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Study Protocol

Direct oral anticoagulant use in hospitalized patients with atrial fibrillation across body mass index categories: design and rationale for a retrospective cohort study

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Fahad Shaikh, Rochelle Wynne, Ronald L. Castelino, Sally C. Inglis, Patricia M. Davidson and Caleb Ferguson

Abstract

Background: Atrial fibrillation (AF) and obesity are common conditions globally; yet, there remains suboptimal pharmacological management contributing to high rates of hospitalization in patients with AF. The altered pathophysiology of both obese and underweight individuals may influence the pharmacology of medications, including those used to manage AF. This, in turn, increases the risk of adverse events and impacts patient risk for stroke and rehospitalization. Despite the well-established complications of obesity, research investigating the relationship between obesity and AF is scant.

Objectives: The primary aim of this study is to describe cardiovascular-related hospitalization in AF patients according to BMI categories. A secondary aim is to describe anticoagulant and antiarrhythmic prescribing practice patterns in patients with AF, according to the BMI category.

Design: A retrospective, exploratory descriptive observational cohort study, using routinely collected electronic medical record data from five public hospitals within a single health district, with a population dominantly that is culturally and linguistically diverse, and has a low socioeconomic status.

Methods and analysis: Data extraction will include a 24-month period (January 2017 to December 2018) with a 12-month follow-up. All adult (⩾18 years) patients at discharge diagnosed with AF, prescribed any oral anticoagulant and/or oral rate/rhythm control agent, will be eligible for inclusion.

Ethics and dissemination: Ethics approval from the health district and the University of Wollongong has been granted. Findings will seek to demonstrate associations between management strategies and patient outcomes, as well as describe patterns of acute care management from prescribers. These data will be used to inform and generate hypotheses for large-scale studies examining the impact of body weight on anticoagulation prescribing at national and global scales.

Plain language summary

Designing a study that examines the use of blood thinners in hospitalised patients with irregular heartbeat at different body weights

Background: Across the world, two of the most common conditions include obesity and a heart disease that causes irregular heartbeat which is known as Atrial Fibrillation (AF).

Correspondence to:
Caleb Ferguson
Centre for Chronic & Complex Care Research, Blacktown Hospital, Western Sydney Local Health District, Blacktown, NSW, Australia

School of Nursing, Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, NSW, Australia
calebf@uow.edu.au

Fahad Shaikh
School of Nursing, Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, NSW, Australia

Rochelle Wynne
School of Nursing, Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, NSW, Australia

The Royal Melbourne Hospital, Parkville, VIC, Australia

Ronald L. Castelino
Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

Pharmacy Department, Blacktown Hospital, Western Sydney Local Health District, Blacktown, NSW, Australia

Sally C. Inglis
Improving Palliative, Aged and Chronic Care through Clinical Research and Translation (IMPACCT), University of Technology Sydney, Sydney, NSW, Australia

Patricia M. Davidson
University of Wollongong, Wollongong, NSW, Australia

Fahad Shaikh
is also affiliated to Centre for Chronic & Complex Care Research, Blacktown Hospital, Western Sydney Local Health District, Blacktown, NSW, Australia

Rochelle Wynne
is currently affiliated to Centre for Quality & Patient Safety, Institute of Health Transformation Western Health Partnership, Western Health Partnership, St Albans, Victoria, Australia; School of Nursing & Midwifery, Deakin University, Geelong, Victoria, Australia

Patricia M. Davidson
is also affiliated to Johns Hopkins University, Baltimore, Maryland, United States of America

As a result of the excessive over or underweight of an individual with AF, can affect how some of the medications used manage AF work, in turn potentially affecting their health.
Purpose: The main purpose of this study is to describe how often people with AF end up in the hospital because of heart-related problems based on their weight category. We also want to describe how doctors prescribe blood thinners and medicines that control the heart rhythm, in patients with AF based on their body weight.
Design and method: To do this we will examine old electronic medical records over a two-year period, from January 2017 to December 2018 from five public hospitals, and we will see what happens after one year if they were hospitalised. These hospitals serve a diverse population with a mix of languages and cultures and are low-income earning households. We will only examine the electronic medical records of adults (18 years and over) who were diagnosed with AF and were prescribed blood thinners and/or heart rate or rhythm-controlling medications at the time of leaving the hospital. All adult (⩾18 years) patients at discharge diagnosed with AF, prescribed any oral anticoagulant and/or oral rate/rhythm control agent, will be eligible for inclusion. We have already gotten approval from the hospital and the University of Wollongong to conduct this study ethically. We anticipate that the results from this study will help us understand how different treatments and body weights are connected, and this knowledge can be used to plan bigger studies on a national and global scale to improve how we care for people with irregular heartbeats.

