A Systematic Review of Anticoagulation Strategies for Patients With Atrial Fibrillation in Critical Care.

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Abstract

Background. Atrial fibrillation (AF) is the most common cardiac arrhythmia in critically ill patients. There is a paucity of data assessing the impact of anticoagulation strategies on clinical outcomes for general critical care patients with AF. Our aim was to assess the existing literature to evaluate the effectiveness of anticoagulation strategies used in critical care for AF.

Methodology. A systematic literature search was conducted using MEDLINE, EMBASE, CENTRAL and PubMed databases. Studies reporting anticoagulation strategies for AF in adults admitted to a general critical care setting were assessed for inclusion.

Results. Four studies were selected for data extraction. A total of 44087 patients were identified with AF, of which 17.8-49.4% received anticoagulation. The reported incidence of thromboembolic events was 0-1.4% for anticoagulated patients, and 0-1.3% in non-anticoagulated patients. Major bleeding events were reported in three studies and occurred in 7.2-8.6% of the anticoagulated patients and in up to 7.1% of the non-anticoagulated patients.

Conclusions. There was an increased incidence of major bleeding events in anticoagulated patients with AF in critical care compared to non-anticoagulated patients. There was no significant difference in the incidence of reported thromboembolic events within studies between patients who did and did not receive anticoagulation. However, the outcomes reported within studies were not standardised, therefore, the generalisability of our results to the general critical care population remains unclear. Further data is required to facilitate an evidence-based assessment of the risks and benefits of anticoagulation for critically ill patients with AF.

Keywords: Atrial fibrillation, anticoagulation, critical care, intensive care, new-onset atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrythmia in the critical care population[1,2]. Nearly one third of patients admitted to critical care have a diagnosis of pre-existing atrial fibrillation (PEAF) or develop new-onset atrial fibrillation (NOAF) during their admission[1]. AF can result in rapid ventricular rates, leading to decreased cardiac output and haemodynamic compromise which may acutely decompensate already unstable critically ill patients[1,3]. Reduced blood velocity in the left atrium, as a result of inefficient atrial systole, predisposes patients with AF to cardiac and systemic emboli, which can cause a significant disease burden both in critical care and long term[4,5]. AF in the critical care setting is associated with a two to fivefold increased risk of mortality, and a twofold increased risk of stroke[1,6].

In addition to well-known risk factors for AF, such as advancing age, hypertension, ischaemic heart disease, heart failure and valvular disease, there are specific factors related to critical illness that predispose patients to the development of NOAF[1,2]. These factors include electrolyte abnormalities, hypoxaemia, adrenergic overstimulation, progressive autonomic dysfunction, acute systemic inflammation, sepsis and shock[1,2]. Changes in autonomic activity, resulting from vasopressor administration and electrolyte disturbances, can lead to increased atrial ectopic impulses and subsequent NOAF[3].

Chronic comorbid conditions associated with AF, such as hypertension, ischaemic heart disease and pulmonary diseases are common in patients admitted to critical care[7]. Furthermore, critical illness predominantly affects adults above the age of 65 years which matches the age-related risk for developing AF in the general population[8].

Oral anticoagulation for thromboembolism prophylaxis is a key component of managing AF in the general population, however, no specific guidelines currently exist for the use of

anticoagulation in the critical care setting[9]. Internationally, clinicians are guided in the management of AF by recommendations from the National Institute for Health and Care Excellence (NICE), the European Cardiology Society and the American Heart Association [10-12]. With regard to anticoagulation for NOAF; these guidelines recommend the use of validated tools to assess thromboembolic risk (e.g. CHA_2DS_2-VASc) and bleeding risk (HAS-BLED) to stratify patients that may benefit from systemic anticoagulation through prevention of thromboembolic events such as stroke[10]. However, the risk-benefit tools used to aid decision making about anticoagulation, including CHA_2DS_2-VASc and HAS-BLED, have not been validated in critical care populations[13]. A recent retrospective study showed that CHA2DS2-VASc and HAS-BLED scores were not associated with stroke or major bleeding and were unable to predict these events [14]. Therefore, decisions around anticoagulation strategies in critical care populations are complex and challenging. There are currently no recommendations relating specifically to the rational therapy of AF in the critical care setting[13,15]. Critically ill patients may be at increased risk of bleeding, whilst simultaneously being hypercoagulable due to the abnormal haemostasis that is associated with critical illness[13]. In critically ill patients thrombocytopenia is seen in is up to 44% of patients and is associated with a four- to fivefold increased risk of bleeding[16]. Other factors contributing to this acquired coagulopathy include severe sepsis, disseminated intravascular coagulation, prolonged global coagulation times and reduced levels of coagulation inhibitors[16]. Additionally, critically ill patients are at a greater risk of thromboembolism due to immobilisation, inflammation, mechanical ventilation and dehydration[17,18]. Furthermore, the potential need for urgent procedures and invasive devices, such as arterial lines and central venous catheters, poses an additional challenge in effectively anticoagulating these patients and must be considered when making anticoagulation decisions[19]. Major bleeding occurs in over 5%

