BMJ Open

Managing new-onset atrial fibrillation in critically ill patients: A systematic narrative review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034774
Article Type:	Original research
Date Submitted by the Author:	08-Oct-2019
Complete List of Authors:	O'Bryan, Liam; University of Oxford, Nuffield Department of Clinical Neurosciences; The University of Melbourne, St Vincent's Department of Medicine Redfern, Oliver; University of Oxford, Nuffield Department of Clinical Neurosciences Bedford, Jonathan; University of Oxford Nuffield Department of Clinical Neurosciences, Kadoorie Centre for Critical Care Research and Education Petrinic, Tatjana; University of Oxford Health Care Libraries, Cairns Library Young, Duncan; University of Oxford, Nuffield Department of Clinical Neurosciences Watkinson, Peter; University of Oxford, Nuffield Department of Clinical Neurosciences
Keywords:	INTENSIVE & CRITICAL CARE, Adult intensive & critical care < ANAESTHETICS, ANAESTHETICS, Adult cardiology < CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Managing new-onset atrial fibrillation in critically ill patients: A systematic narrative review

Liam J O'Bryan[1,3] *: Liam.OBryan@ndcn.ox.ac.uk

Oliver C Redfern[1]: Oliver.Redfern@ndcn.ox.ac.uk

Jonathan Bedford[1]: Jonathan.Bedford@ndcn.ox.ac.uk

Tatjana Petrinic[2]: Tatjana.Petrinic@bodleian.ox.ac.uk

J Duncan Young[1]: Duncan.Young@ndcn.ox.ac.uk

Peter J Watkinson[1]: Peter.Watkinson@ndcn.ox.ac.uk

Authors' details: [1] Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom; [2] Bodleian Health Care Libraries, University of Oxford, Oxford; [3] University of Melbourne St Vincent's Department of Medicine, Melbourne, Australia; *Corresponding author

Word count: 3,470

Abstract:

Objectives: The aim of this review is to summarise the latest evidence on efficacy and safety of treatments for NOAF in critical illness.

Participants: Critically ill adult patients who developed new-onset atrial fibrillation during admission.

Primary and secondary outcomes: Primary outcomes were efficacy in achieving rate or rhythm control, as defined in each study. Secondary outcomes included mortality, stroke, bleeding and adverse events.

Methods: We searched MEDLINE, EMBASE and Web of Knowledge to identify randomised controlled trials and observational studies reporting treatment efficacy for NOAF in critically ill patients. Data were extracted, and quality assessment performed using the Cochrane Risk of Bias Tool, and an adapted Newcastle-Ottawa Scale.

Results: Of 1,406 studies identified, 16 remained after full text screening. Study quality was generally low due to a lack of randomisation, absence of blinding and small cohorts. Amiodarone was the most commonly studied agent (10 studies), followed by beta-blockers (8), calcium channel blockers (6) and magnesium (3). Rates of successful rhythm control using amiodarone varied from 30.0%-95.2%, beta-blockers from 31.8%-92.3%, calcium channel blockers from 30.0%-87.1% and magnesium from 55.2%-77.8%. Adverse effects of treatment were rarely reported (5 studies).

Conclusion: The reported efficacy of beta-blockers, calcium channel blockers, magnesium and amiodarone for achieving rhythm control was highly varied. As there is currently significant variation in how new-onset atrial fibrillation is managed in critically ill patients, we recommend future research focusses on comparing the efficacy and safety of amiodarone, beta-blockers and magnesium. Further research is needed to inform the decision surrounding anticoagulant use in this patient group.

Keywords: New-onset atrial fibrillation; ICU; critical care; treatment

Article summary

Strengths and limitations of this study

- Our systematic review is broad assessment of the evidence surrounding the management of new onset atrial fibrillation in the critically ill patient.
- Our review is a significant update to previous reviews, as our search identified more studies specific to the management of new-onset atrial fibrillation.
- We included studies of non-cardiac critically unwell patients, to ensure that our findings are generalisable to the ICU patient.
- Due to limited randomised trial data and study heterogeneity, we did not conduct a meta-analysis and present a narrative synthesis of evidence.

Background

New-onset atrial fibrillation (NOAF) occurs in 4.5-15% of critically unwell patients[1]; the incidence increases with greater severity of illness and in sepsis[1–3]. NOAF can lead to haemodynamic instability[4] and thromboembolic events[5]. Critically ill patients

with NOAF experience longer intensive care unit (ICU) stay, greater duration of mechanical ventilation and an increased risk of in-hospital mortality[3,6,7].

Extensive guidelines exist for managing atrial fibrillation (AF) in the community and the acute setting[8–10]. However, the safety and efficacy of treatments in critically ill patients are less clear[11]. For example, anticoagulation may fail to prevent stroke in critically ill patients with NOAF[12]. In addition, direct-current cardioversion (DCC) and pharmacological cardioversion are often unsuccessful during critical illness[13,14]. Failure to attain rate or rhythm control in patients with NOAF has been linked with increased in-hospital mortality[2,15].

Two previous systematic reviews have focused on the management of NOAF in the critically ill[1,11]. In 2008, Kanji et al reviewed evidence from randomised controlled trials (RCTs) reporting efficacy of pharmacological treatments[11]. In 2015, Yoshida et al reviewed both RCTs and observational studies of epidemiology, prevention and management[1]. A recent scoping review summarized the epidemiology, prevention and methods of management of NOAF in critically unwell patients[16]. It included patients with pre-existing AF as well as patients outside ICU or in cardiac intensive care. As a scoping review, it did not report the effect on cardiac rhythm of the interventions identified. None of these reviews were able to make specific management or research recommendations due to an absence of high-quality studies and significant population heterogeneity between studies.

The aim of this review is to summarise evidence from observational studies and randomised trials reporting outcomes of individual treatments for NOAF in critically ill adult patients. This review serves as an update, as the most recent review specific to

only the management of NOAF was in 2008. We aim to identify a more relevant studies than previous reviews by including studies of all treatments (including DCC and anticoagulation), observational studies and studies of new-onset supraventricular arrhythmias (SVAs), where AF is the predominant rhythm, in the critically ill.

Methods

We report our review according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (Supplemental Appendix 1)[17].

Study eligibility

We considered all RCTs and observational studies published in peer reviewed journals. We included foreign language papers where an English translation was available. We excluded case reports, conference abstracts, letters to the editor, editorials and any other publication that did not report primary data.

We included studies of adult patients (age ≥16) who developed NOAF during admission to a medical, surgical or general ICU. To improve the search yield, we included studies of sepsis outside the ICU, and of new-onset SVAs where AF was the dominant (>70%) arrhythmia. We defined NOAF as AF occurring during admission in a patient with no history of chronic AF. We excluded studies conducted in specialised (neurosurgical or cardiothoracic) ICUs and studies specific to medical or surgical cardiac patients.

We included all studies reporting data on the outcome of a single intervention. The primary outcome of interest was efficacy in achieving rhythm or rate control, as

defined by each study. Secondary outcomes included mortality, stroke, bleeding and adverse events. No limitation was placed on the timing of outcome assessment.

Search strategy

We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE - OVID interface, 1946 to present), Excerpta Medica (EMBASE - OVID interface, 1974 to present) and Web of Science (Clarivate Analytics interface, 1945 to present) databases on March 11th, 2019, using medical subject headings (MeSH) and key words (full list shown in Supplemental Appendix 2). Search terms were designed to capture all supraventricular arrhythmias, including “atrial fibrillation”, “atrial flutter”, “supraventricular tachycardia” and “atrial arrhythmia”. Terms including “critical care”, “critically ill”, “intensive care” and “sepsis” were used to define the setting. General terms such as “treatment” were used alongside specific treatments including “beta-blocker”, “calcium channel blocker”, “direct current”, “magnesium” and “anticoagulation”. Snowballing was performed by assessing references in relevant review articles. The search strategy was formulated in consultation with a medical librarian (TP).

Study selection

We imported search results into Mendeley Desktop (V1.19.3, Mendeley Ltd.), which was used to identify duplicate publications for removal. Two independent reviewers (LO and JB) then screened titles and abstracts for eligibility. Studies were eligible for full text analysis where the abstract appeared to fulfill our inclusion criteria, or where there was uncertainty. We retrieved full text articles and assessed them for relevance using Rayyan software (Rayyan, HBKU, Qatar) to allow blinding between

the reviewers (LO and JB)[18,19]. We discussed disagreements and consulted a third reviewer (DY) if consensus could not be reached.

Data extraction

One author (LO) performed data extraction; the author was not blinded to study authors or institutions. Data extracted from each study included: design, setting, population, interventions, outcomes, timing of assessment and results (Supplemental Appendix 3). Where studies reported data separately for new or chronic arrhythmias, we extracted only data relating to NOAF. We simplified SVA to NOAF, and grouped drugs by class (beta-blockers, calcium channel blockers or anticoagulants). We extracted outcomes only where the effect of a single intervention was evaluated in a cohort of greater than 10 participants. We extracted percent success for each treatment (with respect to a given outcome) and relative risks or odds ratios where provided. We calculated percent success if it was not reported.

Risk of bias assessment

We conducted a risk of bias assessment for all observational studies using an adapted Newcastle-Ottawa Scale (NOS) (Supplemental Appendix 4)[20,21]. This adaptation was designed for non-randomised trials reporting the incidence of NOAF in critical care[21]. RCTs were assessed using the Cochrane Risk of Bias Tool for Randomised Controlled Trials (Supplemental Appendix 5)[22].

Statistical analysis

The primary outcome was efficacy in rhythm or rate control, expressed as a proportion. Outcome data for RCTs were expressed by calculating an odds ratio using provided data.

Patient and public involvement

No patients were involved in this study which used data from published materials only.

Results

Search results

We identified 1,406 unique studies from our search, of which 97 remained after abstract screening (Figure 1). After full text review, 16 eligible studies were identified (Supplemental Appendix 3). Of these, 13 were of patients treated in ICU and the remaining 3 were of patients with sepsis managed in hospital (ICU and non-ICU), including only the sepsis arm of one study of non-ICU patients[23].

Insert Figure 1 here:

Risk of bias

We identified two RCTs, three prospective cohort and eleven retrospective cohort studies. A high risk of bias was identified in both RCTs (Supplemental Appendix 5) due to an unclear or inadequate randomisation process, failure to conceal patient allocation and failure to blind outcome assessors. We determined that failing to blind participants to the intervention introduced a low risk of bias due to the nature of the critically ill patient population. The quality of cohort studies varied considerably. Risks of bias included small cohorts, retrospective analyses and a failure to standardise outcome measures (Supplemental Appendix 6).

Study characteristics

Studies are described in supplemental appendix 3. Table 1 describes the interventions and outcomes for each of the 16 studies. Amiodarone was the most reported intervention followed by beta-blockers and calcium channel blockers. There were fewer studies of DCC, magnesium and anticoagulation. Studies of less common therapies (pilsicainide, digoxin and propafenone) were grouped. A meta-analysis of RCTs was not performed due to a lack of common interventions.

Rhythm control was the most frequently reported outcome, with rate control data provided in only one study. Although beta-blockers and calcium channel blockers are considered rate control agents, their efficacy was primarily reported in regard to rhythm control. Timing of outcome assessment varied between 2-hours[24] and 7-days[15]. Definitions of "successful rhythm control" varied with regards to how long sinus rhythm (SR) was maintained; the most common definition used was SR maintained for 24-hours. We did not pool study outcomes due to variation in outcome assessment and definition. Of 14 studies assessing rate or rhythm control, 5 stated that electrolyte abnormalities were corrected prior to treatment.

Haemodynamic adverse events (e.g. hypotension and bradycardia) associated with amiodarone, calcium channel blockers, beta-blockers or magnesium were assessed in 5 studies[25–29]. Rates of stroke and bleeding associated with anticoagulation were reported in two studies[12,23]. No other studies reported adverse events following treatment for NOAF.

Table 1: Included studies by treatment and outcome

Therapy	Rhythm control	Rate control	Mortality	Total
Amiodarone	9 studies 1 RCT	0 studies	2 studies 1 RCT	10 studies 1 RCT
Beta-blockers	7 studies 1 RCT	1 study 0 RCTs	1 study 0 RCTs	8 studies 1 RCT
Calcium channel blockers	5 studies 1 RCT	0 studies	2 studies 1 RCT	6 studies 1 RCT
Magnesium	3 studies 1 RCT	0 studies	0 studies	3 studies 1 RCT
DC cardioversion	2 studies 0 RCTs	0 studies	0 studies	2 studies 0 RCTs
Anticoagulation*	N/A	N/A	0 studies	2 studies 0 RCTs
Other† therapies	3 studies 0 RCTs	0 studies	1 study 0 RCTs	4 studies 0 RCTs
Total	13 studies 2 RCTs	1 study 0 RCTs	2 studies 1 RCT	16 studies 2 RCTs

Number of studies where numerical data for each treatment and outcome could be extracted

*Outcomes for anticoagulation in both studies were rates of bleeding and ischaemic stroke; †Other therapies include pilsicainide, digoxin and propafenone; DC = Direct current; RCT = Randomised controlled trial

Study results

Figure 2 shows the odds ratios of treatments compared in each RCT. The efficacy of rhythm control for all studies is shown in Figure 3.

Insert Figure 2 here:

Insert Figure 3 here:

Amiodarone

Overall, amiodarone was the most frequently reported treatment. Studies varied in dosing regimen, timing of outcome assessment and definition of rhythm control. For rhythm control, amiodarone success varied from 3/10 (30.0%)[5] to 177/186 (95.2%)[29]. Mitric et al defined successful rhythm control as any reversion to SR during the ICU stay and reported a high success rate for amiodarone (95.2%), however AF recurred in 51.4%[30]. In the largest studies (n>100) with an outcome of sustained cardioversion, success occurred in 60.0% - 73.5%[4,27,30]. In three comparative observational studies, amiodarone achieved lower rates of rhythm control than beta-blockers, magnesium and calcium channel blockers[5,15,31].

Second-line amiodarone use was associated with high rates success in rate and rhythm control. Amiodarone following initial magnesium therapy resulted in successful rhythm control in 27/29 (93.1%) patients in one study[29]. In another study, amiodarone following initial beta-blocker or calcium channel blocker therapy achieved rate or rhythm control in 11/13 (84.6%)[32].

Hypotension, defined as mean arterial pressure below 60mmHg, was described in one study and occurred in 6.7% of 30 patients managed with amiodarone[25]. Two studies reported no adverse events in response to amiodarone[27,28]. Mayr et al. investigated pulmonary toxicity associated with amiodarone use, defined as changes to the FiO_2/PaO_2 ratio, and found no events in 115 critically ill patients with NOAF[27].

Beta-blockers

Three studies investigated short-acting beta-blockers (e.g. metoprolol, esmolol and landiolol)[24,26,31], and 5 failed to specify the precise agent[4,5,14,15,32]. In one RCT assessing beta-blocker efficacy, Balser et al[24] found 22/26 (85%) non-cardiac surgical ICU patients with SVA who received esmolol reverted to SR after 12-hours. Across all studies, successful rhythm control using beta-blockers was reported in 7/22 (31.8%)[31] to 12/13 (92.3%) patients[30]. The largest studies reporting the efficacy of beta-blockers described sustained rhythm control in 69.2%-84.6% of participants[15,24,26]. The only study reporting rate control efficacy for any agent found a 37.9% heart rate reduction in 39 patients with sepsis and NOAF managed with landiolol[26]. Two observational studies directly compared efficacy of beta-blockers to amiodarone and/or calcium channel blockers, finding higher rates of rhythm control with beta-blockers[15,31].

Hypotension requiring discontinuation of a beta-blocker was identified in 5.9% of 34 patients in one study[24]. Okajima et al. reported none of 39 patients treated with a beta-blocker experienced clinically significant bradycardia[26].

One RCT reported in-hospital mortality in non-cardiac surgical ICU patients, reporting 31% mortality in patients treated with a beta-blocker (n=34), and 38% in patients treated with a calcium channel blocker (n=30)[24]. Walkey et al reported in-hospital mortality, comparing beta-blockers to amiodarone, calcium channel blockers and digoxin in 7,478 propensity-matched septic patients with NOAF[14]. Patients given beta-blockers had lower mortality rates than those given amiodarone (RR 0.67, 95%

CI 0.59-0.77) or digoxin (RR 0.75, 95% CI 0.64 – 0.88). Mortality rates with beta-blockers were similar to calcium channel blockers (RR 0.99, 95% CI 0.86-1.15).

Calcium channel blockers

One RCT investigated calcium channel blockers for efficacy of rhythm control, reporting success in 16/26 (61.5%) patients at 12-hours[24]. Across all studies, successful cardioversion using calcium channel blockers occurred in 10/30 (30%)[5] to 27/31 (87.1%)[25]. Calcium channel blockers were compared with other agents in three studies[5,15,25]. One observational study comparing beta-blockers with calcium channel blockers found greater efficacy in rhythm control with the former[15]. Two studies found calcium channel blockers to be similarly efficacious to amiodarone[5,25], and one study found calcium channel blockers to be more effective than amiodarone, though this study was of lower quality[15]. Hypotension occurred in 1/31 (3.2%) and 1/30 (3.3%) of patients receiving a calcium channel blocker[24,25].