Keywords: antiarrhythmics, anticoagulant, atrial fibrillation, direct oral anticoagulants, obesity, retrospective cohort, study protocol

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Introduction

Atrial fibrillation (AF) and obesity are common conditions worldwide in epidemic proportions in both incidence and prevalence, affecting 60 and 650 million people globally, respectively.[1,2] In the Australian context, an accurate estimation of the burden of AF remains uncertain; however, prevalence rates have been estimated to range from 1.4% to 5%.[3] This is projected to further increase to 6.4% in the next 20 years, and double in people aged over 55 years due to the ageing population of Australia.[3,4]

A similar trend is seen in the obese adult population which has almost doubled between 1995 (18.7%) and 2018 (31.3%).[5] Furthermore, the global ageing population can lead to an increase in the number of elderly people who have multiple comorbidities and persistent acute illnesses demanding frequent hospitalization.[6] This may also have a consequence on the number of patients who have a low body weight, which is a common characteristic of frail elderly patients with multiple comorbidities.[7]

It is estimated that approximately 10–30% of AF patients are admitted to the hospital annually for cardiovascular and non-cardiovascular causes. Subpar management of anticoagulation alone is evident in 40–60% of AF patients.[8,9]

In both obese and underweight individuals, altered pathophysiology may influence the pharmacology of medications, including those used to manage AF, by affecting the volume of distribution (Vd), clearance and, in turn, the elimination of half-life.[10,11] Furthermore, a drug's level of lipophilicity may also cause a lower plasma concentration and a larger Vd in patients who are obese, due to high levels of distribution into adipose tissue.[12] Although these parameters are mainly problematic in morbidly obese (class III)

patients taking highly lipophilic agents (e.g. amiodarone[13,14]), they should not be overlooked. This is particularly pertinent in the context of high-risk medications including those used in the ongoing management of AF, due to the increased risk of medication misadventure leading to bleeding or bradyarrhythmia.[10,11,15] Physiological changes can impact adequate dosing, increasing the risk of adverse events, stroke and rehospitalization.

Despite the epidemic proportions of obesity and AF and strong correlations between the two, there has been little to none, or conflicting guidance provided for the pharmacological management of patients who are obese with AF in international guidelines.[16–20] Furthermore, there are conflicting findings in published systematic reviews on this topic,[21–23] and in clinical trials, such as ARISTOTLE, RELY and ROCKET-AF,[24–26] weight categories were not equally distributed. The majority of patients enrolled in the RELY trial (up to 80%) were between 50 and 100 kg and only 2% were <50 kg.[27] Patients who were >140 kg were under-represented comprising only 1.4% of the sample in the ARISTOTLE trial. As such, the International Society on Thrombosis and Haemostasis recommends not using direct oral anticoagulants (DOAC)'s when the body mass index (BMI) is >40 kg/m^2 or weight >120 kg due to the limited clinical data available.[20] Furthermore, conflicting pharmacokinetic analysis of DOACs and in particular with regards to dabigatran and low body weight add to the complexity of decision-making for prescribers.[28–30]

Socioeconomic disparities further complicate and compound the relationship between obesity and AF, as the prevalence of obesity is highest in low socioeconomic populations. Adults in unskilled and manual professions have a four times greater risk of being obese compared to those in higher socioeconomic groups.[31,32] The Australian Bureau of Statistics estimates that 72% of individuals in low socioeconomic areas are overweight or obese, compared to 62% of those living in high socioeconomic areas.[5] Despite the well-established complications of obesity, research investigating the relationship between obesity and AF is scant. Similarly, the increasing ageing population coupled with low body weight associated with frailty needs to be considered.