of critically ill patients and is associated with a higher risk of in-hospital death. As a consequence, thromboembolic prophylaxis for AF in critical care cannot be managed in the same way as in non-critically ill patients[20]. Hence, further research is required to facilitate the development of management guidelines for AF in the critical care setting.

There is a paucity of data assessing the impact of different anticoagulation strategies on clinical outcomes for general critical care patients with AF, both NOAF and PEAF[21]. A nationwide survey of intensive care clinicians revealed that 63.0% of clinicians would not routinely anticoagulate critically ill patients with NOAF, while 30.8% would consider anticoagulation if NOAF persisted beyond 72 hours, rather than the 48 hours recommended by guidelines[9,12,22]. Despite international guidance, a large variation in practice exists between critical care clinicians, representing the unique challenges of managing AF in critically unwell patients[11,12,22]. A consensus on an effective anticoagulation strategy for AF has therefore not yet been reached, with current practice largely based on observational studies and expert opinion[3]. This systematic review is designed to evaluate the effectiveness of anticoagulation strategies for AF in the critical care setting.

Methods

Protocol and registration

This systematic review was conducted in accordance with The Cochrane Collaboration principles of Systematic Reviews and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[23,24]. The protocol for this systematic review is registered with the International Prospective Register of Systematic

Reviews (PROSPERO) database (registration number: CRD42020158237). A full publication of this protocol is available[25] (PMID: 33082186, doi:10.1136/ bmjopen-2020-037591).

Eligibility criteria

All quantitative studies reporting anticoagulation strategies for AF in adults (>18 years) admitted to a general critical care unit or high dependency unit were assessed for inclusion. Study selection was unrestricted by language. Non-randomised, randomised, prospective and retrospective studies were eligible for inclusion, however, qualitative studies, case studies, editorials, letters, practice guidelines, grey literature, abstract only reports, reviews and commentaries were excluded. In order to comparatively assess the outcome measures, included studies had both an anticoagulated and a non-anticoagulated group of patients with AF in critical care. Studies including patients that had undergone cardiothoracic surgery were excluded, as were studies based in service-specific intensive care units (ICU) (such as coronary care units, surgical ICUs and paediatric ICUs), acute medical units and emergency departments. Studies including patients who had been commenced on anticoagulation for a reason other than AF or had an inherited or pre-existing bleeding or clotting disorder who could not be disentangled from the entire cohort were also excluded.

Data sources and search strategy

A comprehensive broad literature search was conducted with the assistance of a health information specialist. Databases were accessed via NICE Healthcare Database Advanced Search (HDAS) using OpenAthens in October 2019. Studies were identified by searching Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica

database (EMBASE), the Cochrane Central Register of Controlled Trials (CENTRAL) and PubMed. A full description of the search strategy used in HDAS is included (Supplementary Table 1).

Data extraction and study selection

The results of studies identified from the search strategy were exported to Endnote X9 (Clarivate analytics) and any duplicates were removed (AN). All citations were then imported into the Covidence systematic review platform (Veritas Health Innovation, Melbourne, Australia). Two reviewers (AN and GL) independently screened the titles and abstracts of the identified studies from the search strategy and any potentially relevant studies were then screened against inclusion and exclusion criteria. Reference lists of included studies were screened to identify any other eligible studies and authors were contacted if clarification regarding the data and/or methodology was required. Any discrepancies or conflicts in this screening process were resolved by discussion and subsequent input from a third senior reviewer (BWJ). Data was extracted independently by one researcher (AN) and reviewed by a second researcher (GL). The following information was extracted from studies: 1) study characteristic, including title, authors, journal, publication date; 2) study design and methodology, including study type, study period and number of participants; 3) population characteristics: age, sex, setting, patient comorbidities, number of patients with AF; 4) recruitment procedures; and 5) the outcome measures and reported findings in each study. The extracted data was documented in a series of study tables for analysis.

