

Atrieflimren_Behandlingsalgoritme_Versi on 5

National behandlingsvejledning

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Endorsement af SSAI klinisk guideline

<https://ssai.info/wp-content/uploads/acta-anaesthesiol-scand-2023-andreasen-new-onset-atrial-fibrillation-in-critically-ill-adult-patients-an-ssai.pdf>



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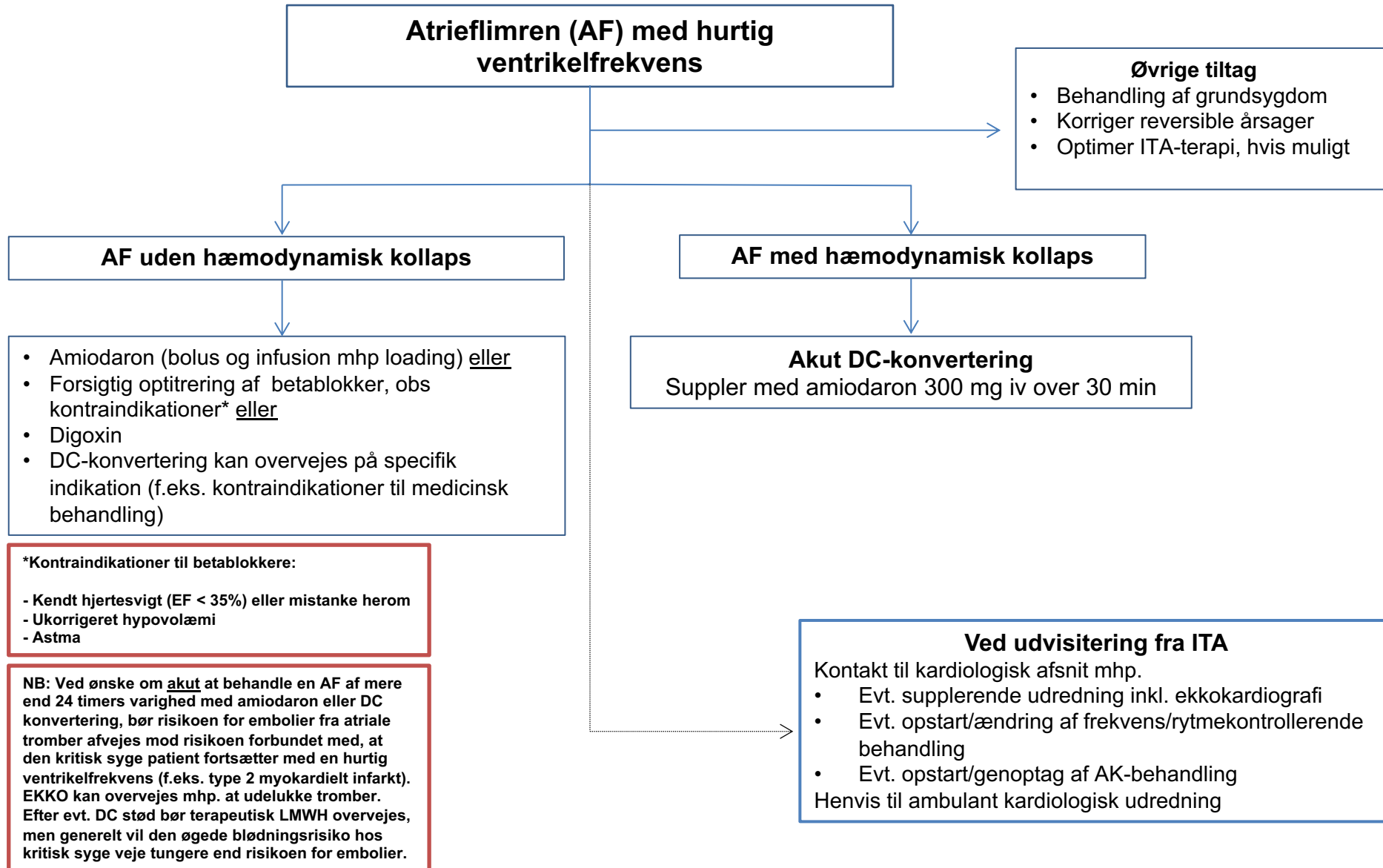
Opsummering af anbefalinger fra SSAI GRADE baseret guideline