Magnesium

Successful rhythm control with magnesium occurred in 55.2%[32] to 77.8%[28] of patients. The only RCT of magnesium reported superior efficacy to amiodarone, with rhythm control achieved in 14/18 (77.8%) patients treated for 24-hours to a target serum concentration of 1.5-2.0mmol/L[28]. A retrospective study of patients receiving magnesium found that 59/91 (64.8%) reverted to SR[5], though the therapeutic target for magnesium level was not reported. A prospective observational study titrated magnesium to a serum concentration of 2.0-3.0mmol/L and reported rhythm control in 16/29 (55%) patients after 1-hour[32]. Magnesium was directly compared to amiodarone and a calcium channel blocker in one observational study which found

the highest success in rhythm control rate with magnesium[5]. No adverse events were identified with magnesium use in any study.

Electrical therapy

DCC was investigated in only two studies, reporting efficacy of 26.9% and 35.1%[4,13]. Mayr et al reported primary success in 13/37 (35.1%) critically ill patients with NOAF at 1-hour[13]. By 24-hours, only 6 (13.5%) of these 37 remained in SR. Another study assessed the efficacy of DCC, reporting success (defined as maintained SR for 24-hours) in 7/26 (26.9%) patients; 18 of these received amiodarone prior to, or during DCC[4].

Other therapies

Successful rhythm control using other treatments ranged from 55.6%[15] to 89.0%[30]. Digoxin use was reported in one efficacy study; rhythm control was achieved in 15/27 (55.6%) patients[15]. Single observational studies investigated the efficacy of pilsicainide and propafenone in rhythm control for this patient population, with success rates of 51/79 (64.6%) and 32/36 (89%) respectively[5,30].

Anticoagulation

We found two studies of anticoagulation in critically ill patients with NOAF. A retrospective analysis of 5,585 patients with sepsis and NOAF found 37.6% were given anticoagulants during admission[12]. Anticoagulant use did not significantly affect the risk of in-hospital stroke (RR 0.85, 95% CI 0.57 – 1.27), or risk of bleeding (RR 0.97, 95% CI 0.83 – 1.14). Another retrospective analysis of 102 critically ill patients with sepsis and NOAF reported rates of ischaemic stroke and bleeding after

3-years follow-up. In patients who were prescribed anticoagulation at discharge, rates of ischaemic stroke were 2/28 (7.1%) compared with 4/73 (5.5%) in those who were not prescribed anticoagulants[23]. Rates of bleeding were 5/25 (20.0%) in the anticoagulated group compared with 15/76 (19.7%) in the control.

Discussion

Our review provides an up-to-date assessment of the evidence for the efficacy of treatments used for managing NOAF in critically ill patients. Our results show that amiodarone, beta-blockers, calcium channel blockers and magnesium achieved similar rates of rhythm control across studies. We therefore recommend further trials focus on comparing these four treatments. Digoxin and DCC achieved lower rates of successful rhythm control in published studies. Our review did not find evidence to support the use of anticoagulation for managing this patient group.

We extracted data from 16 studies reporting treatment outcomes. This includes 9 studies published after the search performed by Yoshida et al. in 2014, who by comparison identified 4 studies providing efficacy data of individual treatments[1]. The 2008 review by Kanji et al.[11] reported on 4 randomised controlled trials, two of which we excluded on the basis of a failure to describe exclusion of participants with pre-existing AF. Our review represents a far broader evidence base than previous systematic reviews. A recent scoping review of all aspects of NOAF in critically ill patients has been undertaken, due to its broad scope, it did not report management strategies within ICU in detail[16]. By focusing solely on management of NOAF in patients admitted to a medical, surgical or general ICU, we present a detailed and modern assessment of the reported effects of different agents in these patients.

Rhythm control

Amiodarone, beta-blockers, calcium channel blockers and magnesium achieved similar rates of sustained rhythm control in critically ill patients with NOAF. Though beta-blockers and calcium channel blockers are considered rate control agents, they appear to be effective in achieving rhythm control. In comparative studies, beta-blockers and magnesium tended to be slightly more successful in achieving rhythm control than calcium channel blockers and magnesium. Magnesium may have an important role as a first-line treatment, reducing the need for higher-risk interventions. While first-line magnesium was successful in only 55% of patients in one study, this may be an underestimate due to the 1-hour end-point used[29]. This study also suggested that the majority of patients who did not convert to SR with magnesium alone, did so with the use of second-line amiodarone. Similarly, Brown et al. reported excellent efficacy in achieving rate and rhythm control with second-line amiodarone following treatment with a beta-blocker[32]. Amiodarone may therefore have an important role as a second-line therapy in patients with NOAF.

Two RCTs compared the efficacy of treatments in regard to rhythm control (figure 2). One of these, comparing magnesium to amiodarone, reported superior efficacy using magnesium[28]. An RCT comparing beta-blockers to calcium channel blockers was underpowered to detect a difference in rhythm control efficacy, despite a tendency towards the beta-blocker[24]. In 4 observational comparative studies, beta-blockers and magnesium tended to be more effective than calcium channel blockers and amiodarone[5,15,25,31]. Further research is needed to compare rhythm control agents in efficacy and safety. In line with previous authors[33], we conclude that digoxin and DCC may be less effective than other therapies in critically ill patients with NOAF.

Although 5 studies reported correction of electrolyte abnormalities prior to treatment, methods and targets of correction were not described. Electrolytes corrected were potassium and magnesium, though some studies failed to specify an electrolyte.

Adverse events

Adverse events associated with treatments were infrequently reported, providing insufficient data to compare event rates for most therapies. Two studies (49 participants) investigated adverse events associated with magnesium use, finding none. Magnesium appeared to carry low risk of adverse outcomes, but larger studies are needed to assess this. Studies reporting adverse events tended to have small cohorts that may not detect uncommon events.

Mortality

Only one retrospective study was sufficiently powered to consider mortality differences between treatments. Walkey et al. reported a reduction in mortality associated with the use of beta-blockers when compared to amiodarone and digoxin in propensity-matched patients with sepsis and NOAF[14]. Patients were matched by year of hospitalization, demographics, comorbidities, acute organ failure, organ-supportive therapy, source of sepsis and hospital characteristics. This finding needs to be interpreted with caution, as septic patients were defined using International Classification of Diseases (ICD) codes and thus may not reflect the general critically ill patient.

Anticoagulation

This review highlights the lack of evidence underlying the use or avoidance of anticoagulants in critically ill patients with NOAF. The only study of sufficient size to investigate the effects of anticoagulation was of patients with sepsis and was not restricted to patients being managed in ICU[12]. This study reported rates of stroke occurring during hospital admission, it is therefore unsurprising that the rate of this uncommon event was not affected by anticoagulant use. Neither study of anticoagulation provided details regarding the duration of treatment.

Limitations of this review

The most significant limitation of this review is a lack of recent RCTs comparing therapies in the critically ill. The majority of studies were observational in design, with small patient cohorts. Studies varied considerably in their patient populations, outcomes and interventions. This variability meant we were unable to pool data for treatment efficacy. Both RCTs in this review are over 20 years old; and no longer reflect current practices in critical care. RCTs were also small, with no common treatment comparisons, rendering a meta-analysis impossible.

Research recommendations

There remains a need for further research to compare treatments for NOAF in critically ill patients. We recommend large cohort studies that report standardised outcomes, before RCTs are conducted. Definitions of NOAF used in future studies need to be agreed. Current recommendations for outcomes used in AF trials are based on the management of chronic AF and have limited relevance to critically ill patients[34,35]. Amiodarone, beta-blockers, calcium channel blockers and magnesium

should be compared for efficacy in studies of sufficient size to be able to detect clinically meaningful differences between individual treatments. Combined therapies with first-line magnesium may also merit further study. The most common definition of rhythm control success in our review was SR maintained for 24-hours. This may make it an appropriate definition for future studies. Secondary outcomes should include mortality, duration of ICU and hospital admission, adverse events and recurrence of AF. The lack of adequate reporting or investigation of adverse events is concerning. Future studies should include hypotension or bradycardia requiring treatment modification and complications associated with amiodarone use (e.g. pulmonary or hepatic toxicity).

Conclusion

Our review has shown similar efficacy of beta-blockers, amiodarone, calcium channel blockers and magnesium in achieving rhythm control, but with limited evidence. First-line magnesium with amiodarone for non-responders achieved high rates of rhythm control in one small study. Electrical cardioversion and digoxin may be less effective in critically ill patients with NOAF. There is insufficient data to inform the use of anticoagulation, this is a deficit that needs to be rectified.

Abbreviations:

NOAF: new-onset atrial fibrillation; ICU: intensive care unit; AF: atrial fibrillation; DCC: direct-current cardioversion; RCT: randomised controlled trial; SVA: supraventricular arrhythmia; PRISMA: preferred reporting items for systematic reviews and meta-analysis; ECG: electrocardiogram; SR: sinus rhythm; USA: United States of America; FDA: Food and Drug Administration

Acknowledgements:

We thank Julie Darbyshire, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford and Rachael Fox, University of Melbourne, Melbourne, Australia for their assistance in manuscript preparation.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. Peter Watkinson is supported by the NIHR Biomedical Research Centre, Oxford

Competing interests: The authors declare that they have no competing interests

Author contributions: All authors made substantial contributions towards the review and drafting of the manuscript. DY and PW conceived and designed the review. TP, JB and LO designed and conducted the search. LO and JB reviewed articles. LO conducted the search, extracted data and performed quality assessment. All authors contributed to the synthesis of, read and reviewed the final manuscript.

Data availability: No additional data available

References

1. Yoshida T, Fujii T, Uchino S, Takinami M. Epidemiology, prevention, and treatment of new-onset atrial fibrillation in critically ill: A systematic review. J Intensive Care. 2015;3(1):19.

2. Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bögelein D, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients

with septic shock: A prospective observational study. Crit Care. 2010;14(3):R108.

3. Klein Klouwenberg PMC, Frencken JF, Kuipers S, Ong DSY, Peelen LM, van Vught LA, et al. Incidence, Predictors, and Outcomes of New-Onset Atrial Fibrillation in Critically Ill Patients with Sepsis. A Cohort Study. Am J Respir Crit Care Med. 2017 Jan;195(2):205–11.

4. Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. J Crit Care. 2012;27(3):326.e1-8.

5. Yoshida T, Uchino S, Yokota T, Fujii T, Uezono S, Takinami M. The impact of sustained new-onset atrial fibrillation on mortality and stroke incidence in critically ill patients: A retrospective cohort study. J Crit Care. 2018;44:267–72.

6. Chen AY, Sokol SS, Kress JP, Lat I. New-Onset Atrial Fibrillation Is an Independent Predictor of Mortality in Medical Intensive Care Unit Patients. Ann Pharmacother. 2015 Mar 10;49(5):523–7.

7. Christian S-A, Schorr C, Ferchau L, Jarbrink ME, Parrillo JE, Gerber DR. Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. J Crit Care. 2008;23(4):532–6.

8. January CT, Stevenson WG, Murray KT, Ezekowitz MD, Alpert JS, Field ME, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. Circulation. 2014;130(23):2071–104.

9. Kirchhof P, Benussi S, Zamorano JL, Aboyans V, Achenbach S, Agewall S, et

al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Russ J Cardiol. 2017;147(7):7–86.

10. National Institute for Health and Care Excellence. Atrial fibrillation: the management of atrial fibrillation. 180th ed. NICE clinical guideline 180. London: NICE Clinical Guidelines; 2014.

11. Kanji S, Stewart R, Fergusson DA, McIntyre L, Turgeon AF, Hébert PC. Treatment of new-onset atrial fibrillation in noncardiac intensive care unit patients: A systematic review of randomized controlled trials. Crit Care Med. 2008;36(5):1620–4.

12. Walkey AJ, Quinn EK, Winter MR, McManus DD, Benjamin EJ. Practice patterns and outcomes associated with use of anticoagulation among patients with atrial fibrillation during sepsis. JAMA Cardiol. 2016 Sep 1;1(6):682–90.

13. Mayr A, Ritsch N, Knotzer H, Dünser M, Schobersberger W, Ulmer H, et al. Effectiveness of direct-current cardioversion for treatment of supraventricular tachyarrhythmias, in particular atrial fibrillation, in surgical intensive care patients. Crit Care Med. 2003;31(2):401–5.

14. Walkey AJ, Evans SR, Winter MR, Benjamin EJ. Practice patterns and outcomes of treatments for atrial fibrillation during sepsis a propensity-matched cohort study. Chest. 2016;149(1):74–83.

15. Liu WC, Lin WY, Lin CS, Huang H Bin, Lin TC, Cheng SM, et al. Prognostic impact of restored sinus rhythm in patients with sepsis and new-onset atrial fibrillation. Crit Care. 2016;20(1):373.

16. Wetterslev M, Haase N, Hassager C, Belley-Cote EP, McIntyre WF, An Y, et al. New-onset atrial fibrillation in adult critically ill patients: a scoping review. Intensive Care Med. 2019 Jul;45(7):928–38.

17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339.

18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.

19. Elmagarmid A, Fedorowicz Z, Hammady H, Ilyas I, Khabsa M, Ouzzani M. Rayyan: a systematic reviews web app for exploring and filtering searches for eligible studies for Cochrane Reviews. In: Evidence-Informed Public Health: Opportunities and Challenges Abstracts of the 22nd Cochrane Colloquium. John Wiley & Sons; 2014. p. 9.

20. Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute. 2010.

21. Bedford J, Harford M, Petrinic T, Young JD, Watkinson PJ. Risk factors for new-onset atrial fibrillation on the general adult ICU: Protocol for a systematic review. BMJ Open. 2018 Sep;8(9):e024640.

22. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al.

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct;343(7829):d5928.

23. Quon MJ, Behlouli H, Pilote L. Anticoagulant Use and Risk of Ischemic Stroke and Bleeding in Patients With Secondary Atrial Fibrillation Associated With Acute Coronary Syndromes, Acute Pulmonary Disease, or Sepsis. JACC Clin Electrophysiol. 2018;4(3):386–93.

24. Balser JR, Martinez EA, Winters BD, Perdue PW, Clarke AW, Huang W, et al. B-Adrenergic Blockade Accelerates Conversion of Postoperative Supraventricular Tachyarrhythmias. Anesthesiology. 1998 Nov;89(5):1052–9.

25. Gerlach AT, Kane-Gill SL, Dasta JF, Steinberg S, Martin LC, Cook CH. Diltiazem versus amiodarone for new-onset atrial arrhythmias in non-cardiac post surgical patients: A cohort study. Crit Care Shock. 2008;11(3):94–106.

26. Okajima M., Takamura M. TT. Landiolol, an ultra-short-acting β1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis. World J Crit Care Med. 2015;4(3):251–7.

27. Mayr AJ, Dünser MW, Ritsch N, Pajk W, Friesenecker B, Knotzer H, et al. High-dosage continuous amiodarone therapy to treat new-onset sapraventricular tachyarrhythmias in surgical intensive care patients: An observational study. Wien Klin Wochenschr. 2004;116(9–10):310–7.

28. Moran JL, Gallagher J, Peake SL, Cunningham DN, Salagaras M, Leppard P. Parenteral magnesium sulfate versus amiodarone in the therapy of atrial tachyarrhythmias: a prospective, randomized study. Crit Care Med. 1995

Nov;23(11):1816–24.

29. Sleeswijk ME, Tulleken JE, Van Noord T, Meertens JHJM, Ligtenberg JJM, Zijlstra JG. Efficacy of magnesium-amiodarone step-up scheme in critically ill patients with new-onset atrial fibrillation: A prospective observational study. J Intensive Care Med. 2008;23(1):61–6.

30. Mitrić G, Udy A, Bandeshe H, Clement P, Boots R. Variable use of amiodarone is associated with a greater risk of recurrence of atrial fibrillation in the critically ill. Crit Care. 2016;20(1):90.

31. Balik M, Kolnikova I, Maly M, Waldauf P, Tavazzi G, Kristof J. Propafenone for supraventricular arrhythmias in septic shock—Comparison to amiodarone and metoprolol. J Crit Care. 2017;41:16–23.

32. Brown M, Nassoiy S, Chaney W, Plackett TP, Blackwell RH, Luchette F, et al. Impact and treatment success of new-onset atrial fibrillation with rapid ventricular rate development in the surgical intensive care unit. J Surg Res. 2018;229:66–75.

33. Walkey AJ, Hogarth DK, Lip GYH. Optimizing Atrial fibrillation management from ICU and beyond. Chest. 2015;148(4):859–64.