Outcome measures

The primary outcome measures were the percentage of patients anticoagulated for treatment of AF in a critical care setting and the anticoagulation strategy they received. Secondary outcome measures included the incidence of any thromboembolic events (defined as stroke, transient ischaemic attacks (TIAs), mesenteric ischaemia, acute limb ischaemia and pulmonary embolism) during critical care admission; the development of a major bleeding event (defined by the included study); length of stay (LOS) on ICU; and mortality on ICU, mortality at 28 days, 90 days and 365 days post discharge to identify both short and long term mortality. Other data abstracted included the use of any risk stratification scores for anticoagulation such as CHA_2DS_2-VASc and HAS-BLED, and risk stratification scores for critical illness such as APACHE II or SOFA.

Assessment of bias

Risk of bias in the identified studies was assessed using a modified Newcastle-Ottawa Scale (NOS), a scoring system for non-randomised trials[26]. The NOS is used to assess a study on three broad perspectives: the selection of the study groups; the comparability of groups; and the ascertainment of the outcome of interest. Although we did not identify any randomised controlled trials, we had planned to use the revised Cochrane Collaborations Risk of Bias (RoB2) tool to assess bias in those studies[25], using the criteria outlined in the Cochrane Handbook of Systematic Reviews of Invention[27].

Results

Study identification

Our literature search identified 1119 studies, of which 1081 were excluded following title and abstract screening. Full text review was undertaken for the 38 remaining studies and a further 34 studies were excluded. Four studies were progressed for data abstraction. We did not undertake meta-analysis due to the limited number of studies and their heterogeneity, which would have made statistical comparisons unmeaningful. As such, the results are presented as a narrative synthesis of the available data. Figure 1 represents a flowchart of the study identification process including the reasons for exclusion after full text review.

Study characteristics

One prospective and three retrospective observational studies were included in our review (Table 1); the respective patient population sizes of each study were 115[21], 325[15], 38582[28] and 57110[29] (Table 2). We contacted all authors for clarification of individual methodology and outcomes of their study, particularly mortality at 30 and 365 days, illness severity scores, and type of therapeutic anticoagulants used. However, no additional data could be made available for further analysis. We included one study, by Walkey et al., representing a patient population not exclusively based in ICU[28]. However, all 38,582 patients included in this study had sepsis and AF. Of these, 62% of study participants were ICU patients and 39% received vasopressors during their admission, highlighting that the majority of these patients were critically ill and haemodynamically unstable[28]. This study matched the eligibility criteria on all other aspects, and represents a population of predominantly critically ill patients, thus providing a large invaluable data set amongst the limited number of studies available. In the largest study by Gamst et al.[29], the adult population was defined as 15+ years, which was outside the limits of our inclusion criteria of adults ≥18 years. Exact figures for the population between 15 and 18 years in this

study were not documented, and therefore could not be disaggregated from the data. It was established by communication with the author that the 15 to 18 year old patients included in the study would have minimal effect on the results obtained, hence the study was included. There were considerable differences within the methodology of each paper, precluding progression to meta-analysis. The assessment of risk of bias for each study is outlined in Table 3[26]. There were two high quality studies scoring seven stars[28,29], one fair quality study scoring five stars[21] and one poor quality study scoring four stars out of a maximum of nine stars[15].

Anticoagulation use and exposure

Table 4 summarises the patient characteristics of individual studies. Anticoagulation use in patients and the risk scores associated with the corresponding patient populations is shown in Table 5. The reported percentages of patients receiving therapeutic anticoagulation for AF in the four studies was 17.8%[15], 30.4%[21], 35.3%[29] and 49.4%[28]. Anticoagulant exposure in the study by Kanji et al.[15] included therapeutic doses of unfractionated heparin (UH), low molecular weight heparin (LMWH) and enteral anticoagulants. The study by Walkey et al.[28] included patients receiving an initial therapeutic dose of parenteral (subcutaneous or intravenous) anticoagulation and patients with PEAF who initially received oral anticoagulants. The results from the patients receiving oral anticoagulation[28] in this study were not robust enough to perform instrumental variable estimations of risk of stroke or bleeding events. As such, the results regarding oral anticoagulation have to be interpreted with caution[28]. The study by Darwish et al.[21] included warfarin, UH, and enoxaparin and identified that warfarin and UH dosing was challenging, with subtherapeutic levels in up to 50% of patients during their ICU admission. Warfarin was the most common oral anticoagulant, prescribed in two studies to 69%[21] and 89%[28] of patients

during their ICU admission. All patients receiving anticoagulation in the study by Gamst et al.[29], were prescribed vitamin K antagonists (VKA) pre-admission to ICU, however the administration of other anticoagulants was not recorded. Enoxaparin was the most common initial parenteral anticoagulant, prescribed for 50% of patients in the study by Walkey et al[28].