Recommendation	Strength of the recommendation	Desirable and undesirable effects	Certainty of evidence	Comments
1. We were unable to provide any recommendations or suggestions on the better first-line pharmacological agent for the treatment of NOAF in critically ill patients in the ICU	NA	Unknown	NA	No direct or indirect relevant data from RCTs were available. Amiodarone is the most used agent.
2. We were unable to provide any recommendations or suggestions on whether we should use DC cardioversion in critically ill adult patients with NOAF and hemodynamic instability caused by atrial fibrillation	NA	Unknown	NA	No direct or indirect relevant data from RCTs were available. Considerable practice variation.
3. We suggest against routine use of therapeutic dose anticoagulant therapy as compared to no anticoagulant therapy in critically ill adult patients with NOAF	Weak	Increased incidence of major bleeding in anticoagulated patients with AF compared with non-anticoagulated patients. No significant difference or uncertainty in the remaining outcomes.	Very low due to risk of bias, inconsistency and indirectness	No direct or indirect relevant data from RCTs were available. A systematic review of observational studies informed the recommendation. Uncertain feasibility and acceptability. Considerable practice variation.
4. We recommend routine follow-up by a cardiologist after hospital discharge for critically ill adult patients with one or more episodes of atrial fibrillation	Best practice statement	Unknown	NA	No direct or indirect relevant data from RCTs were available. The criteria for a best practice statement were fulfilled. Uncertain feasibility and acceptability. Considerable practice variation.

Abbreviations: AF, atrial fibrillation; DC, direct current; ICU, intensive care unit; NA, not applicable; NOAF, new-onset atrial fibrillation; RCTs, randomized clinical trials.

Figur 1. Forslag til behandlingsalgoritme ved ønske om frekvens- eller rytmekontrol

Grundet manglende evidens for bedste behandling af atrieflimren hos kritisk syge bør man vælge den behandlingsmodalitet og de præparater, som man har mest erfaring med og/eller som er afdelingens standardpraksis.



Tabel 1: Reversible årsager

Potentielt arytmogene triggere til atrieflimren ved kritisk sygdom

Hypoxi

Respiratorbehandling

Kardiel iskæmi

Anæmi

Hypotension

Sympatomimetika (adrenalin, noradrenalin, dobutamin)

Elektrolytforstyrrelser (specielt hypokaliæmi, hypomagnesæmi)






Hypo- og hypervolæmi

Inflammation

Modificeret fra:

- Wetterslev et al. PMID: 31089761
- Sibley et al. PMID: 40323451

New-onset atrial fibrillation in critically ill adult patients—an SSAI clinical practice guideline

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Abstract

Background: Acute or new-onset atrial fibrillation (NOAF) is the most common cardiac arrhythmia in critically ill adult patients, and observational data suggests that NOAF is associated to adverse outcomes.

Methods: We prepared this guideline according to the Grading of Recommendations Assessment, Development and Evaluation methodology. We posed the following clinical questions: (1) what is the better first-line pharmacological agent for the treatment of NOAF in critically ill adult patients?, (2) should we use direct current (DC) cardioversion in critically ill adult patients with NOAF and hemodynamic instability caused by atrial fibrillation?, (3) should we use anticoagulant therapy in critically ill adult patients with NOAF?, and (4) should critically ill adult patients with NOAF

This guideline has been prepared in collaboration with MAGIC and is available online.

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receive follow-up after discharge from hospital? We assessed patient-important outcomes, including mortality, thromboembolic events, and adverse events. Patients and relatives were part of the guideline panel.

Results: The quantity and quality of evidence on the management of NOAF in critically ill adults was very limited, and we did not identify any relevant direct or indirect evidence from randomized clinical trials for the prespecified PICO questions. We were able to propose one weak recommendation against routine use of therapeutic dose anticoagulant therapy, and one best practice statement for routine follow-up by a cardiologist after hospital discharge. We were not able to propose any recommendations on the better first-line pharmacological agent or whether to use DC cardioversion in critically ill patients with hemodynamic instability induced by NOAF. An electronic version of this guideline in layered and interactive format is available in MAGIC: <https://app.magicapp.org/#/guideline/7197>.

