BJA

British Journal of Anaesthesia, 128 (5): 759–771 (2022)

doi: 10.1016/j.bja.2021.11.016
Advance Access Publication Date: 13 December 2021
Review Article

CARDIOVASCULAR

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

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Abstract

Background: 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.

Methods: Of 1782 studies, 30 were eligible for inclusion, including 4 RCTs and 26 observational studies. Efficacy of direct current cardioversion, amiodarone, β-adrenergic receptor antagonists, calcium channel blockers, digoxin, magnesium, and less commonly used agents such as ibutilide are reported.

Results: Cardioversion rates of 48% were reported for direct current cardioversion; however, re-initiation of NOAF was as high as 23.4%. Amiodarone was the most commonly reported intervention with cardioversion rates ranging from 18% to 96% followed by β-antagonists with cardioversion rates from 40% to 92%. Amiodarone was more effective than diltiazem (odds ratio [OR]=1.91, P=0.32) at cardioversion. Short-acting β-antagonists esmolol and landiolol were more effective compared with diltiazem for cardioversion (OR=3.55, P=0.04) and HR control (OR=3.2, P<0.001).

Conclusion: There was significant variation between studies with regard 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 studying the role of anti-coagulation in critically unwell patients are required. There is also an urgent need for a core outcome dataset for studies of new onset atrial fibrillation to allow comparisons between different anti-arrhythmic strategies.

Clinical trial registration: PROSPERO CRD42019121739.

Keywords: arrhythmia; atrial fibrillation; cardioversion; critical care; critically unwell patients; intensive care; new onset atrial fibrillation; systematic review

Received: 22 July 2021; **Accepted:** 9 November 2021

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Editor's key points

- New onset atrial fibrillation (NOAF) is the most common arrhythmia in critically unwell patients. It remains unclear whether clinicians should target rhythm or rate control, whether direct current cardioversion is more effective than drug treatment, and whether patients developing NOAF require anticoagulation.
- A review of the literature on the management of NOAF in critically unwell patients found a paucity of high-quality experimental evidence, and significant heterogeneity between studies.
- There is a need for development of a core clinical outcome set for use in future trials to allow comparison between interventions and patient-centred outcomes.

New onset atrial fibrillation (NOAF) is the most common arrhythmia encountered in critically unwell patients. NOAF complicates between 4% and 15% of all ICU admissions, and up to 40% of patients admitted with septic shock.[1–3] 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) after ICU discharge.[1–6]

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 UK, USA, and Europe respectively.[7–10] 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 HR, 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 with inflammation, electrolyte disturbances, and administration of vasopressors in critically unwell patients.[2,11,12] 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 patients.[11]

The risk *vs* benefit of each intervention may differ significantly in critically unwell patients compared with patients developing NOAF in the community. Administration of β-antagonists or calcium channel blockers (CCBs) 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. Although amiodarone infusion has been associated with hypotension that may exacerbate shocked patients admitted to ICU.[11,13,14] 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 anticoagulation.[15–17]

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 (EDs), 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 HR below 110 beats min^{-1}). Secondary objectives explored recurrence of AF and adverse events after treatment with antiarrhythmic agents or cardioversion, mortality associated with developing NOAF, and 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) statement.[19] 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), and the US National Institutes of Health Register (www.ClinicalTrials.gov) and the 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. The 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) and observational studies in critically ill patients who developed NOAF or paroxysmal AF and were treated with any combination of anti-arrhythmic, rate control medication, or direct current conversion *vs* placebo or standard care. New onset AF, including paroxysmal AF, defined as rhythm classification by continuous ECG monitoring or 12-lead ECG, were included.

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

Table 1 Eligibility criteria. NOAF is defined as atrial fibrillation (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. A+E, emergency department; AF, atrial fibrillation; AMU, acute medical unit; DCCV, direct current cardioversion; ESC, European Society of Cardiology; HDU, high dependency unit; NICE, National Institute of Health and Care Excellence; NOAF, new-onset atrial fibrillation.

