**Management of new onset atrial fibrillation in critically unwell adult patients: a systematic review and narrative synthesis**

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**Abstract**

New onset atrial fibrillation (NOAF) is the most common arrhythmia affecting critically unwell patients. NOAF can lead to worsening haemodynamic compromise, heart failure, thromboembolic events and increased mortality. The aim of this systematic review and narrative synthesis is to evaluate the non-pharmacological and pharmacological management strategies for NOAF in critically unwell patients.

From 1782 studies 30 were eligible, including 4 RCTs and 26 observational studies. Efficacy of direct current cardioversion (DCCV), amiodarone, β-antagonists, calcium channel blockers (CCB), digoxin, magnesium and less commonly used agents such as ibutilide are reported. Cardioversion rates of 48% were reported for DCCV however, re-initiation of NOAF was as high as 23.4%. Amiodarone was the most commonly reported intervention with cardioversion rates ranging between 18% to 95.8% followed by β-antagonists with cardioversion rates between 40% to 92.3%. Amiodarone was more effective than Diltiazem (OR 1.91 p=0.32) at cardioversion. Short acting β-antagonists, esmolol and landiolol were more effective compared to diltiazem at cardioversion (OR 3.55 p=0.04) and heart rate control (OR 3.2 p=0.0005).

There was significant variation between studies with regards to the definition of successful cardioversion and heart rate control making comparisons between studies and interventions difficult. Future RCTs comparing individual anti-arrhythmic agents, in particular magnesium, amiodarone and β-antagonists and the role of anticoagulation among critically unwell patients are required. There is also an urgent need for a core outcome dataset for NOAF studies to allow comparison between different anti-arrhythmic strategies.

**Keywords:**

New onset atrial fibrillation; critical care; management strategy; systematic review

**Introduction**

New onset atrial fibrillation (NOAF) is the most common arrhythmia encountered in critically unwell patients. NOAF complicates between 4% to 15% of all intensive care unit (ICU) admissions, and up to 40% of patients admitted with septic shock1–3. Development of NOAF is associated with adverse outcomes including increased mortality, increased incidence of stroke and thromboembolic events, increased length of hospital stay and increased incidence of permanent atrial fibrillation (AF) following ICU discharge1–6.

The National Institute of Health and Care Excellence (NICE), The American College of Cardiology/American Heart Association (AHA/ACC) and the European Society of Cardiology (ESC) have developed guidelines for the management of NOAF in the United Kingdom (UK), United States and Europe respectively7–10. All three international guidelines recommended direct current cardioversion (DCCV) for the management of NOAF in haemodynamically unstable patients but they differ in recommendations for pharmacological management of fast heart rate, rhythm control and thromboembolic event prevention. Existing guidelines tend to focus on NOAF or permanent AF developing in the community setting or in isolation rather than secondary to critical illness. These patient groups differ significantly in terms of epidemiology and traditional risk factors; hypertension and valvular heart disease appear to play less of a role in the development of NOAF when compared to inflammation, electrolyte disturbances, and administration of vasopressors in critically unwell patients2 11 12. Despite its frequency and association with poor outcomes, there is little evidence for how best to manage NOAF in critically unwell patients. Current guidelines are based upon observational studies and expert consensus in patient populations that are not representative of critically unwell patients11.

The risk versus benefit of each intervention may differ significantly in critically unwell patients compared to patients developing NOAF in the community. Administration of β-antagonists or calcium channel blockers (CCB) may have negative inotropic and vasodilatory actions that may worsen hypotension and organ dysfunction; digoxin may be less effective in states of increased sympathetic tone or when co-administrated with vasopressors. Whilst amiodarone infusion has been associated with hypotension that may exacerbate shocked patients admitted to ICU11 13 14. Similarly, there is minimal evidence to support the routine use of anticoagulation in critically unwell patients who may be at increased risk of bleeding complications from anticoagulation15–17.

**Aim and Objectives**

The aim of this review was to determine the most effective management strategy for NOAF in critically unwell patients and evaluate the effectiveness of non-pharmacological (DCCV) and pharmacological (anti-arrhythmic medication) treatments for NOAF. To address this knowledge gap, an extensive systematic review of the published literature of trials reporting treatment of NOAF in critically unwell patients treated in emergency departments (ED), acute medical units and ICU was performed.

The primary objective of the review was to determine which anti-arrhythmic strategies resulted in rhythm control (defined as conversion to sinus rhythm) in NOAF or rate control (defined as heart rate below 110 bpm). Secondary objectives explored recurrence of AF and adverse events after treatment with antiarrhythmic agents or cardioversion, mortality associated with developing NOAF, length of ICU and hospital stay.

**Methods**

The review followed methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions 18 and was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement19. The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database as CRD42019121739. Review methods were described fully in the published protocol and are summarised here 20.

***Search strategy***

Electronic databases Cochrane Central Register of Controlled Trials (CENTRAL), Embase (OVID), MEDLINE, Science Citation Index Expanded (Web of Science), metaRegister of Controlled trials ([www.controlled-trials.com](http://www.controlled-trials.com)) and the US National Institutes of Health Register ([www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)) and the World Health Organization (WHO) International Clinical Trials Registry platform (ICTRP)  were searched for studies published since 1990 up to May 2020. Grey literature was searched using ‘Google Scholar’ and Web of Science databases. Reference lists of all included studies and review authors’ personal collections were also screened. Based upon previous reviews we anticipated a lack of high-quality randomised trials meeting our inclusion criteria, therefore our review included quasi and randomised controlled trials (RCTs) as well as observational studies in critically ill patients who developed NOAF or paroxysmal atrial fibrillation and were treated with any combination of anti-arrhythmic, rate control medication or direct current conversion versus placebo or standard care. New onset AF, including paroxysmal AF, defined as rhythm classification by continuous ECG monitoring or 12 lead ECG will be included.