Risk identification

The annual risk of stroke in patients with AF, as determined by $CHADS_2$ or CHA_2DS_2-VAS_c scoring systems, was reported in two studies[21,28]. Darwish et al.[21] revealed anticoagulated patients had a mean $CHADS_2$ score of 3.43, whilst non-anticoagulated patients had a mean score of 3.05. The $CHADS_2$ scores reported in both populations place them in the 'high risk of stroke' category, but only 30% of these patients received anticoagulation. The most common reason that anticoagulation was not continued in ICU was an increased INR (>3), with 24% of patients having had their warfarin discontinued on admission to ICU[21]. There was no significant difference in CHA_2DS_2-VAS_c scores for the anticoagulated and non-anticoagulated populations in the study by Walkey et al.[28], with poor discrimination of the risk of ischaemic stroke during sepsis between these populations (C statistic = 0.526). Walkey et al. demonstrated that the anticoagulated population were younger ($p< 0.001$) and less likely to have prior bleeding events ($p<0.001$), acute haematological failure ($p<0.001$), acute kidney failure ($p<0.001$), chronic kidney disease ($p<0.001$), cancer ($p<0.001$) or metabolic acidosis ($p<0.002$)[28]. Patients who received parenteral anticoagulation had significantly fewer comorbidities and acute conditions than the non-anticoagulated population[28]. There is no indication in either of these studies that calculated risk scores were used to aid the decision of whether anticoagulation should be prescribed. Table 6 summarises the primary and secondary study outcomes.

Thromboembolic events

The definition of thromboembolic events varied in the studies reviewed. Thromboembolic events included were defined as the following: a diagnosis of ischaemic stroke; embolism or thrombosis in extremities, mesenteric arteries or any unspecified arteries[29]; ICD-9CM codes for ischaemic stroke[28]; embolic stroke[15]; and the incidence of any stroke type during ICU admission[21]. The study by Gamst et al.[29] calculated the adjusted cumulative risk ratio (CRR) for arterial thromboembolism at 30 and 365 days post-admission to critical care among patients with PEAF who took VKAs pre-admission compared to those who did not. The adjustments for confounding were the risk factors included in the CHA_2DS_2-VAS_c score: congestive heart failure, hypertension, age, diabetes mellitus, previous stroke, vascular disease and sex. Patients anticoagulated with a VKA pre-admission to critical care were found to have an adjusted CRR of 0.57 (95% CI 0.26- 1.25) at 30 days and 0.76 (95% CI 0.50-1.16) at 365 days post-admission to critical care, indicating a reduced risk of arterial thromboembolic events. Walkey et al.[28] carried out a propensity-score matched analysis including 13505 patients with AF who had or had not received parenteral anticoagulation and demonstrated that there was no significant difference in the incidence of ischaemic stroke; 1.3% of parentally anticoagulated patients and 1.4% of non-anticoagulated patients developed an ischaemic stroke, with a relative risk (RR) of 0.94 (95% CI 0.77-1.15)[28]. Patients who received initial oral anticoagulants experienced lower rates of stroke (0.5% compared to 1.3% in patients not receiving oral anticoagulation, RR 0.46, 95% CI 0.32-0.66)[28]. No patients were diagnosed with stroke in the studies by Darwish et al. and Kanji et al., though their populations were much smaller in size, totalling 115[21] and 325[15] patients respectively.

Bleeding events

Bleeding complications were more frequent in the anticoagulated patients than in the non-anticoagulated patients in the three studies that reported bleeding events. Walkey et al.[28] defined clinically significant bleeding using ICD-9CM bleeding codes and reported that bleeding occurred more often in the parentally anticoagulated population (8.6%) compared to in the non-anticoagulated population (7.2%) (RR 1.21, 95% 1.10-1.32). Patients receiving oral anticoagulation in this study experienced lower rates of bleeding compared to matched patients who did not receive any anticoagulation (5.2% and 6.0% respectively, RR 0.85, 95% CI 0.74-0.97)[28]. Kanji et al.[15] reported 8.6% of patients receiving anticoagulation reported bleeding, requiring interruption of their anticoagulation and blood transfusion. Incidence of bleeding was not recorded for the non-anticoagulated population of this study[15]. Darwish et al.[21] reported one fatal central nervous system haemorrhage and one non-fatal gastrointestinal haemorrhage in the group of 35 patients who were anticoagulated; there were no incidents of bleeding in the group of 80 non-anticoagulated patients.

