**Prevalence of atrial fibrillation and outcomes in older long-term care residents: A systematic review**

**ABSTRACT**

**Background**

Anticoagulation is integral to stroke prevention for atrial fibrillation (AF) but there is evidence of under-treatment in older people in long-term care (LTC).

**Objective**

To synthesise evidence on the prevalence and outcomes (stroke, mortality or bleeding) of AF in LTC, and factors associated with the prescription of anticoagulation.

**Methods**

Studies were identified from Medline, CINAHL, PsycINFO, Scopus and Web of Science from inception to 31st October 2019. Two reviewers independently applied selection criteria and assessed the quality of studies using the Newcastle Ottawa Scale.

**Results**

Twenty-nine studies were included. Prevalence of AF was reported in 21 studies, ranging from 7%-38%. Two studies reported on outcomes based on the prescription of anticoagulation or not; one reported a reduction in the ischaemic stroke event rate associated with anticoagulant prescription (2.84 per 100 person years, 95% Confidence Interval [CI] 1.98-7.25 vs. 3.95, 95% CI 2.85-10.08) and a non-significant increase in intracranial haemorrhage rate (0.71 per 100 person years, 95% CI 0.29-2.15 vs. 0.65, 95% CI 0.29-1.93). The second study reported a 76% lower chance of ischaemic stroke with anticoagulant prescription and a low incidence of bleeding (n=4 events). Older age, dementia/cognitive impairment and falls/falls risk were independently associated with non-prescription of anticoagulation. Conversely, previous stroke/transient ischaemic attack and thromboembolism were independently associated with increased prescription of anticoagulation.

**Conclusions**

Estimates of AF prevalence and factors associated with anticoagulant prescription varied extensively. Limited data on outcomes prevents the drawing of definitive conclusions. We recommend panel data collection and systems for linkage to create longitudinal cohorts to provide more robust evidence.

**PROSPERO registration number**

CRD42020164963

**Keywords**

Atrial fibrillation, long-term care, prevalence, anticoagulation, systematic review

**Key points**

* Anticoagulation is often under-prescribed in long-term care residents with atrial fibrillation
* Prevalence of atrial fibrillation in long-term care is variable given the diversity across residents and facilities
* Current evidence is insufficient to be definitive about the net risk-benefit of anticoagulation in long-term care residents
* Older age, dementia/cognitive impairment, and falls/falls risk are associated with non-prescription of anticoagulation
* Previous stroke/transient ischaemic attack and thromboembolism are associated with increased prescription of anticoagulation

**INTRODUCTION**

Atrial fibrillation (AF) represents a global health burden that disproportionally affects older people, with evidence to suggest a rise in prevalence by 22% in people aged ≥ 65 years, from 7.6 million in 2016 to 14.4 million in 2060 (1). There is a higher incidence of AF in long-term care (LTC) facilities and one in four individuals who have an AF-related thromboembolic event are unable to return to independent living and become residents in LTC (2, 3). Whilst the incidence of AF-related thromboembolic disease has declined in the last 50 years, likely owing to improved case detection and widespread use of anticoagulation for stroke prophylaxis (4-9), data suggest a non-inclusive distribution of anticoagulant use across all demographic strata. Older people with multiple co-morbidities are often not prescribed anticoagulation in the absence of contraindications, likely due to clinicians’ concerns of iatrogenic harm and doubt over the net clinical benefit of pharmacological intervention (10). Conversely, this population is likely to benefit most from anticoagulant therapy as older age and more frequent multi-morbidity places them at an increased stroke risk (11).

A multi-level framework (individualised care and public policy) to mitigate future AF burden in this vulnerable cohort must be guided by: (1) accurate estimation of disease prevalence, (2) understanding determinants driving sub-optimal implementation of stroke prevention strategies and (3) evidence-based guidance on the net risk-benefit of anticoagulation in the LTC population. Therefore, this systematic review aims to estimate the prevalence of AF in LTC, explore the factors associated with prescription/non-prescription of anticoagulation and outcomes (mortality, stroke and bleeding) of individuals living in LTC with and without AF, and with AF based on anticoagulation status.

**Methods**

The systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12) and a completed PRISMA checklist is provided (Appendix 1). The study protocol was registered with PROSPERO (CRD42020164963).

**Criteria for considering studies for the review**

Observational studies were eligible for inclusion if they reported the prevalence of AF or outcomes (mortality, stroke and bleeding) of residents when compared to a control group (residents with vs. without AF, or residents with AF prescribed anticoagulation vs. not prescribed anticoagulation) in the setting of LTC. Studies that examined factors associated with prescription and non-prescription of anticoagulation in LTC were also eligible for inclusion. We included all types of AF (paroxysmal, persistent and permanent) and of any aetiology. For this review “LTC” was restricted to facilities that provided accommodation for people who could not live independently (nursing homes, skilled nursing facilities and assisted living facilities). Studies conducted in sheltered housing, extra care housing, close care, retirement villages, home-share schemes and independent living facilities were excluded. Hybrid homes housing independent and dependent individuals were also excluded. Facilities with dependency were chosen since this is a marker of frailty and these individuals are often excluded from clinical trials for the management of AF. All studies conducted in LTC facilities in any country with abstracts and/or full texts available in the English language were included. Where authors published more than one study with relevant outcomes on the same cohort, all studies were included but data were reported from the most relevant study.

**Search strategy**

Electronic databases, Ovid Medline, CINAHL, PsycINFO, Scopus, and Web of Science were searched from inception to 31st October 2019. Exploded Medical subject headings (MesH) terms and synonyms for “atrial fibrillation” were combined with “long-term care” using the appropriate Boolean operators, proximity operators, truncation and wildcards for each database (Appendix 2). The OpenGrey repository was searched for unpublished literature/dissertations. This was complemented by “hand-searching” two geriatric cardiology journals (*The Journal of Geriatric Cardiology* and the *American Journal of Geriatric Cardiology*) and Google Scholar. International Scientific Indexing conference proceedings were searched for conference abstracts and bibliographies of identified articles were reviewed for any additional relevant studies.