There was no language and publication status restriction in the search. The search strategy is presented in supplementary material.

***Study selection***

Citations for all studies identified through electronic database searches were exported to EndNote X9 and into Covidence systematic review platform (Veritas Health Innovation, Melbourne, Australia). Duplicate citations were removed using the automated features of EndNote and Covidence before screening. Title and abstract screening for eligibility were performed by two reviewers independently (BWJ and CSC). Full text articles were retrieved and reviewed against inclusion and exclusion criteria (table 1) by the same reviewers (BWJ and CSC). Studies retrieved but excluded following full text review are reported in table 9, supplementary material. Study authors were contacted in cases where further discussion and a judgement was required to make an eligibility decision. Disagreements were resolved where necessary, in consultation with a third reviewer (RD).

**[INSERT TABLE 1 HERE]**

***Data extraction***

Two reviewers (BWJ and CSC) extracted data independently. The custom data extraction form generated in Microsoft Excel was piloted on 10% of included studies and amendments to the form were made. Data extracted included study design/methodology, study population characteristics, interventions and outcomes. Where studies reported data separately for new or chronic arrhythmias, only data related to NOAF were extracted. We simplified supraventricular arrhythmias (SVA) to NOAF and grouped drugs by classes (beta-blockers, calcium channel blockers or anticoagulants). Where necessary, inconsistencies were resolved through discussion with a third reviewer (RH).

***Risk of bias assessment***

Two reviewers (BWJ and CSC) assessed the risk of bias and resolved disagreements by discussion with a third reviewer (RD). RCTs were assessed using the Cochrane Collaborations Risk of Bias (RoB) tool (handbook version 5.1) 18, non-randomised studies were assessed using the Newcastle-Ottawa scale (NOS) tool 21 and case series were assessed using a modified version of the NOS 22.

***Data synthesis***

Our planned network meta-analysis of data was not possible for this review due to significant differences in study designs, methods, timing of assessment and definition of outcomes 20. Consequently, a narrative synthesis was performed adhering to the synthesis without meta-analysis (SWiM) guidelines23.

We present primary and secondary outcomes for randomised controlled trials in table 2. Due to the variability and lack of reporting of secondary outcomes of interest in observational studies we present only primary outcomes from observational studies in the main manuscript (table 3). We present secondary outcomes and further information such as dosing and timing of pharmacological and non-pharmacological interventions for RCTs and observational studies in supplementary material (table 6). Study and patient characteristics of included studies are reported in two tables ordered by study design and date of publication (supplementary material table 4 and 5). Achieving rate and/or rhythm control were reported as dichotomous data, and criteria used for achieving control in the studies were noted. The number of participants experiencing the respective outcome were analysed in each group. Where reported or where data permit these to be calculated, we presented odds ratios (OR) with 95% confidence intervals (CI). For secondary outcomes, we presented dichotomous data as number of participants experiencing the outcome and OR with 95% CI when reported. For continuous data, report arithmetic means and standard deviations with 95% CI for each outcome together with the numbers analysed in each group. We also extracted medians and ranges when provided.

**Results**

***Search results***

The searches resulted in identification of 1782 citations (Figure 1). Following title and abstract screening, 139 studies progressed to full text screening, of which 30 studies met the eligibility criteria and were included in the review3 24–51.

**[INSERTED FIGURE 1 HERE]**

***Study Characteristics***

Study characteristics are presented in supplementary data table 4. Of the 30 studies included, 4 were RCTs (n=317 participants) 14 24 45 46, 8 were prospective observational studies (n=818 participants) 3 25 27 47–49 51 52, and 18 were retrospective observational studies (n=12814 participants)26 28–34 36 37 39–44 53 54.

Nineteen of the 30 studies were conducted in mixed medical/surgical ICU settings 24 26–29 33 34 37 39–41 43 44 47 50 51 53–55. Medical ICUs accounted for five studies 14 36 42 46 49, of which two included cardiology patients 42 49. Surgical ICU settings accounted for five studies 3 25 31 45 48. One study was conducted on a mobile intensive care unit in France, that primarily treated patients with life threatening NOAF 30.

Age, gender, comorbidities and illness severity scores of patients included in studies are presented in supplementary material table 5. Co-morbidities were reported in 23 of 30 studies 3 14 24 25 27 31 33 34 36 37 39–45 47–49 51 53 54. There was significant variation in co-morbidities reported between studies. Hypertension, coronary artery disease/ischaemic heart disease and congestive cardiac failure were the most commonly described co-morbidities.

The most commonly used anti-arrhythmic interventions were Amiodarone (15 studies)14 26 28 30 32 33 36 37 41 44 46 48 49 52 54, β-antagonists (9 studies)24 32 33 36 39–41 45 54, and CCB (7 studies) 14 33 36 40 45 48 54. Fewer studies reported outcomes for Digoxin (3 studies) 29 36 54, Magnesium (3 studies)33 46 52, Propafenone (2 studies)32 49, Nifekalant (1 study)51, Pilsicainide (1 study)33 and Ibutilide (2 studies)42 43. DCCV was reported in six studies 25 33 36 41 51 53, and four studies reported a combination of interventions 3 31 34 47. We report the outcomes of these studies in table 6. supplementary material for information only. Studies reporting second line agents were not included in our analysis as it would not be possible to disentangle the pharmacological agent responsible for rate or rhythm control. Where available we report drug classification, specific drug within that classification and dose in table 6, supplementary material. Overall information regarding drugs and dosing were poorly reported. There was variability in reporting of 24-hour cumulative doses or doses required to achieve rate or rhythm control. The lack of standardised reporting makes comparison between drug classifications and studies difficult, similarly it is difficult to report if participants received adequate loading or infusion doses.