Aim

The primary aim of this study is to establish the prevalence of cardiovascular-related rehospitalization in AF patients according to BMI. For this study, rehospitalization is defined as representation and or readmission within 12 months of the index admission from which patients in AF were discharged. The secondary aims are to describe anticoagulant and antiarrhythmic prescribing practice patterns in patients with existing AF according to BMI and to identify risk factors associated with rehospitalization.

Hypothesis

It is hypothesized that obese patients with an existing AF diagnosis will have a higher rate of cardiovascular-related rehospitalization compared to healthy and underweight patients.

Methods

Design

A retrospective, exploratory descriptive observational cohort study, using routinely collected health service electronic medical record (eMR) data, has been designed. Data extraction will focus on index admissions from January 2017 to December 2018 with a 12-month follow-up.

Setting

The retrospective data will be extracted from eMRs for patient admissions from five public hospitals within a single health district with a population dominantly that is culturally and linguistically diverse and have low socio-economic status, indexed as per the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD). In 2017–2018, there were over 6300 index admissions and 360 deaths associated with AF in this district.[33] Almost two-thirds (64.9%) of the population in this district is considered to be overweight or obese, not unlike the national Australian population average (67%).[34] In addition to the high prevalence of obesity, there are socioeconomic disparities within the district with suburbs such as Blacktown, Mt Druitt and Auburn considered to be of marked socioeconomic disadvantage.[35]

Research questions (RQ) and objectives (O)

To accurately assess the relationship between AF and outcomes according to BMI, in patients rehospitalized in acute care services within a single low socio-economic healthcare district in Western Sydney, the following research questions and specific research objectives have been predefined.

RQ1. Do rates of rehospitalization (representation ± readmission) differ according to BMI in patients with AF?

Oi. To compare the prevalence of rehospitalization at 12-month follow-up according to BMI in patients with AF.

RQ2. What are the anticoagulant and antiarrhythmic prescribing practices for AF patients in different BMI categories?

Oi. To establish the proportion of AF patients prescribed anticoagulants and antiarrhythmic agents.

Oii. To describe commonly prescribed anticoagulant and antiarrhythmic agents used in patients with AF according to BMI.

Oiii. To identify and describe dose modifications made for patients with AF according to BMI.

RQ3. Do risk factors for rehospitalization differ according to BMI in patients with AF?

Oi. To examine risk factors associated with rehospitalization over 12 months according to BMI in patients with AF.

Sample

The study will include all patients who have a new or existing diagnosis of AF (or atrial flutter) in their discharge summary, aligned with the following International Classification of Diseases codes (ICD-10, 2019 revision): 148.0, 148.1, 148.2, 148.3, 148.4, 148.9. Data for the variables of interest will be extracted by the clinical analytics team from the district.

Inclusion criteria

Adult patients (⩾18 years) at index admission with a diagnosis of AF as per ICD coding who are prescribed any oral anticoagulant (rivaroxaban, apixaban, dabigatran and warfarin) and/or oral rate/rhythm control agents (atenolol, metoprolol, sotalol, amiodarone, digoxin, flecainide, disopyramide, verapamil and diltiazem). See Supplemental Table 6 for anatomical therapeutic chemical (ATC) codes.

Exclusion criteria

Non-AF-related indication for anticoagulation (e.g. venous thromboembolism, hip/knee replacement).

Sample size

As eMR data represent routinely collected clinical data, there is a level of uncertainty to consider in sample size calculations. Based on the sample size of previous studies[36–40] that have explored a similar topic within the same health district, a sample size of approximately 300 patients is anticipated. The Pearson product–moment correlation coefficient will be used to examine the relationship between the rate of rehospitalization and BMI. A G*Power *post hoc* calculation for this test indicates this sample size should enable the detection of a large effect with 1.0 power and 0.05 probability.