**Study selection**

Literature search results were exported into EndNoteX9 and duplicates were removed. Two researchers (OO and LR) independently identified relevant articles by initial title screening. In the second stage, abstracts and full texts were screened to identify articles deemed to be potentially relevant. Disagreements were resolved by discussion with another reviewer (DL/SH).

**Data extraction**

For relevant studies, a data extraction form was populated with the following information: authors, study period, design and size, method of recruitment, number of residents with AF, number and proportion of residents on anticoagulation, relevant control group, type and number of LTC facilities, method of AF diagnosis, country of study, age and gender distribution, proportion and effect measure for stroke (ischaemic and haemorrhagic), bleeding, mortality, length of follow up and reasons for anticoagulant prescription/non-prescription. Attempts were made to contact three authors for further information, but no response was received.

**Quality assessment and data synthesis**

Two reviewers (OO and LR) independently assessed the quality and risk of bias of cohort studies using the Newcastle Ottawa scale (NOS) (13). For cross-sectional studies, a published modified NOS was used (14). This replaces the selection of non-exposed cohort, outcome not present at start and follow-up domains with sample size, non-respondents and statistical test.

All included studies were reported using qualitative synthesis. Prevalence of AF was reported as a percentage and for studies reporting on outcomes, the number of events (with percentages), event rates or relative risk [RR] with 95% confidence intervals [CI] were reported. Factors associated with prescription/non-prescription of anticoagulation were reported as odds ratios [OR] or hazard ratios [HR] with 95% CIs. There were insufficient studies with comparable outcomes/methodology and this did not allow for quantitative analysis.

**RESULTS**

**Screening**

The searches resulted in 8431 studies identified for screening after removal of duplicates (Figure 1). After reviewing the title and abstract, 8397 (99.6%) were removed and full-text screening was carried out for 34 studies. Five studies (10, 15-18) were excluded due to lack of a control group (n=1) (15), incorrect study setting (n=1) (10), recruitment of a subset of participants (n=2) with glaucoma or post-stroke (16, 18) or both no control group and recruitment of a subset of participants (n=1) post-stroke (17). Twenty-nine studies met the eligibility criteria and were included in the review. Two authors had published two studies each reporting on the same cohort, Reardon et al (19, 20) and Shurrab et al (21, 22), while Aronow et al (23-26) published four studies using the same cohort from one LTC facility but at different points in time and applying different inclusion criteria (Figure 1).

**Included studies**

In the 29 studies, there were approximately 249,779 LTC residents and 269 physicians included. Studies reporting on the same cohort (Reardon et al (19, 20) and Shurrab et al (21, 22) were only accounted for once to calculate the total number of LTC residents. Similarly, only one study by Aronow et al (23) (with the largest sample size) was included. The exact number of residents could not be calculated because one study (19) only provided an estimate of the sample size.

Most studies were conducted in the United States (US) (18 studies, n=223,707 residents) (3, 19, 20, 23-37), five studies were conducted in Canada (n=11,299 residents and 269 physicians) (21, 22, 38-40), three in Australia (n=3835 residents) (41-43), and one each in France (n=10,660 residents) (44), the United Kingdom (UK) (n=53 residents) (45) and the Republic of Ireland (n=225 residents) (46). Twenty-one studies were cross-sectional (3, 19-22, 26-33, 37, 39-41, 43-46), seven were cohort studies (23-25, 34-36, 42) and one study was a survey (38). The number of LTC facilities recruited from ranged from one (29) to 9133 (35). Five studies [12, 17, 18, 21, 26] did not report the number of LTC facilities included. Table 1 summarises the characteristics of the included studies.

**Assessment of study quality**

All cohort studies (23, 25, 34-36) were graded as ‘good’ quality by the Newcastle Ottawa Scale except two (24, 42). One study ranked as ‘poor’ owing to selection bias, inadequate comparability to controls and follow-up (42), and the other study ranked as ‘fair’ owing to selection bias and inadequate follow-up (Appendix 3). Ten cross-sectional studies (19, 20, 22, 30, 32, 33, 39, 40, 43, 44) were awarded the maximum quality assessment score (10/10), with most of the remaining studies scoring very highly (9/10) (26, 27, 31) or highly (7-8/10) (3, 21, 29, 37, 38, 46). Only three studies scored lower (5/10) (45) or (6/10) (28, 41). The survey by Monette et al (38) was quality assessed as a cross-sectional study because the survey data was collected at one point in time and rated highly (7/10) (Appendix 3).

**Prevalence of AF in LTC residents**

Twenty-one studies reported the prevalence of AF, ranging from 7.1%-38% (3, 19-23, 25, 26, 28-33, 37, 39, 40, 42, 44-46). Aronow et al reported a different prevalence of AF in three studies that recruited from the same LTC facility due to different time-points and applying different inclusion criteria (13.7% (23), 13% (25) and 10% (26)). Three studies reported an AF prevalence <10% (28, 37, 40), 13 had a prevalence between 10-15% (19-23, 25, 26, 32, 33, 39, 42, 44, 45) and five reported a >15% prevalence (3, 29-31, 46) (Table 1). There was no association between mean/median resident age (years) and prevalence of AF. The median [IQR] resident age was 85 [77-89] years for the highest prevalence of AF (38%) (41) and the mean [SD] resident age was 87.7 [6.5] years for the lowest prevalence of AF (7.1%) (28).

**Outcomes in LTC residents with AF**

Only one study (25) investigated the outcomes of LTC residents with AF (n=283) compared to residents without AF (n=1818). During follow-up, there was a higher incidence of ischaemic stroke events in residents with AF compared to residents without AF (131, 46% vs. 303, 17%, P <0.0001) and in multivariate analyses, AF was an independent predictor of ischaemic stroke (RR 3.3, 95% CI 2.4-4.5) (Table 2). No information was reported on other health-related outcomes (all-cause mortality, intracranial haemorrhage or other bleeding events).