There was significant variation in reported outcomes between studies. Of primary outcomes, cardioversion to sinus rhythm was reported by 24 studies 14 25–27 31–33 36 37 39 41–51 53 56 however the time point at which cardioversion was recorded varied between 40 min to within 72 hours 41 49. Outcomes for heart rate control was reported by 11 studies however, 7 studies did not define successful heart rate control 26 29 31 39 45 46 57 and only 2 studies defined heart rate control as <110bpm as per our protocol 40 50. Other definitions for heart rate control included less than 100 bpm 49, between 69 - 94 bpm 24, >20% reduction in baseline heart rate 24 and >30% reduction in baseline heart rate 14. Secondary outcomes of interest were poorly reported overall, mortality was reported by 16 studies 24 29 31–36 38 40 41 44 45 47 53 56. Mortality was most commonly reported between patients that cardioverted to SR versus those that remained in NOAF rather than for specific pharmacological agents, making it difficult to estimate the effect of individual antiarrhythmic medications on mortality. ICU and/or hospital LoS was reported by 13 studies26 28 29 32 34 36 37 40 42 45 47 48 53. Studies reporting use of anticoagulation lacked information regarding dose, route or type of anticoagulation used 14 27 33 41 43 47 49 54.

***Methodological quality / Risk of Bias***

Of the four RCTs, we judged two studies as having a high risk of bias in relation to blinding of study participants14 24, three as unclear in terms of risk of bias from randomisation14 45 46, and all studies as unclear in terms of risk of allocation concealment14 24 45 46 (table 7. supplementary material). Of the 26 observational studies, we judged 13 as having a NOS score greater or equal to 7 (absence of substantial bias)3 26 28 30 32 36 37 41 44 47 49 51 54 (table 8. supplementary material).

***Primary study outcomes by intervention***

***DCCV***

***Cardioversion to SR***

Six observational studies reported outcomes for DCCV 25 33 36 41 51 53. The effectiveness of DCCV in achieving immediate cardioversion to sinus rhythm ranged from 41/85 patients (48%) to 37/37 patients (100%) 25 53. Despite high rates of cardioversion, re-initiation of NOAF was common, with Kanji reporting recurrence of NOAF in 4/26 patients (15.4%) by 24 hours and Mayr reporting recurrence of NOAF in 6/37 patients (16.2%) by 24 hours25 41. Hayashi investigated the use of Nifekalant following unsuccessful DCCV and reported a DCCV failure rate of 27/64 patients (42.2%%) prior to Nifekalant: 12/64 (18.7%) due to failure of initial DCCV and 15/64 (23.4%) due to re-initiation of NOAF51.

**[INSERT TABLE 2 HERE]**

***Amiodarone***

***Cardioversion to SR***

Two RCTs reported the use of Amiodarone 14 46. Delle Karth reports a non-significant difference favouring amiodarone bolus followed by infusion compared to amiodarone bolus alone (OR 1.22 (95% CI 0.32-4.31) p=0.75) or diltiazem (OR 1.91 (95% CI 0.52-7.00) p=0.33) at cardioversion to sinus rhythm 14. Conversely, Moran et al reported that amiodarone was not as effective as magnesium at achieving cardioversion of NOAF to sinus rhythm (OR 0.53 (95% CI 0.11-2.59) p=0.44))14 46. Neither studies reported data on mortality or LoS.

Cardioversion to SR was reported in 11 observational studies 26 30 33 37 40 41 44 48–50. Outcome reporting time differed significantly between studies and ranged from 40 mins to 72 hours 30 41. Success rates of cardioversion to SR ranged from 18% at 40 minutes post infusion 30 to 94.2% 49. Amiodarone appeared as effective as diltiazem at cardioversion (87.1% vs 86.7%) 48 in one study. Sleeswijk reported magnesium may be more effective than amiodarone (55% vs 38%) 50 whilst Milojevic reported superiority of esmolol compared to amiodarone (18% vs 44%) 30. Three observational studies that investigated amiodarone reported outcomes for multiple or combinations of treatments33 36 41. In these studies, it was not possible to disentangle which anti-arrhythmic agent was responsible for the observed effect (table 6. supplementary material) 33 36 41.

***Heart rate control***

In a RCT comparing diltiazem and amiodarone, Delle Karth et al defined heart rate control, as >30% heart rate reduction within 4 hours sustained for 4 hours, and reported a non-significant difference in rates of HR control. Patients received either amiodarone bolus alone or amiodarone bolus and infusion vs diltiazem. Amiodarone bolus and infusion resulted in greater rates of HR control 15/20 vs 11/20 OR 2.45 (95% CI 0.64-9.39) p=0.18) compared to amiodarone bolus alone or diltiazem 15/20 vs 14/20, OR 1.29 (95% CI 0.32-5.17) p=0.7214.

Three observational studies reported heart rate control with amiodarone as an outcome 26 49 50. Milojevic et al reported that amiodarone bolus plus infusion achieved a heart rate <100bpm in only 50/200 (25%) of patients with the primary end point of heart rate control at 40 minutes 30. Esmolol performed better than amiodarone; successfully achieving heart rate control (<100bpm) in 64/100 (64%) patients at 40 min post infusion30. Magnesium lead to a decrease in HR <110 in 9/29 (31%) of patients 50 whilst continuous amiodarone infusion resulted in a decrease in HR from 137 +/- 26 to 91 +/- 17bpm by 12 hrs with a lower heart rate being sustained for 48 hours 26.