Conclusions: The body of evidence on the management of NOAF in critically ill adults is very limited and not informed by direct evidence from randomized clinical trials. Practice variation appears considerable.

KEYWORDS

clinical practice guideline, MAGIC, new-onset atrial fibrillation

1 | BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia.¹ New-onset atrial fibrillation (NOAF) can be defined as a newly detected irregular cardiac rhythm with the absence of P waves and irregular RR intervals, but no uniform definition exists.² In critically ill patients, acute or new-onset AF has a reported frequency ranging between 2% and 44%.^{2,3}

Observational data suggest that AF related to critical illness is associated with adverse outcomes, including prolonged hospitalization, hemodynamic instability, increased risk of thromboembolic events and higher mortality rates.⁴ The mechanisms by which AF is associated to worse outcomes are unknown, but may be due to hemodynamic instability, heart failure, stroke, or they may represent a marker of underlying pathophysiology that leads to worse outcomes.²

Despite NOAF being common and associated with adverse outcomes, recently published studies have highlighted considerable practice variation in the management of NOAF in the intensive care unit (ICU).^{2,4-6} Moreover, the body of evidence informing the management of NOAF in critically ill patients is sparse, and specific clinical practice recommendations are missing. Current recommendations on the management of AF in critically ill patients are mainly derived from non-critically ill patient populations,⁷ and it is questionable if these recommendations can be extrapolated to patients with organ failure(s) in the ICU.

Accordingly, the Clinical Practice Committee of the Scandinavian Society of Anesthesiology and Intensive care medicine (SSAI) initiated this clinical practice guideline on the management of NOAF in critically ill adult patients. The aim was to summarize the available evidence and provide recommendations according to current standards for trustworthy guidelines.⁸⁻¹⁰

2 | METHODS

2.1 | Organization

This clinical practice guideline was initiated and sponsored by the Clinical Practice Committee of the SSAI.

2.2 | Scope

The clinical practice guideline applies to critically ill adults in an ICU setting. The guideline does not apply to cardiac surgery patients, patients outside the ICU or to children.

2.3 | Target audience

The target users of this guideline are healthcare workers who care for critically ill adult patients in an ICU setting, including critical care physicians, advanced practice providers, nurses, and pharmacists.

2.4 | Guideline panel

The Clinical Practice Committee of the SSAI selected and invited the panel members. The panel comprised a total of 15 stakeholders including patient representatives, content experts, academic critical care physicians, nurses, methodologists, and frontline clinicians.

We aimed for diversity in the panel, including gender, age, profession, and geography.¹¹ A clinical chair (A.S.A.) and a methods chair

TABLE 1 The clinical questions and PICO questions used in this guideline.

(A) What is the better first-line pharmacological agent for the treatment of new onset atrial fibrillation (NOAF) in critically ill adult patients?	
PICO 1	Description
Population	Critically ill adult patients with NOAF
Intervention	Amiodarone, digoxin, beta-blockers, magnesium, or placebo
Comparator	Amiodarone, digoxin, beta-blockers, magnesium, or placebo
Outcomes	Mortality at longest follow-up, adverse events, NOAF recurrence, hospital length of stay (LOS), intensive care unit (ICU) LOS, thromboembolic events, health-related quality of life
(B) Should we use direct current (DC) cardioversion in critically ill adult patients with new onset atrial fibrillation (NOAF) and hemodynamic instability caused by atrial fibrillation (AF)?	
PICO 2	Description
Population	Critically ill adult patients with NOAF and hemodynamic instability caused by AF
Intervention	DC cardioversion
Comparator	No DC cardioversion (pharmacological therapy only)
Outcomes	Mortality at longest follow-up, adverse events, NOAF recurrence, hospital length of stay (LOS), intensive care unit (ICU) LOS, thromboembolic events, health-related quality of life
(C) Should we use direct current (DC) cardioversion in critically ill adult patients with new onset atrial fibrillation (NOAF) and hemodynamic instability caused by atrial fibrillation (AF)?	
PICO 3	Description
Population	Critically ill adult patients with NOAF and hemodynamic instability caused by AF
Intervention	DC cardioversion
Comparator	DC cardioversion and subsequent pharmacological therapy
Outcomes	Mortality at longest follow-up, adverse events, NOAF recurrence, hospital length of stay (LOS), intensive care unit (ICU) LOS, thromboembolic events, health-related quality of life
(D) Should we use anticoagulant therapy in critically ill adult patients with new onset atrial fibrillation (NOAF)?	
PICO 4	Description
Population	Critically ill adult patients with NOAF
Intervention	Anticoagulant therapy
Comparator	No anticoagulant therapy
Outcomes	Mortality at longest follow-up, adverse events, NOAF recurrence, hospital length of stay (LOS), intensive care unit (ICU) LOS, bleeding events, thromboembolic events, health-related quality of life
(E) Should critically ill adult patients with new onset atrial fibrillation (NOAF) receive follow-up after discharge from hospital?	
PICO 5	Description
Population	Critically ill adult patients with NOAF
Intervention	Follow-up after hospital discharge
Comparator	No follow-up after hospital discharge
Outcomes	Mortality at longest follow-up, adverse events, NOAF recurrence, hospital length of stay (LOS), intensive care unit (ICU) LOS, thromboembolic events, health-related quality of life