34. Breithardt G, Kirchhof P, Hohnloser S, Kappenberger L, Lip GYH, Olsson B, et al. Outcome parameters for trials in atrial fibrillation: executive summary: Recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA). Eur Heart J. 2007 Sep 25;28(22):2803–17.

35. Berti D, Van Vlasselaer X, Moons P, Heidbuchel H. Prioritized outcomes to evaluate the effectiveness of atrial fibrillation disease management: A systematic review and Delphi study. Vol. 202, International journal of cardiology. Netherlands; 2016. p. 500–3.

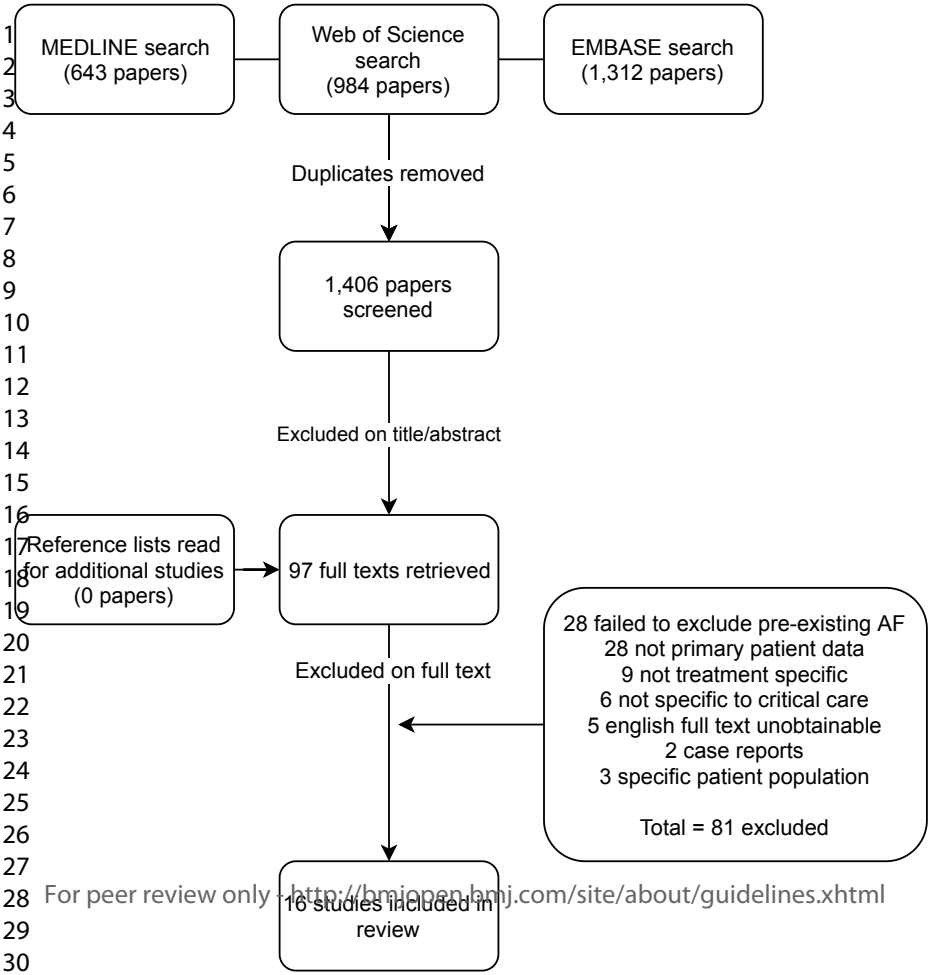
Figures legend

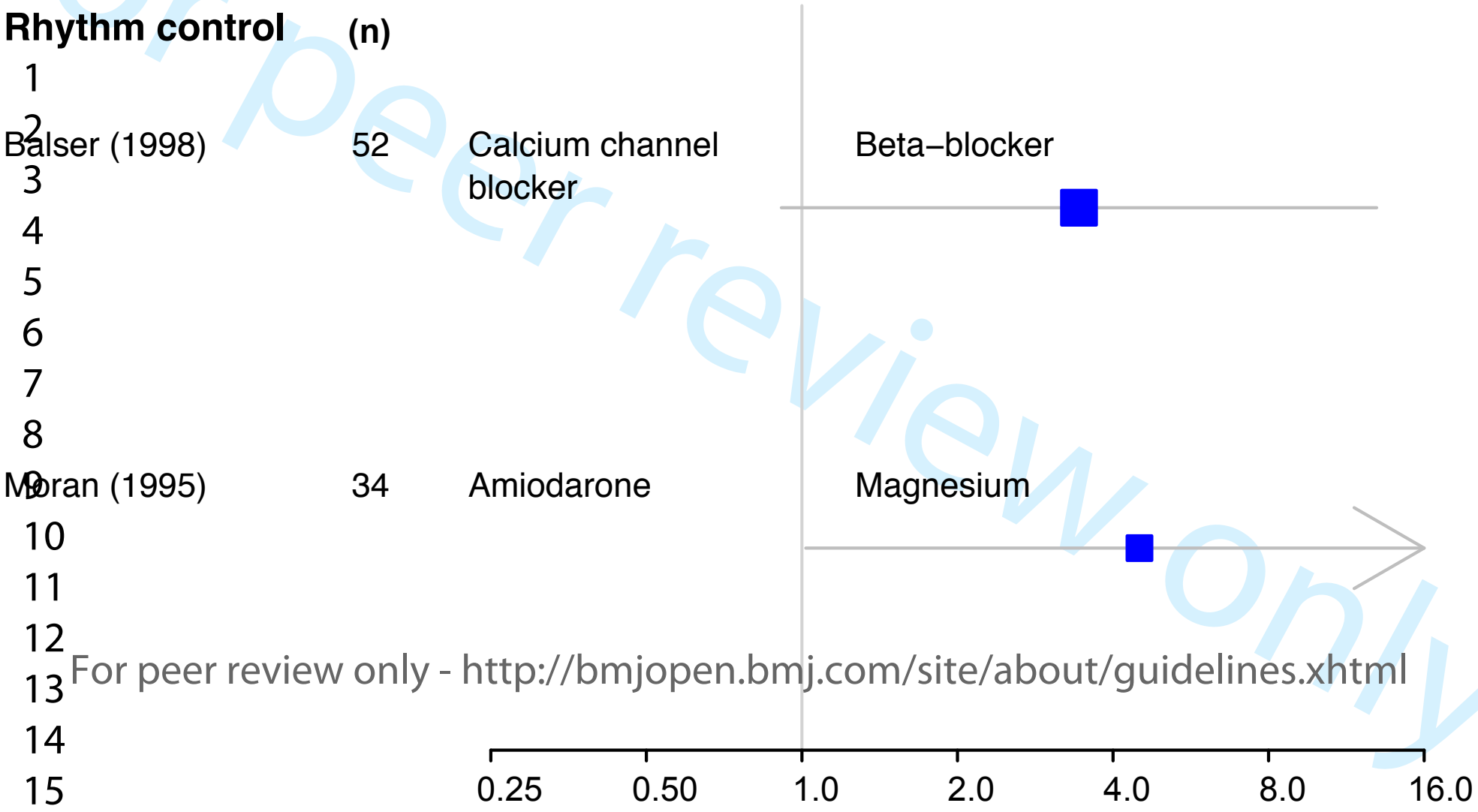
- Figure 1: PRISMA diagram; PRISMA flowchart of search results and screening
- Figure 2: Rate or rhythm control success (RCTs); Odds ratio comparing agents assessed in randomised controlled trials
- Figure 3: Rate or rhythm control success (all studies); Efficacy of each agent as reported in all studies, both randomised and observational, reported as % success

Supplementary materials

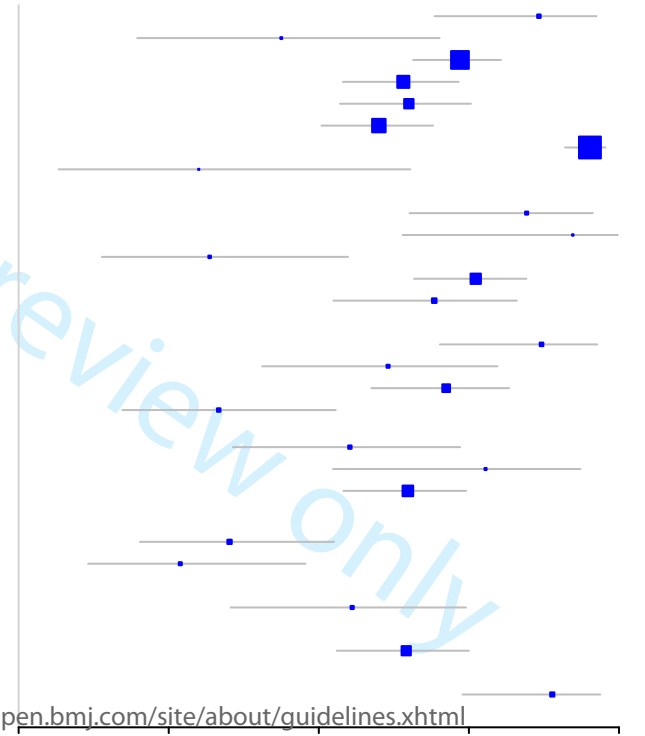
- Supplemental Appendix 1: PRISMA checklist; Completed PRISMA checklist
- Supplemental Appendix 2: Search strategy; Search terms used for MEDLINE, EMBASE and Web of Knowledge, with results
- Supplemental Appendix 3: Included study characteristics; Data extracted from all included studies in regard to author, design, population, setting, interventions, outcomes, follow-up and results
- Supplemental Appendix 4: Modified Newcastle-Ottawa Scale; Description of criteria in the modified Newcastle-Ottawa Scale used for assessing risk of bias in included observational studies
- Supplemental Appendix 5: Risk of bias assessment (RCTs); Assessment for risk of bias in included randomised trials using Cochrane Risk of Bias Tool
- Supplemental Appendix 6: Risk of bias assessment (observational); Assessment for risk of bias in included observational studies using the modified Newcastle-Ottawa Scale

Figure 1





Rhythm control			(n)
Amiodarone	Gerlach (2008)	Prospective cohort	30
	Moran (1995)	RCT	16
	Balik (2017)	Retrospective cohort	151
	Kanji (2012)	Retrospective cohort	103
	Liu (2016)	Retrospective cohort	80
	Mayr (2004)	Retrospective cohort	115
	Mitric (2016)	Retrospective cohort	186
	Yoshida (2018)	Retrospective cohort	10
Beta−blocker	Balser (1998)	RCT	26
	Balik (2017)	Retrospective cohort	13
	Brown (2018)	Retrospective cohort	22
	Liu (2016)	Retrospective cohort	88
	Okajima (2015)	Retrospective cohort	39
Calcium channel blocker	Gerlach (2008)	Prospective cohort	31
	Balser (1998)	RCT	26
	Liu (2016)	Retrospective cohort	66
	Yoshida (2018)	Retrospective cohort	30
Magnesium	Sleeswijk (2008)	Prospective cohort	29
	Moran (1995)	RCT	18
	Yoshida (2018)	Retrospective cohort	91
DC Cardioversion	Mayr (2003)	Prospective cohort	37
	Kanji (2012)	Retrospective cohort	26
Digoxin	Liu (2016)	Retrospective cohort	27
Flecainide	Yoshida (2018)	Retrospective cohort	79
Propafenone	Balik (2017)	Retrospective cohort	36



Supplemental Appendix 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page line 1-3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2 line 1 – page 3 line 6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3 lines 19 – page 4 line 20
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4 lines 21 – page 5 line 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5 lines 8-23
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6 lines 1-14
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 line 15 – 23
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7 lines 1-11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 7 lines 1-11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 7 lines 12-17
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 7 lines 18-21
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 7 lines 18-21
Risk of bias across	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective	Supplemental

studies		reporting within studies).	appendices 5 and 6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1: Page 8 line 12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplemental appendix 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplemental appendices 5 and 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2 and 3: Page 10 lines 7 and 9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplemental appendices 5 and 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 14 line 21 – page 15 line 16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 17 lines 9-16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 18 lines 1-8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 20 lines 2-4

Supplemental Appendix 2: Search strategies

MEDLINE:

1	ATRIAL FIBRILLATION/	49041
2	ATRIAL FLUTTER/	5599
3	SUPRAVENTRICULAR TACHYCARDIA/	5605
4	("atrial fibrillation*" or AF).ab,ti.	74164
5	"atrial flutter*".ab,ti.	5322
6	"atrial arrhythmia*".ab,ti.	3064
7	"supraventricular tachycardia*".ab,ti.	6374
8	"NOAF*".ab,ti.	59
9	"atrial tachyarrhythmia*".ab,ti.	1432
10	INTENSIVE CARE UNITS/	48874
11	CRITICAL CARE/	48388
12	SEPSIS/	55156
13	SEPTIC SHOCK/	21272
14	"intensive care".ab,ti.	127344
15	(ITU* or ICU* or HDU*).ab,ti.	52744
16	(sepsis or "septic shock").ab,ti.	99233
17	("critically unwell" or "critically ill").ab,ti.	39586
18	("intensive care unit*" or "high dependenc*" or "intensive therapy unit*").ab,ti.	102135
19	ELECTRIC COUNTERSHOCK/	14154
20	ANTI ARRHYTHMIA AGENTS/	26612
21	ANTIHYPERTENSIVE AGENTS/	62664
22	ADRENERGIC BETA ANTAGONISTS/	39179
23	CALCIUM CHANNEL BLOCKERS/	36001
24	Anticoagulants/	70256
25	(manag* or treat* or therap*).ti.	2352258
26	"beta block*".ti.	9471
27	"anti coagula*".ti.	382
28	"cardiover*".ab,ti.	18003
29	"anticoagula*".ab,ti.	85126
30	"beta block*".ab,ti.	34631
31	"calcium channel".ab,ti.	26861
32	"amiodarone".ab,ti.	8952
33	"calcium antagonist".ab,ti.	5375
34	"beta antagonist".ab,ti.	778
35	"rate control".ab,ti.	2996
36	"rhythm control".ab,ti.	1403
37	"electrolyte".ab,ti.	50920
38	"magnesium".ab,ti.	53872
39	"potassium".ab,ti.	128991
40	"fluid*".ab,ti.	446933

41	("DC" or "direct current").ab,ti.	61847
42	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	96717
43	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	316301
44	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41	3261491
45	42 and 43 and 44	711
46	limit 45 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)")	66
47	45 not 46	643

EMBASE:

1	ATRIAL FIBRILLATION/	43839
2	ATRIAL FLUTTER/	8265
3	SUPRAVENTRICULAR TACHYCARDIA/	18074
4	("atrial fibrillation*" or AF).ab,ti.	128623
5	"atrial flutter*".ab,ti.	8106
6	"atrial arrhythmia*".ab,ti.	5106
7	"supraventricular tachycardia*".ab,ti.	8529
8	"NOAF*".ab,ti.	137
9	"atrial tachyarrhythmia*".ab,ti.	2237
10	INTENSIVE CARE UNITS/	90170
11	CRITICAL CARE/	91142
12	Sepsis/	140969
13	SEPTIC SHOCK/	45930
14	"intensive care".ab,ti.	184193
15	(ITU* or ICU* or HDU*).ab,ti.	107345
16	(sepsis or "septic shock").ab,ti.	149567
17	("critically unwell" or "critically ill").ab,ti.	58766
18	("intensive care unit*" or "high dependenc*" or "intensive therapy unit*").ab,ti.	146350
19	ELECTRIC COUNTERSHOCK/	17812
20	ANTI ARRHYTHMIA AGENTS/	27886
21	ANTIHYPERTENSIVE AGENTS/	75315
22	ADRENERGIC BETA ANTAGONISTS/	98724
23	CALCIUM CHANNEL BLOCKERS/	56064
24	Anticoagulants/	86960
25	(manag* or treat* or therap*).ti.	2801451
26	"beta block*".ti.	13652
27	"anti coagula*".ti.	569
28	"cardiover*".ab,ti.	27376
29	"anticoagula*".ab,ti.	127479
30	"beta block*".ab,ti.	51955
31	"calcium channel".ab,ti.	34858

32	"amiodarone".ab,ti.	13152
33	"calcium antagonist".ab,ti.	6499
34	"beta antagonist".ab,ti.	891
35	"rate control".ab,ti.	4399
36	"rhythm control".ab,ti.	2318
37	"electrolyte".ab,ti.	51390
38	"magnesium".ab,ti.	62433
39	"potassium".ab,ti.	146940
40	"fluid*".ab,ti.	542188
41	("DC" or "direct current").ab,ti.	79411
42	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	162475
43	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	508124
44	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41	3925641
45	42 and 43 and 44	2379
46	limit 45 to conference abstracts	989
47	limit 45 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years>)	96
48	46 or 47	1051
49	45 not 48	1312

Web of Science:

(TS=(atrial fibrillation OR atrial flutter OR supraventricular tachycardia* OR AF OR atrial arrhythmia*)) AND (TS=(intensive care* OR critical care OR sepsis OR septic shock OR ICU OR ITU OR HDU OR critically unwell OR critically ill OR high dependenc* OR intensive therapy unit)) AND (TI=(manag* OR treat* OR therap*) OR TS=(beta block* OR anticoagula* OR anti coagula* OR calcium channel OR rate control OR rhythm control OR electrolyte OR magnesium OR potassium OR DC OR direct current OR beta antagonist OR calcium antagonist))

Supplemental appendix 3: Study characteristics

AUTHOR (YEAR)	DESIGN	SETTING (COUNTRY)	POPULATION (N)	INTERVENTIONS	OUTCOMES	FOLLOW-UP	RESULTS
BALIK (2017)	Retrospective cohort study	Single centre mixed ICU (Czech Republic)	Sepsis and NOAF (200)	Amiodarone Propafenone Beta-blocker DC cardioversion	Rhythm control	24h	**Rhythm control success:** 74% amiodarone 89% propafenone 92% beta-blocker
BALSER (1998)	Randomised controlled trial	Single centre surgical ICU (USA)	NOAF (55)	Calcium channel blocker Beta-blocker	Rhythm control Recurrence of AF	2h 12h	**Rhythm control success:** 59% beta-blocker (2h) 33% calcium channel blocker (2h) 85% beta-blocker (12h) 69% calcium channel blocker (12h) **Recurrence of AF:** 5.3% beta-blocker **Mortality:** 31% beta-blocker 38% calcium channel blocker **Hypotension:** 3.3% calcium channel blocker
BROWN (2018)	Retrospective cohort study	Single centre surgical ICU (USA)	Post-surgical NOAF (33)	Beta-blocker	Rhythm control	24h	**Rhythm control success:** 27% beta-blocker
GERLACH (2008)	Prospective cohort study	Single centre surgical ICU (USA)	NOAF (61)	Calcium channel blocker Amiodarone	Rhythm control Hypotension	24h	**Rhythm control success:** 87.1% calcium channel blocker 86.7% amiodarone **Hypotension:** 6.7% amiodarone 3.2% calcium channel blocker
KANJI (2012)	Retrospective cohort study	3 centre mixed ICUs (Canada)	NOAF (139)	Amiodarone DC cardioversion	Rhythm control	24h	**Rhythm control success:** 64.1% amiodarone 27.0% DC cardioversion **Recurrence of AF:** 42.2% amiodarone
LIU (2016)	Retrospective cohort study	Single centre medical ICU (Taiwan)	NOAF (265)	Beta-blocker Amiodarone Calcium channel blocker Digoxin DC cardioversion	Rhythm control	7d	**Rhythm control success:** 76.1% beta-blocker 65% amiodarone 71.2% calcium channel blocker 55.6% digoxin

							50% DC cardioversion
MAYR (2004)	Retrospective cohort study	Single centre mixed ICU (Austria)	NOAF (131)	Amiodarone	Rhythm control Hypotension	12h 24h 48h	**Rhythm control success:** 54.2% amiodarone (12h) 60.0% amiodarone (24h) 72.1% amiodarone (48h) **Hypotension:** 0% amiodarone
MAYR (2003)	Prospective cohort study	Single centre surgical ICU (Austria)	NOAF (37)	DC cardioversion	Rhythm control Recurrence of AF	48h	**Rhythm control success:** 35% DC cardioversion **Recurrence of AF:** 61.5% DC cardioversion
MITRIC (2016)	Retrospective cohort study	Single centre mixed trauma ICU (Australia)	NOAF (186)	Amiodarone	Rhythm control Recurrence of AF	Hospital admission	**Rhythm control success:** 95.2% amiodarone **Recurrence of AF:** 51.4% amiodarone
MORAN (1995)	Randomised controlled trial	Single centre mixed ICU (Australia)	NOAF (34)	Magnesium Amiodarone	Rhythm control Hypotension	24h	**Rhythm control success:** 77.8% magnesium 50.0% amiodarone **Hypotension:** 0% magnesium 0% amiodarone
OKAJIMA (2017)	Retrospective cohort study	Single centre mixed ICU (Japan)	Sepsis and NOAF (61)	Beta-blocker Other therapy (not specified)	Rhythm control Bradycardia	24h	**Rhythm control success:** 69.2% beta-blocker 36.4% other therapy **Bradycardia:** 0% beta-blocker
QUON (2018)	Retrospective cohort study	Outpatient (Canada)	NOAF secondary to ACS, acute pulmonary disease or sepsis (2,304)	Anticoagulants	Stroke Bleeding	3y	**Bleeding:** 17.4% anticoagulation 6.4% no anticoagulation **Stroke:** 5.0% anticoagulation 4.3% no anticoagulation
SLEESWIJK (2008)	Prospective cohort study	Single centre mixed ICU (Netherlands)	NOAF (29)	Magnesium Amiodarone	Rhythm control Recurrence of AF Hypotension	24h	**Rhythm control success:** 55.2% magnesium 93.1% magnesium + amiodarone **Recurrence of AF:** 12.5% magnesium 38.5% magnesium + amiodarone **Hypotension** 0% magnesium + amiodarone

WALKEY (2015)	Retrospective cohort study	Mixed hospitals (USA)	Sepsis and NOAF (7,487)	Beta-blocker Calcium channel blocker Digoxin Amiodarone	Mortality	Hospital admission	**Mortality:** Beta-blocker vs amiodarone, RR 0.67 (0.59 – 0.77) Beta-blocker vs calcium channel blocker RR 0.99 (0.86 – 1.15) Beta-blocker vs digoxin RR 0.75 (0.64 – 0.88)
WALKEY (2016)	Retrospective cohort study	Mixed hospitals (USA)	Sepsis and NOAF (7,522)	Anticoagulants	Stroke Bleeding	Hospital admission	**Stroke:** Anticoagulation vs no anticoagulation RR (95%CI) = 0.85 (0.57 – 1.27) **Bleeding:** Anticoagulation vs no anticoagulation RR (95%CI) = 0.97 (0.83 – 1.14)
YOSHIDA (2018)	Retrospective cohort study	Single centre mixed ICU (Japan)	NOAF (151)	Calcium channel blocker Beta-blocker Magnesium Amiodarone Pilsicainide DC cardioversion	Rhythm control	6h	**Rhythm control success:** 33.3% calcium channel blocker 64.8% magnesium 30% amiodarone 64.6% pilsicainide 66.7% DC cardioversion

ICU: Intensive care unit, DC: Direct current, NOAF: New-onset atrial fibrillation, ACS: acute coronary syndrome, RR: relative risk, CI: confidence interval

Supplemental appendix 4: Modified Newcastle-Ottawa Scale

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1. Representativeness of the study population
    a. Truly representative of the general adult ICU population ★
    b. Somewhat representative of the general adult ICU population ★
    c. Poorly representative of the general adult ICU population
    d. No description of the derivation of the cohort
2. Demonstration that the outcome of interest was not present at the start of the study
    a. Exclusion of AF (current and historic) described ★
    b. AF (current and historic) excluded but no description
3. Ascertainment of the presence of risk factor
    a. Medical record or investigation result ★
    b. Structured interview ★
    c. Written self-report
    d. No description or none of the above
4. Study size
    a. ≥100 participants in each group ★
    b. <100 participants in each group

Comparability

1. Comparability of the cohorts on the basis of the design or analysis
    a. Study design controls for confounding factors ★
    b. Study controls for confounding factors in data analysis ★

Outcome

1. Study design
    a. Prospective ★
    b. Retrospective
2. Assessment of outcome
    a. Independent assessment of heart rhythm from primary source (e.g. monitor/ECG) ★
    b. Non-independent assessment or heart rhythm identified from secondary source (e.g. patient records)
    c. Other identification of heart rhythm
    d. No description
3. Adequacy of follow up of cohorts
    a. Complete follow up – all subjects accounted for ★
    b. Subjects lost to follow up unlikely to introduce bias – small number lost, ≥90% follow up or description of those lost ★
    c. Follow up rate < 90% and no description of those lost
    d. No statement

Supplemental appendix 5: Risk of bias assessment (RCTs)

AUTHOR (YEAR)	DOMAIN	SUPPORT FOR JUDGEMENT	RISK
BALSER (1998)	Random sequence generation	Quote: "randomized to receive intravenous diltiazem or intravenous esmolol" Comment: No description of randomisation method	Unclear
	Allocation concealment	Comment: No description of allocation concealment	Unclear
	Blinding participants and personnel	Quote: "were prospectively randomised to receive either intravenous diltiazem or intravenous esmolol for ventricular rate control (unblinded)" Comment: Lack of blinding unlikely to influence outcome in critically ill patient group	Low
	Blinding outcome assessment	Quote: "these tracings were subsequently reviewed by a cardiologist blinded to patient treatment"	Low
	Incomplete outcome data	Quote: "we studied a total of 64 cases of SVT, with 34 patients randomized to receive esmolol and 30 to receive diltiazem […] Because of enrolment errors or patient intolerance, 55 patients with nonsinus tachyarrhythmias continued to receive rate control therapy until the primary 2h end point (31 esmolol, 28 diltiazem)." Quote: "Three patients (two esmolol, one diltiazem) did not have ECGs at the 12-h endpoint and were therefore excluded from the 12-h statistical analysis" Comment: Patients data was excluded in similar numbers and for the same reasons between groups	Low
	Selective reporting	Comment: No available protocol and no clear evidence of pre-specified outcomes, however no evidence that outcomes were not pre-specified	Unclear

	Other sources of bias	Comment: No other clear sources of bias	Low
MORAN (1995)	Random sequence generation	Quote: “Patients were prospectively randomised to the two treatment groups, using a random permuted block design (blocks of two patients)” Comment: No description of method of sequence generation for randomisation	Unclear
	Allocation concealment	Comment: No description of allocation concealment	Unclear
	Blinding participants and personnel	Comment: No mention of blinding participants. Lack of blinding unlikely to influence outcome in critically ill patient group	Low
	Blinding outcome assessment	Quote: “Conversion to sinus rhythm was documented with a repeat 12-lead electrocardiogram” Comment: No description of blinding in outcome assessment.	Unclear
	Incomplete outcome data	Quote: “For magnesium sulphate, n = 18; for amiodarone, n = 16, except for time = 24 hrs where n = 14 (2 deaths)” Comment: Missing data unlikely to influence outcomes	Low
	Selective reporting	Quote: “Patients were also stratified according to the presence or absence of chronic dysrhythmias […] conversion to sinus rhythm was documented with a repeat 12-lead electrocardiogram” Comment: Outcomes specific to this review appear to be pre-specified in the article	Low
	Other sources of bias	Comment: No other clear sources of bias	Low

Supplemental appendix 6: Risk of bias assessment (observational studies)

AUTHOR (YEAR)	DOMAIN	CRITERIA	JUDGEMENT	REASONING
BALIK (2017)	Selection bias	Representativeness of the study population	×	Population of sepsis, not general ICU patients
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Groups < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓	Multivariate analysis for confounders
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	×	No described ECG use
		Adequacy of follow up	×	Significant cross over between groups
BROWN (2018)	Selection bias	Representativeness of the study population	✓	General surgical ICU, consecutive patients
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Groups < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	××	No comparability on basis of design or analysis
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	✓	ECG assessment by cardiologist

		Adequacy of follow up	✓	No significant loss to follow up
GERLACH (2008)	Selection bias	Representativeness of the study population	✓	General surgical ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Groups < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	✓	Prospective design
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
KANJI (2012)	Selection bias	Representativeness of the study population	✓	General surgical ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	Medical records with ICD coding used for diagnosis
		Study size	✓	N = 103
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective design
		Assessment of outcomes	×	No description of ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
LIU (2016)		Representativeness of the study population	×	Sepsis population

	Selection bias	Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Group sizes < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective design
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
MAYR (2004)	Selection bias	Representativeness of the study population	✓	General surgical ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	✓	N = 131
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective design
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
MAYR (2003)	Selection bias	Representativeness of the study population	✓	General surgical ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF

		Study size	×	Group sizes < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓	Difference in age not corrected for
	Outcomes	Study design	✓	Prospective design
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
MITRIC (2017)	Selection bias	Representativeness of the study population	✓	Mixed ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	✓	N = 486
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective design
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
OKAJIMA (2017)	Selection bias	Representativeness of the study population	×	Sepsis population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Group sizes < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective design

		Assessment of outcomes	×	No evidence of ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
QUON (2018)	Selection bias	Representativeness of the study population	✓	Range of critical illnesses included
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	Hospital records and ICD-10 coding used
		Study size	✓	N = 1,304
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	✓	Hospital records used for bleeding and stroke
		Adequacy of follow up	✓	No significant loss to follow up
SLEESWIJK (2008)	Selection bias	Representativeness of the study population	✓	Mixed ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	ECG assessment and exclusion of prior history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Group sizes < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	✓	Prospective
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
WALKEY (2015)		Representativeness of the study population	×	Sepsis population

	Selection bias	Demonstration that the outcome of interest was not present at the start of the study	✓	Subgroup analysis of NOAF (based on medical records)
		Ascertainment of the presence of exposure	✓	ICD-9 coding used
		Study size	✓	N = 7,487
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	✓	Hospital records for mortality outcomes
		Adequacy of follow up	✓	No significant loss to follow up
WALKEY (2016)	Selection bias	Representativeness of the study population	×	Sepsis population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Subgroup analysis of NOAF (based on medical records)
		Ascertainment of the presence of exposure	✓	ICD-9 coding used
		Study size	✓	N = 7,522
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	✓	Hospital records for mortality outcomes
		Adequacy of follow up	✓	No significant loss to follow up
YOSHIDA (2018)	Selection bias	Representativeness of the study population	✓	General surgical ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	ECG assessment and exclusion of prior history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF

		Study size	×	Group sizes < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up

BMJ Open

Managing new-onset atrial fibrillation in critically ill patients: A systematic narrative review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-034774.R1
Article Type:	Original research
Date Submitted by the Author:	17-Jan-2020
Complete List of Authors:	O'Bryan, Liam; University of Oxford, Nuffield Department of Clinical Neurosciences; The University of Melbourne, St Vincent's Department of Medicine Redfern, Oliver; University of Oxford, Nuffield Department of Clinical Neurosciences Bedford, Jonathan; University of Oxford Nuffield Department of Clinical Neurosciences, Kadoorie Centre for Critical Care Research and Education Petrinic, Tatjana; University of Oxford Health Care Libraries, Cairns Library Young, Duncan; University of Oxford, Nuffield Department of Clinical Neurosciences Watkinson, Peter; University of Oxford, Nuffield Department of Clinical Neurosciences
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Anaesthesia, Cardiovascular medicine
Keywords:	INTENSIVE & CRITICAL CARE, Adult intensive & critical care < ANAESTHETICS, ANAESTHETICS, Adult cardiology < CARDIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Managing new-onset atrial fibrillation in critically ill patients: A systematic narrative review

Liam J O'Bryan[1,3] *: Lobrya.2@gmail.com

Oliver C Redfern[1]: Oliver.Redfern@ndcn.ox.ac.uk

Jonathan Bedford[1]: Jonathan.Bedford@ndcn.ox.ac.uk

Tatjana Petrinic[2]: Tatjana.Petrinic@bodleian.ox.ac.uk

J Duncan Young[1]: Duncan.Young@ndcn.ox.ac.uk

Peter J Watkinson[1]: Peter.Watkinson@ndcn.ox.ac.uk

Authors' details: [1] Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom; [2] Bodleian Health Care Libraries, University of Oxford, Oxford; [3] University of Melbourne St Vincent's Department of Medicine, Melbourne, Australia; *Corresponding author

Word count: 4,120

Abstract:

Objectives: The aim of this review is to summarise the latest evidence on efficacy and safety of treatments for new-onset atrial fibrillation (NOAF) in critical illness.

Participants: Critically ill adult patients who developed NOAF during admission.

Primary and secondary outcomes: Primary outcomes were efficacy in achieving rate or rhythm control, as defined in each study. Secondary outcomes included mortality, stroke, bleeding and adverse events.

Methods: We searched MEDLINE, EMBASE and Web of Knowledge on March 11th, 2019 to identify randomised controlled trials and observational studies reporting treatment efficacy for NOAF in critically ill patients. Data were extracted, and quality assessment performed using the Cochrane Risk of Bias Tool, and an adapted Newcastle-Ottawa Scale.

Results: Of 1,406 studies identified, 16 remained after full text screening including 2 randomised control trials. Study quality was generally low due to a lack of randomisation, absence of blinding and small cohorts. Amiodarone was the most commonly studied agent (10 studies), followed by beta-blockers (8), calcium channel blockers (6) and magnesium (3). Rates of successful rhythm control using amiodarone varied from 30.0%-95.2%, beta-blockers from 31.8%-92.3%, calcium channel blockers from 30.0%-87.1% and magnesium from 55.2%-77.8%. Adverse effects of treatment were rarely reported (5 studies).