***β-Antagonists***

Ten studies reported outcomes for β-antagonists. Two RCTs reported outcomes for the short acting β-antagonists esmolol and landiolol 24, 45. Four observational studies reported outcomes for β-antagonists including metoprolol, landiolol and sotalol 30 32 39 40. Two observational studies report outcomes for β-antagonists but failed to specify individual agents 33 36 41 44.

***Cardioversion to SR***

Balser reported a significant difference in rates of successful cardioversion to SR between esmolol and diltiazem 20/34 (59%) vs 10/30 (33%) OR 2.86 (95% CI 1.03-7.93) p=0.04)) at 2 hours and 12 hours (22/26 (85%) vs 16/26 (62%) ) 45. However Balser et al noted that between 2-12 hours, 11/26 (42%) of patients also received treatment with Magnesium and 6/26 (23%) patients received treatment with digoxin as well as esmolol, making it difficult to determine the true efficacy of esmolol 45.

Landiolol, metoprolol and esmolol were investigated in observational studies. Okajima reported a significant difference in rates of cardioversion to SR at 24 hours between landiolol and control (27/39 (69.7%) vs 8/22 (36.4%) p=0.05) 39. Balik compared cardioversion rates at 24 hours between amiodarone, propafenone and metoprolol 32. Cardioversion rates for metoprolol were 12/13 (92.3%) compared to amiodarone 111/151 (73.5%) and propafenone 32/36 (88.9%) 32. Milojevic reported a significant difference in rates of cardioversion to SR between esmolol and amiodarone (44/100 (44%) vs 36/200 (18%) p<0.01) 30. However, Milojevic reported cardioversion to SR at shortly after commencement of treatment at 40 min30

Yoshida et al, Liu et al, Xie et al and Kanji et al reported outcomes for cardioversion to sinus rhythm for β-antagonists but did not specify agents. Efficacy at achieving sinus rhythm ranged from 2/5 (40%) to 67/88 (77%) 33 36 41 44.

***Heart rate control***

Kakihana et al compared landiolol to placebo and found a significant difference for heart rate control, defined as achieving a heart rate of 60-94 bpm, (41/76 (55%) vs 25/75 (33%) p<0.003) OR3.2 (95% CI 1.66-6.31) p=0.0005 24. Kakihana did not report any outcomes with regard to cardioversion to sinus rhythm24.

Personett et al compared achievement of heart rate control, defined as heart rate < 110bpm, between metoprolol and diltiazem and reported that metoprolol achieved heart rate control in 35/66 (53%) of patients compared to 42/55 (72%) for diltiazem 40. However, 22/66 patients continued another unspecified β-antagonists (26/66), 3/66 continued a CCB (3/66) and 6/66 continued another non-specified antiarrhythmic (6/66) 40.

***Magnesium***

***Cardioversion to SR***

Moran et al in a RCT reported that magnesium was more effective at achieving cardioversion to SR than amiodarone (18/21 (85.7%) vs 16/21 (76.1%) OR 1.86 (95% CI 0.38-9.12 p=0.44)) 46. Sleeswijk et al reported similar results, with magnesium achieving sinus rhythm in 11/29 (37.9%) compared to 7/29 (24.1%) for amiodarone 50. In another observational study the efficacy of cardioversion with magnesium was 59/91 (30.9%), although this study reported combinations of anti-arrhythmic medications 33.

***Heart rate control***

Sleeswijk reported that Magnesium was effective in 9/29 (31%) at achieving a HR < 110bpm50. No other studies investigating magnesium reported outcomes for control of HR.

***Calcium channel blockers***

***Cardioversion to SR***

Studies of CCB reported primary outcomes of interest in seven studies 14 33 36 40 44 45 48. Balser and Delle Karth compared diltiazem to esmolol and amiodarone respectively14 45. Rates of cardioversion to SR are reported above.

Two observational studies compared diltiazem with amiodarone or metoprolol respectively 40 48. Gerlach et al reported similar efficacy between amiodarone and diltiazem at achieving cardioversion to SR (26/30 (86.7%) vs 27/31 (87.1) 48.

Liu et al and Yoshida et al reported rates of cardioversion of 47/66 (71%) and 10/30 (33%) respectively but did not specify a specific CCB and included combinations of anti-arrhythmic medications33 36

***Heart rate control***

Few studies report rates of heart rate control for calcium channel blockers, Delle Karth in and RCT reported a non-significant difference between diltiazem and amiodarone as reported above 14.

In observational studies diltiazem was more effective than metoprolol at achieving heart rate control, defined as heart rate <110 bpm (42/55 (73%) vs 35/66 (53%))40.

***Digoxin***

Three observational studies reported outcomes for digoxin 29 36 54. Only Liu et al reported outcomes for rates of cardioversion to SR with an efficacy of 15/27 (55.6%) 36. Digoxin appeared more effective at achieving heart rate control, defined as a heart rate <100 bpm, in 174/180 (96.6%) of patients following 250mcg – 500mcg bolus of digoxin in septic patients with NOAF 29.

[INSERT TABLE 3 HERE]

**Discussion**

This systematic review assessed the efficacy of a wide range of treatments including DCCV and pharmacological rhythm and rate control. The most commonly reported pharmacological agents were Amiodarone, β-antagonists and CCB. We also presented findings for less commonly used agents such as Ibutilide, Nifekalant, Propafenone, Pilsicainide and studies reporting combinations of treatment. Thirty studies met the eligibility criteria including a further 2 RCTs and 15 observational studies published since the most recent systematic reviews by O’Bryan et al and Yoshida et al respectively33 58. In particular we included studies that present emerging data related to newer β-antagonist drugs such as Landiolol which may gain importance in the future management of NOAF in critically unwell patients 24 39.