Length of stay

Mean LOS on ICU was only reported in one study[21] and was 8.7 ± 9.2 days for non-anticoagulated and 7.2 ± 6.7 days for anticoagulated patients. This difference was not statistically significant (p=0.718)[21].

Mortality

We initially planned to investigate short- and long-term mortality in patients at 28 days, 90 days and 365 days. However, long term mortality data was only reported by Gamst et al.[29] who reported mortality at 30 days and 365 days. We chose to modify our outcome measures to report mortality on ICU, at 30 days and 365 days. Darwish et al.[21] reported no significant difference in mortality on ICU, where 26% of the anticoagulated population and 34% of the non-anticoagulated population died during admission[21]. Gamst et al.[29] reported a significantly lower mortality and relative risk (RR) of death at 30 days and 365 days post-admission to ICU for the patients anticoagulated with VKA pre-admission compared to the non-VKA users[29]. 30-day mortality was 22.9% (21.3-24.6) in the pre-admission VKA users and 30.6% (28.9-32.4) in the non-VKA users (RR 0.91, 95% CI 0.82-1.00)[29]. 365-day mortality was 35.4 % (33.5-37.3), in the pre-admission VKA users and 46.3% (44.4-44.8) in the non-VKA users (RR 0.91, 95% CI 0.85-0.97)[29]. The RR of death was adjusted for age, sex, comorbidities and services provided by the general practitioner.

Discussion

This is the first systematic review assessing the current evidence for anticoagulation strategies in critically ill patients with AF. Previous reviews have investigated the epidemiology, treatment and prevention of AF and the risk factors, treatment and outcomes of NOAF, however, there is a lack of literature focusing specifically on anticoagulation in the critical care setting[30,31]. This systematic review demonstrates that an array of anticoagulation strategies are used for AF in critical care, and only 17.8- 49.4% of the patients received therapeutic anticoagulation. In the studies reporting the specific anticoagulants prescribed, the most common were warfarin and enoxaparin. Anticoagulated populations had lower 30 and 365 day mortality rates post-admission

to critical care; however, this data was only extracted from one study[29]. This study by Gamst et al. included patients with PEAF who were anticoagulated with VKA pre-admission to critical care and did not consider other forms of anticoagulation initiated or discontinued in critical care nor patients that developed NOAF[29]. This must be taken into consideration when interpreting the results. Critically ill patients are subject to bleeding events due to the associated coagulopathy, thrombocytopenia and platelet dysfunction that may occur in critical illness[20]. There was an increase in clinically significant bleeding in the anticoagulated population compared to the non-anticoagulated population[15,21], however, there was no difference in the rate of thromboembolic events between patients receiving and not receiving anticoagulation[28].

Anticoagulant exposure varied between the studies and only two studies specified the anticoagulant doses prescribed[15,28]. The variation in type of anticoagulant, the lack of clarity about doses and monitoring practices used, in addition to the potential for other factors such as augmented renal clearance to alter the effectiveness of anticoagulation, may all have influenced the incidence of thromboembolic and bleeding events documented in the studies[32]. Therefore, the effects of anticoagulation on the adverse outcomes (arterial thromboembolic events in ICU, bleeding events, 30-day and 365-day mortality) remain unclear. Given the low number of selected studies and their retrospective nature, it was not possible to investigate outcomes of different anticoagulants, for example, parenteral versus oral anticoagulants. The four studies did not clearly define treatment doses of individual anticoagulants and therefore the safety and efficacy of different anticoagulant prescriptions could not be assessed. Future prospective studies should define clear outcome measures including dosing regimens of anticoagulants to allow comparison between different cohort studies and to increase the validity of conclusions drawn.

Additionally, there were different definitions of outcome measures within the four studies included in this review. Thromboembolic events recorded were based on a variety of thromboembolic outcomes including a diagnosis of ischaemic stroke; embolism or thrombosis in extremities, mesenteric arteries or any unspecified arteries[29]; ICD-9CM codes for ischaemic stroke[28]; embolic stroke[15]; and the incidence of any stroke type during ICU admission[21]. Similarly, there was variation in the defined outcomes of bleeding events in the three studies reporting haemorrhage. Walkey et al.[28] defined clinically significant bleeding using ICD-9CM bleeding codes, Kanji et al.[15] reported bleeding requiring interruption of anticoagulation and blood transfusion and Darwish et al.[21] did not provide a defined outcome of bleeding events. Therefore, It is difficult to draw meaningful and valid conclusions regarding events such as bleeding/haemorrhage and thromboembolic events, as there was significant heterogeneity in defining these outcomes in the four studies. Not all studies reported the proposed outcome measures, therefore the sample size available for analysis and inferences was limited.