(M.H.M.) led the guideline process. Two methodologists (M.W. and A.A.) provided methodologic support to the panel.

Five patient representatives—three patients and two relatives—provided valuable insights regarding values and preferences as well as outcome selection and prioritization.¹²

Conflicts of interests

We assessed and managed conflicts of interests as described elsewhere.¹³ All panel members completed an electronic conflicts of

interest form. No panel members declared financial conflicts of interests, and one panel member had potential academic conflict of interests. This was acknowledged and managed in the panel discussions, and in the formulation of the recommendations.¹³

2.5 | Guideline questions

The guideline panel addressed the following questions:

1. What is the better first-line pharmacological agent for the treatment of NOAF in critically ill adult patients?

2. Should we use direct current (DC) cardioversion in critically ill adult patients with NOAF and hemodynamic instability caused by AF?
3. Should we use anticoagulant therapy in critically ill adult patients with NOAF?
4. Should critically ill adult patients with NOAF receive follow-up after discharge from hospital?

2.6 | Population

The population of interest was critically ill adult patients in an ICU setting with NOAF, as defined by the included studies (Table 1).

2.7 | Intervention(s) and comparator(s)

We assessed the following interventions/comparators: (1) amiodarone, (2) digoxin, (3) beta-blockers, (4) magnesium, (5) placebo/no treatment, (6) DC cardioversion, (7) anticoagulant therapy, and (8) follow-up after hospital discharge (Table 1).

2.8 | Outcome(s)

The outcomes selected and prioritized as critical¹⁴ by the panel were: (1) mortality at longest follow-up, (2) adverse events, (3) recurrence of NOAF, (4) bleeding events, (5) thromboembolic events, (6) hospital length of stay (LOS), (7) ICU LOS, and (8) health-related quality of life (Table 1).

2.9 | The evidence

We systematically searched PubMed, Cochrane Library, and Epistemonikos for systematic reviews or randomized clinical trials (RCTs) according to the PICO questions (Table 1) on September 14, 2021. No language restriction was employed. The search strategy is available in the Supporting Information S1.

2.10 | Statistics

We planned to use conventional meta-analyses to generate summary estimates, but this proved not to be relevant due to the lack of data.

2.11 | The certainty of evidence

We assessed the certainty of evidence on an outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.¹⁵ In brief, we downgraded the certainty of evidence (our confidence in the effect-estimates) for an intervention for identified risks of bias, inconsistency (unexplained heterogeneity), indirectness (including extrapolation from other patient populations or use of

surrogate outcomes), imprecision (wide confidence interval around the effect estimate) or publication bias. Accordingly, the certainty of evidence was rated from 'high' to 'very low'.

2.12 | Moving from evidence to recommendation

We used GRADEpro GDT (GRADEpro Guideline Development Tool [Software]. McMaster University, 2015, developed by Evidence Prime, Inc.) to complete the Evidence-to-decision (EtD) framework. In brief, the panel addressed the balance and magnitude of the desirable and undesirable effects, the certainty of evidence, patients' values and preferences, costs and resources, feasibility, and acceptability, and we used the recently published informative statements to communicate the findings.^{12,16}

As direct published literature from RCTs was absent, an expert evidence survey was administered to the healthcare personnel in the panel about their unpublished observations and case series.¹⁷ The focus of this survey was on collecting data about cases and outcome, not panel opinions.