***Heart rhythm control using DCCV cardioversion or anti-arrhythmic medication***

Current international guidelines recommend DCCV in haemodynamically unstable patients 7–9. Despite these recommendations, no RCTs reported outcomes for DCCV and observational studies revealed that DCCV often was not immediately successful and re-initiation of NOAF was common. No studies reported outcomes for use of antiarrhythmic medications prior to DCCV. However, the significant rates of failure and re-initiation of AF has led some authors to recommend concomitant administration of pharmacological rate or rhythm control therapies 11. We noted that Kyo et al reported that potassium levels greater than 3.8mmol/L impacted upon the success of DCCV and four DCCV studies reported potassium levels within the range of 3.5 – 4.2mmol/L prior to attempting DCCV 25 36 41 51. However, none of these studies addressed whether potassium levels impacted upon the success of DCCV as a primary or secondary outcome 25 36 41 51.

We did not include electrolyte levels as a specific outcome measure in our review however, future studies should explore this intervention and whether electrolyte supplementation in addition to DCCV or other pharmacological intervention impacts upon cardioversion or rate control.

Pharmacological rhythm control was reported in 23 studies including 4 RCTs. Amiodarone was the most commonly used agent with success rates ranging between 18% to 94%30 49. Time to restoration of sinus rhythm with Amiodarone was poorly reported but ranged from 4 hours to 72 hours and amiodarone bolus followed by continuous infusion appeared to be more effective 14 41 52. Similar rates of cardioversion were reported for Magnesium, β-antagonists, CCBs, and Digoxin. Magnesium decreases cardiac automaticity and prolongs AV node delay without significant side effects such as hypotension, which is commonly observed after administration of agents such as beta-antagonists, CCB and Amiodarone11. Of note, Sleeswijk et al added Amiodarone to treatment in patients that failed to respond to Magnesium alone to achieve cardioversion in a further 38% of patients at a median of 4 hours (2-78)52. Such a magnesium / amiodarone step up regimen deserves further investigation given the safety profile of magnesium and the familiarity of clinicians with amiodarone as a first line agent for NOAF, particularly in the UK 59.

Two RCTs compared rates of cardioversion between diltiazem and esmolol or amiodarone respectively 14 45. In both studies, diltiazem appeared to be inferior at conversion to sinus rhythm. Observational studies reflect these findings, with esmolol appearing more effective at achieving cardioversion than amiodarone (44% vs 18%) 30.

***Heart rate control***

There was significant heterogeneity in the definition of heart rate control between studies (table 2). A number of studies reported heart rate before and after pharmacological treatment but without heart rate control being a defined outcome 29 31 39 45 46. Two observational studies reported heart rate before and after cardioversion as a combined outcome measure 31 39.

Amiodarone and Diltiazem were effective in achieving a heart rate reduction of > 30% of baseline heart rate14. Diltiazem (73%) appeared more effective compared to Metoprolol (53%) in achieving a heart rate reduction to <110bpm in one observational study 40. β-antagonists, Esmolol and Landiolol appeared to be as effective as Amiodarone and Diltiazem at achieving HR rate control in one RCT and three observational studies 24 30 48 52. Mayr et al investigated heart rates before and after high dose Amiodarone infusion and reported that Amiodarone was effective at lowering heart rate even in patients that failed cardioversion into sinus rhythm 26. Digoxin was equally effective at achieving heart rate control (<110 bpm) in septic patients admitted to ICU with success rates of up to 96.6% within 12 hours and provided good haemodynamic stability 29.

The initial management goals in the treatment of NOAF depend upon whether the deleterious effects of NOAF are due to high heart rates, in which a rate control strategy may be effective; or loss of atrial systole, in which a rhythm control strategy may be beneficial 11. Overall, we were unable to offer a recommendation for a particular pharmacological agent to achieve either heart rate or rhythm control, mainly because of significant variation in definition of heart rate control (**Table 2**). Newer ultra-short acting beta-antagonists such as Esmolol and Landiolol offer the advantage of rapid onset, titration and short half-life compared to other agents60. Furthermore, studies have suggested that short acting β-antagonists may enhance arterial elastance and improve ventricular-arterial coupling in septic patients leading to improved haemodynamic parameters and patient outcomes 61. Coupled with a favourable safety profile and minimal impact upon blood pressure Landiolol may offer an advantage over other β-antagonists at controlling heart rate 24 39.

***Strengths and weaknesses***

We believe our study to be the most comprehensive and up to date assessment of the literature on the management of NOAF in critically unwell patients. We present a wider range of evidence than previous reviews as we did not limit our searches geographically and included critically unwell patients admitted to any acute care setting including HDU, ICU, CCU, Emergency Departments and Acute medical units.

A formal assessment of certainty of the evidence could not be performed given that assessment of GRADE domains such as inconsistency and imprecision was hindered by underreporting of precision estimates such as 95% confidence intervals in the studies published. Despite the extensive systematic literature review, we were unable to define the superiority of any anti-arhythmic for rhythm or rate control in NOAF. Our review was limited by the lack of high-quality RCTs assessing the impact of therapeutic interventions versus placebo. Similarly, observational studies were often single centre and at high risk of bias. Few studies reported outcomes for anticoagulation and therefore we are unable to make any recommendations regarding the use of anticoagulation in critically unwell patients that develop NOAF (Supplementary material). Whilst it is established that achieving cardioversion or rate control conveys a mortality advantage, few studies reported mortality or length of stay data for specific rate or rhythm control strategies. We are therefore unable to determine if specific agents convey a mortality advantage or the observed differences are reflective of being in either sinus rhythm or AF. Whether individual agents improve mortality requires further investigation.