There were two studies reporting the risk of stroke using the CHA_2DS_2-VAS_c or $CHADS_2$. Both studies included patients who reached the threshold score for commencing anticoagulation therapy, however, there is no indication in either of these studies that calculated risk scores were used to aid the decision of whether anticoagulation should be prescribed. There remains a lack of clarity in initiating anticoagulation in these "at risk" patients, which is also reflected in other studies. A recent study reported AF outcomes for critically ill patients admitted to step down units. CHA_2DS_2-VAS_c scores were not associated with the occurrence of stroke or TIA and failed to predict these thromboembolic events[14].

This systematic review aimed to assess both NOAF and PEAF together to cumulate the outcomes associated with AF during critical care admission. However, the data for post-admission mortality at 30 and 365 days are based solely on one study[29], which included only patients with PEAF. Although there is evidence that NOAF is an independent risk factor for increased mortality and risk of stroke during critical illness and sepsis[1,33], the available data did not allow discrimination between these two subtypes of AF with regards to outcomes.

Mortality at 28 days and 90 days was not reported in any of the studies, therefore it was excluded from analysis. The protocol for this review outlined the intention to review the incidence of thromboembolic events, including stroke[25], TIAs, mesenteric ischaemia, acute limb ischemia and pulmonary embolism. Only one study[29] reported the risk of arterial thromboembolism (including embolism or thrombosis in the extremities), whilst the other three studies reported stroke incidence only[15,21,28]. Diagnosis of stroke may have been underreported as clinical examination and diagnostic testing in critically ill patients receiving mechanical ventilation and sedative medications may be limited[34]. The two studies by Darwish et al. and Walkey et al.[21,28] focused on septic patients only, which may have affected the outcome results in these studies. There is evidence that sepsis affects the coagulation cascade with both prothrombotic and antithrombotic effects, therefore, it is impossible to determine whether the adverse outcomes documented in these studies are related to anticoagulation strategies or the underlying sepsis[35].

The largest study by Gamst et al.[29] with 5065 patients did not report the incidence of thromboembolic events, incidence of major haemorrhage or other anticoagulation-related complications, LOS and mortality on ICU, thus limiting its comparability with other studies. For analysis of the data reported, percentage values were used for universal comparisons between

studies. In order to avoid overrepresentation of outcomes in the small cohort studies by Kanji et al. and Darwish et al.[15,21], careful interpretation is required when comparing these to the large cohort studies by Walkey et al. and Gamst et al.[28,29]. Adjustment for confounding factors were made by both authors[28,29] through propensity-score matched analysis and calculation of relative risk respectively. This may have introduced bias in comparison with the other studies[15,21] as a result of unadjusted confounding factors, such as age, sex, diabetes mellitus, previous stroke and hypertension.

Clinical diversity was evident with variability in the participants, interventions, settings and the measured outcomes in each study. The largest study[29] included admissions with sepsis inside and outside ICU, while the other studies[15,21,28] reported mixed ICU populations (surgical versus medical versus cardiac surgery). Due to this variability and the limited number of studies, the data available for extraction was insufficient to perform statistical analysis between studies, and as such meta-analysis was not feasible. Given the nature of the study designs, power analysis was not included. Our systematic review also identified methodological diversity with varying risk of bias scores as reflected in the Newcastle Ottawa assessment scores. The varying bias in the studies further jeopardises the reliability of inferences made collectively on the effectiveness of anticoagulation strategies for AF in the general critical care setting.

Conclusion

A variety of anticoagulation regimens are currently used to treat critically ill patients with AF. There is limited evidence available regarding anticoagulation strategies in critically ill patients. We cannot confirm an optimal strategy due to the limited number of available studies, variation in study methodology, differences between patient populations included, and a lack of

standardisation of study outcomes. We could not identify any randomised clinical trials for this review, which clearly represents a gap in the available evidence. Further high quality studies and well planned randomised trials investigating the effectiveness and safety of anticoagulation in critically ill patients with AF are urgently needed, , with standardised outcomes to facilitate comparison and the development of evidence based guidance.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Conflicts of interest

The authors declare there are no competing interests.

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Authors' contributions

The protocol was conceived and designed by IW, BWJ and AW. AN conducted primary screening and data collection, reviewed by BJW and GL. Data extraction, analysis and

preparation of the manuscript was conducted by AN. IW, BWJ, AW and AN read and approved the final manuscript.

