AF burden

INTERNATIONAL CONSENSUS WORKSHOP

TMA

AF burden
INTERNATIONAL CONSENSUS WORKSHOP

MUNICH, GERMANY
FEBRUARY 23-24 2023

International Consensus Workshop

Determining a Consensus Definition of of AF Burden and its Clinical and Research Relevance

AIMS AND SCOPE OF THE WORKSHOP

The aim of the workshop is to propose a consensus on the definition of atrial fibrillation (AF) burden as a fundamental clinical concept. This consensus aims to inform clinicians and health care workers, trialists, industry representatives and health-care policy makers on a clinically applicable concept of AF burden:

- **Why is an assessment of AF burden necessary? – What is the purpose of a definition of AF burden?**
- **What is AF burden – one or more definitions?**
- **What influences AF burden?**
- **How should AF burden be assessed?**
- **How variable is AF burden and what influences the variability?**
- **What is the clinical relevance of AF burden and what are meaningful actionable thresholds?**
- **What are current knowledge gaps on AF burden?**

The output from this workshop will advance the clinical understanding of AF with the goal:

- **to define innovative targets for future research of clinical and technological concepts,**
- **to encourage validation of assessment of AF burden in clinical studies,**
- **to advance the academic interdisciplinary discussion on AF burden and related clinical conditions.**

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AF burden INTERNATIONAL CONSENSUS WORKSHOP

MUNICH, GERMANY FEBRUARY 23-24 2023

SESSION STRUCTURE, CONSENSUS PROCEDURES, DISSEMINATION

The workshop will address specific individual aspects that define the characteristics of AF burden from a diagnostic, therapeutic, regulatory and technological perspective and discuss key questions in a structured agenda. The main categories that will be addressed are:

What is AF burden?	**Principle concepts**
How to measure AF burden?	**(Patho-)physiologic and technical perspectives**
AF burden – clinical relevance	**Diagnostics,** **Risk assessment in relation to diseases** **Therapeutic decision making.**
AF burden – clinical trial relevance	**AF as an outcome variable** **Assessment methods and technology** **Endpoint definitions**

Structured discussion:

These main topics above will be discussed in separate sessions starting with an introductory impulse presentation (no global data review), followed by structured discussion of defined key questions (see details below), followed by a consensus voting. A Delphi procedure will be pursued for consensus development using the on-site discussion and subsequent manuscript review of the written report from the workshop (supported by scientific writing).

Voting procedure

A pre-defined consensus process (statement - vote - modifying debate - revote) will include the entire faculty and will be applied to each question. As a result of this process, consensus options can be either accepted, modified, or rejected. The voting for consensus is recorded according to predefined levels of consensus.

Level of consensus: 100%: unanimous consensus
90-99%: strong consensus,
75-89%: moderate consensus,
50-74%: weak consensus, majority agreement,
<50%: no consensus

Outcome and dissemination

A consensus statement will be drafted based on the outcome for the discussion and the consensus process.

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MUNICH, GERMANY FEBRUARY 23-24 2023

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Day 1

Main Topic 1: What is AF burden?

A fundamental approach to define AF burden will be discussed, based on a temporal load but possibly including additional variables. AF burden is widely applied in relation to the risk of stroke secondary to paroxysmal AF. The concept of AF burden may, however, be applicable as a primary rhythm assessment with clinical implications beyond stroke for a range of clinical conditions and morbidities.

Key questions:

- **Can AF burden be defined as a function of time in AF?**
- **Is AF burden the absolute time spent in AF during a period of monitoring (in min and hours, e.g. 6 hours during an observation of 24 hours) or is it the current proportion of time spent in AF (in %) or a combination of absolute time (in min/h) and relative time (in % of recording time)?**
- **What are modifying rhythm variables of AF burden (e.g., continuous vs cumulative AF duration, duration vs frequency of episodes, heart rate in AF)?**
- **Are further ECG variables relevant for AF burden analysis (number of irregular beats, degree of ventricular irregularity, SR-bradycardia or ventricular pauses following an episode of AF, etc.)?**
- **Do the temporal patterns making up the burden have any relevance (legato versus staccato)?**
- **How do modifying non-cardiac variables contribute to the dynamic nature of AF burden (impact of age, lifestyle, immobilisation, nutrition, sleep, drugs)?**

Proposal 1 | **example consensus statement**

AF burden is an ECG measurement of the time spent in AF during a specified period. AF burden is an ECG-derived metric which may support risk assessment and diagnostic or therapeutic decision-making for improvement of clinical outcome or symptoms related to AF.