Inclusion criteria (if all of the following conditions are met)	Exclusion criteria (if any of the following is 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 yr, 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	3. Insufficient information (e.g. study only available as a conference proceeding/abstract)
4. (a) 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 beats min^{-1}). (b) Secondary outcomes included: i. Development of permanent atrial fibrillation ii. Development of recurrent paroxysmal atrial fibrillation that terminates within 48 h as defined by the ESC[9] iii. Any thromboembolic events (such as stroke pulmonary embolism, deep vein thrombosis, left atrial thrombus) during critical care admission iv. Development of major bleeding events after administration of therapeutic anticoagulation as recommended in NICE guidelines[7] v. Any complication documented secondary to the intervention vi. Last reported mortality vii. ICU mortality viii. Length of stay in critical care and length of hospital stay	
5. RCT, quasi-RCT, and prospective or retrospective observational studies published in peer-reviewed journals	

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 after full-text review are reported in Supplementary Table S1. 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).

Data extraction

Two reviewers (BWJ and CSC) extracted data independently. The custom data extraction form generated in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) 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, CCBs, 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 because of 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) guidelines.[23]

We present primary and secondary outcomes for RCTs in Table 2. Owing to the variability and lack of reporting of

Table 2 Primary and secondary outcomes of randomised controlled trials. [†]HR control (defined as HR 60–94 beats min^{-1} after 24 h). [‡]The 28-day mortality was stratified by whether the primary outcome was met: landiolol 9% (6/65) *vs* placebo 24% (18.76), RR=0.39 (95% CI, 0.16–0.92). [¶]Cardioversion to SR at 4 h. [§]HR reduction >30% of baseline for within a 4-h period and sustained for >4 h. [‖]Hypotension defined as mean arterial blood pressure <60 mm Hg over 10 min. [#]Bradycardia defined as HR <60 beats min^{-1} over 30 min. [**]Sixty-four patients included in intention-to-treat analysis, with nine patients intolerant of intervention. [††]Between 2 and 12 h, 40% of patients in both groups received magnesium infusion that may impact upon cardioversion to SR rates. CI, confidence interval; LoS, length of stay; n/r, not reported; pAF, paroxysmal atrial fibrillation; PEAF, permanent atrial fibrillation; RR, relative risk; SR, sinus rhythm; SVT, supraventricular tachycardia; TE, thromboembolic events.

First author (year)	Participants	Arrhythmia	Intervention	Cardioversion to SR	HR control	ICU LoS	Hospital LoS	Mortality	pAF/ PEAF	TE	Adverse events
Kakihana (2020)[24]	151	Atrial fibrillation Atrial flutter SVT	Landiolol	n/r	41/76 (55%)[†]	14.6* (8.6%)	1.6* (3.8%)	12%[‡] 20%[‡]	n/r	n/r	Hypotension: Landiolol 9/77 (12%), Control 0/74(0%)
			Placebo		25/75 (33%)[†]	13.3* (9.1%)	1.8* (4.2%)	HR=0.59 (0.26–1.37)			Delirium: Landiolol 7/77 (9%), Control 3/74 (4%)
					Between-group difference 23.1% (95% CI, 7.1–37.5; P=0.0031	P=0.55 *ICU-free days	P=0.91 *Hospital-free days	P=0.22 28-day mortality			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)[14]	60	Atrial fibrillation Atrial flutter	Diltiazem Amiodarone:	6/20 (30%)[¶] 8/20 (40%)[¶]	14/20 (70%)[§] 11/20 (55%)[§]	n/r	n/r	35%	n/r	n/r	Bradycardia[‖]: Diltiazem 1/20, Amiodarone 0/40
		Atrial tachycardia	Bolus only					35%			Hypotension[#]: Diltiazem 6/20
			Bolus+Infusion	9/20 (45%)[¶] P=0.61	15/20 (75%)[§] P=0.34			35% In-hospital mortality			Amiodarone bolus only 0/20 Amiodarone bolus and infusion 1/20
Balser (1998)[25]	64**	Atrial fibrillation Atrial flutter Unspecified SVT	Esmolol Diltiazem	2 h: 20/34 (59%)[††] 2 h: 10/30 (33%)[††] P=0.049 12 h: 22/66 (85%)[††] 12 h: 16/26 (62%)[††] P=0.067	n/r	8.4 (9.5) days 10.6 (13.4) days	n/r	31% 38% In-hospital mortality	n/r	n/r	Hypotension: Esmolol 2/34 (6%) Diltiazem 1/30 (3)
Moran (1995)[26]	42	Atrial tachyarrhythmia (>1 h)	Magnesium Amiodarone	18/21 (85.7%) 16/21 (76.1%)	n/r	n/r	n/r	n/r	n/r	n/r	n/r