Only two studies (24) (34) examined the effect of anticoagulation status on health outcomes of LTC residents with AF (Table 2). Aronow et al (24) compared outcomes between residents on warfarin therapy (n=187, 59.9%) vs. no oral anticoagulant (OAC) therapy (aspirin 325mg daily) (n=125, 40%), followed-up for a mean [SD] of 34 [16] and 37 months [18], respectively. Warfarin use was associated with fewer ischaemic stroke events during follow-up (40 (32%) residents on warfarin vs. 122 (65.2%) on aspirin, P <0.001). After adjustment, warfarin use was associated with a 76% lower chance of incident ischaemic stroke (24). The incidence of bleeding was low: one intracranial haemorrhage and one report of gross haematuria for residents on warfarin, but no difference in gastrointestinal bleeding events for residents on aspirin compared to those on warfarin (4 [2.1%] vs. 2 [1.6%]) (Table 2).

Gill et al (34) compared outcomes between residents on warfarin, dabigatran or rivaroxaban therapy (n=7919) vs. no OAC therapy (n=13958), followed-up for 339 days [IQR 131-747]. In bivariate analyses, when multiple events occurring in the same person-month were counted as one event, ischaemic stroke events were recorded in 102 residents on OAC vs. 324 residents on no therapy. Analogous figures for intracranial haemorrhage events were 22 residents vs. 55 residents respectively. This translated into an ischaemic stroke event rate of 2.94 vs. 4.10 per 100 person years and an intracranial haemorrhage event rate 0.63 vs. 0.70 per 100 person years, for OAC vs. no therapy, respectively.

In multivariate analyses adjusted for age, sex, co-morbidities (stroke, bleeding, hypertension, and congestive heart failure) and hospitalisations for ischaemic stroke or intracranial haemorrhage within the last month, prescription of OAC was associated with a significant reduction in ischaemic stroke event rate (2.84, 95% CI 1.98-7.25 vs. 3.95, 95% CI 2.85-10.08 per 100 person years) but no significant association was noted between OAC and the intracranial haemorrhage event rate (0.71, 95% CI 0.29-2.15 vs. 0.65, 95% CI 0.29-1.93 per 100 person years) (Table 2).

**Factors associated with anticoagulant prescription in LTC residents with AF**

Seventeen studies explored factors associated with the prescription/non-prescription of anticoagulation (3, 19, 22, 24, 27, 32-36, 38-44) (Table 3). Ten studies reported multivariate analyses (3, 32-36, 39, 40, 43, 44), five reported bivariate analyses only (19, 22, 24, 38, 42) and two performed no statistical tests but provided a breakdown of different resident characteristics and the numbers of residents prescribed/not prescribed anticoagulation (27, 41).

Congestive heart failure (CHF) (32, 34), previous stroke/transient ischaemic attack (TIA) (32-34, 40, 43), thromboembolism (TE) (32, 34, 43), valvular disease (32) and polypharmacy (32) were independent predictors of receiving a prescription for anticoagulation. Conversely, older age (32, 34, 35, 40, 43, 44) (described categorically by all studies except one (44) as ages ≥85 years (34, 35, 40, 43) and ≥90 years (32)), male gender (34, 36), non-White (32)/Hispanic (36)/Other (34)/Black (34, 35) (vs. White) ethnicities, dementia/cognitive impairment (22, 34-36, 40), falls/falls risk (34, 43, 44), anaemia (34), gastrointestinal bleeding (32, 33), internal bleeding (35), history of bleeding (35, 44), increased bleed risk (3, 43), concomitant use of antiplatelets (32) and frailty (34) were independent predictors of non-prescription of anticoagulation. However, for the majority of these factors there were also studies that reported no independent association with prescription/non-prescription of anticoagulation (CHF n=2 (33, 39), previous stroke/TIA n=1 (39), TE n=1 (39), older age n=2 (36, 39), Black [vs. White] ethnicity n=1 (36), dementia/cognitive impairment n=1 (44), anaemia n=1 (35, 39), history of bleeding n=1 (39), increased bleed risk n=2 (29, 36) and concomitant use of antiplatelets n=2 (34, 39)) (Table 3).

Three studies considered the effect of facility characteristics (34, 35, 38) on the prescription and non-prescription of anticoagulation (Table 3). Calendar year in LTC was not independently associated with anticoagulant prescription (34). In addition, chain affiliated facilities, facilities with “poor” quality of care or pharmacy-related deficiencies were not found to be independently associated with anticoagulant prescription (35). There was only one study that investigated the effect of physician characteristics on the prescription and non-prescription of anticoagulation (38). Characteristics such as year of graduation, proportion of work in the LTC setting and number of LTC patients were not found to be associated with their decision to prescribe anticoagulation or not. Physicians who identified themselves as geriatricians were found to be more likely to prescribe warfarin in one of the clinical scenarios sent as part of the survey (OR 1.27, 95% CI 1.03-1.55) but not in another (38).

**DISCUSSION**

In this systematic review, our principal findings are as follows: AF prevalence ranged from 7.1%-38% (3, 19-23, 25, 26, 28-33, 37, 39, 40, 42, 44-46); ischaemic stroke events were over two and a half times more common in LTC residents with AF than those without AF (25); the prescription of anticoagulation was associated with an approximately three-fold reduction in ischaemic stroke events, with very low incidence of intracranial haemorrhage (one event) in one study (24) and in another, a non-significant increase in intracranial haemorrhage event rate was seen (34). Lastly, older age (32, 34, 35, 40, 43, 44), dementia/cognitive impairment (34-36, 40, 43) and falls/falls risk (43, 44) were independently associated with non-prescription of anticoagulation. Conversely, previous stroke/TIA (32-34, 40, 43) and TE (32, 34, 43) were independently associated with increased prescription of anticoagulation. To date, there have been no other systematic reviews that have considered the available evidence for these three major objectives, which underpin the management of AF in older people in LTC.