Conclusion: The reported efficacy of beta-blockers, calcium channel blockers, magnesium and amiodarone for achieving rhythm control was highly varied. As there

is currently significant variation in how new-onset atrial fibrillation is managed in critically ill patients, we recommend future research focusses on comparing the efficacy and safety of amiodarone, beta-blockers and magnesium. Further research is needed to inform the decision surrounding anticoagulant use in this patient group.

Keywords: New-onset atrial fibrillation; ICU; critical care; treatment

Article summary

Strengths and limitations of this study

- Our systematic review is broad assessment of the evidence surrounding the management of new onset atrial fibrillation in the critically ill patient.
- Our review is a significant update to previous reviews, as our search identified more studies specific to the management of new-onset atrial fibrillation.
- We included studies of non-cardiac critically unwell patients, to ensure that our findings are generalisable to the ICU patient.
- Due to limited randomised trial data and study heterogeneity, we did not conduct a meta-analysis and present a narrative synthesis of evidence.

Background

New-onset atrial fibrillation (NOAF) occurs in approximately 14% of critically unwell patients[1]; the incidence increases with greater severity of illness and in sepsis[2–4]. NOAF can lead to haemodynamic instability[5] and thromboembolic events[6]. Critically ill patients with NOAF experience longer intensive care unit (ICU) stay, greater duration of mechanical ventilation and an increased risk of in-hospital mortality[4,7,8].

Extensive guidelines exist for managing atrial fibrillation (AF) in the community and the acute setting[9–11]. However, the safety and efficacy of treatments in critically ill patients are less clear[12]. For example, anticoagulation may fail to prevent stroke in critically ill patients with NOAF[13]. In addition, direct-current cardioversion (DCC) and pharmacological cardioversion are often unsuccessful during critical illness[14,15]. Failure to attain rate or rhythm control in patients with NOAF has been linked with increased in-hospital mortality[3,16].

Two previous systematic reviews have focused on the management of NOAF in the critically ill[2,12]. In 2008, Kanji et al reviewed evidence from randomised controlled trials (RCTs) reporting efficacy of pharmacological treatments[12]. In 2015, Yoshida et al reviewed both RCTs and observational studies of epidemiology, prevention and management[2]. A recent scoping review summarized the epidemiology, prevention and methods of management of NOAF in critically unwell patients[1]. It included patients with pre-existing AF as well as patients outside ICU or in cardiac intensive care. As a scoping review, it did not report the effect on cardiac rhythm of the interventions identified. None of these reviews were able to make specific management or research recommendations due to an absence of high-quality studies and significant population heterogeneity between studies.

Objective

The aim of this review is to summarise evidence from observational studies and randomised trials reporting outcomes of individual treatments for NOAF in critically ill adult patients. This review serves as an update, as the most recent review specific to only the management of NOAF was in 2008. We aim to identify a more relevant

studies than previous reviews by including studies of all treatments (including DCC and anticoagulation), observational studies and studies of new-onset supraventricular arrhythmias (SVAs), where AF is the predominant rhythm, in the critically ill.

Methods

We report our review according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (Supplemental Appendix 1)[17]. Whilst the methods of our review were specified a priori, no protocol was published.

Study eligibility

We considered all RCTs and observational studies published in peer reviewed journals. We included foreign language papers where an English translation was available. We excluded case reports, conference abstracts, letters to the editor, editorials and any other publication that did not report primary data.

We included studies of adult patients (age ≥16) who developed NOAF during admission to a medical, surgical or general ICU. To improve the search yield, we included studies of sepsis outside the ICU, and of new-onset SVAs where AF was the dominant (>70%) arrhythmia. We defined NOAF as AF occurring during admission in a patient with no history of chronic AF. We excluded studies conducted in specialised (neurosurgical or cardiothoracic) ICUs and studies specific to medical or surgical cardiac patients.

We included all studies reporting data on the outcome of a single intervention. The primary outcome of interest was efficacy in achieving rhythm or rate control, as

defined by each study. Secondary outcomes included mortality, stroke, bleeding and adverse events. No limitation was placed on the timing of outcome assessment.

Search strategy

We searched the Medical Literature Analysis and Retrieval System Online (MEDLINE - OVID interface, 1946 to present), Excerpta Medica (EMBASE - OVID interface, 1974 to present) and Web of Science (Clarivate Analytics interface, 1945 to present) databases on March 11th, 2019, using medical subject headings (MeSH) and key words (full list shown in Supplemental Appendix 2). Search terms were designed to capture all supraventricular arrhythmias, including “atrial fibrillation”, “atrial flutter”, “supraventricular tachycardia” and “atrial arrhythmia”. Terms including “critical care”, “critically ill”, “intensive care” and “sepsis” were used to define the setting. General terms such as “treatment” were used alongside specific treatments including “beta-blocker”, “calcium channel blocker”, “direct current”, “magnesium” and “anticoagulation”. Snowballing was performed by assessing references in relevant review articles. The search strategy was formulated in consultation with a medical librarian (TP).

Study selection

We imported search results into Mendeley Desktop (V1.19.3, Mendeley Ltd.), which was used to identify duplicate publications for removal. Two independent reviewers (LO and JB) then screened titles and abstracts for eligibility. Studies were eligible for full text analysis where the abstract appeared to fulfill our inclusion criteria, or where there was uncertainty. We retrieved full text articles and assessed them for relevance using Rayyan software (Rayyan, HBKU, Qatar) to allow blinding between

the reviewers (LO and JB)[18,19]. We discussed disagreements and consulted a third reviewer (DY) if consensus could not be reached.

Data extraction

One author (LO) performed data extraction; the author was not blinded to study authors or institutions. Data extracted from each study included: design, setting, population, interventions, outcomes, timing of assessment and results (Supplemental Appendix 3). Where studies reported data separately for new or chronic arrhythmias, we extracted only data relating to NOAF. We simplified SVA to NOAF, and grouped drugs by class (beta-blockers, calcium channel blockers or anticoagulants). We extracted outcomes only where the effect of a single intervention was evaluated in a cohort of greater than 10 participants. We extracted percent success for each treatment (with respect to a given outcome) and relative risks or odds ratios where provided. We calculated percent success if it was not reported.

Risk of bias assessment

We conducted a risk of bias assessment for all observational studies using an adapted Newcastle-Ottawa Scale (NOS) (Supplemental Appendix 4)[20,21]. This adaptation was designed for non-randomised trials reporting the incidence of NOAF in critical care[21]. RCTs were assessed using the Cochrane Risk of Bias Tool for Randomised Controlled Trials (Supplemental Appendix 5)[22].

Statistical analysis

The primary outcome was efficacy in rhythm or rate control, expressed as a proportion. Outcome data for RCTs were expressed by calculating an odds ratio using provided data.

Patient and public involvement

No patients were involved in this study which used data from published materials only.

Results

Search results

We identified 1,406 unique studies from our search, of which 97 remained after abstract screening (Figure 1). After full text review, 16 eligible studies were identified (Supplemental Appendix 3). Of these, 13 were of patients treated in ICU and the remaining 3 were of patients with sepsis managed in hospital (ICU and non-ICU), including only the sepsis arm of one study of non-ICU patients[23].

Insert Figure 1 here:

Risk of bias

We identified two RCTs, three prospective cohort and eleven retrospective cohort studies. Thirteen of these studies reported an outcome of treatment efficacy in achieving rate or rhythm control. Of two RCTs reporting this outcome, both had unclear risk of bias in allocation concealment and randomisation (Supplemental Appendix 5)[24,25]. One RCT also had unclear blinding of outcome assessment[25] while the other had an unclear risk of selective reporting[24].Observational studies reporting rate and rhythm control for critically ill patients with NOAF were varied in quality (Supplemental Appendix 6). The most common reasons for risk of bias in these studies are outlined in table 1.

Studies reporting outcomes of stroke and bleeding associated with anticoagulation were of higher methodological quality, with less risk of bias[13,23]. Risks of bias in each of these studies were due to retrospective study design and basis in a population of patients with sepsis rather than a generally critically unwell patient group. One study of mortality associated with rate and rhythm control agents used in septic patients with NOAF was of high methodological quality but with risks of bias due to retrospective design and a septic patient population[15].

Table 1: Summary of risks of bias in observational studies reporting efficacy in rate or rhythm control

Domain of bias	Criteria	Main issues
Selection bias	Representativeness of study population	Population of sepsis less representative of generally critically unwell[16,26,27]
	Study size	Treatment group size (n<100)[6,16,26–31]
Comparability	Comparability of cohorts based on study design or analysis	Groups not adequately comparable by study design or analysis[14,26,28]
Outcomes	Study design	Retrospective design[5,6,16,26–28,30,32]
	Assessment of outcomes	Failure to describe ECG use for outcome assessment[5,26,27]
	Adequacy of follow up	No study reported significant loss to follow up

Study characteristics

Studies are described in supplemental appendix 3. Table 2 describes the interventions and outcomes for each of the 16 studies. Amiodarone was the most reported intervention followed by beta-blockers and calcium channel blockers. There were fewer studies of DCC, magnesium and anticoagulation. Studies of less common therapies (pilsicainide, digoxin and propafenone) were grouped. A meta-analysis of RCTs was not performed due to a lack of common interventions.

Rhythm control was the most frequently reported outcome. Although beta-blockers and calcium channel blockers are considered rate control agents, their efficacy was primarily reported in regard to rhythm control. Timing of outcome assessment varied between 2-hours[24] and 7-days[16]. Definitions of successful rhythm control varied with regards to how long sinus rhythm (SR) was maintained; the most common definition used was SR maintained for 24-hours. We did not pool study outcomes due to variation in outcome assessment and definition. Of 14 studies assessing rate or rhythm control, 5 stated that electrolyte abnormalities were corrected prior to treatment.

Study outcomes pertaining to rate control were heterogenous. Due to the inconsistent reporting of rate control efficacy in included studies, we were unable to present these data.

Haemodynamic adverse events (e.g. hypotension and bradycardia) associated with amiodarone, calcium channel blockers, beta-blockers or magnesium were assessed in 5 studies[25,27,29–31]. Rates of stroke and bleeding associated with anticoagulation

were reported in two studies[13,23]. No other studies reported adverse events following treatment for NOAF.

Table 2: Included studies by treatment and outcome

Therapy	Rhythm control	Rate control	Mortality	Total
Amiodarone	9 studies 1 RCT	0 studies	2 studies 1 RCT	10 studies 1 RCT
Beta-blockers	7 studies 1 RCT	1 study 0 RCTs	1 study 0 RCTs	8 studies 1 RCT
Calcium channel blockers	5 studies 1 RCT	0 studies	2 studies 1 RCT	6 studies 1 RCT
Magnesium	3 studies 1 RCT	0 studies	0 studies	3 studies 1 RCT
DC cardioversion	2 studies 0 RCTs	0 studies	0 studies	2 studies 0 RCTs
Anticoagulation*	N/A	N/A	0 studies	2 studies 0 RCTs
Other† therapies	3 studies 0 RCTs	0 studies	1 study 0 RCTs	4 studies 0 RCTs
Total	13 studies 2 RCTs	1 study 0 RCTs	2 studies 1 RCT	16 studies 2 RCTs

Number of studies where numerical data for each treatment and outcome could be extracted

*Outcomes for anticoagulation in both studies were rates of bleeding and ischaemic stroke; †Other therapies include pilsicainide, digoxin and propafenone; DC = Direct current; RCT = Randomised controlled trial

Study results

Figure 2 shows the odds ratios of treatments compared in each RCT. The efficacy of rhythm control for observational studies is shown in Figure 3.

Insert Figure 2 here:

Insert Figure 3 here:

Amiodarone

Overall, amiodarone was the most frequently reported treatment. Studies varied in dosing regimen, timing of outcome assessment and definition of rhythm control. The only RCT of amiodarone reported it was inferior to amiodarone in obtaining rhythm control.

In observational studies, amiodarone success in terms of rhythm control varied from 3/10 (30.0%)[6] to 177/186 (95.2%)[31]. Mitric et al defined successful rhythm control as any reversion to SR during the ICU stay and reported a high success rate for amiodarone (95.2%), however AF recurred in 51.4%[32]. In the largest studies (n>100) with an outcome of sustained cardioversion, success occurred in 60.0% - 73.5%[5,30,32]. In three comparative observational studies, amiodarone achieved lower rates of rhythm control than beta-blockers, magnesium and calcium channel blockers[6,16,26].

Second-line amiodarone use was associated with high rates success in rate and rhythm control. Amiodarone following initial magnesium therapy resulted in successful rhythm control in 27/29 (93.1%) patients in one study[31]. In another study, amiodarone following initial beta-blocker or calcium channel blocker therapy achieved rate or rhythm control in 11/13 (84.6%)[28].

Hypotension, defined as mean arterial pressure below 60mmHg, was described in one study and occurred in 6.7% of 30 patients managed with amiodarone[29]. Two studies reported no adverse events in response to amiodarone[25,30]. Mayr et al. investigated pulmonary toxicity associated with amiodarone use, defined as changes to the FiO_2/PaO_2 ratio, and found no events in 115 critically ill patients with NOAF[30].

Beta-blockers

Three studies investigated short-acting beta-blockers (e.g. metoprolol, esmolol and landiolol)[24,26,27], and 5 failed to specify the precise agent[5,6,15,16,28]. In one RCT assessing beta-blocker efficacy, Balser et al[24] found 22/26 (85%) non-cardiac surgical ICU patients with SVA who received esmolol reverted to SR after 12-hours. In observational studies, successful rhythm control using beta-blockers was reported in 7/22 (31.8%)[26] to 12/13 (92.3%) patients[32]. The largest studies reporting the efficacy of beta-blockers described sustained rhythm control in 69.2%-84.6% of participants[16,24,27]. The only study reporting rate control efficacy for any agent found a 37.9% heart rate reduction in 39 patients with sepsis and NOAF managed with landiolol[27]. Two observational studies directly compared efficacy of beta-blockers to amiodarone and/or calcium channel blockers, finding higher rates of rhythm control with beta-blockers[16,26].

Hypotension requiring discontinuation of a beta-blocker was identified in 5.9% of 34 patients in one study[24]. Okajima et al. reported none of 39 patients treated with a beta-blocker experienced clinically significant bradycardia[27].

One RCT reported in-hospital mortality in non-cardiac surgical ICU patients, reporting 31% mortality in patients treated with a beta-blocker (n=34), and 38% in patients treated with a calcium channel blocker (n=30)[24]. Walkey et al reported in-hospital mortality, comparing beta-blockers to amiodarone, calcium channel blockers and digoxin in 7,478 propensity-matched septic patients with NOAF[15]. Patients given beta-blockers had lower mortality rates than those given amiodarone (RR 0.67, 95% CI 0.59-0.77) or digoxin (RR 0.75, 95% CI 0.64 – 0.88). Mortality rates with beta-blockers were similar to calcium channel blockers (RR 0.99, 95% CI 0.86-1.15).

Calcium channel blockers

One RCT investigated calcium channel blockers for efficacy of rhythm control, reporting success in 16/26 (61.5%) patients at 12-hours[24]. Observational studies reported successful cardioversion using calcium channel blockers in 10/30 (30%)[6] to 27/31 (87.1%)[29]. Calcium channel blockers were compared with other agents in three studies[6,16,29]. One observational study comparing beta-blockers with calcium channel blockers found greater efficacy in rhythm control with the former[16]. Two studies found calcium channel blockers to be similarly efficacious to amiodarone[6,29], and one study found calcium channel blockers to be more effective than amiodarone, though this study was of lower quality[16]. Hypotension occurred in 1/31 (3.2%) and 1/30 (3.3%) of patients receiving a calcium channel blocker[24,29].

Magnesium

The only RCT of magnesium reported superior efficacy to amiodarone, with rhythm control achieved in 14/18 (77.8%) patients treated for 24-hours to a target serum concentration of 1.5-2.0mmol/L[25]. Across all studies, successful rhythm control with magnesium occurred in 55.2%[28] to 77.8%[25] of patients. A retrospective study of patients receiving magnesium found that 59/91 (64.8%) reverted to SR[6], though the therapeutic target for magnesium level was not reported. A prospective observational study titrated magnesium to a serum concentration of 2.0-3.0mmol/L and reported rhythm control in 16/29 (55%) patients after 1-hour[28]. Magnesium was directly compared to amiodarone and a calcium channel blocker in one observational study which found the highest success in rhythm control rate with magnesium[6]. No adverse events were identified with magnesium use in any study.

Electrical therapy

DCC was investigated in only two observational studies, reporting efficacy of 26.9% and 35.1%[5,14]. Mayr et al reported primary success in 13/37 (35.1%) critically ill patients with NOAF at 1-hour[14]. By 24-hours, only 6 (13.5%) of these 37 remained in SR. Another study assessed the efficacy of DCC, reporting success (defined as maintained SR for 24-hours) in 7/26 (26.9%) patients; 18 of these received amiodarone prior to, or during DCC[5].