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 Table S2. The study and patient characteristics are reported in two tables ordered by study design and date of publication (Supplementary Tables S3 and S4). Achieving rate control, rhythm control, or both 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 permitted 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, we 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 (Fig 1). After title and abstract screening, 139 studies progressed to full text screening, of which 30 studies met the eligibility criteria and were included in the review.[3,24–35,37–44,46–51]

Study characteristics

Study characteristics are presented in Supplementary Table S3. Of the 30 studies included, four were RCTs (n=317 participants),[14,24–26] eight were prospective observational studies (n=818 participants),[3,27–33] and 18 were retrospective observational studies (n=12 814 participants).[34,35,37–43,45–51]

Nineteen of the 30 studies were conducted in mixed medical/surgical ICU settings.[24,27,30,31,33–36,39,41,43–48,50–52] Medical ICUs accounted for five studies,[14,26,29,42] of which two included cardiology patients.[29,49] Surgical ICU settings accounted for five studies.[3,25,28,32,38] One study was conducted on a mobile ICU in France, that primarily treated patients with life-threatening NOAF.[37]

Age, sex, comorbidities and illness severity scores of patients included in studies are presented in Supplementary Table S4. Co-morbidities were reported in 23 of 30 studies.[3,14,24,25,27–29,31–33,36,38,39,42–49,51] 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),[14,29,30,34,37,39,40,42–44,46,48,50] β-antagonists (nine studies),[24,25,39,40,42,44,45,47,48] and CCBs (seven studies).[14,25,28,39,42,44,47] Fewer studies reported outcomes for digoxin (three studies),[35,42,44] magnesium (three studies),[26,30,39] propafenone (two studies),[29,40] nifekalant (one study),[31] pilsicainide (one study),[39] and ibutilide (two studies).[49,51] DCCV was reported in six studies,[31,32,36,39,42,48] and four studies reported a combination of interventions.[3,27,38,41] We report the outcomes of these studies in Supplementary Table S2 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 Supplementary Table S2. Overall information regarding drugs and dosing were poorly reported. There was variability in reporting of 24 h 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[14,25–33,38–40,42,43,45,46,48–51] however the time point at which cardioversion was recorded varied between 40 min and within 72 h.[29 48] Outcomes for HR control was reported by 11 studies; however, seven studies did not define successful HR control,[25,26,35,38,45,50,53] and only two studies defined HR control as <110 beats min^{-1} as per our protocol.[30 47] Other definitions for HR control included less than 100 beats min^{-1},[29] between 69 and 94 beats min^{-1},[24] >20% reduction in baseline HR,[24] and >30% reduction in baseline HR.[14] Secondary outcomes of interest were poorly reported overall; mortality was reported by 16 studies.[3,14,24,25,27,35,36,38–42,44,46–48] Mortality was most commonly reported between patients that cardioverted to SR *vs* 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 length of stay (LoS), hospital LoS, or both was reported by 13 studies.[25,27,28,34–36,40–43,47,49,50] Studies reporting use of anticoagulation lacked information regarding dose, route, or type of anticoagulation used.[14,27,29,33,39,44,48,51]

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 participants,[14,24] three as unclear in terms of risk of bias from randomisation,[14,25,26] and all studies as unclear in terms of risk of allocation concealment[14,24–26] (Supplementary Table S5). Of the 26 observational studies, we judged 13 as having an NOS score greater than or equal to 7 (absence of substantial bias)[3,27,29,31,34,37,40,42–44,46,48,50] (Supplementary Table S6).

Primary study outcomes by intervention

DCCV — cardioversion to sinus rhythm

Six observational studies reported outcomes for DCCV.[31,32,36,39,42,48] The effectiveness of DCCV in achieving immediate cardioversion to sinus rhythm ranged from 41/85 patients (48%) to 37/37 patients (100%).[32,36] Despite high rates of cardioversion, re-initiation of NOAF was common, with Kanji and colleagues[48] reporting recurrence of NOAF in 4/26 patients (15.4%) by 24 h and Mayr and colleagues[32] reporting recurrence of NOAF in 6/37 patients (16.2%) by 24 h. Hayashi and colleagues[31] investigated the use of nifekalant after an unsuccessful DCCV and reported a DCCV failure rate of 27/64 patients (42.2%%) before nifekalant: 12/64 (18.7%) attributed to failure of initial DCCV and 15/64 (23.4%) owing to re-initiation of NOAF.