AF Burden can -/- should be expressed as:
(a) continued (or total cumulative?) time in AF (in minutes and hours), or
(b) relative time of observed AF based on the overall observation time (in %)
(c) a combination of absolute and relative time (the length of longest AF episode plus % time in AF)

Potential further points to include in the consensus statement:
- More details on the timing of AF burden needed to define AF burden.
- Other ECG variables that contribute to AF burden?
- Other non-ECG variables (clinical, personal, ...) that contribute to AF burden?
- Address knowledge gaps

AF burden INTERNATIONAL CONSENSUS WORKSHOP

MUNICH, GERMANY FEBRUARY 23-24 2023

SCIENTIFIC AGENDA

Day 1

NOTES Topic 1: What is AF burden?

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MUNICH, GERMANY FEBRUARY 23-24 2023

SCIENTIFIC AGENDA

Day 1

Main Topic 2: How to measure AF burden?

In clinical reality, a wide range of assessment methods for AF detection and recording exists and the definition of AF burden may need to acknowledge this variety of assessment methods.
This session will address the different approaches for AF detection regarding validity and applicability (reproducibility, availability, complexity, costs, compliance). The aim is to identify clinical and technical needs to provide meaningful measurements to assess AF burden (including current limitations).

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Key questions:

- **How much time must be sampled to accurately (sufficiently) assess AF burden?**
- **How do different assessment concepts compare (repeated short ECGs [e.g., once daily], extended ECG monitoring [days...weeks], permanent monitoring [CIED]?**
- **What is the value of lay devices e.g., Apple Watch, ICART ring, Kardia Mobile, etc.; medical-grade vs consumer-grade devices?**
- **Analytical challenges of assessment of AF burden (functional capabilities and limits)?**
- **Current status and outlook on qualified expert analysis vs. AI analytics (predictive accuracy from non-continued assessment methods)?**

Proposal 2 | **example consensus statement**

Measurement of AF burden requires extended ECG monitoring with longer monitoring resulting in higher precision.

The ultimate assessment would be derived from (semi-) permanent continued ECG monitoring (e.g., by CIED).

If ECG recording is maintained for a limited period of time, it is important to define AF burden in relation to the time of the rhythm monitoring.

Potential further points to include in the consensus statement:
- Categories of low/ -medium-/-high AF burden (e.g., categories for duration of AF episodes)
- A minimum time of rhythm monitoring needed to assess AF burden.
- Address methodological / technical requirements to define AF burden.
- Address knowledge gaps

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AF burden INTERNATIONAL CONSENSUS WORKSHOP

MUNICH, GERMANY FEBRUARY 23-24 2023

SCIENTIFIC AGENDA

Day 1

NOTES Topic 2: How to measure AF burden?

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MUNICH, GERMANY FEBRUARY 23-24 2023

SCIENTIFIC AGENDA

Day 2

Main Topic 3: Clinical value of measuring AF burden (stroke, heart failure, kidney injury, cognitive impairment, QoL)

In the current literature, a range of cut-points for AF duration regarding an incremental thromboembolic risk have been investigated ranging from 30 seconds, 60 minutes to 24 hours. The discussion is ongoing as to the relevance of the temporal association of AF and stroke event, including the debate of AF as a marker or mediator of stroke risk). Additional factors (clinical risk profile, comorbidities) also modify AF related-risk of stroke (or other sequelae), but the interdependence of AF burden and such risk factors is less well understood.

