF burden is associated with HF; the association is stronger with HFpEF than HFrEF.** | Strong |
| 3.7 | **In patients with HF, increasing AF burden is associated with an increasing risk of HF decompensation and/or hospitalization.** | Unanimous |
| 3.8 | **There is an apparent association between increasing AF burden and the progression of renal failure.** | Unanimous |
| 3.9 | **AF burden reflects AF progression or regression more precisely than categorical AF patterns (paroxysmal, persistent, permanent AF).** | Strong |
| 3.10 | **AF burden reduction may be associated with improvement of QoL.** | Strong |
| 3.11 | **There is an association between increasing AF burden and increased mortality.** | Unanimous |

Recent data show that AF burden, assessed as a per cent of monitoring period, has a greater impact on QoL than AF episode duration or the number of AF episodes, and is the only AF variable associated with lower QoL.[115] The inverse relationship between AF burden and health-related QoL seems clear and has in fact been shown in the CAPTAF trial.[31] Indeed, every 10% increase in AF burden resulted in a 1.3-point decrease of the Vitality score of SF-36.[115] The strength of the association between higher AF burden and reduction of QoL seems to vary not only according to the AF population studied but also depending on the monitoring duration and the various definitions applied for AF burden assessment. Atrial fibrillation burden was measured as absolute time in AF per day in some trials (ASPECT,[116] TRENDS,[66] ATTEST[113]) or time in AF per months in others.[117] A reduction of AF burden was generally reported in these studies to carry a beneficial effect on QoL,[31] whereas AF recurrence as defined by 30 s of arrhythmia had no clinical relevance.[118] Due to the differences in the current ways of AF burden assessment and the different monitoring periods, comparability of treatment efficacy between individual trials is very limited and validated actionable thresholds are lacking. The ability of AF burden reduction to improve QoL in patients with relevant comorbidities such as advanced HF or renal failure needs to be determined.

The degree of AF burden reduction required to achieve a clinically meaningful improvement in QoL remains to be determined. The strong association of health-related QoL with AF burden rather than with time to first recurrence of AF underscores the need of a reproducible and comparable assessment of AF burden as a contributor to QoL.

## Applying atrial fibrillation burden in clinical trials

Treatment of AF is designed to reduce major cardiovascular events (MACEs), reduce symptoms, and improve QoL. An adequate measure of antiarrhythmic therapeutic success should correlate closely with one or all of these objectives. The assessment of rhythm-related variables as endpoints in clinical trials is determined by the two methodological constraints: the choice of a valid rhythm-related variable and the mode of monitoring, including the duration and frequency of ECG monitoring. A variety of rhythm-related variables have been applied in clinical trials such as time to recurrence of an AF episode of a pre-defined duration, the number of AF episodes, the LEAF duration, AF density, or AF burden during a defined period of time.

### Recurrence of an atrial fibrillation episode vs. a quantitative measure of atrial fibrillation burden

The standard binary primary endpoint in trials evaluating antiarrhythmic therapy for AF is the time to the first recurrence of an episode of AF, documented for at least 30 s of ECG rhythm strip or a complete 12-lead ECG showing AF.[119] The classical emphasis on the recurrence of 'symptomatic AF' was based on the relatively easy monitoring techniques, such as event-driven ECG monitoring, that could be implemented for assessing symptom control. Large clinical trials necessary to assess MACE outcomes were not thought necessary because antiarrhythmic therapy was demonstrably successful in relieving symptoms. On the other hand, when it became clear that AF is often asymptomatic and that successful suppression of AF might also reduce MACEs and improve QoL, it was argued that all AF recurrences should be documented and that a better surrogate for MACEs might be the time to the first recurrence of AF or the frequency of AF recurrences. However, this requires more intensive rhythm monitoring. Initially, systematic regular ECG recording was added to the recording of symptomatic events. Then, the duration of monitoring was progressively increased to allow (near-) all AF episodes to be recorded.