Amiodarone — cardioversion to sinus rhythm

Two RCTs reported the use of amiodarone.[14,26] Delle Karth and colleagues[14] reported a non-significant difference favouring

Table 3 Primary outcomes of prospective and retrospective observational studies. *Patients may be treated with one or more anti-arrhythmic agents. †Interventions included propafenone and amiodarone; only data for first administered agents (propafenone and amiodarone) have been extracted. ‡Ibutilide therapy after failure of amiodarone therapy. ¶Twenty-six patients with PEAF received amiodarone. §Six patients with PEAF received propafenone. ‖Two patients with PEAF received metoprolol. **Mayr and colleagues included 131 cardiac and non-cardiac patients. Only data on noncardiac patients were extracted n=70. DCCV, direct current cardioversion; LoS, length of stay; n/r, not reported; pAF, paroxysmal atrial fibrillation; PEAF, permanent atrial fibrillation; SR, sinus rhythm; SVT, supraventricular tachycardia; TE, thromboembolic events.

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)[27]	412	Atrial fibrillation	Multiple/ combination*	Cardioversion to SR	Unable to disentangle individual treatment effect
Meierhenrich (2010)[3]	49	Atrial fibrillation in sepsis	Multiple/ combination*	Cardioversion to SR	Unable to disentangle individual treatment effect
Gerlach (2008)[28]	61	Atrial fibrillation Atrial flutter Atrial tachycardia	Diltiazem Amiodarone	Cardioversion to SR (within 24 h)	Diltiazem 26/30 (86.7) Amiodarone 27/31 (87.1%)
Milicevic (2008)[29]	140	Atrial fibrillation	Amiodarone† 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)[30]	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)[31]	64	Atrial fibrillation	DCCV	Cardioversion to SR	37/64 (57.8%)
Mayr (2003)[32]	37	Atrial fibrillation SVT	DCCV	Cardioversion to SR	11/37 (29.7%
Hennersdorf (2002)[33]	26	Atrial fibrillation Atrial flutter	Ibutilide‡	Cardioversion to SR (in <90 min)	21/26 (81%)
Retrospective observational studies					
Betthauser (2019)[34]	239	Atrial fibrillation	Amiodarone	Does not report primary outcomes	No primary outcomes reported
Herasevich (2019)[35]	180	Atrial fibrillation Atrial flutter Atrial tachycardia SVT	Digoxin	Haemodynamic profile of digoxin	174/180 (96.6%), P<0.001
Kyo (2019)[36]	85	Atrial fibrillation	DCCV	Cardioversion to SR	41/85 (48%)
Milojevic (2019)[37]	300	Atrial fibrillation	Esmolol Amiodarone	Cardioversion to SR (SR within 40 min) 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)[38]	33	Atrial fibrillation	Multiple/ combination*	Cardioversion to SR (within 48 h) HR control (no definition of successful HR control)	Unable to disentangle individual treatment effect

Continued

Table 3 Continued

Author (year)	Number in analysis	Type of arrhythmia	Interventions/ comparators	Primary outcomes Cardioversion to SR HR control (as per study definition)	Key findings
Yoshida (2018)[39]	151	Atrial fibrillation	Multiple/ combination* DCCV, *n*=3 Amiodarone, *n*=10 Diltiazem, *n*=30 Pilscainide, *n*=79 Magnesium, *n*=91	Cardioversion to SR (within 6 h)	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)[40]	234	SVT	Amiodarone (*n*=151) Propafenone (*n*=36) Metoprolol (*n*=13)	Cardioversion to SR (within 24 h)	111/151 (74%)¶ 32/36 (88.9%)§ 12/13 (92.3%)‖
Duby (2017)[41]	191	Atrial fibrillation	Multiple/ combination*	Does not report primary outcomes	Unable to disentangle individual treatment effect
Liu (2016)[42]	240	Atrial fibrillation	Multiple/ combination* DCCV, *n*=8 Amiodarone, *n*=88 Digoxin, *n*=27 β-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)[43]	186	Atrial fibrillation	Amiodarone	Cardioversion to SR (within 12 h)	86/186 successful (49%)
Walkey (2016)[44]	39 693	Atrial fibrillation during sepsis	Multiple/ combination*	Does not report primary outcomes	No primary outcomes reported
Okajima (2015)[45]	61	Atrial fibrillation Atrial flutter SVT	Landiolol, *n*=9 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