The inconsistent and varied estimates of AF prevalence across included studies likely reflects heterogeneity in the methods of AF diagnosis used in the studies, comprised of electrocardiography alone (23, 25, 26, 28, 29, 40, 45), medical records alone (3, 20-22, 33, 39, 42), electrocardiography and medical records (37, 44, 46) and database diagnostic codes (31, 32, 36). The highest prevalence of AF (38%) (46) was recorded in a high dependency residential unit providing nursing care. These residents had extensive multi-morbidity and a high proportion (45%) were documented to have hypertension which is responsible for physiological alterations that pre-dispose to AF (47).

The limited number of available studies examining outcomes of LTC residents with and without AF (n=1) (25) and with AF based on anticoagulant prescription (n=2) (24, 34) restricts any conclusions that can be drawn to provide evidence based guidance on the net risk-benefit of anticoagulation in the LTC population with AF. Further investigation of treatment outcomes is paramount to inform the development of treatment guidelines specific to this care setting; it is well recognised that anticoagulant use in LTC residents is complex and must take into account polypharmacy, frailty, dementia, multi-morbidity, falls risk, altered pharmacokinetics and pharmacodynamics and a simultaneously heightened stroke and bleeding risk profile (48).

Studies varied widely in the number of factors investigated to examine their effect on the prescription/non-prescription of anticoagulation. Resident characteristics were predominantly considered and only a small number of studies (n=3) examined the effect of physician (38) and facility characteristics (34, 35, 38). There were inconsistencies in the results reported and again, this is likely a reflection of significant diversity in the LTC population and type of LTC facility. In another systematic review of older people with AF which examined the effect of frailty of OAC prescription, irregularities were also evident; meta-analysis showed frailty was significantly associated with a lower odds of OAC prescription at hospital admission but not at hospital discharge, and an increased odds of OAC prescription in the community (49). Furthermore, significant heterogeneity owing to different analyses, different categories/cut-offs used to define older age and variation in methods used to determine bleed/stroke risk, dependency in activities of daily living and co-morbidity burden also limits the conclusions that can be drawn.

**Limitations**

We were unable to perform a meta-analysis of the results due to extensive heterogeneity amongst included studies. Whilst most studies ranked highly on the quality assessment, four studies scored poorly, and even studies of good quality may contain bias. Selection bias is a limitation of studies using database diagnostic codes; it is recognised that reporting of diagnoses in administrative data may vary depending on the condition being investigated, patient age, other co-morbidities, severity of illness, length of hospital stay and in-hospital mortality (50). Most studies did not provide a clear description of the type of LTC facility which limited interpretation of the results.

**Conclusions**

Estimates of AF prevalence and the factors associated with the prescription/non-prescription of anticoagulation varied extensively. Future research would benefit from stratification by type of LTC facility to account for diversity in resident age and comorbidities. The limited number of studies examining outcomes of LTC residents with AF also prevents the drawing of any definitive conclusions. Without more robust evidence, the risk-treatment paradox in this often-neglected population who are at high-risk of AF and adverse AF-related outcomes still exists. We recommend data collection on health outcomes, for example using a panel design, and data linkage with routinely collected health and social data to create longitudinal LTC cohorts (51, 52). Establishment of data capture systems about different LTC facilities will also help to address the issue of heterogeneity found amongst the included studies.

**Funding**

None.

**Figure 1. PRISMA flow diagram.**

## Screening

## Included

## Eligibility

## Identification

Records screened  
(n = 8431)

Records after duplicates removed  
(n = 8431)

Hand-searching of bibliographies  
(n=3)

Studies included in qualitative synthesis  
(n = 29)

Full-text articles assessed for eligibility  
(n = 34)

Records excluded  
(n = 8397)

Authors reporting on the same cohort in more than one study (number of studies)

Aronow et al (n=4)

Reardon et al (n=2)

Shurrab et al (n=2)

Full-text articles excluded because of no control group (n=1), incorrect study setting (n=1), recruitment of a subset of participants (n=2) and no control group and recruitment of a subset of participants (n=1)

Records identified through database searching  
(n = 9644)