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Figure captions

Figure 1: PRISMA flowchart of studies selected in the systematic review.

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Table 1: Study characteristics

Author, year	Study design	Study period	Journal	Number of patients	Setting
Kanji et al., 2012	Retrospective, observational	2006	Journal of Critical Care	325	Mixed medical/surgical ICU
Darwish et al., 2013	Retrospective, observational	2004-2009	Annals of Pharmacotherapy	115	General ICU
Gamst et al., 2015	Prospective, observational	2005-2011	Journal of the American Medical Association: Cardiology	57110	All ICU centres
Walkey et al., 2016	Retrospective, observational	2010-2013	Journal of the American Medical Association: Cardiology	38582	NS

535 *ICU* intensive care unit, *NS* not specified

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Table 2 Eligibility criteria, intervention and outcome measures of studies

Author, year	Intervention	Comparators	Inclusion	Exclusion	Illness Severity Analysis	Risk score analysis	Outcome measures
Kanji et al., 2012	Direct current cardioversion, pharmacological rhythm conversion, pharmacological rate control and systemic anticoagulation for thromboembolism prevention	No treatment plus standard care	Adults admitted to ICU with AF	Patients recovering from cardiac surgery	APACHE II	NS	Incidence and time of rate and rhythm control, development of a pulmonary embolism, embolic stroke or MI, LOS in hospital and ICU, disposition and mortality.
Darwish et al., 2013	Anticoagulation for thromboembolism prevention	No treatment plus standard care	Adults admitted to general ICU with AF and sepsis	Patients with contraindications for anticoagulation	Patients requiring mechanical ventilation	$CHADS_2$	Incidence of bleeding, HIT, stroke, LOS in hospital and ICU and mortality

Gamst et al., 2015	ICU therapies including RRT, inotropes, NIV, mechanical ventilation. Preadmission therapies including statins, aspirin, VKA, beta blockers, CCB, digoxin and amiodarone	Patients admitted to ICU without a diagnosis of AF	Adults* admitted to general ICU with AF	NS	NS	CHA_2DS_2-VAS_c	Arterial thromboembolism and mortality at 30 days and 365 days post ICU admission
Walkey et al., 2016	Anticoagulation for thromboembolism prophylaxis	No treatment plus standard care	Adults with sepsis and AF	Patients with other indications for anticoagulation	NS	CHA_2DS_2-VAS_c	In-hospital ischaemic stroke and bleeding incidence

*Age 15+ years. *AF* atrial fibrillation, *ICU* intensive care unit, *NS* not specified, *MI* myocardial infarction, *LOS* length of stay, *HIT* heparin induced thrombocytopenia, *NIV* non-invasive ventilation, *VKA* vitamin K antagonist, *RRT* renal replacement therapy, *CCB* non dihydropyridine calcium channel blocker.

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Table 3 Newcastle Ottawa Assessment Scale for assessment of bias.

	Selection[a]	Comparability[b]	Outcomes[c]	Total
Kanji et al., 2012	***	-	*	4
Darwish et al., 2013	****	-	*	5
Gamst et al., 2015	***	*	***	7
Walkey et al., 2016	****	**	*	7

* Represents the number of stars appointed after assessment

[a] Selection was assessed based on the representativeness of the anticoagulated cohort, identification of the non-anticoagulated cohort, ascertainment of anticoagulant exposure and demonstration that the measured primary outcomes were not present at the start of the study. The maximum score for the selection component is 4.

[b] Comparability was assessed by examining whether the study controlled for age, sex and patient comorbidities. The maximum score for comparability is 2.

[c] Outcomes were assessed by examining how the outcome was assessed, the follow-up period and follow up response. The maximum score for outcomes is 3.

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Table 4 Characteristics of patients with atrial fibrillation in selected studies

Author, year	Mean age, years (range)		Number of Patients with AF	Male sex with AF, n (%)	Comorbidities of patients with AF, n (%)
Kanji et al., 2012	NOAF	PEAF	325	189 (58)	CHF: 61 (19) HTN: 87 (58) Stroke: 43 (13) DM: 74 (23) CAD: 126 (39) VHD: 22 (7) Asthma: 23 (7) COPD on HO: 17 (5) Cardiomyopathy: 22 (7) Chronic renal insufficiency: 40 (12) Chronic renal failure: 14 (4)
	72 (12.5)	74 (9.2)			
Darwish et al., 2013	81 (9.5)		115	47 (41)	CHF: 64 (56) HTN: 95 (83) Stroke/TIA: 78 (68)
Gamst et al., 2015	75 (67-81)[a]		5065	3162 (62)	CHF: 1714 (34) HTN: 2457 (49) TIA: 359 (7) DM: 830 (27) VHD: 1215 (24) PAD: 824 (16) MI: 1056 (20) CLD: 1136 (26) CKD: 518 (10)