In future trials, core outcomes, including heart rate control boundaries and conversion into sinus rhythm need to be clearly defined, taking into account the time interval until rate and/or rhythm control is achieved as well as recurrences or permanent treatment failure. So far, neither uniform reporting tools nor standardisation of outcome measures for NOAF exist, making the development of a core outcome set a priority to allow comparison of different treatment strategies.

***Conclusion***

In this review we are unable to distinguish a hierarchy of effectiveness between DCCV, amiodarone, β-antagonists, CCB and magnesium at achieving cardioversion to SR or heart rate control in NOAF. There is a paucity of high-quality RCT evidence for DCCV in the management of NOAF. Despite initially high success rates of conversion to SR with DCCV in observational studies, the rates of re-initiation of NOAF were significant. There is little evidence to recommend a particular pharmacological agent for the management of NOAF in critically unwell patients and treatment decisions should be individualised taking into account the potential side effects of specific anti-arrhythmic medications. Conclusions are limited due to the heterogeneity between studies in the definition of NOAF and the lack of standardised outcomes that allow comparison between anti-arrhythmic strategies. Future studies therefore require clearly defined outcomes with reference to successful cardioversion to sinus rhythm and clinically relevant heart rate control. Similarly, studies should uniformly report anti-arrhythmic medication side effects, adverse events and treatment failure. There is an urgent need for the development of a core clinical outcome set that would allow for comparison between agents in a clinically meaningful and patient-centred manner.

***Author contributions:***

Idea and study concept: BWJ, IFW, DFM, BB

Study design: BWJ, RH, RD, CSC, IW

Title/abstract, full text screening and data extraction: BWJ, CSC

Disagreement resolution: RH, RD

Preparation and submission of manuscript: BWJ, CSC, RH, RD, BB, DFM, IDW

***Declaration of interests***

The authors report no conflicts of interest to declare.

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| --- | --- |
| **Table 1. Eligibility criteria** | |
| Inclusion criteria (if all of the following met) | Exclusion criteria (if any of the following met) |
| 1. Population comprised adults admitted to a critical care setting (ICU, HDU, A+E, AMU) who have developed or develop NOAF including paroxysmal AF (rhythm classification by continuous ECG monitoring or 12 lead ECG) | 1. Population includes patients younger than 18 years, pregnant women, patients with known AF or a history of previous episodes of AF, patients who have undergone or are scheduled to undergo cardiac surgery, permanent pacemaker insertion or surgical ablation, or patients post cardiac/thoracic surgery |
| 2. Intervention was any anti-arrhythmic or rate control medication (including but not limited to beta antagonists, calcium channel antagonists, Digoxin, Amiodarone, Magnesium), DCCV, or any combination of these interventions | 2. Case reports and studies with no original data presented (e.g., design/protocol paper, [systematic] review, meta-analysis, commentary/editorial) |
| 3. Comparator was any of the interventions above, placebo, standard care or no comparator | 4. Insufficient information (e.g., study only available as a conference proceeding/abstract) |
| 4.   1. Primary outcome measures included achievement of heart rhythm control/cardioversion to sinus rhythm or achievement of heart rate control (defined as heart rate less than 110 bpm); 2. Secondary outcomes included:    1. development of permanent atrial fibrillation,    2. development of recurrent paroxysmal atrial fibrillation that terminates within 48 h as defined by the ESC 9,    3. any thromboembolic events (such as stroke pulmonary embolism, deep vein thrombosis, left atrial thrombus) during critical care admission,    4. development of major bleeding events after administration of therapeutic anticoagulation as recommended in NICE guidelines 7,    5. any complication documented secondary to the intervention,    6. last reported mortality,    7. ICU mortality,    8. length of stay in critical care and length of hospital stay |  |
| 5. RCTs, quasi-RCTs and prospective or retrospective observational studies published in peer-reviewed journals |  |
| NOAF defined as AF occurring during admission in a patient with no history of chronic AF. We also included studies of new-onset supraventricular arrhythmias (SVAs) where AF was the dominant arrhythmias  AF=atrial fibrillation; ECG= electrocardiogram; ESC= European Society of Cardiology; HDU=high dependency unit; ICU=intensive care unit; A+E=emergency department; AMU=acute medical unit; NICE=National Institute of Health and Care Excellence; NOAF=new onset atrial fibrillation; RCT=randomised controlled trial; DCCV=direct current cardioversion | |