Continued

Table 3 Continued

Author (year)	Number in analysis	Type of arrhythmia	Interventions/ comparators	Primary outcomes Cardioversion to SR HR control (as per study definition)	Key findings
Xie (2015)[46]	2586	Atrial fibrillation	Amiodarone Amiodarone (*n*=66) β-Antagonists (*n*=14) CCBs (*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)[47]	121	Atrial fibrillation Atrial flutter	Diltiazem *n*=55 Metoprolol *n*=66	HR control (defined as HR <110 beats min^{-1})	Diltiazem: 42/55 (73%) Metoprolol: 35/66 (53%)
Kanji (2012)[48]	348	Atrial fibrillation	Multiple/ combination* DCCV, *n*=64 Amiodarone, *n*=103 Sotalol, *n*=2	Cardioversion to SR at 24 and 72 h HR control not reported (no definition of successful HR control)	DCCV: 37/64 (50%) Amiodarone: 66/ 103 (24 h), 90/103 (72 h) Sotalol: 2/2 (24 h) Patients may have had multiple/ combinations of interventions. Cardioversion success rates may reflect combinations of agents.
Delle Karth (2005)[49]	17	Atrial fibrillation Atrial flutter	Ibutilide	Cardioversion to SR (within 60 min)	14/17 (82.4%)
Mayr (2004)[50]	131** 70**	SVT	Amiodarone	Cardioversion to SR HR at 12, 24, and 48 h (no definition of successful HR control)	52/70 (74.3%) 137 (26) (0 h) 91 (17) (12 h) 91 (18) (24 h) 86 (16) (48 h)
Varriale (2000)[51]	34	Atrial fibrillation Atrial flutter	Ibutilide	Cardioversion to SR	27/34 (79.4%)

amiodarone bolus followed by infusion compared with 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. Conversely, Moran and colleagues[26] 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] Neither study reported data on mortality or LoS.

Cardioversion to SR was reported in 11 observational studies.[28–30,37,39,43,46–48,50] Outcome reporting time differed significantly between studies and ranged from 40 min to 72 h.[37,48] Success rates of cardioversion to SR ranged from 18% at 40 min after infusion[37] to 94.2%.[29] Amiodarone appeared as effective as diltiazem at cardioversion (87.1% *vs* 86.7%)[28] in one study. Sleeswijk and colleagues[30] reported that magnesium may be more effective than amiodarone (55% *vs* 38%), whereas Milojevic and colleagues[37] reported the superiority of esmolol compared with amiodarone (18% *vs* 44%). Three observational studies that investigated amiodarone reported outcomes for multiple or combinations of treatments.[39,42,48] In these studies, it was not possible to disentangle which antiarrhythmic agent was responsible for the observed effect (Supplementary Table S6).[39,42,48]

Amiodarone — HR control

In an RCT comparing diltiazem and amiodarone, Delle Karth and colleagues[14] defined HR control, as >30% HR reduction within 4 h sustained for 4 h 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 with amiodarone bolus alone or diltiazem (15/20 *vs* 14/20; OR=1.29; 95% CI, 0.32–5.17; *P*=0.72.

