



Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Original article

Long-term trends in antithrombotic drug prescriptions among adults aged 80 years and over from primary care: a temporal trends analysis using electronic health records

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ARTICLE INFO

Article history:

Received 23 December 2017

Accepted 13 March 2018

Available online xxx

Keywords:

Anticoagulants

Antiplatelets

Elderly

Prevention

Primary care

ABSTRACT

Purpose: This study aimed to estimate trends in antithrombotic prescriptions from 2001 to 2015 among people aged 80 years and over within clinical indications.

Methods: A prospective cohort study with 215,559 participants registered with the UK Clinical Practice Research Datalink from 2001 to 2015 was included in the analyses. The prevalence and incidence of antiplatelet and anticoagulant drugs were estimated for each year and by five clinical indications.

Results: The prevalence rate of antithrombotic prescriptions among patients aged over 80 years and diagnosed with atrial fibrillation increased from 53% in 2001 to 77% in 2015 ($P_{\text{trend}} < .001$). Anticoagulant prescriptions rates also increased five-fold in older adults with atrial fibrillation from around 10% in 2001 to 46% in 2015 ($P_{\text{trend}} < .001$). Clopidogrel-prescribing rates in patients aged over 80 years and with venous thrombosis increased from 0.4% in 2001 to 10% in 2015 ($P_{\text{trend}} < .001$). Warfarin-prescribing rates in older patients with venous thrombosis increased from 13% in 2001 to 21% in 2015 ($P_{\text{trend}} < .001$).

Conclusions: The use of antithrombotic drugs increased from 2001 to 2015 in people aged 80 years and over across multiple clinical indications. Assessing the benefits and harms of antithrombotic drugs across different clinical indications in older people is a priority.

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Aging is associated with increased risk of cardiovascular diseases (CVD), including coronary heart disease (CHD), venous thromboembolism (VTE), atrial fibrillation (AF), peripheral arterial disease (PAD), and stroke. Antithrombotic therapies (ATT) (i.e., antiplatelet and anticoagulant drugs) have been shown to be effective at reducing the risk and/or recurrence of major CVD events in younger populations (aged < 80 years) [1–5]. The use of ATT in patients aged over 80 years remains controversial, however, given their potential association with increased risk of bleeding [2,6–9]. Valid data on the prevalence of anticoagulant and antiplatelet therapies among adults aged over 80 years in the presence of comorbidities and frailty is of major clinical relevance. Comorbidity and frailty are associated with polypharmacy [10] and are important factors influencing the risk of potential complications (i.e.,

bleeding) associated with antithrombotic drugs in very old patients [11,12]. The evidence about long-term trends in the prescription of antiplatelet and anticoagulant use in adults aged over 80 years is scarce and of varying standards (i.e., small samples, self-reports) [13]. Reliable data on the use of ATT across different subgroups of very old patients are essential to inform clinical practice and for future planning of health care resources. The present study used a large primary care database to investigate patterns in the prescription of ATT drugs from 2001 to 2015 in patients aged 80 years and over. In particular, the study compared ATT prescriptions patterns across the main indications (e.g., AF, VTE, PAD, and major CVD) and patient characteristics (e.g., frailty, age).

Methods

Study design

A prospective sequential cohort study was implemented in the UK Clinical Practice Research Datalink (CPRD), the world's largest

Conflict of interest: The authors declare that there is no conflict of interest.

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<https://doi.org/10.1016/j.annepidem.2018.03.006>

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database of primary care electronic health records, covering approximately 7% of the UK population [14]. The CPRD population is considered to be representative of the UK population and includes comprehensive clinical, referral, and pharmacological data recorded in primary care, which have been validated in several studies [15]. Prescriptions are not directly linked to a clinical diagnosis in CPRD (may be linked to Read codes via a unique ID consultation number), and the study considered only prescriptions issued within the first four weeks as being likely to be related to the same condition [16].

Study participants

The sample was drawn from the April 2017 release of CPRD. Stratified sampling by age, sex, and study year was used to ensure adequate representation of older ages. Eligible participants were selected from patients aged at least 80 years old and registered with the UK CPRD at anytime between January 1, 2001 and the December 31, 2015. The study excluded 2016 information because delays in practice data update by the CPRD could fail to capture recent data. For each calendar year from 2001 to 2015, and for each single year of age from 80 to 105 years, 1000 patients were sampled without replacement, from the population of patients registered during that year. This yielded a cohort of 215,599 patients whose primary care electronic health records were investigated. As per study protocol, the sample size was sufficient to estimate a proportion with precision (confidence interval width) of less than $\pm 1\%$.