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With the option of prolonged and continuous ECG recording, the standard endpoint of 'time to first AF recurrence' is questionable. It is highly variable and arbitrary, and recurrences of short AF episodes are poorly related to QoL and MACE outcomes. Other measures of AF recurrence such as the number or frequency of AF recurrences, etc. might provide better information on the efficacy of an antiarrhythmic therapy aimed at improving QoL. However, it is more likely that the integral of frequency and duration of AF recurrences, an estimate of AF burden, might better correlate with MACE outcomes and QoL estimates.[120,121]

The efficacy of AF ablation was shown to progressively decline when the endpoint 'time to the first AF episode recurrence' was used, whereas it remained stable when AF burden was used as the endpoint during follow-up.[120] Thus, the first episode of AF relapse is considered a less optimal endpoint than the reduction in AF burden, especially when aiming for long-term success.[122] The rhythm outcomes of AF ablation vary depending on the definitions used for AF duration cut-off and the methods of rhythm monitoring.[123] Efficacy, as measured by freedom from paroxysmal AF, ranged from 28 to 72% at 1 year, depending on the AF duration cut-off (ranging from over 6 min to over 23 h) and whether intermittent or continuous monitoring was employed. In contrast, efficacy remained stable at 99.6% when measured as a reduction in AF burden. In the LINQ-AF study, four different methods of rhythm outcome assessment were compared (time to AF recurrence, discontinuous recurrence analysis, AF burden, and rhythm profiles). Applying these different rhythm assessment methods resulted in a large variation in the ablation success rates (ranging from 46 to 79%). However, AF burden and individual rhythm profiles were the least affected, with successful treatment observed in 60 to 70% of patients.[34]

Comparability of AF burden assessment between clinical studies is a clear unmet need. The here proposed unified definition of AF burden assessment will allow for better standards in clinical trial design and ensure comparability of treatment effects.

## Atrial fibrillation burden as an endpoint in clinical outcome trials

Atrial fibrillation burden can itself be an outcome by which to judge the efficacy of an antiarrhythmic therapy or to predict adverse MACE outcomes, such as stroke or HF. When considering the direct evaluation of an antiarrhythmic therapy, AF burden assessment can accurately quantify the amount of AF. If some patients, however, develop sustained symptomatic arrhythmia which requires cardioversion or ablation, the value of the burden assessment will be compromised since these patients may undergo a heart rhythm intervention to terminate AF, and hence to modify AF burden at a time decided by the physician or patient. These patients might be censored from the AF burden outcome and contribute to another outcome event, such as 'medical intervention' or remain within the burden outcome but with a nominal pre-specified burden. Such a manoeuvre may be necessary because the time of the cardioversion, and hence, the AF burden of a sustained arrhythmia would otherwise depend largely on the choice of the physician or patient. Similar considerations should apply when patients who are assessed for ablation efficacy using AF burden estimates if other antiarrhythmic therapy is added.

When an AF burden assessment is made to evaluate the risk of an adverse outcome thought to be caused or aggravated by AF such as stroke, dementia, and HF, the AF burden to which the patient is exposed is the appropriate measure. If a sustained arrhythmia occurs while awaiting cardioversion, the AF burden estimate should include this entire period. There is growing interest in the relationship between AF burden and MACE AF-related outcomes (such as mortality and hospitalization) particularly in AF populations with comorbidities such as HF.[79,124,125] A recent substudy of the CIRCA-DOSE trial, on a general AF population, found that higher AF burden was significantly associated with increased emergency department visits, rate of hospitalizations and cardioversions, and repeated AF ablation procedures at a 3-year follow-up.[126] Several studies on data from CIEDs have demonstrated that higher AF burden is associated with increased mortality,[83,127] worsened cardiovascular outcomes[4] a higher risk of new-onset HF, or increased risk of HF-related hospitalization in patients with HF.[75]

Data from the interventional CASTLE-AF trial showed that AF ablation treatment successfully reduced mortality and HF hospitalization in patients with HF, and this treatment effect was associated with reduction of AF burden, but not with the re-occurrence of AF episodes exceeding 30 s.[15] This evidence supports the conclusion that AF burden may represent the most suitable outcome measure to study efficacy of rhythm control treatments.[128] Therefore, the assessment of AF burden in a unified way to allow comparability between individual clinical studies should be adopted as a new standard assessment of rhythm endpoints in clinical trials.

**Clinical Consensus Statements (4): AF burden as outcome in clinical trials**

| No | AF burden as outcome in clinical trials | % Agreement |
|---|---|---|
| 4.1 | **In clinical trials of AF on rhythm control, AF burden should become a standard outcome for measuring antiarrhythmic effects.** | Unanimous |
| 4.2 | **AF burden is an important secondary outcome in clinical trials of AF patients where the treatment may be hypothetically antiarrhythmic.** | Unanimous |
| 4.3 | **In proof of concept/phase II trials AF burden can be a primary outcome.** | Unanimous |

# Current knowledge gaps on atrial fibrillation burden

The proposed unified definition of AF burden will allow for comparability of data between clinical studies assessing the clinical impact of therapy for intermittent AF occurring in various clinical circumstances, and to identify clinically meaningful actionable thresholds of AF burden. Such a standardized concept for the assessment of AF burden will help to address current knowledge gaps in the field of diagnostic or treatment of rhythm-related clinical conditions. A list of important current knowledge gaps is given below.