**Table 1. Characteristics of included studies in long-term care reporting on (one or more of)** **prevalence of atrial fibrillation, outcomes for residents with AF and factors associated with the prescription/non-prescription of anticoagulation.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author, country (year)** | **Description of long-term care facility, (n)** | a**Sample size**  b**Proportion of females, n (%)**  c**Age (mean [SD] or median [IQR])** | **Prevalence of AF, n (%)** | **Number and proportion of participants with AF on anticoagulation** |
| **Cross-sectional** | | | | |
| Savickas et al, UK (2019) (45) | Care homes (4) linked to two general practices | a53  b40/53 (76%)  c90 (mean) [†] | 7 (14%) | † |
| Alcusky et al, USA (2019) (27) | Nursing homes (†) | a37787  b24939/37787 (66%)  c84 [IQR 78-90] | † | Warfarin 9320/37787 (24.7%), NOACs 8734/37787 (23.1%) |
| Shurrab et al, Canada (2017 (22), 2019 (21)) | Long-term care facilities (government-regulated centres where elderly care is provided under continuous nursing supervision at intensity guided by the clinical status of the resident) (25) | a3378  b293/433 (68% of females with AF)  c87 [SD 7] (participants with AF) | 433 (13%) | Warfarin 114/433 (26.3%), rivaroxaban 71/433 (16.4%), apixaban 62/433 (14.3%), dabigatran 26/433 (6%)d |
| Frain et al, Australia (2018) (43) | Government-funded residential aged-care facility (†) | a1952  b1290/1952 (66.1%)  c86.5 [SD 6.9] | † | Warfarin or dabigatran 567/1952 (29%) |
| Chaskes et al, USA (2018) (28) | Nursing home (†) | a211  b175/211 (82.9%)  c87.7 [SD 6.5] | 15 (7.1%) | † |
| O'Caoimh et al, Southern Ireland (2017) (46) | High dependency unit providing nursing care (4) | a225  b134/225 (60%)  c85 [IQR 77-89] | 86 (38%) | Warfarin 15/86 (17%) |
| Wiesel et al, USA (2017) (29) | Nursing homes (1) | a261  b48/101 (47.5% of females screened for AF)  c77.7 (mean) [†] (participants screened for AF) | 47 (18%) | † |
| Nishtala et al, Australia (2016) (41) | Low- and high-care residential aged care facilities from a single Residential Medication Management Review provider (†) | a146  b93/146 (63.7%)  c88.4 [SD 7.5] | † | Warfarin 37/146 (25.3%), dabigatran 5/146 (3.4%) |
| Oo et al, USA (2015) (30) | Long-term care facility, staffed by 10 physicians (1) | a400  b253/400 (63.2%)  c83.2 [SD 11.7] | 85 (21.3%) | Anticoagulantse only 36/85 (42.4%), anticoagulants and antiplatelets 22/85 (25.9%) |
| Bahri et al, France (2015) (44) | Nursing homes (104) | a10660  b796/1085 (73.4% of females with AF)  c87.1 [SD 5.3] (participants with AF) | 1085 (10.1%) | Warfarin 541/1085 (49.9%) |
| Reardon et al, USA (2012 (20)f, 2013 (19)) | Nursing homes (1500 from NNHS database, ~200 from AnalytiCare database) | NNHS database (first) and AnalytiCare database (second)  a13507, ~100,000  b1018/1452 (70% of females with AF), 2384/3757 (63.5% of females with AF)  c85 (median) [†] (participants with AF), 83 (median) [†] (participants with AF) | 1454 (10.8% of participants from NNHS database), †AnalytiCare database | Warfarin 502/1454 (34%, 95% CI 31.1-36.8% of participants with AF from NNHS database), warfarin 1674/3757 (45%, 95% CI 43-46.1% of participants with AF from AnalytiCare database) |
| Moore et al, USA (2012) (31) | Nursing homes (1174) | a11788  b8785/11788 (74.5%)  c84 [SD 8] | 2947 (25%) | † |
| Ghaswalla et al, USA (2012) (32) | Nursing homes (†) | a13507  b1259/1767 (71% of females with AF who were eligible for warfarin therapy)  c85.6 [SD 7.4] (participants with AF who were eligible for warfarin therapy) | 1904 (14%) | Warfarin 537/1904 (28.2%) |
| Latif et al, USA (2005) (33) | Nursing homes (2 inner city, 4 among inner and outer ring surburbs, all had at least 100 beds and at least 3 physicians) (6) | a934  b82/117 (70.7% of females with AF)  c84.6 (mean) [†] (participants with AF) | 117 (12.5%) | Warfarin 54/117 (46%) |
| Lau et al, Canada (2004) (39) | Long-term care institutions (17) | a2421  b167/265 (63% of females with AF)  c85 (mean) [†] (participants with AF) | 265 (11%) | Warfarin 152/265 (57.4%) |
| McCormick et al, USA (2001) (3) | Community-based long term care facilities, all certified by Medicare and Medicaid (21) | a2587  b336/429 (78% of females with AF)  c87 [SD 7.1] (participants with AF) | 429 (17%) | Warfarin 180/429 (42%) |
| Gurwitz et al, Canada (1997) (40) | Community-based nursing homes (23), university-affiliated facilities (5), US department of veterans affairs nursing home care units (2) | a5500  b272/413 (65.9% of females with AF)  c†g | 413 (7.5%) | Warfarin 130/413 (31%) |
| Lackner et al, USA (1995) (37) | Nursing homes (5) | a902  b67/85 (78.8% of females with AF)  c†h | 85 (9.4%) | Warfarin 17/85 (20%) |
| **Survey** | | | | |
| Monette et al, Canada (1997) (38) | Community based nursing homes (23), university-affiliated long-term care facilities (5), US Veterans Health Administration nursing homes (2) | a269  b†  c† | † | † |
| **Cohort** | | | | |
| Gill et al, USA (2019) (34) | CMS certified long-term care facility (provide short- and long-term care for people who need 24-hour nursing  care and who cannot be cared for at home) (†) | a21877  b16596/21877 (75.9%)  c†g | † | Prevalence across all study years: Warfarin, rivaroxaban or dabigatran, 36.2% (95% CI 35.6-36.8%) |
| Dutcher et al, USA (2015) (35) | Nursing homes (for-profit facility) (9133) | a16174  b12353/16174 (76.4%)  c84.5 [SD 7.4] | † | Average monthly prevalence of prescription: warfarin 82215 (37.4%), heparin 875 (0.4%), low molecular weight heparini 1886 (0.9%) |
| Patel et al, USA (2013) (36) | Nursing homes (200) | a148  b102/148 (69%)  c84 (median) [†] | † | † |
| Singh et al, Australia (2011) (42) | Aged-care facilities (29) | a1737  b178/262 (67.9% of females with AF)  c86.5 [SD 6.6] (participants with AF) | 262 (15%) | Warfarin 80/262 (30.5%), phenindione 1/262 (0.4%) |
| Aronow et al, USA (2002) (23)j | Long-term health facility (1) | a3624  b2464/3624 (68%)  c80 [SD 8] (male participants), 81 [SD 8] (female participants) | 495 (13.7%) | † |

AF, atrial fibrillation; CMS, Centers for Medicare and Medicaid Services; IQR, interquartile range; NNHS, National Nursing Home Survey; SD, standard deviation.

†not reported

dtaken from Shurrab et al 2017 (22), Shurrab et al 2019 (21) provides distributions for NOACs collectively

eanticoagulants included oral (warfarin and dabigatran) and injectable dosage forms (heparin and enoxaparin, assumed to be treatment doses)

freports AF prevalence from NNHS database only that is also reported in Reardon et al 2013 (19)

gage reported as percentage of participants for different age categories

hmean age reported for different subsets of participants according to anticoagulation status

iheparin and low molecular weight heparin (dalteparin, enoxaparin, tinzaparin) assumed to be treatment doses