We followed the recommendations by the GRADE working group on when best practice statements should be issued.¹⁸

A strong recommendation was considered when virtually all informed patients would choose the recommended management strategy. A suggestion, that is, a weak/conditional recommendation, applies when fully informed patients would choose different management strategies, and reflects a close call between benefits and harms, uncertainty regarding treatment effects, questionable cost-effectiveness or variability in values and preferences.^{10,19} The author group agreed upon all the recommendations in this guideline.

An electronic version of this guideline in layered and interactive format is available in MAGIC: <https://app.magicapp.org/#/guideline/7197>.

3 | RESULTS

The results and recommendations based on the PICOs are presented below (A–D) and in Table 2.

3.1 | (A) What is the better first-line pharmacological agent for the treatment of NOAF in critically ill adult patients?

3.1.1 | Recommendation

We were unable to provide any recommendations or suggestions on the better first-line pharmacological agent for the treatment of NOAF in critically ill adult patients in an ICU setting.

3.1.2 | Rationale

We did not identify any relevant RCTs comparing the interventions of interest in critically ill adult patients with NOAF.

TABLE 2 Key recommendations.

Recommendation	Strength of the recommendation	Desirable and undesirable effects	Certainty of evidence	Comments
1. We were unable to provide any recommendations or suggestions on the better first-line pharmacological agent for the treatment of NOAF in critically ill patients in the ICU	NA	Unknown	NA	No direct or indirect relevant data from RCTs were available. Amiodarone is the most used agent.
2. We were unable to provide any recommendations or suggestions on whether we should use DC cardioversion in critically ill adult patients with NOAF and hemodynamic instability caused by atrial fibrillation	NA	Unknown	NA	No direct or indirect relevant data from RCTs were available. Considerable practice variation.
3. We suggest against routine use of therapeutic dose anticoagulant therapy as compared to no anticoagulant therapy in critically ill adult patients with NOAF	Weak	Increased incidence of major bleeding in anticoagulated patients with AF compared with non-anticoagulated patients. No significant difference or uncertainty in the remaining outcomes.	Very low due to risk of bias, inconsistency and indirectness	No direct or indirect relevant data from RCTs were available. A systematic review of observational studies informed the recommendation. Uncertain feasibility and acceptability. Considerable practice variation.
4. We recommend routine follow-up by a cardiologist after hospital discharge for critically ill adult patients with one or more episodes of atrial fibrillation	Best practice statement	Unknown	NA	No direct or indirect relevant data from RCTs were available. The criteria for a best practice statement were fulfilled. Uncertain feasibility and acceptability. Considerable practice variation.

Abbreviations: AF, atrial fibrillation; DC, direct current; ICU, intensive care unit; NA, not applicable; NOAF, new-onset atrial fibrillation; RCTs, randomized clinical trials.

Some observational studies in critically ill adult patients were identified,²⁰ but given the considerable risk of confounding in observational studies assessing intervention effects,²¹ the panel decided not to use observational studies to inform this recommendation.

The panel also decided not to use indirect evidence from other populations, including non-critically ill patients and patients in the emergency department, as causes of AF and the desirable and undesirable effects of anti-arrhythmic agents in critically ill patients with organ failure(s) were judged to be significantly different than in non-critically ill patients with no or limited organ dysfunction(s).

The results from the discussion of the EtD framework are available in the Supporting Information S1.

The results from the expert evidence survey showed that all panel members had most experience with amiodarone (Supporting Information S1).

3.2 | (B) Should we use DC cardioversion in critically ill adult patients with NOAF and hemodynamic instability caused by AF?

3.2.1 | Recommendation

We were unable to provide any recommendations or suggestions on whether we should use DC cardioversion in critically ill adult patients with NOAF and hemodynamic instability caused by AF.

3.2.2 | Rationale

We did not identify any relevant RCTs comparing the interventions of interest in critically ill adult patients with NOAF.