Outcome measures

The main measures for the study were antiplatelet (e.g., aspirin, clopidogrel, dipyridamole, ticagrelor, prasugrel) and anticoagulant (e.g., warfarin, heparin, dabigatran, rivaroxaban, apixaban) drug prescriptions. Ticagrelor and prasugrel were available for analysis from 2012 onward, whereas dabigatran and apixaban were available from 2010 onward. Gemscript codes capturing drugs based on the British National Formulary were used to identify antiplatelet and anticoagulant drugs prescribed during the study period from January 1, 2001 to December 31, 2015. Only prescriptions who were coprescribed on the same date of a relevant diagnosis (i.e., AF, VTE, PAD, CHD, cerebrovascular accident) or in the following 28 days were considered. Each outcome variable was constructed as a binary (yes/no) independent measure based on all relevant drugs available for prescription during the study period. An overall ATT outcome variable was developed reflecting either anticoagulant or antiplatelet drug prescriptions during the study period. To explore trends in most commonly prescribed ATT drugs, separate binary variables were developed for aspirin, clopidogrel, dipyridamole, ticagrelor, warfarin, heparin, and dabigatran. The study considered both oral and injectable ATTs to offer a more comprehensive understanding about prescription patterns over time.

Indication exposure

Read codes used by general practitioners to record a clinical diagnosis in primary care were used to develop specific binary variables (yes/no) representing common indications for ATT prescriptions including AF, VTE, PAD, cerebrovascular diseases (including, ischemic stroke and transient ischemic attack), and CHD (e.g., myocardial infarction, angina). The validity and accuracy of Read medical codes have been documented extensively [17–20].

Covariate measures

Characteristics known to be associated with variation in antithrombotic prescribing were selected and included gender, 5-year age group, and frailty. Frailty status was assessed using a previously published 36-item electronic frailty index (eFI) [21]. The eFI was constructed from the cumulative deficit frailty model with the eFI score calculated by the presence or absence of individual deficits as a proportion of the total possible [22]. Quantitative traits, including blood pressure, and polypharmacy were omitted from the eFI score for this study. Categories of fit, mild, moderate, and severe frailty were defined following the study by Clegg et al. [21]. Gender was developed as a binary variable (men vs. women), and based on their age at each sampling year, study participants were grouped into the following age categories: 80–84, 85–89, 90–94, 95–99, and 100 and over.

Statistical analysis

Descriptive statistics were used to calculate prevalence and inception rates for antiplatelet and anticoagulant drugs separately for each study year. The crude prevalence of ATT prescription was estimated by dividing the total number of ATT prescriptions recorded during each study calendar year by the total number of patients with a relevant clinical indication registered in CPRD during that calendar year. The number of ATT prescriptions was calculated for each calendar year of follow-up for each individual based on their clinical condition. Annual proportions were calculated for overall (e.g., ATT, anticoagulants, antiplatelet) and specific (e.g. aspirin, clopidogrel, ticagrelor, dipyridamole, warfarin, heparin, and dabigatran) drugs, stratified by the clinical indication (e.g., AF, PAD, VTE, CHD, cerebrovascular accident). Linear regression analyses were conducted to analyze trends in proportion by each clinical condition, and the *P* for trend was calculated. Piecewise linear regression has been used to estimate a potential nonlinear relationship between ATT prescriptions and time to identify any potential inflection points in ATT prescribing trends. The crude incidence (inception) of ATT was estimated per 100-person-years at risk for each clinical indication separately. Each patient contributed person-years from the start date for each calendar year (defined as latest of the first of January of each study sampling year [2001–2015], aged 80 years, practice up-to-date standard, or start of the participant's record in the CPRD) to the end date (defined as the earliest of date of ATT prescription, date of death, the end of CPRD record, or the 31st of December of each calendar year). The incidence rate was estimated by totaling the number of patients with a first recording of ATT in each specific year, and then dividing this number by the total person-years of follow-up for all patients during a specific year. The person-time denominator included all patients with the clinical indication of interest registered in CPRD during a specific calendar year whether or not they were prescribed an ATT medication. These estimations have been performed separately for overall and each specific prescription, stratified by clinical indication. For inception analyses, patients with a relevant (i.e., antiplatelet or anticoagulant) drug prescription anytime before 2001 or the year they turned 80 years of age were excluded. Drug prescriptions (not patients) issued before a condition diagnosis (e.g., AF, VTE, CHD) were excluded. A series of sensitivity analyses were performed to evaluate whether the trends in ATT proportions varying with patients age or frailty status within each clinical condition. The proportion of patients who were prescribed both antiplatelet and anticoagulant agents ranged from around 17% in 2001 to around 6% in 2014. For the present study purposes, however, these

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