Three observational studies reported HR control with amiodarone as an outcome.[29,30,50] Milojevic and colleagues[37] reported that amiodarone bolus plus infusion achieved a HR of <100 beats min^{-1} in only 50/200 (25%) of patients with the primary endpoint of HR control at 40 min.[30] Esmolol performed better than amiodarone, successfully achieving HR control (<100 beats min^{-1}) in 64/100 (64%) patients at 40 min after infusion.[37] Magnesium led to a decrease in HR <110 in 9/29 (31%) of patients,[30] whereas continuous amiodarone infusion resulted in a decrease in HR from 137 (26) to 91 (17) beats min^{-1} by 12 h with a lower HR being sustained for 48 h.[50]

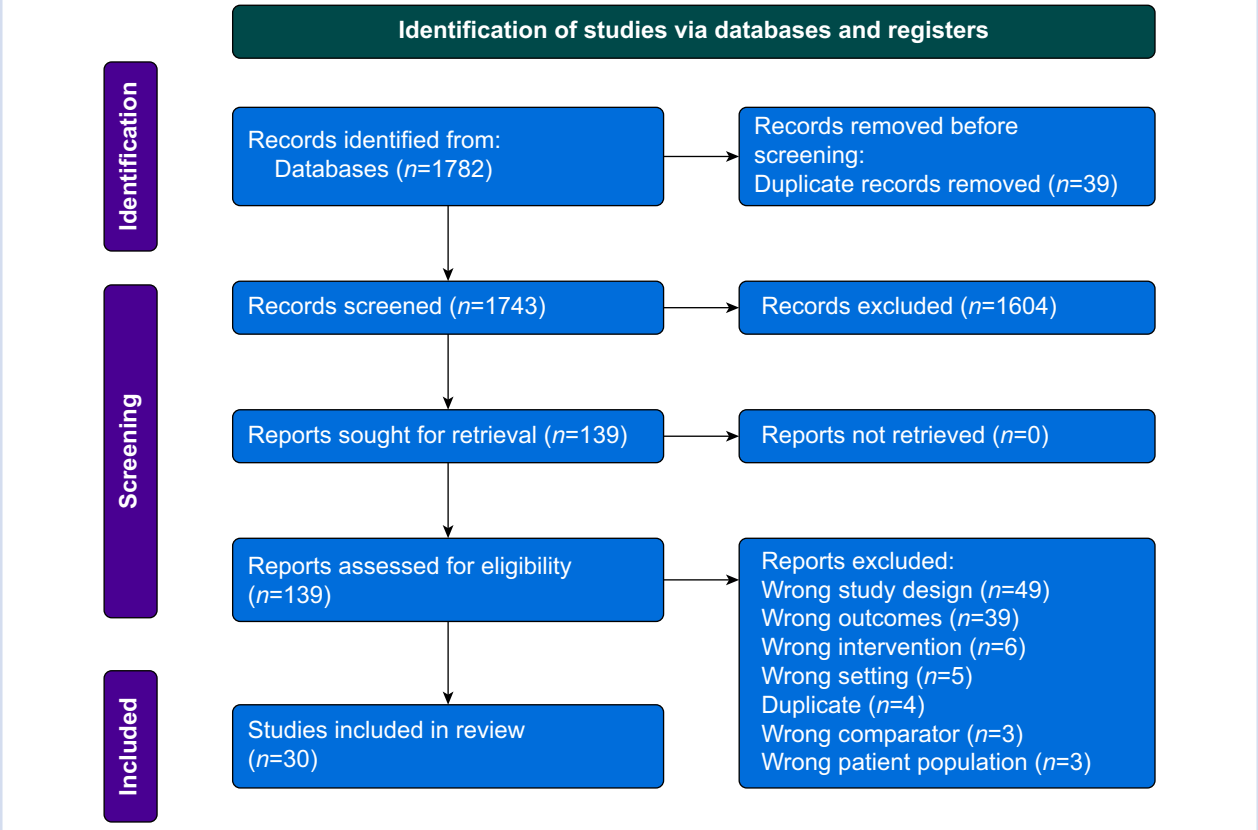


Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart of search results. From Page and colleagues.[19]

β-Adrenergic antagonists — cardioversion to sinus rhythm

Ten studies reported outcomes for β-antagonists. Two RCTs reported outcomes for short-acting β-antagonists, esmolol and landiolol.[24,25] Four observational studies reported outcomes for β-antagonists including metoprolol, landiolol, and sotalol.[37,40,45,47] Two observational studies report outcomes for β-antagonists but failed to specify individual agents.[39,42,46,48]

Balser and colleagues[25] 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 and 12 h (22/26 [85%] *vs* 16/26 [62%]). However, Balser and colleagues[25] noted that between 2 and 12 h, 11/26 (42%) of patients also received treatment with magnesium, and 6/26 (23%) patients received treatment with digoxin and esmolol, making it difficult to determine the true efficacy of esmolol.[25]