Key questions:

- **Does the definition of clinically relevant AF burden vary in relation to risk of subsequent morbidities (e.g., (recurrent) stroke, heart failure, kidney injury, cognitive impairment, etc.)?**
- **What is the particular relevance of AF burden in relation to stroke risk?**
- **Can we define "actionable thresholds" (cut-points, limits) for AF burden in relation to the risk of stroke? If so, is there a difference of AF burden in primary vs secondary stroke prevention?**
- **Are "actionable thresholds" possible for other risks (heart failure, renal function, cognitive dysfunction, etc.)?**
- **Should the combination of AF burden and clinical risk factors be applied to quantify risk (using a 2-dimensional risk score matrix of AF burden x risk factors)?**
- **What is the relevance of temporal association of an AF episode and ischemic stroke?**
- **Is it AF burden (AF=mediator) or atrial cardiomyopathy (AF = marker) that is the major determinant of thromboembolic risk?**

Proposal 3 | **example consensus statement**

AF burden may have different implications for clinical conditions, (i.e., stroke, heart failure, renal failure, impaired cognitive function, impaired quality of life).

A particular clinical relevance of AF burden has been established for assessing the risk of stroke. For assessment of AF-related stroke risk, AF burden should be combined with individual patient's clinical characteristics.

A population of low -/- moderate -/- high stroke risk related to AF burden can be defined as:
For the risk of stroke: ...

Potential further points to include in the statement:

- Risk categories for other clinical conditions than stroke
- Address knowledge gaps

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SCIENTIFIC AGENDA

Day 2

NOTES Topic 3: Clinical value of measuring AF burden

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MUNICH, GERMANY FEBRUARY 23-24 2023

SCIENTIFIC AGENDA

Day 2

Main Topic 4: AF burden as an outcome in clinical trials

AF burden may be used as an outcome variable in a clinical trial with both diagnostic and therapeutic targets. The debate is ongoing to define key characteristics and clinical patterns of AF – and AF burden – as an endpoint in clinical trials. Regulatory authorities (FDA, EMA) identify only two reasons for preventing AF recurrence: reduction of symptoms and MACE events. They also argue that the relationship between burden and MACE event is not yet well understood, and they take up inconsistent positions on asymptomatic burden being irrelevant to the patient. The session will discuss the relevance and the clinical and technical aspects of AF burden as an endpoint variable in future clinical trials. .

Key questions:

- **Is AF burden a relevant outcome variable in diagnostic and interventional trials? Diagnostic trials: AF screening for risk assessment; therapeutic trials: AF burden as a target of medical or interventional therapy for a) MACE or b) AF-related symptom limitation (QoL)?**
- **Which time-related aspects of AF burden are relevant outcomes in clinical trials (time to first AF re-occurrence, reduction of AF burden [absolute or relative time]; which additional time-related measurements of AF burden should be analysed? AI-based ECG analysis?)**
- **Can quantitative measures (cut-points) be proposed as an endpoint (AF y/n vs. reducing AF burden below actionable thresholds, better than AF duration ≥30 seconds)?**
- **Relevance of symptomatic vs. asymptomatic AF as applicable outcome?**
- **Weighing AF burden reduction vs. clinical outcomes?**
- **Technical perspective: which ECG variables may contribute to advanced AF burden analysis, what can be assessed and what are current (technical) limitations?**

Proposal 4 | **example consensus statement**

AF burden is a relevant outcome variable in diagnostic, as well as in interventional trials.

- Clinically and technically meaningful cut-points (actionable thresholds) for risk levels related to AF burden for the risk of stroke are: ...
- Those cut-points may vary depending on the type and the goal of the clinical trial:
  Diagnostic trials: actionable thresholds
  Interventional trials: clinically relevant risk reduction for symptomatic or outcome endpoints

Potential further points to include in the statement:

- Address knowledge gaps

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SCIENTIFIC AGENDA

Day 2

NOTES Topic 4: AF burden as an outcome in clinical trials

AF burden INTERNATIONAL CONSENSUS WORKSHOP

MUNICH, GERMANY FEBRUARY 23-24 2023

SCIENTIFIC AGENDA

Day 2

Final session :

This session will aim to provide an integrated definition of AF burden to inform clinicians with a clinically applicable definition to support risk assessment and therapeutic decision making and to instruct trialists on meaningful endpoint characteristics to test innovative diagnostic and therapeutic concepts. Finally, gaps in current evidence and unmet needs in the evaluation of AF burden will be summarized.