Primary outcomes

The primary outcome is the rate of cardiovascular-related equivalent ICD-10 codes to those outlined by Wetmore *et al.*,[41] rehospitalization within 12 months of the date of discharge from the index admission. Relevant cardiovascular conditions include the following:

- Stroke (ischaemic or haemorrhagic), systemic or pulmonary embolism
- Any bleeding events (i.e. major, clinically significant non-major or minor bleeding, haemorrhagic or thromboembolic events) as per ICD coding
- Transient ischaemic attack

Secondary outcomes

Secondary outcome measures include identifying the proportion of patients with existing AF prescribed anticoagulant and antiarrhythmic agents, types of anticoagulant and antiarrhythmic agents prescribed, the dose administered, and frequency of medication-related adverse events, according to BMI category. Time to first rehospitalization, the reason for rehospitalization and the frequency of all-cause rehospitalization will be established. Length of stay during rehospitalization, number

of major adverse clinical events (MACE: composite of myocardial infarction, all-cause death, stroke, systemic or pulmonary embolism) within 12 months and rate of all-cause in-hospital mortality within 12 months will be examined.

Data extraction

Baseline data will be collected at index admission, with a follow-up at 12 months. Variables of interest include sample characteristics (medical history, serum creatinine (SCr), estimated glomerular filtration rate (eGFR), age, ethnicity, residence postcode, sex, BMI), medication(s) at discharge, international normalized ratio, anti-Xa or dilute thrombin time, hospital readmission/representation diagnosis/presenting problem and date. The variables of interest will be collected at baseline and index readmission(s)/representation(s). However, variables such as hospital readmission/representation diagnosis/presenting problem and date will be collected at all subsequent readmission/representations following index admission.

Data management

The overall quantity and quality of the data are difficult to estimate. It is anticipated that conventional methods such as listwise deletion and imputation will be used to manage incomplete and missing data (i.e. $<5\%$) depending on completeness. All patients will be deidentified and allocated a unique ID code number, after which the dataset will be separated from the linkage file and a re-identifiable dataset will be used by the research team for analysis. The dataset will be saved in a password-protected file, on a password-protected hard drive, on an self-sovereign identity (SSI)-encrypted health district computer. Any data extracted for this study will be in a digital format. Data will not be shared with any third party and access to information will be strictly restricted to the research team. Data will be stored for a minimum of 5 years following the final presentation or publication of information associated with this study, after which it will be deleted from the computer on which it is stored.

Data analysis

Statistical analysis will be performed using IBM SPSS® (Version 28.0).[42] For continuous variables, assumptions of normality will be tested graphically with histograms and using the Shapiro–Wilk or Kolmogorov–Smirnoff test. Continuous data will be presented as mean (*M*) with standard deviation (SD), or median (Med) and quartiles (Q1, Q3) if not normally distributed. Continuous data will be analysed using univariate descriptive tests and bivariate tests such as two-sample *t*-tests or analysis of variance ((ANOVA) for parametric data, and Mann–Whitney or Kruskal–Wallis test for non-parametric data. Categorical variables will be presented as frequency (*N*) and proportion (%) and analysed using chi-square or Fisher's exact tests where appropriate.

The primary outcome measure will be analysed using Pearson product–moment correlation if there are no violations of assumptions of normality, linearity and homoscedasticity. Cohen's *d* will be used to assess the strength of the relationship and the coefficient of determination calculated to examine shared variance. BMI will be categorized as underweight (BMI $<18.5\,kg/m^2$), normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), obese class I (BMI 30.0–34.9 kg/m^2), obese class II (BMI 35.0–39.9 kg/m^2) or obese class III (BMI $\geqslant 40\,kg/m^2$). Univariate analyses will be used to identify unadjusted risk factors for rehospitalization. Survival analysis based on the Kaplan-Meier method will be used to illustrate freedom from rehospitalization for the 12-month follow-up interval. Cases will be right-censored if they did not experience the event by the end of the follow-up period, that is, 12 months. If there is an adequate incidence of rehospitalization, univariate predictors of rehospitalization risk will be examined using a Cox proportional hazards regression model to compare the hazard of rehospitalization between obese and non-obese patients. All tests will be two-tailed and a *p*-value of <0.05 will be considered statistically significant.