Some observational studies in critically ill adult patients were identified but given the considerable risk of confounding in observational studies assessing intervention effects,²¹ the panel agreed not to use observational studies to inform this recommendation.

The panel also agreed not to use indirect evidence from other populations, including non-critically ill patients and patients in the emergency department, as the causes of AF and the desirable and undesirable effects of DC cardioversion in critically ill patients with organ failure(s) were judged to be significantly different than in non-critically ill patients with no or limited organ dysfunction(s).

The results from the discussion of the EtD framework are available in the Supporting Information S1.

The results of the expert evidence survey indicated significant practice variation with some panel members using DC cardioversion on a regular basis, whereas some rarely use it (Supporting Information S1).

3.3 | (C) Should we use anticoagulant therapy in critically ill adult patients with NOAF?

3.3.1 | Recommendation

We suggest against routine use of therapeutic dose anticoagulant therapy as compared to no anticoagulant therapy in critically ill adult patients with NOAF (weak recommendation, very low certainty of evidence).

Remark: therapeutic dose anticoagulant therapy can be used based on other indications than NOAF, including manifest thromboembolism.

3.3.2 | Rationale

We did not identify any relevant RCTs comparing the interventions of interest in critically ill adult patients with NOAF.

The panel agreed to use a recently published systematic review of observational studies to inform this recommendation.²² The guideline panel believed that the results from this systematic review could be extrapolated to critically ill adult patients with NOAF.

The systematic review comprised four observational studies and 44,087 patients with AF assessing the effects of anticoagulant therapy in critically ill patients with either NOAF or preexisting AF. The systematic review reported an increased incidence of major bleeding in anticoagulated patients with AF compared with non-anticoagulated patients, while no significant difference in the reported incidence of thromboembolic events were observed.²² As for mortality and ICU length of stay, the body of evidence was more uncertain.

Based on the results of the systematic review, the panel felt that there is uncertainty about the balance between the desirable and undesirable effects of anticoagulant treatment in critically ill adult patients with NOAF, but that anticoagulant therapy may increase the risk of bleeding events. Therefore, if clinicians prefer to use anticoagulant therapy in critically ill adults with NOAF and no other indication

for anticoagulation, the panel recommends that this is done in the context of RCTs.

The panel was uncertain about whether implementation of anticoagulant therapy would be acceptable to healthcare workers, patients, and relatives, but that implementation would likely be feasible (Supporting Information S1).

The results of the expert evidence survey indicated significant practice variation with some panel members never using anticoagulant therapy and some always using it (Supporting Information S1).

The certainty of evidence was very low (downgraded for risk of bias, indirectness, and inconsistency).

3.4 | (D) Should critically ill adult patients with NOAF receive follow-up after discharge from hospital?

3.4.1 | Recommendation

We recommend routine follow-up by a cardiologist after hospital discharge for critically ill adult patients with one or more episodes of NOAF (best practice statement).

Remark: the episode(s) of NOAF should last 30 s or more and be documented by 12-lead ECG and/or print from monitor and be available to the cardiologist at follow-up.

3.4.2 | Rationale

We did not identify any relevant RCTs or observational studies comparing the interventions of interest in critically ill adult patients with NOAF.

The panel agreed not to use indirect evidence from other non-critically ill populations, as the causes and treatment of AF in critically ill patients with organ failure(s) were judged to be significantly different than in non-critically ill patients with no or limited organ dysfunction(s).

The question fulfilled the criteria for a best practice statement,¹⁸ why a best practice statement was issued by the panel.

The panel was uncertain about whether routine referral to cardiologist follow-up would be acceptable and feasible to implement (Supporting Information S1).

The results of the expert evidence survey indicated substantial practice variation with some panel members never referring to cardiologist follow-up after hospital discharge, whereas others always do this (Supporting Information S1).

4 | DISCUSSION

The quantity and quality of evidence on the management of NOAF in critically ill adults was very limited, and we did not identify any relevant RCTs for any of the questions. Because causes and treatments of NOAF in critically ill patients with organ failure(s) are significantly

different than in non-critically ill patients with no or limited organ dysfunction(s), it was only deemed relevant to use indirect evidence for the question on anticoagulant therapy.