jAronow et al have three other publications using the same cohort that report on AF prevalence (25, 26), health outcomes (24, 25) and factors associated with the prescription of anticoagulation (24), all are cohort studies with the exception of one which is cross-sectional (26)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author, country (year) | Gill et al, USA (2019) (34) | | Aronow et al, USA (1999) (24) | Aronow et al, USA (1996) (25) |
| Comparator | OAC therapy with warfarin, rivaroxaban or dabigatran vs. no OAC therapy for AF | | OAC therapy with warfarin vs. no OAC therapy (aspirin 325mg daily) for AF | AF vs. no AF |
| aParticipants with AF, n  bParticipants without AF, n  cParticipants with AF on OAC, n (%)  dParticipants with AF not on OAC, n (%) | a21877  b†  c7919 (36.2%, 95% CI 35.6-36.8%)  d13958 (63.8%) | | a312  b†  c187 (59.9%)  d125 (40%) | a283  b1818  c†  d† |
| Follow up (mean [SD]/median [IQR]) | 339 days [IQR 131-747] | | 34 months [SD 16] (OAC therapy) vs. 37 months [SD 18] (no OAC therapy) | 31 months [SD 18] (AF) vs. 44 months [SD 27] (no AF) |
| Ischaemic stroke events, n (%) | **Bivariate** | **Multivariate** | 40 (32%) vs. 122 (65.2%), p <0.001h,i | 131 (46%) vs. 303 (17%), p <0.0001j , Relative Risk 3.3, 95% CI 2.4-4.5k |
| 102 vs. 324 (event rate 2.94 vs. 4.10)e,f,g | Event rate 2.84 (95% CI 1.98-7.25) vs. 3.95 (95% CI 2.85-10.08)e,f,g |
| Intracranial haemorrhage events, n (%) | **Bivariate** | **Multivariate** | 1 (0.8%) vs. 0 (0%) | † |
| 22 vs. 55(event rate 0.63 vs. 0.7)e,f,g | Event rate 0.71 (95% CI 0.29-2.15) vs. 0.65 (95% CI 0.29-1.93)e,f,g |
| Other bleeding events, n (%) | † | | Gastrointestinal: 2 (1.6%) vs. 4 (2.1%)  Gross haematuria: 1 (0.8%) vs. 0 (0%) | † |
| All-cause mortality, n (%) | † | | † | † |

|  |
| --- |
| **Table 2. Outcomes of individuals living in long-term care with or without atrial fibrillation or with atrial fibrillation based on anticoagulation status.** |

AF, atrial fibrillation; IQR, interquartile range; OAC, oral anticoagulant; SD, standard deviation

†not reported

emultiple events occurring in the same person-month were classed as a single event, 3469 person years on OAC, 7708 person years not on OAC

fevent rate reported per 100 person-years

gGill et al (34) also looked at severe ischaemic stroke and intracranial haemorrhage (defined as length of hospital stay of 3 days or more)

hcalculated using chi-square test or Fisher’s exact test

iafter adjustment for gender, smoking, hypertension, diabetes mellitus, obesity, prior myocardial infarction, prior stroke, history of congestive heart failure, mitral stenosis, mitral annular calcium, left atrial enlargement, left ventricular hypertrophy, left ventricular ejection fraction, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides, age, and use of warfarin or aspirin and time to the development of a new thromboembolic stroke, warfarin use was associated with a 76% lower chance of incident ischaemic stroke.

jcalculated using chi-square test

kcalculated using multivariate cox regression model but confounders adjusted for not reported