Other therapies

Successful rhythm control using other treatments ranged from 55.6%[16] to 89.0%[32]. Digoxin use was reported in one efficacy study; rhythm control was achieved in 15/27 (55.6%) patients[16]. Single observational studies investigated the efficacy of

pilsicainide and propafenone in rhythm control for this patient population, with success rates of 51/79 (64.6%) and 32/36 (89%) respectively[6,32].

Anticoagulation

We found two observational studies of anticoagulation in critically ill patients with NOAF. A retrospective analysis of 5,585 patients with sepsis and NOAF found 37.6% were given anticoagulants during admission[13]. Anticoagulant use did not significantly affect the risk of in-hospital stroke (RR 0.85, 95% CI 0.57 – 1.27), or risk of bleeding (RR 0.97, 95% CI 0.83 – 1.14). Another retrospective analysis of 102 critically ill patients with sepsis and NOAF reported rates of ischaemic stroke and bleeding after 3-years follow-up. In patients who were prescribed anticoagulation at discharge, rates of ischaemic stroke were 2/28 (7.1%) compared with 4/73 (5.5%) in those who were not prescribed anticoagulants[23]. Rates of bleeding were 5/25 (20.0%) in the anticoagulated group compared with 15/76 (19.7%) in the control.

Discussion

Our review provides an up-to-date assessment of the evidence for the efficacy of treatments used for managing NOAF in critically ill patients. Our results show that amiodarone, beta-blockers, calcium channel blockers and magnesium achieved similar rates of rhythm control across studies. We therefore recommend further trials focus on comparing these four treatments. Digoxin and DCC achieved lower rates of successful rhythm control in published studies. Our review did not find evidence to support the use of anticoagulation for managing this patient group.

We extracted data from 16 studies reporting treatment outcomes. This includes 9 studies published after the search performed by Yoshida et al. in 2014, who by comparison identified 4 studies providing efficacy data of individual treatments[2]. The 2008 review by Kanji et al.[12] reported on 4 randomised controlled trials, two of which we excluded on the basis of a failure to describe exclusion of participants with pre-existing AF. Our review represents a far broader evidence base than previous systematic reviews. A recent scoping review of all aspects of NOAF in critically ill patients has been undertaken, due to its broad scope, it did not report management strategies within ICU in detail[1]. By focusing solely on management of NOAF in patients admitted to a medical, surgical or general ICU, we present a detailed and modern assessment of the reported effects of different agents in these patients.

Rhythm control

Amiodarone, beta-blockers, calcium channel blockers and magnesium achieved similar rates of sustained rhythm control in critically ill patients with NOAF. Though beta-blockers and calcium channel blockers are considered rate control agents, they appear to be effective in achieving rhythm control. In comparative studies, beta-blockers and magnesium tended to be slightly more successful in achieving rhythm control than calcium channel blockers and magnesium. Magnesium may have an important role as a first-line treatment, reducing the need for higher-risk interventions. While first-line magnesium was successful in only 55% of patients in one study, this may be an underestimate due to the 1-hour end-point used[31]. This study also suggested that the majority of patients who did not convert to SR with magnesium alone, did so with the use of second-line amiodarone. Similarly, Brown et al. reported excellent efficacy in achieving rate and rhythm control with second-

line amiodarone following treatment with a beta-blocker[28]. Amiodarone may therefore have an important role as a second-line therapy in patients with NOAF.

Two RCTs compared the efficacy of treatments in regard to rhythm control (figure 2). One of these, comparing magnesium to amiodarone, reported superior efficacy using magnesium[25]. An RCT comparing beta-blockers to calcium channel blockers was underpowered to detect a difference in rhythm control efficacy, despite a tendency towards the beta-blocker[24]. In 4 observational comparative studies, beta-blockers and magnesium tended to be more effective than calcium channel blockers and amiodarone[6,16,26,29]. Further research is needed to compare rhythm control agents in efficacy and safety. In line with previous authors[33], we conclude that digoxin and DCC may be less effective than other therapies in critically ill patients with NOAF.

Although 5 studies reported correction of electrolyte abnormalities prior to treatment, methods and targets of correction were not described. Electrolytes corrected were potassium and magnesium, though some studies failed to specify an electrolyte.

Rate control:

In patients with atrial fibrillation, rate control is an equally important outcome as rhythm control[34]. It is possible that for critically ill NOAF patients treated with beta-blockers or calcium channel blockers, rate control leads to rhythm control by allowing for spontaneous cardioversion[29]. Despite this, studies of treatment efficacy report rate control data inconsistently. Balser et al report a mean ventricular rate following drug therapy but fail to report the pre-treatment rates or the proportion of people in whom rate control occurred[24]. Two included studies report rate and rhythm control as a combined outcome[28,31], while another three studies report outcomes for rate

control without separating results for the treatments given[5,25,30]. Two studies provide the mean heart rate prior to and after treatment but fail to report the proportion of patients in whom treatment was successful[27,29]. Due to the heterogenous reporting of rate control data, we were unable to provide detailed results of treatment efficacy in bringing about rate control. It is therefore essential for future studies to report rate control data in a standardised manner to enable robust comparison of treatment efficacy for critically ill patients with NOAF.

Adverse events

Adverse events associated with treatments were infrequently reported, providing insufficient data to compare event rates for most therapies. Two studies (49 participants) investigated adverse events associated with magnesium use, finding none. Magnesium appeared to carry low risk of adverse outcomes, but larger studies are needed to assess this. Studies reporting adverse events tended to have small cohorts that may not detect uncommon events.

Mortality

Only one retrospective study was sufficiently powered to consider mortality differences between treatments. Walkey et al. reported a reduction in mortality associated with the use of beta-blockers when compared to amiodarone and digoxin in propensity-matched patients with sepsis and NOAF[15]. Patients were matched by year of hospitalization, demographics, comorbidities, acute organ failure, organ-supportive therapy, source of sepsis and hospital characteristics. This finding needs to be interpreted with caution, as septic patients were defined using International

Classification of Diseases (ICD) codes and thus may not reflect the general critically ill patient.

Anticoagulation

This review highlights the lack of evidence underlying the use or avoidance of therapeutic-dose anticoagulants in critically ill patients with NOAF. The only study of sufficient size to investigate the effects of anticoagulation was of patients with sepsis and was not restricted to patients being managed in ICU[13]. This study reported rates of stroke occurring during hospital admission for patients treated with therapeutic doses of intravenous or subcutaneous anticoagulant medications. The rate of this uncommon event was not significantly affected by anticoagulant use during admission. The second study of anticoagulant use reported rates of stroke and bleeding over 3 years in patients prescribed anticoagulants upon discharge from hospital; this was underpowered to report a difference in complications[23]. Neither study of anticoagulation provided details regarding the duration of treatment.

Limitations of this review

The findings of our review were limited by a lack of recent RCTs comparing therapies in the critically ill. The majority of studies were observational in design, with small patient cohorts. Studies varied considerably in their patient populations, outcomes and interventions. This variability meant we were unable to pool data for treatment efficacy. Both RCTs in this review are over 20 years old; and no longer reflect current practices in critical care. RCTs were also small, with no common treatment comparisons, rendering a meta-analysis impossible. We were unable to

account for rates of spontaneous cardioversion that occurred in studies, which serves as a confounder to our reported rates of successful rhythm control.

Research recommendations

There remains a need for further research to compare treatments for NOAF in critically ill patients. We suggest that large cohort studies are conducted using standardised outcomes to identify the key treatments of interest and to guide the design of subsequent RCTs. Definitions of NOAF used in future studies need to be agreed. Amiodarone, beta-blockers, calcium channel blockers and magnesium should be compared for efficacy in studies of sufficient size to be able to detect clinically meaningful differences between individual treatments. Combined therapies with first-line magnesium may also merit further study.

The most common definition of rhythm control success in our review was SR maintained for 24-hours. This may make it an appropriate definition for future studies. The reporting of rate control efficacy should be brought into line with current guidance. A review of trial data comparing outcomes for rate control in chronic AF found that a target resting rate < 110 was a valid outcome for detecting symptoms and complications from disease[35]. These findings were not specific to a critically ill patient population. To our knowledge there are no recommendations for the use of percentage change in heart rate or change in mean heart rate as an outcome for rate control in AF. We recommend future studies adopt a target HR of <110bpm and report the proportion of patients in whom this target was successfully reached at a time point of 24 hours. This would bring the reporting of rate control data into line with existing studies reporting the efficacy in terms of rhythm control._Secondary

outcomes reported should include mortality, duration of ICU and hospital admission and adverse events. The lack of adequate reporting or investigation of adverse events is concerning. Future studies should include hypotension or bradycardia requiring treatment modification and complications associated with amiodarone use (e.g. pulmonary or hepatic toxicity).

Conclusion

Our review has shown similar efficacy of beta-blockers, amiodarone, calcium channel blockers and magnesium in achieving rhythm control, but with limited evidence. First-line magnesium with amiodarone for non-responders achieved high rates of rhythm control in one small study. Electrical cardioversion and digoxin may be less effective in critically ill patients with NOAF. There is insufficient data to inform the use of anticoagulation, this is a deficit that needs to be rectified. We suggest standardised outcomes for future studies to guide practice in managing this important condition.

Abbreviations:

NOAF: new-onset atrial fibrillation; ICU: intensive care unit; AF: atrial fibrillation; DCC: direct-current cardioversion; RCT: randomised controlled trial; SVA: supraventricular arrhythmia; PRISMA: preferred reporting items for systematic reviews and meta-analysis; ECG: electrocardiogram; SR: sinus rhythm; USA: United States of America; FDA: Food and Drug Administration

Acknowledgements:

We thank Julie Darbyshire, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford and Rachael Fox, University of Melbourne, Melbourne, Australia for their assistance in manuscript preparation.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. Peter Watkinson is supported by the NIHR Biomedical Research Centre, Oxford

Competing interests: The authors declare that they have no competing interests

Author contributions: All authors made substantial contributions towards the review and drafting of the manuscript. DY and PW conceived and designed the review. TP, JB, OR and LO designed the search. LO and JB reviewed articles. LO and OR conducted the search, extracted data and performed quality assessment. OR produced the figures. All authors contributed to the synthesis of, read and reviewed the final manuscript.

Data availability: No additional data available

References

1. Wetterslev M, Haase N, Hassager C, Belley-Cote EP, McIntyre WF, An Y, et al. New-onset atrial fibrillation in adult critically ill patients: a scoping review. Intensive Care Med. 2019 Jul;45(7):928–38.

2. Yoshida T, Fujii T, Uchino S, Takinami M. Epidemiology, prevention, and

treatment of new-onset atrial fibrillation in critically ill: A systematic review. J Intensive Care. 2015;3(1):19.

3. Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bögelein D, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: A prospective observational study. Crit Care. 2010;14(3):R108.

4. Klein Klouwenberg PMC, Frencken JF, Kuipers S, Ong DSY, Peelen LM, van Vught LA, et al. Incidence, Predictors, and Outcomes of New-Onset Atrial Fibrillation in Critically Ill Patients with Sepsis. A Cohort Study. Am J Respir Crit Care Med. 2017 Jan;195(2):205–11.

5. Kanji S, Williamson DR, Yaghchi BM, Albert M, McIntyre L. Epidemiology and management of atrial fibrillation in medical and noncardiac surgical adult intensive care unit patients. J Crit Care. 2012;27(3):326.e1-8.

6. Yoshida T, Uchino S, Yokota T, Fujii T, Uezono S, Takinami M. The impact of sustained new-onset atrial fibrillation on mortality and stroke incidence in critically ill patients: A retrospective cohort study. J Crit Care. 2018;44:267–72.

7. Chen AY, Sokol SS, Kress JP, Lat I. New-Onset Atrial Fibrillation Is an Independent Predictor of Mortality in Medical Intensive Care Unit Patients. Ann Pharmacother. 2015 Mar 10;49(5):523–7.

8. Christian S-A, Schorr C, Ferchau L, Jarbrink ME, Parrillo JE, Gerber DR. Clinical characteristics and outcomes of septic patients with new-onset atrial fibrillation. J Crit Care. 2008;23(4):532–6.

9. January CT, Stevenson WG, Murray KT, Ezekowitz MD, Alpert JS, Field ME, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. Circulation. 2014;130(23):2071–104.

10. Kirchhof P, Benussi S, Zamorano JL, Aboyans V, Achenbach S, Agewall S, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Russ J Cardiol. 2017;147(7):7–86.

11. National Institute for Health and Care Excellence. Atrial fibrillation: the management of atrial fibrillation. 180th ed. NICE clinical guideline 180. London: NICE Clinical Guidelines; 2014.

12. Kanji S, Stewart R, Fergusson DA, McIntyre L, Turgeon AF, Hébert PC. Treatment of new-onset atrial fibrillation in noncardiac intensive care unit patients: A systematic review of randomized controlled trials. Crit Care Med. 2008;36(5):1620–4.

13. Walkey AJ, Quinn EK, Winter MR, McManus DD, Benjamin EJ. Practice patterns and outcomes associated with use of anticoagulation among patients with atrial fibrillation during sepsis. JAMA Cardiol. 2016 Sep 1;1(6):682–90.

14. Mayr A, Ritsch N, Knotzer H, Dünser M, Schobersberger W, Ulmer H, et al. Effectiveness of direct-current cardioversion for treatment of supraventricular tachyarrhythmias, in particular atrial fibrillation, in surgical intensive care patients. Crit Care Med. 2003;31(2):401–5.

15. Walkey AJ, Evans SR, Winter MR, Benjamin EJ. Practice patterns and outcomes of treatments for atrial fibrillation during sepsis a propensity-matched

cohort study. Chest. 2016;149(1):74–83.

16. Liu WC, Lin WY, Lin CS, Huang H Bin, Lin TC, Cheng SM, et al. Prognostic impact of restored sinus rhythm in patients with sepsis and new-onset atrial fibrillation. Crit Care. 2016;20(1):373.

17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339.

18. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.

19. Elmagarmid A, Fedorowicz Z, Hammady H, Ilyas I, Khabsa M, Ouzzani M. Rayyan: a systematic reviews web app for exploring and filtering searches for eligible studies for Cochrane Reviews. In: Evidence-Informed Public Health: Opportunities and Challenges Abstracts of the 22nd Cochrane Colloquium. John Wiley & Sons; 2014. p. 9.

20. Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute. 2010.

21. Bedford J, Harford M, Petrinic T, Young JD, Watkinson PJ. Risk factors for new-onset atrial fibrillation on the general adult ICU: Protocol for a systematic review. BMJ Open. 2018 Sep;8(9):e024640.

22. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct;343(7829):d5928.

23. Quon MJ, Behlouli H, Pilote L. Anticoagulant Use and Risk of Ischemic Stroke and Bleeding in Patients With Secondary Atrial Fibrillation Associated With Acute Coronary Syndromes, Acute Pulmonary Disease, or Sepsis. JACC Clin Electrophysiol. 2018;4(3):386–93.

24. Balser JR, Martinez EA, Winters BD, Perdue PW, Clarke AW, Huang W, et al. B-Adrenergic Blockade Accelerates Conversion of Postoperative Supraventricular Tachyarrhythmias. Anesthesiology. 1998 Nov;89(5):1052–9.

25. Moran JL, Gallagher J, Peake SL, Cunningham DN, Salagaras M, Leppard P. Parenteral magnesium sulfate versus amiodarone in the therapy of atrial tachyarrhythmias: a prospective, randomized study. Crit Care Med. 1995 Nov;23(11):1816–24.

26. Balik M, Kolnikova I, Maly M, Waldauf P, Tavazzi G, Kristof J. Propafenone for supraventricular arrhythmias in septic shock—Comparison to amiodarone and metoprolol. J Crit Care. 2017;41:16–23.

27. Okajima M., Takamura M. TT. Landiolol, an ultra-short-acting β1-blocker, is useful for managing supraventricular tachyarrhythmias in sepsis. World J Crit Care Med. 2015;4(3):251–7.

28. Brown M, Nassoiy S, Chaney W, Plackett TP, Blackwell RH, Luchette F, et al. Impact and treatment success of new-onset atrial fibrillation with rapid

ventricular rate development in the surgical intensive care unit. J Surg Res. 2018;229:66–75.

29. Gerlach AT, Kane-Gill SL, Dasta JF, Steinberg S, Martin LC, Cook CH. Diltiazem versus amiodarone for new-onset atrial arrhythmias in non-cardiac post surgical patients: A cohort study. Crit Care Shock. 2008;11(3):94–106.

30. Mayr AJ, Dünser MW, Ritsch N, Pajk W, Friesenecker B, Knotzer H, et al. High-dosage continuous amiodarone therapy to treat new-onset supraventricular tachyarrhythmias in surgical intensive care patients: An observational study. Wien Klin Wochenschr. 2004;116(9–10):310–7.