For the question on the preferred pharmacological treatment of NOAF in critically ill adult patients, we were not able to provide any strong or conditional recommendations. According to the expert evidence survey, the most widely used anti-arrhythmic agent is amiodarone (Supporting Information S1). This is supported by data from a recent international inception cohort study²³ and survey,²⁴ as amiodarone appears to be the preferred choice in 45%. Importantly, there are no direct evidence available from RCTs to inform clinical practice, so whether amiodarone, beta-blockers, digoxin, magnesium or no pharmacological agent is the better treatment option in critically ill adult patients with NOAF is unknown and a research priority.

We were also not able to provide any recommendations for the use of DC cardioversion in adult critically ill patients with NOAF, as no direct evidence from RCTs were available. The expert evidence survey indicated significant practice variation. This is again supported by data from the recent international inception cohort study²³ and survey,²⁴ where DC cardioversion was used in 51%. Whether DC cardioversion is indicated in some adult critically ill patients with NOAF remains to be determined.

We proposed a weak recommendation against routine use of therapeutic dose anticoagulant therapy in adult critically ill patients with NOAF based on very low certainty of evidence. This was informed by a systematic review of observational studies in critically ill patients with NOAF or preexisting AF in which there was a suggestion of an increased risk of major bleeding episodes with either no difference or uncertainty for other outcomes.²² The panel believed that the results from this systematic review could be extrapolated to critically ill adult patients with NOAF and felt that the possible risk of harm warranted a weak recommendation against routine use of therapeutic dose anticoagulant therapy, if no other specific indication for anticoagulation exists. The expert evidence survey and the international inception cohort study and survey indicated practice variation with two thirds preferring routine anticoagulant therapy.²⁴ With no direct evidence from RCTs, the panel agreed that this question is also a research priority.

We issued a best practice statement for routine follow-up by a cardiologist after hospital discharge for critically ill adult patients with one or more episodes of AF, as no direct or indirect relevant evidence was identified and since the criteria for a best practice statement were fulfilled.¹⁸ Whether routine follow-up by all patients with NOAF is feasible and acceptable is uncertain and likely depends on local resources and prioritization. The expert evidence survey, and the international survey indicated significant practice variation with some panel members never referring to cardiological follow-up after hospital discharge, whereas others routinely do this.²⁴ Importantly, the patients and relatives on the panel valued an option for routine follow-up by a cardiologist after hospital discharge for patients with NOAF.

As witnessed by the limited body of evidence on the management of NOAF in critically ill adults, there is considerable

uncertainty about the balance between the desirable and undesirable effects of different management options in this population and there are many knowledge gaps. Several interventions, which are common practice in the ICU, have been adopted based on the perception of improved physiological parameters and physiological reasoning. This has the eminent risk of overestimating benefit and underestimating harm.²⁵ In a recently published systematic review, eight critical care interventions used in clinical practice were shown to increase mortality, and several others proved to have no effect at all.²⁶ We recommend that clinicians who treat adult critically ill patients with NOAF consider doing this in the context of high-quality RCTs. Furthermore, systematic and meticulous monitoring and evaluation of adult critically ill patients with NOAF is warranted.

The management of adult critically ill patients with NOAF in specific settings should be based on existing adaptation frameworks, including the balance between the desirable and undesirable effects, the available resources, and the clinical context.¹²

This guideline will be updated if new potentially practice changing trials are published.

We prepared this clinical practice guideline according to current standards for trustworthy guidelines, that is, the GRADE methodology which support a systematic and transparent process.¹² We included patients and relatives on the panel. Our recommendations were in general restricted to those that can be based on findings from RCTs exclusively, however observational studies may potentially provide evidence to help form some recommendations although they are often biased.²⁷ We assessed some of the most widely used antiarrhythmic drugs internationally, but other treatment options, including calcium-blockers are also used in patients with NOAF.²⁴

In conclusion, the body of evidence on the management of NOAF in critically ill adults is very limited and not informed by direct evidence from randomized clinical trials. We were able to propose one weak recommendation against routine use of therapeutic dose anticoagulation therapy and one best practice statement for routine follow-up by a cardiologist after hospital discharge. The management of NOAF in critically ill adults should be a research priority.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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