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 3. Summary of studies conducting bivariate/multivariate analysis to investigate the factors associated anticoagulant prescription/non-prescription\*.** | | | | | | | | | | | | | | | | | | |
| **Factors associated with AC prescription/non-prescription**  **Key:**  ++ Independent predictor, increases prescription  -- Independent predictor, increases non-prescription  xx Non-significant multivariate analysis  + Significant bivariate analysis only, increases prescription  - Significant bivariate analysis only, increases non-prescription  x Non-significant bivariate analysis only | | | | **Ghaswalla 2012 (32)** | **Gurwitz 1997 (40)** | **Gill 2019 (34)** | **Bahri 2015 (44)** | **Patel 2013**  **(36)** | **Singh 2011 (42)** | **Dutcher 2015 (35)** | **Reardon 2013 (19)** | **Lau 2004 (39)** | **Latif 2005 (33)** | **Aronow 1999 (24)** | **Shurrab 2017 (22)** | **Frain 2018 (43)** | **Monette 1997 (38)** | **McCormick 2001 (3)** |
| **Resident characteristics** | Older agea | | | -- | -- | -- | -- | xx | - | -- | -/xb | xx | x | x | x | -- |  |  |
| Body weight | | |  |  |  |  | xx |  |  |  |  |  | x |  |  |  |  |
| Male gender | | | x | x | --C | x | --C |  | xx | x | x | x | x | x |  |  |  |
| Ethnicity | Non-white (vs. White) | | -- |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hispanic (vs. White) | |  |  |  |  | -- |  | xx | x |  |  |  |  |  |  |  |
| Other (vs. White) | |  |  | -- |  |  |  | xx | x |  |  |  |  |  |  |  |
| Black (vs. White) | |  |  | -- |  | xx |  | -- | x |  |  |  |  |  |  |  |
| White, African or American Hispanic | |  |  |  |  |  |  |  |  |  | x |  |  |  |  |  |
| **Medical history** | Congestive heart failure | | | ++ |  | ++ | + |  |  |  | +/xd | xx | xx | x | x |  |  |  |
| Previous stroke/TIA | | | ++ | ++ | ++ | x |  |  |  | +/xe | xx | ++ | + | x | ++ |  |  |
| Thromboembolism | | | ++ |  | ++ | + |  |  |  | + | xx |  |  | x | ++ |  |  |
| Hypertension | | |  |  | xx | + |  |  |  |  | xx | xx |  |  |  |  |  |
| Diabetes Mellitus | | | x |  | xx | + |  |  |  | +/xd | xx | xx | x |  |  |  |  |
| Myocardial Infarction | | | x |  |  |  |  |  |  |  |  |  | + |  |  |  |  |
| Dementia/cognitive impairment | | | x | -- | -- | xx | -- |  | -- | - |  | x |  | x | -- |  |  |
| Falls/falls risk | | | x | x | --/xxf | -- |  |  | xx | x |  | x |  |  | -- |  |  |
| Anaemia | | |  |  | -- |  |  |  | xx | -/xg | xx | x |  |  |  |  |  |
| Gastrointestinal bleeding | | | -- |  |  |  |  |  |  | -/xg |  | -- |  |  |  |  |  |
| Internal bleeding | | |  |  | -- |  |  |  |  | x |  |  |  |  |  |  |  |
| Valvular disease | | | ++ |  |  | +/xh |  |  |  | + | xx |  | + |  |  |  |  |
| History of bleeding | | |  | x |  | -- |  |  | -- |  | xx |  |  |  |  |  |  |
| Coronary artery disease | | | x |  |  |  |  |  |  | x | xx | x |  |  |  |  |  |
| Peripheral vascular disease | | |  |  | xx |  | xx |  |  | x |  | x |  |  |  |  |  |
| Malignancy | | | x |  | xx |  |  |  |  | x | xx |  |  |  |  |  |  |
| Liver/kidney disease | | | x |  | xx |  |  |  | xx | x | xx |  |  |  |  |  |  |
| Peptic ulcer disease | | |  |  |  |  |  |  |  |  | xx | x |  |  |  |  |  |
| Increasing stroke risk | | | + |  |  | xx | xx | + | xx | + | xx |  |  | x | xx | +/xi | xx |
| Increasing bleeding risk | | |  |  |  |  | xx |  |  | - | xx |  |  |  | -- |  | -- |
| **Medicines** | Polypharmacy | | | ++ |  |  | + |  |  |  |  | + |  |  | + |  |  |  |
| Use of antiplatelets | | | -- |  | xx |  |  |  |  | - | xx |  |  |  |  |  |  |
| Use of NSAIDs | | | + |  |  |  |  |  |  | x | xx |  |  |  |  |  |  |
| **Other** | Hospice residency/short life expectancy | | |  |  |  |  |  |  | -- | - |  |  |  |  |  |  |  |
| Length of stay in long-term care | | | x |  | xx |  |  |  |  |  |  |  |  |  |  |  |  |
| Less dependency in ADLs | | |  | x |  |  |  |  |  | + |  | x |  | x |  |  |  |
| Frailty | | |  |  | -- |  |  |  |  |  |  |  |  | x |  |  |  |
| Lower co-morbidity burden | | |  | x |  | + |  |  | ++ |  |  |  |  |  |  |  |  |
| Region in USA | | Midwest (vs. West) |  |  | ++ |  |  |  |  |  |  |  |  |  |  |  |  |
| South (vs. West) |  |  | xx |  |  |  |  |  |  |  |  |  |  |  |  |
| North East (vs. West) |  |  | xx |  |  |  |  |  |  |  |  |  |  |  |  |
| Midwest (vs. South) |  |  |  |  |  |  | ++ |  |  |  |  |  |  |  |  |
| Northeast (vs. South) |  |  |  |  |  |  | ++ |  |  |  |  |  |  |  |  |
| Midwest (vs. East) |  |  |  |  | -- |  |  |  |  |  |  |  |  |  |  |
| South-Central (vs. East) |  |  |  |  | xx |  |  |  |  |  |  |  |  |  |  |
| West (vs. South) |  |  |  |  |  |  | ++ |  |  |  |  |  |  |  |  |
| West (vs. East) |  |  |  |  | xx |  |  |  |  |  |  |  |  |  |  |

AC, anticoagulant; ADL, activities of daily living; NSAID, non-steroidal anti-inflammatory drug; TIA, transient ischaemic attack.

\*Factors were only included in the table if reported on by two or more studies in bivariate or multivariate analyses. Where studies conducted bivariate and multivariate analyses for the same factor, only results from multivariate analyses are reported in the table

aWhere studies reported the ages categorically, results of multivariate/bivariate analyses for the highest age category are reported

bReardon (19) significant p-value for trend reported for ages 75-84 and ≥85 years (<75 referent) for cohort from AnalytiCare database, but not for cohort from NNHS database

cGill (34) male gender independent predictor of AC non-prescription, Patel (36) female gender independent predictor of reduced AC discontinuation

dReardon (19) CHF and DM significantly associated with increased AC prescription for cohort from AnalytiCare database, but non-significant for cohort from NNHS database

eReardon (19) previous stroke significantly associated with increased AC prescription for cohort from NNHS database, but non-significant for cohort from AnalytiCare database

fGill (34) fall in the prior month independent predictor of AC non-prescription but falls history not

gReardon (19) anaemia and GI bleeding significantly associated with AC non-prescription for cohort from AnalytiCare database, but non-significant for cohort from NNHS database

hBahri (44) mitral insufficiency significantly associated with increased AC prescription but aortic stenosis and aortic insufficiency not

**i**Monette (38) each increase of 1 unit in the risk ratio (stroke risk/haemorrhagic risk) significantly associated with increased AC prescription for one clinical scenario presented to physicians as part of a survey (scenario 1), but not for another (scenario 2)

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**Appendices**

**Appendix 1- Supplementary materials: 2009 PRISMA Checklist (53)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | |  |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 1, 2 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4 |
| **METHODS** | | |  |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 4 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4, 5 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 5, 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 29 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 5, 6 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5, 6 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 5. 6 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 6, 7 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | 6, 7 |

Page 1 of 2

|  |  |  |  |
| --- | --- | --- | --- |
| **Section/topic** | **#** | **Checklist item** | **Reported on page #** |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 6, 7 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |
| **RESULTS** | | |  |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 7, 15 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 7, 8, 16 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 8, 31, 32 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 8, 9, 10, 11 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | N/A |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 31, 32 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | N/A |
| **DISCUSSION** | | |  |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 11, 12 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13, 14 |
| **FUNDING** | | |  |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 14 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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**Appendix 2- Supplementary materials: Search strategy**