Landiolol, metoprolol, and esmolol were investigated in observational studies. Okajima and colleagues[45] reported a significant difference in rates of cardioversion to SR at 24 h between landiolol and control (27/39 [69.7%] *vs* 8/22 [36.4%], *P*=0.05). Balik and colleagues[40] compared cardioversion rates at 24 h between amiodarone, propafenone, and metoprolol. Cardioversion rates for metoprolol were 12/13 (92.3%) compared with 111/151 (73.5%) for amiodarone and 32/36 (88.9%) for propafenone.[40] Milojevic and colleagues[37] reported a significant difference in rates of cardioversion to SR between esmolol and amiodarone (44/100 [44%] *vs* 36/200 [18%], *P*<0.01). However, Milojevic and colleagues[37] reported cardioversion to SR at shortly after commencement of treatment at 40 min.

Yoshida and colleagues,[39] Liu and colleagues,[42] Xie and colleagues,[46] and Kanji and colleagues[48] reported outcomes for cardioversion to sinus rhythm for β-antagonists but did not specify agents. The efficacy at achieving sinus rhythm ranged from 2/5 (40%) to 67/88 (77%).

β-Adrenergic antagonists — HR control

Kakihana and colleagues[24] compared landiolol with placebo and found a significant difference for HR control, defined as achieving a HR of 60–94 beats min^{-1} (41/76 [55%] *vs* 25/75 [33%], *P*<0.003) (OR=3.2; 95% CI, 1.66–6.31; *P*=0.0005). Kakihana and colleagues[24] did not report any outcomes with regard to cardioversion to sinus rhythm.

Personett and colleagues[47] compared achievement of HR control (defined as HR <110 beats min^{-1}), between metoprolol and diltiazem and reported that metoprolol achieved HR control in 35/66 (53%) of patients compared with 42/55 (72%) for diltiazem. However, 22/66 patients continued another unspecified β-antagonist (26/66), 3/66 continued a CCB (3/66), and 6/66 continued another non-specified anti-arrhythmic agent (6/66).[47]

Magnesium — cardioversion to sinus rhythm

Moran and colleagues[26] in an 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). Sleeswijk and colleagues[30] reported similar results, with magnesium achieving sinus rhythm in 11/29

(37.9%) compared with 7/29 (24.1%) for amiodarone. In another observational study, the efficacy of cardioversion with magnesium was 59/91 (30.9%), although this study reported combinations of anti-arrhythmic medications.[39]

Magnesium — HR control

Sleeswijk and colleagues[30] reported that magnesium was effective in 9/29 (31%) at achieving a HR <110 beats min^{-1}. No other studies investigating magnesium reported outcomes for control of HR.

Calcium channel blockers — cardioversion to sinus rhythm

Studies of CCB reported primary outcomes of interest in seven studies.[14,25,28,39,42,46,47] Balser and colleagues[25] and Delle Karth and colleagues[14] compared diltiazem with esmolol and amiodarone, respectively. Rates of cardioversion to SR are reported above.

Two observational studies compared diltiazem with amiodarone or metoprolol respectively.[28,47] Gerlach and colleagues[28] reported similar efficacy between amiodarone and diltiazem at achieving cardioversion to SR (26/30 [86.7%] *vs* 27/31 [87.1]).

Liu and colleagues and Yoshida and colleagues[39] 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 medications.

Calcium channel blockers — HR control

Few studies report rates of HR control for CCBs, Delle Karth and colleagues,[14] in an RCT, reported a non-significant difference between diltiazem and amiodarone as reported above.