| **Table 2. Primary and secondary outcomes of randomised controlled trials** | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author/Year** | **Participants** | **Arrhythmia** | **Intervention** | **Cardioversion to SR** | **HR control** | **ICU LoS** | **Hospital LoS** | **Mortality** | **pAF/**  **PEAF** | **TE** | **Adverse events** |
| **Kakihanna (2020)**24 | 151 | Atrial fibrillation  Atrial flutter  SVT | Landiolol  Placebo | n/r | 41/76 (55%) a  25/75 (33%) a  Between grp difference 23.1% (95%CI 7.1-37.5; p=0.0031 | 14.6\* (8.6%)  13.3\* (9.1%)  p=0.55  \*ICU Free Days | 1.6\* (3.8%)  1.8\* (4.2%)  p=0.91  \*Hospital  Free  Days | 12%b  20%b  HR 0.59 (0.26-1.37) p=0.22  28d mortality | n/r | n/r | Hypotension:  Landiolol 9/77 (12%), Control 0/74(0%)  Delirium:  Landiolol 7/77 (9%), Control 3/74 (4%)  Constipation:  Landiolol 5/77 (6%), Control 3/74 (4%)  Diarrhoea:  Landiolol 5/77 (6%), Control 2/74 (3%)  Hypokalaemia:  Landiolol 5/77 (6%), Control 1/74 (1%)  Contact dermatitis:  Landiolol 4/77 (5%), Control 4/74 (5%)  Insomnia  Landiolol 2/77 (3%), Control 5/74 (7%)  Hypophosphatemia:  Landiolol 2/77 (3%), Control 3/74 (4%)  Erythema:  Landiolol 0, Control 3/74 (4%) |
| **Delle Karth (2001)**35 | 60 | Atrial fibrillation  Atrial flutter  Atrial tachycardia | Diltiazem  Amiodarone  Bolus only  Bolus+Infusion | 6/20 (30%) c  8/20 (40%) c  9/20 (45%) c  p=0.61 | 14/20 (70%) d  11/20 (55%) d  15/20 (75%) d  p=0.34 | n/r | n/r | 35%  35%  35%  In-hospital mortality | n/r | n/r | Bradycardiae:  Diltiazem 1 /20, Amiodarone 0/40  Hypotensionf:  Diltiazem 6/20  Amiodarone bolus only 0/20  Amiodarone bolus and infusion 1/20 |
| **Balser (1998)**45 | 64g | Atrial fibrillation  Atrial flutter  Unspecified SVT | Esmolol  Diltiazem | 2hr: 20/34 (59%)h  2hr: 10/30 (33%)h  p=0.049  12hr: 22/66 (85%)h  12hr: 16/26 (62%)h  p=0.067 | n/r | 8.4d +/-9.5d  10.6 +/- 13.4d | n/r | 31%  38%  In-hospital mortality | n/r | n/r | Hypotension:  Esmolol 2/34 (6%) Diltiazem 1/30 (3) |
| **Moran (1995)**46 | 42 | Atrial tachyarrhythmia (>1 hr) | Magnesium  Amiodarone | 18/21 (85.7%)  16/21 (76.1%) | n/r | n/r | n/r | n/r | n/r | n/r | n/r |
| Abbreviations: SR Sinus rhythm, HR Heart rate, ICU Intensive Care Unit, LoS Length of stay, pAF paroxysmal atrial fibrillation, PEAF permanent atrial fibrillation, TE thromboembolic events, SVT, Supraventricular tachycardia, n/r Not reported,  a HR control (defined as HR 60-94bpm after 24 hours)  b 28-day mortality. Mortality stratified by whether or not the primary outcome was met: Landiolol 9% (6/65) vs Placebo 24% (18.76) RR0.39 (95%CI 0.16-0.92)  c Cardioversion to SR at 4 hours  d HR reduction >30% of baseline for within a 4hr period and sustained for >4hr  e Hypotension defined as mean arterial blood pressure <60mmHg over 10 mins  f Bradycardia defined as HR <60 beats/min over 30 min  g 64 patients included in intention to treat analysis, 9 patients intolerant of intervention  h between 2hr and 12hr 40% of patients in both groups received Magnesium infusion that may impact upon cardioversion to SR rates. | | | | | | | | | | | |