Medline (ovid)

|  |
| --- |
| 1. exp atrial fibrillation/  2. exp atrial flutter/  3. AF.mp  4. a-fib.mp  5. atrial fibrillation\*.mp  6. atrium fibrillation\*.mp  7. (atri\* adj5 fibrillat\*).mp  8. (auricular\* adj5 fibrillat\*).mp  9. (auricular\* adj5 flutter\*).mp  10. (atri\* adj5 arrhytm\*).mp  11. (atri\* adj5 flutter\*).mp  12. (atri\* adj5 tachy\*).mp  13. 1-12/OR  14. exp care home/  15. exp nursing home/  16. exp hospice/  17. home\* for the aged.mp  18. halfway house\*.mp  19. ((nurs\* or care\* or long$term or geriatri\* or old\* or age\* or elder\* or senior\* or group\* or extend\*) adj5 (home\* or facilit\* or cent\* or institut\*)).mp.  20. 14–19/OR |

Cinhal Plus

|  |  |  |
| --- | --- | --- |
| (atrial N5 fibrillat\*) or (atrial N5 flutter\*) or (auricular N5 fibrillat\*) or (auricular N5 flutter\*) or (AF) or (afib) or (a-fib) | AND | (nursing home$) or (nursing facilit\*) or (nursing care) or (long-term facilit\*) or (long-term home$) or (long term facilit\*) or (long term home$) or (residential care) or (residential home$) or (residential facilit\*) or (geriatric home$) or (geriatric care) or (geriatric facilit\*) or (age$ care) or (age$ home$) or (age$ facilit\*) or (elder$ care) or (elder$ home$) or (elder$ facilit\*) or (intermediate care) or (intermediate home$) or (intermediate facilit\*) |

Web of science

|  |  |  |
| --- | --- | --- |
| (atrial N5 fibrillat\*) or (atrial N5 flutter\*) or (auricular N5 fibrillat\*) or (auricular N5 flutter\*) or (AF) or (afib) or (a-fib) | AND | (nursing home$) or (nursing facilit\*) or (nursing care) or (long-term facilit\*) or (long-term home$) or (long term facilit\*) or (long term home$) or (residential care) or (residential home$) or (residential facilit\*) or (geriatric home$) or (geriatric care) or (geriatric facilit\*) or (age$ care) or (age$ home$) or (age$ facilit\*) or (elder$ care) or (elder$ home$) or (elder$ facilit\*) or (intermediate care) or (intermediate home$) or (intermediate facilit\*) |

Scopus

|  |
| --- |
| ( ALL ( nursing AND home$ OR nursing AND facilit\* OR nursing AND care OR long-term AND facilit\* OR long-term AND home$ OR long AND term AND facilit\* OR long AND term AND home$ OR residential AND care OR residential AND home$ OR residential AND facilit\* OR geriatric AND home$ OR geriatric AND care OR geriatric AND facilit\* ) AND ALL ( ( atrial AND n5 AND fibrillat\* ) OR ( atrial AND n5 AND flutter\* ) OR ( auricular AND n5 AND fibrillat\* ) OR ( auricular AND n5 AND flutter\* ) OR ( af ) OR ( afib ) OR ( a-fib ) ) ) |

**Appendix 3- Supplementary tables: Quality assessment of included studies.**

**Table 1. Quality assessment of the included cohort studies using the Newcastle Ottawa Scale (13).**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Selection** | | | | **Comparability** | **Outcome** | | | **Total** | **Ranking** |
| Representative of exposed cohort | Selection of non-exposed cohort | Ascertainment of exposure | Outcome not present at start | Controls and adjusted | Ascertainment of outcome | Was follow up long enough | Adequate follow up |
| Gill 2019 (34) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 | Good |
| Dutcher 2015 (35) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 9 | Good |
| Patel 2013 (36) | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 8 | Good |
| Singh 2011 (42) | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 3 | Poor |
| Aronow 2002 (23) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 7 | Good |
| Aronow 1999 (24) | 0 | 1 | 0 | 1 | 2 | 1 | 1 | 0 | 6 | Fair |
| Aronow 1996 (25) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 7 | Good |

**Table 2. Quality assessment of the included cross-sectional studies using the modified Newcastle Ottawa Scale (14).**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Selection** | | | | **Comparability** | **Outcome** | | **Total** |
| Representative of exposed cohort | Sample size | Non-respondents | Ascertainment of exposure | Controls and adjusted | Ascertainment of outcome | Statistical test |
| Savickas 2019 (45) | 0 | 0 | 0 | 2 | 1 | 1 | 1 | 5 |
| Alcusky 2019 (27) | 1 | 1 | 1 | 2 | 2 | 2 | 0 | 9 |
| Shurrab 2019 (21) | 1 | 0 | 0 | 2 | 1 | 2 | 1 | 7 |
| Frain 2018 (43) | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 10 |
| Chaskes 2018 (28) | 0 | 0 | 0 | 2 | 1 | 2 | 1 | 6 |
| Shurrab 2017 (22) | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 10 |
| O'Caoimh 2017 (46) | 1 | 1 | 0 | 2 | 1 | 2 | 1 | 8 |
| Wiesel 2017 (29) | 1 | 1 | 0 | 2 | 1 | 2 | 1 | 8 |
| Nishtala 2016 (41) | 1 | 0 | 1 | 2 | 0 | 2 | 0 | 6 |
| Oo et al 2015 (30) | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 10 |
| Bahri 2015 (44) | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 10 |
| Reardon 2013 (19) | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 10 |
| Reardon 2012 (20) | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 10 |
| Moore 2012 (31) | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 9 |
| Ghaswalla 2012 (32) | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 10 |
| Latif 2005 (33) | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 10 |
| Lau 2004 (39) | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 10 |
| McCormick 2001 (3) | 1 | 1 | 1 | 2 | 0 | 2 | 1 | 8 |
| Gurwitz 1997 (40) | 1 | 1 | 1 | 2 | 2 | 2 | 1 | 10 |
| Monette 1997 (38) | 1 | 1 | 0 | 1 | 2 | 1 | 1 | 7 |
| Lackner 1995 (37) | 1 | 1 | 1 | 2 | 1 | 2 | 0 | 8 |
| Aronow 1987 (26) | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 9 |

**Appendix 4- Supplementary references: Full reference list**

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