31. Sleeswijk ME, Tulleken JE, Van Noord T, Meertens JHJM, Ligtenberg JJM, Zijlstra JG. Efficacy of magnesium-amiodarone step-up scheme in critically ill patients with new-onset atrial fibrillation: A prospective observational study. J Intensive Care Med. 2008;23(1):61–6.

32. Mitrić G, Udy A, Bandeshe H, Clement P, Boots R. Variable use of amiodarone is associated with a greater risk of recurrence of atrial fibrillation in the critically ill. Crit Care. 2016;20(1):90.

33. Walkey AJ, Hogarth DK, Lip GYH. Optimizing Atrial fibrillation management from ICU and beyond. Chest. 2015;148(4):859–64.

34. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002 Dec;347(23):1825–33.

35. Van Gelder IC, Rienstra M, Crijns HJGM, Olshansky B. Rate control in atrial

1 fibrillation. Lancet (London, England). 2016 Aug;388(10046):818–28.

2

3

Figures legend

- Figure 1: PRISMA diagram; PRISMA flowchart of search results and screening
- Figure 2: Rate or rhythm control success (RCTs); Odds ratio comparing agents assessed in randomised controlled trials
- Figure 3: Rate or rhythm control success (observational); Efficacy of each agent as reported in observational studies, reported as percentage success

Supplementary materials

- Supplemental Appendix 1: PRISMA checklist; Completed PRISMA checklist
- Supplemental Appendix 2: Search strategy; Search terms used for MEDLINE, EMBASE and Web of Knowledge, with results
- Supplemental Appendix 3: Included study characteristics; Data extracted from all included studies in regard to author, design, population, setting, interventions, outcomes, follow-up and results
- Supplemental Appendix 4: Modified Newcastle-Ottawa Scale; Description of criteria in the modified Newcastle-Ottawa Scale used for assessing risk of bias in included observational studies
- Supplemental Appendix 5: Risk of bias assessment (RCTs); Assessment for risk of bias in included randomised trials using Cochrane Risk of Bias Tool
- Supplemental Appendix 6: Risk of bias assessment (observational); Assessment for risk of bias in included observational studies using the modified Newcastle-Ottawa Scale

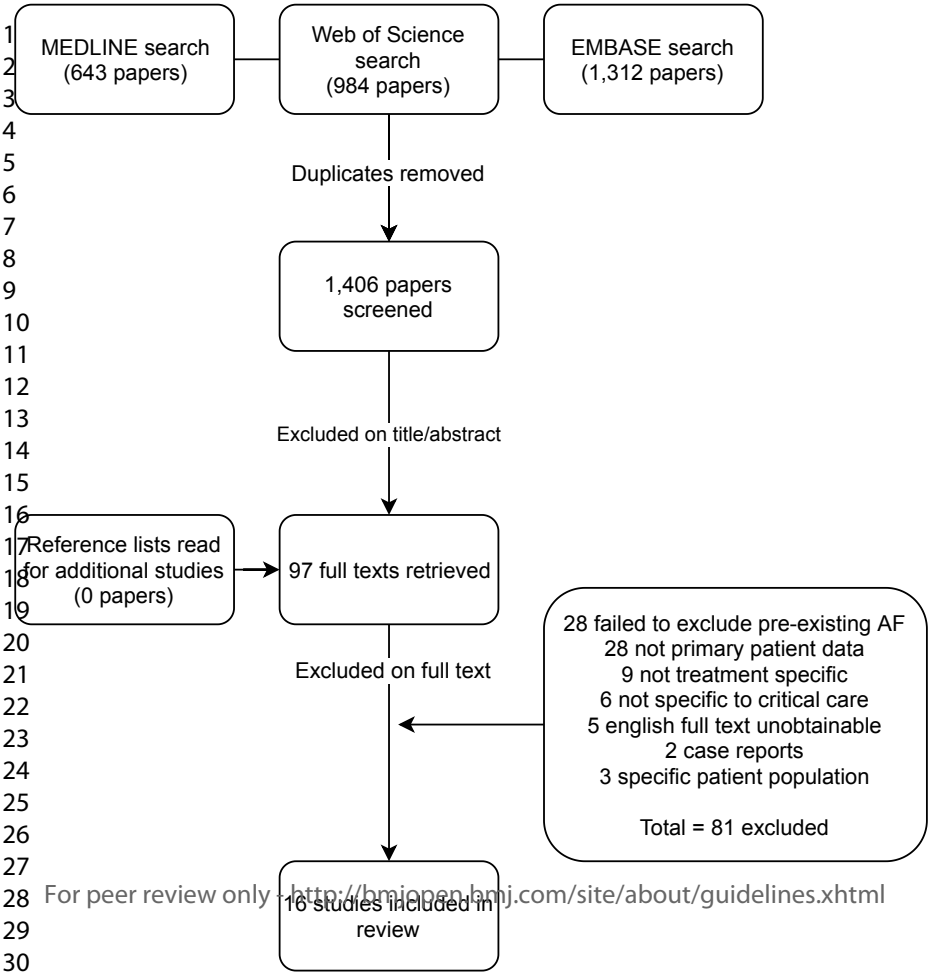


Figure 2:

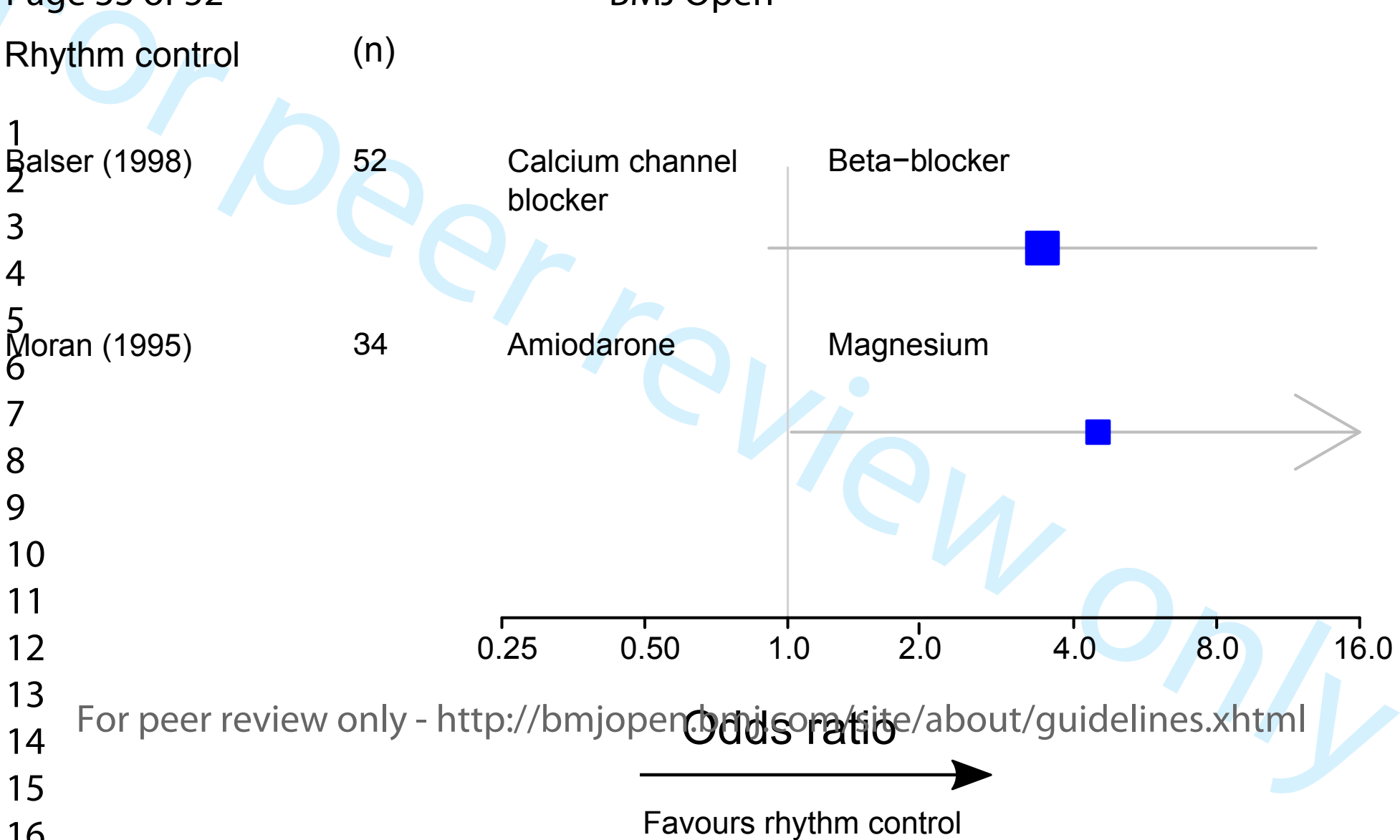
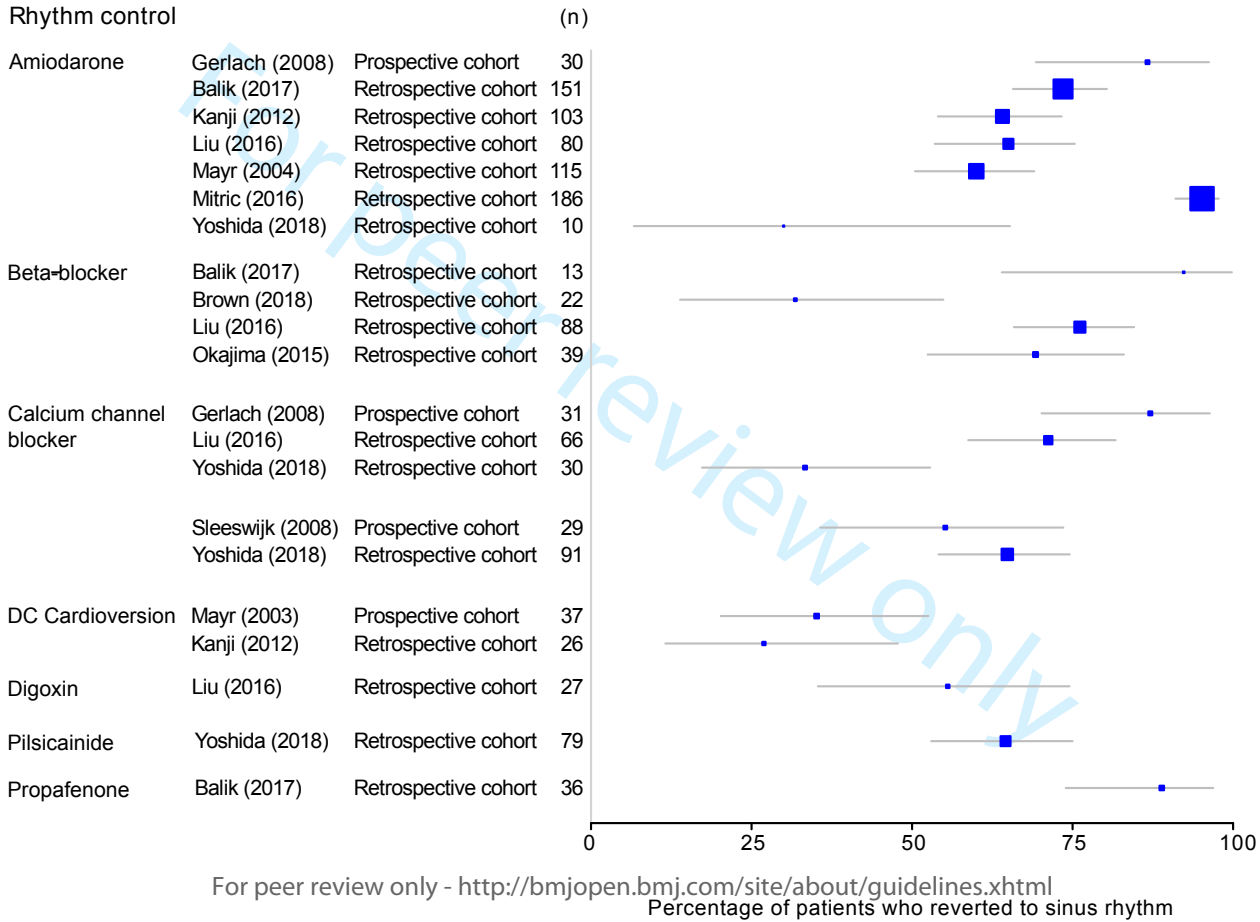


Figure 3:



Supplemental Appendix 1: PRISMA Checklists

The PRISMA for Abstracts Checklist

Section/topic	Checklist item	Reported on page #
1. Title:	Identify the report as a systematic review, meta-analysis, or both.	Title page line 1-3
Background		
2. Objectives:	The research question including components such as participants, interventions, comparators, and outcomes.	Page 2 lines 2-3
Methods		
3. Eligibility criteria:	Study and report characteristics used as criteria for inclusion.	Page 2 lines 5-10
4. Information sources:	Key databases searched and search dates.	Page 2 lines 8-9
5. Risk of bias:	Methods of assessing risk of bias.	Page 2 lines 10-12
Results		
6. Included studies:	Number and type of included studies and participants and relevant characteristics of studies.	Page 2 line 13-20
7. Synthesis of results:	Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals.	Page 2 line 13-20
8. Description of the effect:	Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients.	Page 2 line 13-20
Discussion		
9. Strengths and Limitations of evidence:	Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence)	Page 2 line 21 – page 3 line 4
10. Interpretation:	General interpretation of the results and important implications	Page 2 line 21 – page 3 line 4
Other		
11. Funding:	Primary source of funding for the review.	N/A; page 20 lines 2-4
12. Registration:	Registration number and registry name.	N/A

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page line 1-3
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2 line 1 – page 3 line 4
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3 lines 17 – page 4 line 18
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4 line 19 – page 5 line 3
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5 line 7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5 lines 8-23
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 6 lines 1-14
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplemental appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 6 line 15 – 23
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7 lines 1-11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 7 lines 1-11
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 7 lines 12-17
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 7 lines 18-21
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 7 lines 18-21
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Supplemental appendices 5 and 6

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 7 lines 18-21
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1: Page 8 line 12
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplemental appendix 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1; Supplemental appendices 5 and 6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2 and 3: Page 11 lines 8 and 10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplemental appendices 5 and 6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 16 lines 1-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 20 lines 3-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 21 lines 16-22
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 22 lines 12-14

Supplemental Appendix 2: Search strategies

MEDLINE:

1	ATRIAL FIBRILLATION/	49041
2	ATRIAL FLUTTER/	5599
3	SUPRAVENTRICULAR TACHYCARDIA/	5605
4	("atrial fibrillation*" or AF).ab,ti.	74164
5	"atrial flutter*".ab,ti.	5322
6	"atrial arrhythmia*".ab,ti.	3064
7	"supraventricular tachycardia*".ab,ti.	6374
8	"NOAF*".ab,ti.	59
9	"atrial tachyarrhythmia*".ab,ti.	1432
10	INTENSIVE CARE UNITS/	48874
11	CRITICAL CARE/	48388
12	SEPSIS/	55156
13	SEPTIC SHOCK/	21272
14	"intensive care".ab,ti.	127344
15	(ITU* or ICU* or HDU*).ab,ti.	52744
16	(sepsis or "septic shock").ab,ti.	99233
17	("critically unwell" or "critically ill").ab,ti.	39586
18	("intensive care unit*" or "high dependenc*" or "intensive therapy unit*").ab,ti.	102135
19	ELECTRIC COUNTERSHOCK/	14154
20	ANTI ARRHYTHMIA AGENTS/	26612
21	ANTIHYPERTENSIVE AGENTS/	62664
22	ADRENERGIC BETA ANTAGONISTS/	39179
23	CALCIUM CHANNEL BLOCKERS/	36001
24	Anticoagulants/	70256
25	(manag* or treat* or therap*).ti.	2352258
26	"beta block*".ti.	9471
27	"anti coagula*".ti.	382
28	"cardiover*".ab,ti.	18003
29	"anticoagula*".ab,ti.	85126
30	"beta block*".ab,ti.	34631
31	"calcium channel".ab,ti.	26861
32	"amiodarone".ab,ti.	8952
33	"calcium antagonist".ab,ti.	5375
34	"beta antagonist".ab,ti.	778
35	"rate control".ab,ti.	2996
36	"rhythm control".ab,ti.	1403
37	"electrolyte".ab,ti.	50920
38	"magnesium".ab,ti.	53872
39	"potassium".ab,ti.	128991
40	"fluid*".ab,ti.	446933

41	("DC" or "direct current").ab,ti.	61847
42	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	96717
43	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	316301
44	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41	3261491
45	42 and 43 and 44	711
46	limit 45 to ("all infant (birth to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)")	66
47	45 not 46	643

EMBASE:

1	ATRIAL FIBRILLATION/	43839
2	ATRIAL FLUTTER/	8265
3	SUPRAVENTRICULAR TACHYCARDIA/	18074
4	("atrial fibrillation*" or AF).ab,ti.	128623
5	"atrial flutter*".ab,ti.	8106
6	"atrial arrhythmia*".ab,ti.	5106
7	"supraventricular tachycardia*".ab,ti.	8529
8	"NOAF*".ab,ti.	137
9	"atrial tachyarrhythmia*".ab,ti.	2237
10	INTENSIVE CARE UNITS/	90170
11	CRITICAL CARE/	91142
12	Sepsis/	140969
13	SEPTIC SHOCK/	45930
14	"intensive care".ab,ti.	184193
15	(ITU* or ICU* or HDU*).ab,ti.	107345
16	(sepsis or "septic shock").ab,ti.	149567
17	("critically unwell" or "critically ill").ab,ti.	58766
18	("intensive care unit*" or "high dependenc*" or "intensive therapy unit*").ab,ti.	146350
19	ELECTRIC COUNTERSHOCK/	17812
20	ANTI ARRHYTHMIA AGENTS/	27886
21	ANTIHYPERTENSIVE AGENTS/	75315
22	ADRENERGIC BETA ANTAGONISTS/	98724
23	CALCIUM CHANNEL BLOCKERS/	56064
24	Anticoagulants/	86960
25	(manag* or treat* or therap*).ti.	2801451
26	"beta block*".ti.	13652
27	"anti coagula*".ti.	569
28	"cardiover*".ab,ti.	27376
29	"anticoagula*".ab,ti.	127479
30	"beta block*".ab,ti.	51955
31	"calcium channel".ab,ti.	34858

32	"amiodarone".ab,ti.	13152
33	"calcium antagonist".ab,ti.	6499
34	"beta antagonist".ab,ti.	891
35	"rate control".ab,ti.	4399
36	"rhythm control".ab,ti.	2318
37	"electrolyte".ab,ti.	51390
38	"magnesium".ab,ti.	62433
39	"potassium".ab,ti.	146940
40	"fluid*".ab,ti.	542188
41	("DC" or "direct current").ab,ti.	79411
42	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	162475
43	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	508124
44	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41	3925641
45	42 and 43 and 44	2379
46	limit 45 to conference abstracts	989
47	limit 45 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years>)	96
48	46 or 47	1051
49	45 not 48	1312

Web of Science:

(TS=(atrial fibrillation OR atrial flutter OR supraventricular tachycardia* OR AF OR atrial arrhythmia*)) AND (TS=(intensive care* OR critical care OR sepsis OR septic shock OR ICU OR ITU OR HDU OR critically unwell OR critically ill OR high dependenc* OR intensive therapy unit)) AND (TI=(manag* OR treat* OR therap*) OR TS=(beta block* OR anticoagula* OR anti coagula* OR calcium channel OR rate control OR rhythm control OR electrolyte OR magnesium OR potassium OR DC OR direct current OR beta antagonist OR calcium antagonist))

Supplemental appendix 3: Study characteristics

AUTHOR (YEAR)	DESIGN	SETTING (COUNTRY)	POPULATION (N)	INTERVENTIONS	OUTCOMES	FOLLOW-UP	RESULTS
BALIK (2017)	Retrospective cohort study	Single centre mixed ICU (Czech Republic)	Sepsis and NOAF (200)	Amiodarone Propafenone Beta-blocker DC cardioversion	Rhythm control	24h	**Rhythm control success:** 74% amiodarone 89% propafenone 92% beta-blocker
BALSER (1998)	Randomised controlled trial	Single centre surgical ICU (USA)	NOAF (55)	Calcium channel blocker Beta-blocker	Rhythm control Recurrence of AF	2h 12h	**Rhythm control success:** 59% beta-blocker (2h) 33% calcium channel blocker (2h) 85% beta-blocker (12h) 69% calcium channel blocker (12h) **Recurrence of AF:** 5.3% beta-blocker **Mortality:** 31% beta-blocker 38% calcium channel blocker **Hypotension:** 3.3% calcium channel blocker
BROWN (2018)	Retrospective cohort study	Single centre surgical ICU (USA)	Post-surgical NOAF (33)	Beta-blocker	Rhythm control	24h	**Rhythm control success:** 27% beta-blocker
GERLACH (2008)	Prospective cohort study	Single centre surgical ICU (USA)	NOAF (61)	Calcium channel blocker Amiodarone	Rhythm control Hypotension	24h	**Rhythm control success:** 87.1% calcium channel blocker 86.7% amiodarone **Hypotension:** 6.7% amiodarone 3.2% calcium channel blocker
KANJI (2012)	Retrospective cohort study	3 centre mixed ICUs (Canada)	NOAF (139)	Amiodarone DC cardioversion	Rhythm control	24h	**Rhythm control success:** 64.1% amiodarone 27.0% DC cardioversion **Recurrence of AF:** 42.2% amiodarone
LIU (2016)	Retrospective cohort study	Single centre medical ICU (Taiwan)	NOAF (265)	Beta-blocker Amiodarone Calcium channel blocker Digoxin DC cardioversion	Rhythm control	7d	**Rhythm control success:** 76.1% beta-blocker 65% amiodarone 71.2% calcium channel blocker 55.6% digoxin

							50% DC cardioversion
MAYR (2004)	Retrospective cohort study	Single centre mixed ICU (Austria)	NOAF (131)	Amiodarone	Rhythm control Hypotension	12h 24h 48h	**Rhythm control success:** 54.2% amiodarone (12h) 60.0% amiodarone (24h) 72.1% amiodarone (48h) **Hypotension:** 0% amiodarone
MAYR (2003)	Prospective cohort study	Single centre surgical ICU (Austria)	NOAF (37)	DC cardioversion	Rhythm control Recurrence of AF	48h	**Rhythm control success:** 35% DC cardioversion **Recurrence of AF:** 61.5% DC cardioversion
MITRIC (2016)	Retrospective cohort study	Single centre mixed trauma ICU (Australia)	NOAF (186)	Amiodarone	Rhythm control Recurrence of AF	Hospital admission	**Rhythm control success:** 95.2% amiodarone **Recurrence of AF:** 51.4% amiodarone
MORAN (1995)	Randomised controlled trial	Single centre mixed ICU (Australia)	NOAF (34)	Magnesium Amiodarone	Rhythm control Hypotension	24h	**Rhythm control success:** 77.8% magnesium 50.0% amiodarone **Hypotension:** 0% magnesium 0% amiodarone
OKAJIMA (2017)	Retrospective cohort study	Single centre mixed ICU (Japan)	Sepsis and NOAF (61)	Beta-blocker Other therapy (not specified)	Rhythm control Bradycardia	24h	**Rhythm control success:** 69.2% beta-blocker 36.4% other therapy **Bradycardia:** 0% beta-blocker
QUON (2018)	Retrospective cohort study	Outpatient (Canada)	NOAF secondary to ACS, acute pulmonary disease or sepsis (2,304)	Anticoagulants	Stroke Bleeding	3y	**Bleeding:** 17.4% anticoagulation 6.4% no anticoagulation **Stroke:** 5.0% anticoagulation 4.3% no anticoagulation
SLEESWIJK (2008)	Prospective cohort study	Single centre mixed ICU (Netherlands)	NOAF (29)	Magnesium Amiodarone	Rhythm control Recurrence of AF Hypotension	24h	**Rhythm control success:** 55.2% magnesium 93.1% magnesium + amiodarone **Recurrence of AF:** 12.5% magnesium 38.5% magnesium + amiodarone **Hypotension** 0% magnesium + amiodarone

WALKEY (2015)	Retrospective cohort study	Mixed hospitals (USA)	Sepsis and NOAF (7,487)	Beta-blocker Calcium channel blocker Digoxin Amiodarone	Mortality	Hospital admission	**Mortality:** Beta-blocker vs amiodarone, RR 0.67 (0.59 – 0.77) Beta-blocker vs calcium channel blocker RR 0.99 (0.86 – 1.15) Beta-blocker vs digoxin RR 0.75 (0.64 – 0.88)
WALKEY (2016)	Retrospective cohort study	Mixed hospitals (USA)	Sepsis and NOAF (7,522)	Anticoagulants	Stroke Bleeding	Hospital admission	**Stroke:** Anticoagulation vs no anticoagulation RR (95%CI) = 0.85 (0.57 – 1.27) **Bleeding:** Anticoagulation vs no anticoagulation RR (95%CI) = 0.97 (0.83 – 1.14)
YOSHIDA (2018)	Retrospective cohort study	Single centre mixed ICU (Japan)	NOAF (151)	Calcium channel blocker Beta-blocker Magnesium Amiodarone Pilsicainide DC cardioversion	Rhythm control	6h	**Rhythm control success:** 33.3% calcium channel blocker 64.8% magnesium 30% amiodarone 64.6% pilsicainide 66.7% DC cardioversion

ICU: Intensive care unit, DC: Direct current, NOAF: New-onset atrial fibrillation, ACS: acute coronary syndrome, RR: relative risk, CI: confidence interval

Supplemental appendix 4: Modified Newcastle-Ottawa Scale

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1. Representativeness of the study population
    a. Truly representative of the general adult ICU population ★
    b. Somewhat representative of the general adult ICU population ★
    c. Poorly representative of the general adult ICU population
    d. No description of the derivation of the cohort
2. Demonstration that the outcome of interest was not present at the start of the study
    a. Exclusion of AF (current and historic) described ★
    b. AF (current and historic) excluded but no description
3. Ascertainment of the presence of risk factor
    a. Medical record or investigation result ★
    b. Structured interview ★
    c. Written self-report
    d. No description or none of the above
4. Study size
    a. ≥100 participants in each group ★
    b. <100 participants in each group

Comparability

1. Comparability of the cohorts on the basis of the design or analysis
    a. Study design controls for confounding factors ★
    b. Study controls for confounding factors in data analysis ★

Outcome

1. Study design
    a. Prospective ★
    b. Retrospective
2. Assessment of outcome
    a. Independent assessment of heart rhythm from primary source (e.g. monitor/ECG) ★
    b. Non-independent assessment or heart rhythm identified from secondary source (e.g. patient records)
    c. Other identification of heart rhythm
    d. No description
3. Adequacy of follow up of cohorts
    a. Complete follow up – all subjects accounted for ★
    b. Subjects lost to follow up unlikely to introduce bias – small number lost, ≥90% follow up or description of those lost ★
    c. Follow up rate < 90% and no description of those lost
    d. No statement

Supplemental appendix 5: Risk of bias assessment (RCTs)

AUTHOR (YEAR)	DOMAIN	SUPPORT FOR JUDGEMENT	RISK
BALSER (1998)	Random sequence generation	Quote: "randomized to receive intravenous diltiazem or intravenous esmolol" Comment: No description of randomisation method	Unclear
	Allocation concealment	Comment: No description of allocation concealment	Unclear
	Blinding participants and personnel	Quote: "were prospectively randomised to receive either intravenous diltiazem or intravenous esmolol for ventricular rate control (unblinded)" Comment: Lack of blinding unlikely to influence outcome in critically ill patient group	Low
	Blinding outcome assessment	Quote: "these tracings were subsequently reviewed by a cardiologist blinded to patient treatment"	Low
	Incomplete outcome data	Quote: "we studied a total of 64 cases of SVT, with 34 patients randomized to receive esmolol and 30 to receive diltiazem […] Because of enrolment errors or patient intolerance, 55 patients with nonsinus tachyarrhythmias continued to receive rate control therapy until the primary 2h end point (31 esmolol, 28 diltiazem)." Quote: "Three patients (two esmolol, one diltiazem) did not have ECGs at the 12-h endpoint and were therefore excluded from the 12-h statistical analysis" Comment: Patients data was excluded in similar numbers and for the same reasons between groups	Low
	Selective reporting	Comment: No available protocol and no clear evidence of pre-specified outcomes, however no evidence that outcomes were not pre-specified	Unclear

	Other sources of bias	Comment: No other clear sources of bias	Low
MORAN (1995)	Random sequence generation	Quote: “Patients were prospectively randomised to the two treatment groups, using a random permuted block design (blocks of two patients)” Comment: No description of method of sequence generation for randomisation	Unclear
	Allocation concealment	Comment: No description of allocation concealment	Unclear
	Blinding participants and personnel	Comment: No mention of blinding participants. Lack of blinding unlikely to influence outcome in critically ill patient group	Low
	Blinding outcome assessment	Quote: “Conversion to sinus rhythm was documented with a repeat 12-lead electrocardiogram” Comment: No description of blinding in outcome assessment.	Unclear
	Incomplete outcome data	Quote: “For magnesium sulphate, n = 18; for amiodarone, n = 16, except for time = 24 hrs where n = 14 (2 deaths)” Comment: Missing data unlikely to influence outcomes	Low
	Selective reporting	Quote: “Patients were also stratified according to the presence or absence of chronic dysrhythmias […] conversion to sinus rhythm was documented with a repeat 12-lead electrocardiogram” Comment: Outcomes specific to this review appear to be pre-specified in the article	Low
	Other sources of bias	Comment: No other clear sources of bias	Low

Supplemental appendix 6: Risk of bias assessment (observational studies)

AUTHOR (YEAR)	DOMAIN	CRITERIA	JUDGEMENT	REASONING
BALIK (2017)	Selection bias	Representativeness of the study population	×	Population of sepsis, not general ICU patients
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Groups < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓	Multivariate analysis for confounders
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	×	No described ECG use
		Adequacy of follow up	×	Significant cross over between groups
BROWN (2018)	Selection bias	Representativeness of the study population	✓	General surgical ICU, consecutive patients
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Groups < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	××	No comparability on basis of design or analysis
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	✓	ECG assessment by cardiologist

		Adequacy of follow up	✓	No significant loss to follow up
GERLACH (2008)	Selection bias	Representativeness of the study population	✓	General surgical ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Groups < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	✓	Prospective design
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
KANJI (2012)	Selection bias	Representativeness of the study population	✓	General surgical ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	Medical records with ICD coding used for diagnosis
		Study size	✓	N = 103
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective design
		Assessment of outcomes	×	No description of ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
LIU (2016)		Representativeness of the study population	×	Sepsis population

	Selection bias	Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Group sizes < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective design
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
MAYR (2004)	Selection bias	Representativeness of the study population	✓	General surgical ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	✓	N = 131
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective design
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
MAYR (2003)	Selection bias	Representativeness of the study population	✓	General surgical ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF

		Study size	×	Group sizes < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓	Difference in age not corrected for
	Outcomes	Study design	✓	Prospective design
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
MITRIC (2017)	Selection bias	Representativeness of the study population	✓	Mixed ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	✓	N = 486
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective design
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
OKAJIMA (2017)	Selection bias	Representativeness of the study population	×	Sepsis population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Group sizes < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective design

		Assessment of outcomes	×	No evidence of ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
QUON (2018)	Selection bias	Representativeness of the study population	✓	Range of critical illnesses included
		Demonstration that the outcome of interest was not present at the start of the study	✓	Exclusion of patients with history of AF
		Ascertainment of the presence of exposure	✓	Hospital records and ICD-10 coding used
		Study size	✓	N = 1,304
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	✓	Hospital records used for bleeding and stroke
		Adequacy of follow up	✓	No significant loss to follow up
SLEESWIJK (2008)	Selection bias	Representativeness of the study population	✓	Mixed ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	ECG assessment and exclusion of prior history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF
		Study size	×	Group sizes < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	✓	Prospective
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up
WALKEY (2015)		Representativeness of the study population	×	Sepsis population

	Selection bias	Demonstration that the outcome of interest was not present at the start of the study	✓	Subgroup analysis of NOAF (based on medical records)
		Ascertainment of the presence of exposure	✓	ICD-9 coding used
		Study size	✓	N = 7,487
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	✓	Hospital records for mortality outcomes
		Adequacy of follow up	✓	No significant loss to follow up
WALKEY (2016)	Selection bias	Representativeness of the study population	×	Sepsis population
		Demonstration that the outcome of interest was not present at the start of the study	✓	Subgroup analysis of NOAF (based on medical records)
		Ascertainment of the presence of exposure	✓	ICD-9 coding used
		Study size	✓	N = 7,522
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	✓	Hospital records for mortality outcomes
		Adequacy of follow up	✓	No significant loss to follow up
YOSHIDA (2018)	Selection bias	Representativeness of the study population	✓	General surgical ICU population
		Demonstration that the outcome of interest was not present at the start of the study	✓	ECG assessment and exclusion of prior history of AF
		Ascertainment of the presence of exposure	✓	ECG diagnosis of NOAF

		Study size	×	Group sizes < 100
	Comparability	Comparability of cohorts on the basis of design or analysis	✓✓	Comparable on both design and analysis
	Outcomes	Study design	×	Retrospective
		Assessment of outcomes	✓	ECG assessment
		Adequacy of follow up	✓	No significant loss to follow up