| **Table 3. Primary outcomes of prospective and retrospective observational studies** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Author / Year** | **Number in Analysis** | **Type of Arrhythmia** | **Interventions / comparators** | **Primary Outcomes**  Cardioversion to SR  HR control (as per study definition) | **Key findings** |
| **Prospective Observational Studies** | | | | | |
| **Uchino (2020)**47 | 412 | Atrial fibrillation | Multiple/combinatione | Cardioversion to SR | Unable to disentangle individual treatment effect |
| **Meierhenrich (2010)**3 | 49 | Atrial fibrillation in sepsis | Multiple/combinatione | Cardioversion to SR | Unable to disentangle individual treatment effect |
| **Gerlach (2008)**48 | 61 | Atrial fibrillation  Atrial flutter  Atrial tachycardia | Diltiazem Amiodarone | Cardioversion to SR (within 24 hours) | Diltiazem 26/30 (86.7)  Amiodarone 27/31 (87.1%) |
| **Milicevic (2008)**49 | 140 | Atrial fibrillation | Amiodarone c  Propafenone | Cardioversion to SR (sequential administration of up to 3 anti-arrhythmic agents) | Amiodarone 16/17 (94.2%)  Propafenone 29/44 (65.9%) |
| **Sleeswijk (2008)**52 | 29 | Atrial fibrillation | Magnesium Amiodarone | Cardioversion to SR  HR control (defined as HR <110) | Magnesium 16/29 (55%)  Amiodarone 11/29 (38%)  Magnesium 9/29 (31%)  Amiodarone HR control not reported |
| **Hayashi (2008)**51 | 64 | Atrial fibrillation | DCCV | Cardioversion to SR | 37/64 (57.8%) |
| **Mayr (2003)**25 | 37 | Atrial fibrillation  SVT | DCCV | Cardioversion to SR | 11/37 (29.7% |
| **Hennersdorf (2002)**27 | 26 | Atrial fibrillation  Atrial flutter | Ibutilided | Cardioversion to SR (in <90min) | 21/26 (81%) |
| **Retrospective Observational Studies** | | | | | |
| **Betthauser (2019)**28 | 239 | Atrial fibrillation | Amiodarone | Does not report primary outcomes | No primary outcomes reported |
| **Herasevich (2019)**29 | 180 | Atrial fibrillation  Atrial flutter  Atrial tachycardia  SVT | Digoxin | Haemodynamic profile of Digoxin | 174/180 (96.6%) p<0.001 |
| **Kyo (2019)**53 | 85 | Atrial fibrillation | DCCV | Cardioversion to SR | 41/85 (48%) |
| **Milojevic (2019)**30 | 300 | Atrial fibrillation | Esmolol  Amiodarone | Cardioversion to SR (SR within 40min)  HR control (defined as HR <100 within 40 min) | Esmolol 44/100 (44%)  Amiodarone 36/200 (18%) p<0.01  Esmolol 64/100 (64%)  Amiodarone 50/200 (25%) p<0.01 |
| **Brown (2018)**31 | 33 | Atrial fibrillation | Multiple/combinatione | Cardioversion to SR (within 48 hours)  HR control (no definition of successful HR control) | Unable to disentangle individual treatment effect |
| **Yoshida (2018)**33 | 151 | Atrial fibrillation | Multiple/combinatione  DCCV n=3  Amiodarone n=10  Diltiazem n=30  Pilscainide n=79  Magnesium n=91 | Cardioversion to SR (within 6 hours) | DCCV: 2/3 p=1.0  Amiodarone: 3/10 p=0.03  β-blocker: 2/5 p=0.34  Diltiazem: 10/30 p=<0.001  Pilsicainide: 51/79 p=0.86  Magnesium, 59/91 p=0.86  Patients may have had multiple/combinations of interventions. Cardioversion success rates may reflect combinations of agents. |
| **Balik (2017)**32 | 234 | SVT | Amiodarone (n=151)  Propafenone (n=36)  Metoprolol (n=13) | Cardioversion to SR (within 24 hours) | 111/151 (74%) f  32/36 (88.9%) g  12/13 (92.3%) h |
| **Duby (2017)**34 | 191 | Atrial fibrillation | Multiple/combinatione | Does not report primary outcomes | Unable to disentangle individual treatment effect |
| **Liu (2016)**36 | 240 | Atrial fibrillation | Multiple/combinatione  DCCV n=8  Amiodarone n=88  Digoxin n=27  b-blocker n=88  CCB n=66 | Cardioversion to SR | DCCV: 4/8 (50%) p=0.25  Amiodarone: 52/80 p=0.38  Digoxin, 15/27 (55%) p=0.12  β-blocker, 67/88 (77%) p=0.06  CCB, 47/66 (28.5%) p=0.61  Patients may have had multiple/combinations of interventions. Cardioversion success rates may reflect combinations of agents. |
| **Mitric (2016)**37 | 186 | Atrial fibrillation | Amiodarone | Cardioversion to SR (within 12 hours) | 86/186 successful (49%) |
| **Walkey (2016)**54 | 39693 | Atrial fibrillation during sepsis | Multiple/combinatione | Does not report primary outcomes | No primary outcomes reported |
| **Okajima (2015)**39 | 61 | Atrial fibrillation  Atrial flutter  SVT | Landiolol n=39  Control n=22 | Cardioversion to SR  HR control not reported (no definition of successful HR control) | Landiolol: 27/39 (69.7%)  Control: 8/22 (36.4%) p<0.05 |
| **Xie (2015)**44 | 2586 | Atrial fibrillation | Amiodarone  Amiodarone (n=66)  β-antagonists (n=14)  CCB (n=7)  Digoxin (n=6) | Cardioversion to SR | 68/71 (95.8%)  Patients may have had multiple/combinations of intervention. Cardioversion success rates may reflect a combination of agents. |
| **Personett (2014)**40 | 121 | Atrial fibrillation  Atrial flutter | Diltiazem n=55  Metoprolol n=66 | HR control (defined as HR <110bpm) | Diltiazem: 42/55 (73%)  Metoprolol: 35/66 (53%) |
| **Kanji (2012)**41 | 348 | Atrial fibrillation | Multiple/combinatione  DCCV n=64  Amiodarone n=103  Sotalol n=2 | Cardioversion to SR at 24 and 72 hours  HR control not reported (no definition of successful HR control) | DCCV: 37/64 (50%)  Amiodarone: 66/103 (24hrs), 90/103 (72 hrs)  Sotalol: 2/2 (24hrs)  Patients may have had multiple/combinations of interventions. Cardioversion success rates may reflect combinations of agents. |
| **Delle Karth (2005)**42 | 17 | Atrial fibrillation  Atrial flutter | Ibutilide | Cardioversion to SR (within 60 min) | 14/17 (82.4%) |
| **Mayr (2004)**26 | 131i  70 i | SVT | Amiodarone | Cardioversion to SR  HR at 12, 24 and 48 hours (no definition of successful HR control) | 52/70 (74.3%)  137 +/- 26 (0hr)  91 +/- 17 (12hr)  91 +/- 18 (24hr)  86 +/- 16 (48hrs) |
| **Varriale (2000)**43 | 34 | Atrial Fibrillation  Atrial flutter | Ibutilide | Cardioversion to SR | 27/34 (79.4%) |
| Abbreviations:  SR Sinus rhythm, HR Heart rate, ICU Intensive Care Unit, LoS Length of stay, pAF paroxysmal atrial fibrillation, PEAF permanent atrial fibrillation, TE thromboembolic events, SVT, Supraventricular tachycardia, n/r Not reported, DCCV Direct current cardioversion  a 64 patients included in intention to treat analysis, 9 patients intolerant of intervention  b All patients were treated with Adenosine prior to Esmolol or Diltiazem  c Interventions included Propafenone, Amiodarone, etc only data for first administered agents (propafenone and amiodarone) have been extracted  d Ibutilide therapy following failure of Amiodarone therapy  e Patients may be treated with one or more antiarrhythmic agents  f 26 patients with PEAF received Amiodarone  g 6 patients with PEAF received Propafenone  h 2 patients with PEAF received Metoprolol  I Mayr et al included 131 cardiac and non-cardiac patients. Only data on non-cardiac patients were extracted n=70 | | | | | |