Planned subgroup and post hoc *analysis*

We will perform subgroup analyses for age, anticoagulant agent, sex, renal impairment [Cockcroft-Gault (based on multiple body weight calculation methods) *versus* eGFR] and social economic status (as per IRSAD indexation). Additionally, given the noted ambiguity in the literature concerning the use of DOACs in special populations,[43–46] we will perform a *post hoc* analysis of DOAC use according to ethnicity

(Supplemental Table 6), sex and renal impairment. The results from the *post hoc* analyses will be published separately.

Dissemination and translation strategy

We intend to publish results in peer-reviewed cardiology journals and present study findings at local, national and international scientific meetings. The reporting of this study and any subsequent publications will conform to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[47]

Furthermore, we intend to provide plain English language summaries to consumers and research end-users *via* the media, through outlets such as The Conversation or The Pulse, which is the health district's own media outlet that provides a health-literacy-friendly media for consumers. Other news outlets with public reach and engagement may also be used. We also intend to produce a short animation video that will be shared across social media platforms.

Strengths and limitations

The main limitation of this study is its retrospective design. Real-world clinical data may potentially be predisposed to unidentifiable confounding factors. In addition, the necessity for complete data entry may impact sample size secondary to missing data. However, accessing existing data is also a strength, as it enables a rapid, efficient strategy for service evaluation and future risk stratification to target care readmission risk reduction. Retrospective data provide rich information to benchmark practice patterns for future research and identify inadequacies in existing practice methods. This district was also the first site in Australia to implement eMR for two full years before it implemented an electronic medication system.[48] As a result, it is anticipated that the likelihood of most of the variables of interest being adequately collected is high compared to other hospitals in the state. Errors in the coding of clinical information could further add to the limitation of using retrospectively collected real-world clinical data, which could affect the veracity of the data that has been extracted. However, to minimize this from occurring, the health district has a health informatics unit that audit the coding to ensure that the documented clinical data are correctly translated into the correct code as per the coding guidelines and requirements.

The second key limitation is that the collected data will not include patients who had AF at discharge and were not prescribed an oral anticoagulant/antiarrhythmic. However, this was to ensure that the patients did not have a self-limiting AF, which could potentially skew endpoint measures.

Conclusion/outcomes

This study will provide a real-world snapshot of anticoagulant and antiarrhythmic prescribing practice patterns and cardiovascular complications in AF patients according to BMI, in a cohort of patients living in a low socio-economic status healthcare district. Prescribing patterns in AF management will be established along with differences in rates of rehospitalization according to BMI. The findings from this study will highlight the impact of actual rather than ideal management strategies on patient outcomes and identify patterns of acute care management from prescribers within this field.

Declarations

Ethics approval and consent to participate

This retrospective study is of low or negligible risk as it relies on data routinely collected as a usual component of clinical care. This activity is consistent with the National Privacy Principle 2.1(a) in that, the secondary purpose of using data for this study is directly related to the primary purpose of collection; thus, the use of this information for this secondary purpose would be within reasonable individual expectations. The study will be purely observational in nature and as such, does not involve any form of intervention being tested on patients or direct contact with patients. The main source of ethical consideration is the breach of patient confidentiality and anonymity and ensuring the dataset is non-identifiable will protect from these risks. The information will be used to compile descriptive data to audit and benchmark practice patterns. The presentation of findings will be in aggregate form that does not identify individuals and is compliant with the health services commissioner's guidelines. The study has received ethics approval from the University of Wollongong and Western Sydney Local Health Disctrict (WSLHD) Ref 2011-05 (approved December 2020).

Consent for publication
Not applicable.

Author contributions
Fahad Shaikh: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Writing – original draft; Writing – review & editing.

Rochelle Wynne: Methodology; Resources; Supervision; Validation; Writing – review & editing.

Ronald L. Castelino: Methodology; Supervision; Writing – review & editing.

Sally C. Inglis: Supervision; Writing – review & editing.

Patricia M. Davidson: Methodology; Supervision; Validation; Writing – review & editing.

Caleb Ferguson: Conceptualization; Methodology; Resources; Supervision; Validation; Writing – review & editing.

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Competing interests
CF is a co-author of the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation 2018. All other authors declare no conflict of interest.

Availability of data and materials
Not applicable.

ORCID iD
Fahad Shaikh https://orcid.org/0000-0003-4875-5771

Supplemental material
Supplemental material for this article is available online.

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