In observational studies, diltiazem was more effective than metoprolol at achieving HR control, defined as HR <110 beats min^{-1} (42/55 [73%] *vs* 35/66 [53%]).[47]

Digoxin

Three observational studies reported outcomes for digoxin.[35,42,44] Only Liu and colleagues[42] reported outcomes for rates of cardioversion to SR with an efficacy of 15/27 (55.6%). Digoxin appeared more effective at achieving HR control, defined as a HR <100 beats min^{-1}, in 174/180 (96.6%) of patients after 250—500 μg bolus of digoxin in septic patients with NOAF.[35]

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 CCBs. We also presented findings for less commonly used agents such as ibutilide, nifekalant, propafenone, and pilsicainide, and studies reporting combinations of treatment. Thirty studies met the eligibility criteria including a further two RCTs and 15 observational studies published since the most recent systematic reviews by O'Bryan and colleagues[54] and Yoshida and colleagues,[39] respectively. 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.[24,45]

Heart rhythm control using direct current 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 before 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 and colleagues[36] reported that potassium levels greater than 3.8 mmol L^{-1} impacted upon the success of DCCV, and four DCCV studies reported potassium levels within the range of 3.5—4.2 mmol L^{-1} before attempting DCCV.[31,32,42,48] However, none of these studies addressed whether potassium levels impacted upon the success of DCCV as a primary or secondary outcome.[31,32,42,48]

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 four RCTs. Amiodarone was the most commonly used agent with success rates ranging from 18% to 94%.[29,37] Time to restoration of sinus rhythm with amiodarone was poorly reported but ranged from 4 to 72 h, and amiodarone bolus followed by continuous infusion appeared to be more effective.[14,30,48] Similar rates of cardioversion were reported for magnesium, β-antagonists, CCBs, and digoxin. Magnesium decreases cardiac automaticity and prolongs atrioventricular node delay without significant side-effects such as hypotension, which is commonly observed after administration of agents such as beta-antagonists, CCBs, and amiodarone.[11] Of note, Sleeswijk and colleagues[30] added amiodarone to treatment in patients who failed to respond to magnesium alone to achieve cardioversion in a further 38% of patients at a median of 4 h (2—78). 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.[55]

Two RCTs compared rates of cardioversion between diltiazem and esmolol or amiodarone, respectively.[14 25] 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%).[37]

Heart rate control

There was significant heterogeneity in the definition of HR control between studies (Table 2). A number of studies reported HR before and after pharmacological treatment but without HR control being a defined outcome.[25,26,35,38,45] Two observational studies reported HR before and after cardioversion as a combined outcome measure.[38,45]

Amiodarone and diltiazem were effective in achieving a HR reduction of >30% of baseline HR.[14] Diltiazem (73%) appeared more effective compared with metoprolol (53%) in achieving a HR reduction to <110 beats min^{-1} in one observational study.[47]

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.[24,28,30,37] Mayr and colleagues[50] investigated HRs before and after high-dose amiodarone infusion, and reported that amiodarone was effective at lowering HR even in patients who failed cardioversion into sinus rhythm. Digoxin was equally effective at achieving HR control (<110 beats min^{-1}) in septic patients admitted to the ICU with success rates of up to 96.6% within 12 h and provided good haemodynamic stability.[35]

The initial management goals in the treatment of NOAF depend upon whether the deleterious effects of NOAF are attributable to high HR, 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 HR or rhythm control, mainly because of significant variation in definition of HR 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 with other agents.[56] 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.[57] Coupled with a favourable safety profile and minimal impact upon blood pressure landiolol may offer an advantage over other β-antagonists at controlling HR.[24,45]

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 (Grading of Recommendations Assessment, Development, and Evaluation) domains such as inconsistency and imprecision was hindered by under-reporting of precision estimates such as 95% CI in the studies published. Despite the extensive systematic literature review, we were unable to define the superiority of any anti-arrhythmic for rhythm or rate control in NOAF. Our review was limited by the lack of high-quality RCTs assessing the impact of therapeutic interventions *vs* 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). Although it is established that achieving cardioversion or rate control conveys a mortality advantage, few studies reported mortality or LoS 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 HR control boundaries and conversion into sinus rhythm need to be clearly defined, taking into account the time interval until rate control, rhythm control, or both is achieved and 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.

Conclusions

In this review we are unable to distinguish a hierarchy of effectiveness between direct current cardioversion, amiodarone, β-antagonists, calcium channel blockers, and magnesium at achieving cardioversion to sinus rythm or heart rate control in NOAF. There is a paucity of high-quality RCT evidence for direct current cardioversion in the management of NOAF. Despite initially high success rates of conversion to sinus rythm with direct current cardioversion 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 because of 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.

Authors' 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

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.11.016.

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Handling editor: Jonathan Hardman