Proposal 5 **on an integrating consensus definition of AF burden.**

- key statements from Topic 1 (what is AF burden?)
- key statements from topic 2 (how to measure AF burden)
- key statements from topic 3 (clinical value of AF burden)
- key statements from topic 4 (AF burden as an outcome in clinical trials)

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SCIENTIFIC AGENDA

Day 2

NOTES Final session :

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SCHEDULE

Day 1

	Thursday, February 23	
13:00-13:30	**Welcome and introduction**	J. Camm/ W.Doehner
	Overview on AF burden as applied in RCT's	T. Potpara
13:30-15:30	**Main Session 1:** **What is AF burden?**	G. Lip
	Impulse presentation Structured discussion of defined questions (Q1, 2, …) Consensus proposal – modifying debate - voting	J. Camm
15:30-16:00	COFFEE BREAK	
16:00-18:00	**Main Session 2:** **How to measure AF burden**	B. Freedmann
	Impulse presentation Structured discussion of defined questions (Q1, 2, …) Consensus proposal – modifying debate - voting	R. Passmann
19:15	DINNER	

Day 2

	Friday, February 24	
8:30-10:30	**Main Session 3:** **Clinical value of measuring AF burden in relation to different clinical diseases**	R. Schnabel
	Impulse presentations stroke / heart failure /renal failure -/- cognitive impairment/, QoL, Structured discussion of defined questions (Q1, 2, …) Consensus proposal – modifying debate - voting	L. Sposato, G. Boriani, T. Potpara KG. Häusler
10:30-10:45	COFFEE BREAK	
10:45-12:45	**Main session 4:** **AF burden in clinical trials**	J. Healey
	Impulse presentation Structured discussion of defined questions (Q1, 2, …) Consensus proposal – modifying debate - voting	C. Blomström-Lundqvist
12:45-13:00	COFFEE BREAK	
13:00-13:30	**Main Session 5:** **Summary on consensus definition of AF burden**	W. Doehner
	Consensus proposal – modifying debate - voting	
13:30-13:45	**Summary and conclusion**	J. Camm/ W. Doehner

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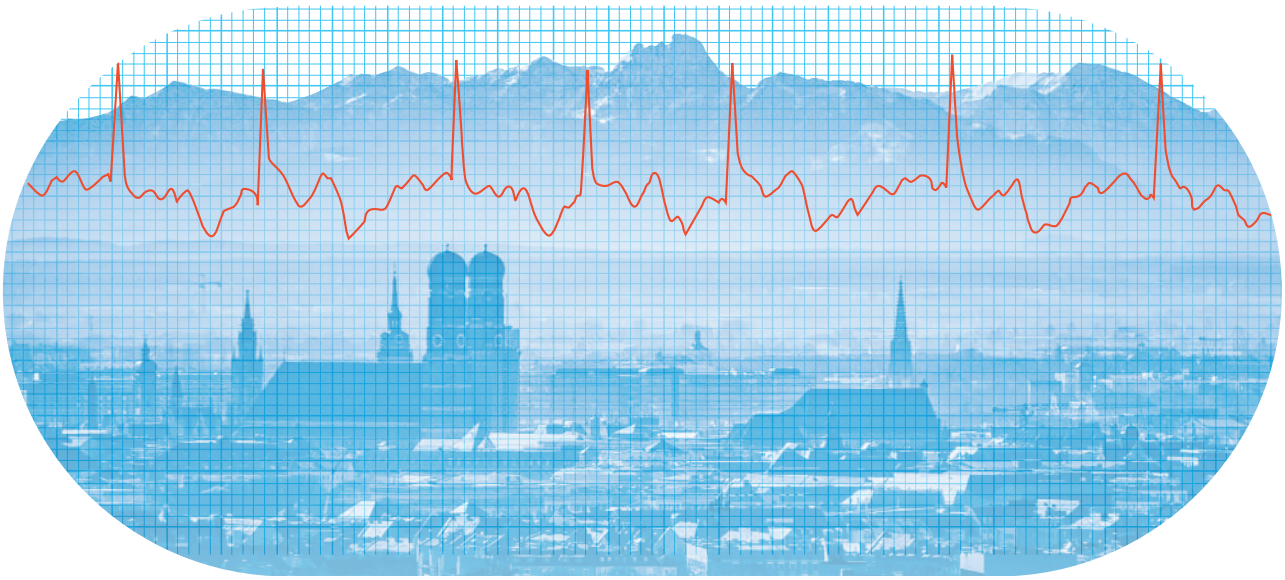

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