					IHD: 1724 (34) Angina pectoris:1506 (30) Cerebrovascular disease: 1217 (24) Hemiplegia: 35 (1) Dementia: 109 (2) Connective tissue disease: 360 (7) Liver disease: 160 (3) Cancer: 1233 (24)
Walkey et al., 2016	A 73 (11.7)	A' 76 (11.7)	38582	18976 (49)	CHF: 15504 (40) HTN: 26839 (70) Stroke: 1316 (3) DM: 13864 (36) CAD/MI: 12502 (32) CLD: 15130 (39) CKD: 12667 (33) VHD: 5358 (14) PVD: 5126 (13) Prior bleeding: 3775 (10) Cancer: 5326 (14) Dementia: 2752 (7)

NOAF new-onset atrial fibrillation, *PEAF* pre-existing atrial fibrillation, *A* anticoagulated patient cohort, *A'* non-anticoagulated patient cohort, *CHF* congestive heart failure, *HTN* hypertension, *TIA* transient ischaemic attack, *DM* diabetes mellitus, *CAD* coronary artery disease, *VHD* valvular heart disease, *PAD* peripheral artery disease, *MI* myocardial infarction, *CLD* chronic lung disease, *CKD* chronic kidney disease, , *PVD* peripheral vascular disease, *COPD on HO* chronic obstructive pulmonary disease on home oxygen, *IHD* ischaemic heart disease.

[a] Median age (interquartile range)

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Table 5 Anticoagulation use and corresponding risk score values

Author, year	Number of patients with AF	Patients receiving anticoagulation, n (%)	Anticoagulation strategy, n (%)	Risk score (mean±SD) A	A'
Kanji et al., 2012	325	58 (17.8)	NS	NS	NS
Darwish et al., 2013	115	35 (30.4)	Warfarin 24 (69) UH 10 (29) LMWH 1 (2)	3.43 ±1.17[a]	3.05 ±1.18[a]
Gamst et al., 2015	5065	2500 (49.4)	VKA 2500 (100)	NS	NS
Walkey et al., 2016	38582	13611[c] (35.3)	Enoxaparin 6991 (50) Heparin 5004 (35) Dalteparin 1296 (9) Fondaparinux 830 (6)	3.40 ±1.5[b]	3.60 ±1.5[b]
		8289[d] (89.2)	Warfarin 8289 (89) Dabigatran 722 (8) Rivaroxaban 282 (3) Apixaban 1 (0)		

AF atrial fibrillation, *A* anticoagulated patient cohort, *A'* non-anticoagulated patient cohort, *SD* standard deviation, *NS* not specified

[a] $CHADS_2$ score

[b] CHA_2DS_2-VAS_c score

[c] Number of patients receiving an initial or subcutaneous anticoagulant in doses greater than prophylactic dose for venous thromboembolism

[d] Number of patients with PEAF receiving an initial oral anticoagulant

Table 6 Study Outcomes

Author, years	Number of patients with AF who received anticoagulation n (%)	Incidence of any thromboembolic event, n (%)		Major bleeding event/ anticoagulation complication, n (%)		Length of stay on ICU, mean (days)		ICU mortality, n (%)		30 day mortality, n (%)		365 day mortality, n (%)	
		A	A'	A	A'	A	A'	A	A'	A	A'	A	A'
Kanji et al., 2012	58 (17.8)	0 (0)	0 (0)	5 (8.6)	NS	NS		NS		NS		NS	
Darwish et al,. 2013	35 (30.4)	0 (0)	0 (0)	2 (5.7)	0 (0)	7.2 ± 6.7	8.7 ± 9.2	9 (26)	27 (34)	NS		NS	
Gamst et al., 2015	2500 (49.4)	NS		NS		NS		NS		573 (23)	785 (31)	885 (35)	1188 (46)
Walkey et al, 2016[a]	13611 (35.3)	174 (1.3)	185 (1.4)	1163 (8.6)	979 (7.2)	NS		NS		NS		NS	

A anticoagulated population *A'* non-anticoagulated population, *NS* not specified

[a] Results reported using propensity matched scores which matched 13505 of 13611 (99.2%) of anticoagulated patients and 13505 of 24971 (54.1%) of non-anticoagulated patients

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