(1) The predictive value of AF burden, defined as the proportion of time spent in AF during a specified period, for various outcomes over a range of clinical backgrounds needs ongoing assessment.
(2) The incremental predictive value of the AF burden assessed in terms of the LEAF needs further assessment for various outcomes over a range of clinical backgrounds.
(3) Atrial fibrillation burden is not 'static' and may change with ageing and co-incident comorbidities or therapy. As many prior studies have focused on a 'one off' assessment, the implications of dynamic changes in AF burden remain uncertain.

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(4) The clinical value of AF density as an additional metric of AF burden needs further assessment.
(5) The association of additional characteristics of AF burden (high heart rate, degree of ventricular rate irregularity, etc.) on the predictive value of AF burden should be measured.
(6) There are different requirements for the minimal extent of continuous monitoring for assessment of AF burden depending on AF related outcomes measured (e.g. disease deterioration vs. mortality).

## Knowledge gaps on clinical endpoints

(7) The scarce and heterogeneously reported data on AF burden and AF burden changes in patients with ischaemic stroke is a major knowledge gap.
(8) The AF burden (per cent of time during a specified period) is less well established than the duration of uninterrupted AF episodes as a risk factor for ischaemic stroke.
(9) It is currently unclear, if the observed lower stroke risk in patients with AF detected after stroke would justify different AF burden actionable thresholds for anticoagulation therapy compared with primary stroke prevention.
(10) Assessment of AF burden in relation to stroke and the impact of AF burden reduction on risk may provide important insight to the ongoing discussion of AF as a marker or mediator of stroke.
(11) The degree of AF burden reduction required to prevent onset or worsening of HF is unknown.
(12) The significance of AF burden for the onset and progression of AF-related cognitive decline is poorly studied as is improvements in cognitive function with reductions in AF burden.
(13) It is unknown if and to what extent monitoring of AF burden in HFrEF patients post-AF ablation will improve their prognosis.
(14) Although a high AF burden post-AF ablation in HFrEF patient implies increased mortality, it is unknown whether resumption of sinus rhythm by re-ablation will improve the prognosis.

# Conclusions

The clinical significance of AF and most of the clinical decisions related to AF are currently based on the categorical recognition of AF being present or absent (with limited further insight from the additional categorical appraisal of paroxysmal AF). There is increasing evidence, however, that a more precise temporal characterization of intermittent AF has a relevant impact on symptoms, onset and progression of AF-related disease, including mortality.

Atrial fibrillation burden has emerged as an innovative measure of intermittent AF in relation to underlying clinical conditions. However, the inconsistent assessment methods of AF burden prevent a wider between-study comparability of AF burden and its validation for standardized clinical use. To address this unmet clinical need a unified definition of AF burden is proposed: AF burden should be primarily reported as the proportion of time spent in AF in relation to the overall monitoring time. The duration of the LEAF should be also reported where clinically relevant. Both measurements may carry significant and independent clinical information. A pivotal requirement for validity and comparability of this proposed definition of AF burden is a sufficient length of the monitoring period that needs to be reported together with the AF burden assessment. It is understood that the true AF burden can only be assessed by continuous or near-continuous ECG monitoring (e.g. by ICM), which is regarded as the reference method, although well performed patch monitoring or medical-grade wearable devices may also provide high-quality information. Limited-time intermittent monitoring requires a duration of at least 4 weeks accumulated monitoring per year in order to achieve statistically comparable accuracy compared with continuous rhythm monitoring. The patients preference should be taken into account when selecting the individualized rhythm monitoring method. Actionable thresholds which are disease specific need to be defined according to the AF-related outcomes.

The proposed unified definition of AF burden will allow for comparability of data between clinical studies and will therefore expand the evidence to validate clinically meaningful actionable thresholds of AF burden and of AF burden dynamics in various clinical conditions. This proposed definition of AF burden will inform risk evaluation and clinical treatment decisions in AF-related disease, it will further support clinical trial development to derive meaningful and comparable evidence on the significance of intermittent AF. Finally, a unified definition of AF burden will support the technology development of heart rhythm monitoring towards validated technology to meet clinical needs.

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## Data availability

No new data were generated or analysed in support of this research.

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