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Systematic Review/Meta-analysis

Risk of Hospital Admissions in Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis

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See editorial by Samuel and Brophy, pages 1291–1293 of this issue.

ABSTRACT

Background: Atrial fibrillation (AF) is associated with multiple comorbidities and various adverse outcome events, suggesting a high risk of hospital admissions in this patient population. However, its exact incidence and potential underlying causes are not well defined. The objective of this systematic review was to investigate the incidence and risk factors for hospital admissions in patients with AF.

Methods: We systematically searched MEDLINE, EMBASE, and CENTRAL for studies providing information on all-cause hospital admissions. Studies were included if they provided information on the incidence of all-cause hospital admissions in $\geq$ 100 patients with AF, and had $\geq$ 1 year of follow-up. Incidence estimates were pooled using random-effects models. Meta-regression analysis was performed to identify characteristics associated with between-study heterogeneity.

Results: Thirty-five studies (n = 311,314 patients) were included. The pooled incidence of all-cause hospital admissions was 43.7 (95% confidence interval [CI], 38.5-48.9; I^2 = 99.9%) per 100 person-years. In 24 studies (n = 234,028 patients) that provided information on admission causes, cardiovascular hospitalizations were more

RÉSUMÉ

Contexte : La fibrillation auriculaire (FA) est associée à de multiples maladies concomitantes et à diverses issues défavorables, ce qui donne à penser qu'un risque élevé d'hospitalisation existe au sein de la population de patients qu'elle touche. Cependant, son incidence exacte et ses causes sous-jacentes potentielles ne sont pas bien définies. Le présent article propose une revue systématique des données sur l'incidence et les facteurs de risque d'hospitalisation chez les patients atteints de FA.

Méthodologie : Nous avons effectué dans MEDLINE, EMBASE et CENTRAL une recherche systématique d'études fournissant des renseignements sur les hospitalisations toutes causes confondues. Les études retenues pour les besoins de notre revue de données devaient fournir des renseignements sur l'incidence des hospitalisations toutes causes confondues chez $\geq$ 100 patients atteints de FA et comporter une période de suivi d'au moins un an. Les estimations de l'incidence ont été regroupées à l'aide de modèles à effets aléatoires. Une analyse de métarégression a été effectuée afin de cerner les caractéristiques associées à l'hétérogénéité interétude.

Atrial fibrillation (AF) affects more than 3% of the general adult population, and its prevalence is expected to further increase over the next decades.[1-3] Patients with AF have an increased risk of death, stroke, and heart failure, and they also seem to have a higher risk of non-cardiovascular diseases.[4-8] Accordingly, patients with AF have a higher risk of being admitted to the hospital compared with individuals without AF.[9] Hospital admissions seem to account for the highest proportion of direct health care expenditure.[10-12] A recent systematic review estimated that in patients with AF, 50% to 70% of the annual direct costs were directly attributable to hospitalizations and inpatient care.[13]

Unfortunately, precise data on the incidence and underlying causes of hospital admissions in AF patients are not readily available. Such information would be of major interest, as they may help to plan resource use, develop prevention

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common than noncardiovascular hospitalizations (pooled incidence 26.3 [95% CI, 22.7-29.9; I^2 = 99.9%] vs 15.7 [95% CI, 12.5-18.9; I^2 = 99.8%] per 100 person-years). In meta-regression analyses, older age (β = 1.4 [95% CI, 0.33-2.53], P = 0.01, R^2 = 15.7%) and prevalence of chronic pulmonary disease (β = 1.5 [95% CI, 0.57-2.45], P = 0.005, R^2 = 49.8%) were associated with an increased rate of all-cause hospital admissions.

Conclusions: Patients with AF have a very high risk of being admitted to the hospital, both for cardiovascular and noncardiovascular causes. The development and implementation of preventive strategies should be a public health priority.

Résultats : Trente-cinq études (n = 311 314 patients) ont été retenues. L'incidence des hospitalisations toutes causes confondues chez ces patients après regroupement des données s'est établie à 43,7 (intervalle de confiance [IC] à 95 % de 38,5 à 48,9; I^2 = 99,9 %) par 100 années-personnes. Dans 24 études (n = 234 028 patients) qui comportaient des renseignements sur les causes d'admission, les hospitalisations attribuables à des causes cardiovasculaires étaient plus fréquentes que les hospitalisations attribuables à des causes autres que cardiovasculaires (incidence après regroupement des données de 26,3 [IC à 95 % de 22,7 à 29,9; I^2 = 99,9 %] vs 15,7 [IC à 95 % de 12,5 à 18,9; I^2 = 99,8 %] par 100 années-personnes). Dans les analyses de métarégression, l'âge avancé (β = 1,4 [IC à 95 % de 0,33 à 2,53], P = 0,01, R^2 = 15,7 %) et la prévalence de maladies pulmonaires chroniques (β = 1,5 [IC à 95 % de 0,57 à 2,45], P = 0,005, R^2 = 49,8 %) étaient associés à une augmentation du taux d'hospitalisation toutes causes confondues.

Conclusions : Les patients atteints de FA courent un risque très élevé d'hospitalisation tant pour des causes cardiovasculaires que non cardiovasculaires. L'élaboration et la mise en œuvre de stratégies de prévention devraient être une priorité de santé publique.

strategies to minimize the risk of costly hospital admissions, and improve outcomes among AF patients.[14]

We therefore conducted a comprehensive systematic review and meta-analysis to summarize the available information on the risk of hospital admissions and underlying causes among patients with AF.

Methods

This systematic review and meta-analysis was not registered but complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) standards.[15,16]

Eligibility criteria

Studies were included if they fulfilled all of the following criteria: (1) They were cohort studies or randomized controlled trials, (2) reported data on at least 100 patients with AF, (3) reported the incidence of all-cause hospital admissions in patients with AF or sufficient information to calculate it, and (4) had at least 1 year of follow-up. To minimize the risk of reporting bias, we excluded studies that reported only on cause-specific hospital admissions, such as hospitalizations for heart failure.

Search methods

We developed a search strategy in collaboration with an experienced research librarian and systematically searched MEDLINE (via PubMed), CENTRAL (Cochrane Central Register of Controlled Trials), and EMBASE (via Ovid) from database inception to December 21, 2017. In addition, we screened reference lists of studies fulfilling inclusion criteria for additional relevant articles. In case of incomplete data, we contacted the corresponding study authors to provide us with additional information. For our search, we used Medical Subject Heading (MeSH) terms and keywords such as "hospital admission," "hospitalization," and "atrial fibrillation." No language or geographical restrictions were applied to the search, and abstracts were included. The complete search strategy is outlined in Supplemental Figure S1.

Two independent reviewers (P.M. and Se.B.) screened titles and abstracts of all articles identified in the initial search. Full texts of all potentially eligible manuscripts were reviewed by the same authors for eligibility. Disagreements were resolved through discussion or third-party arbitration (St.B.).

Data extraction and outcome assessment

From each eligible study, we extracted in duplicate the following information using a standardized case report form: study design, participating country, year of publication, total number of patients, AF type, follow-up time, average age of patients, number and percentages of male patients, cardiovascular risk factors (hypertension, diabetes), cardiovascular comorbidities including coronary artery disease, heart failure, previous stroke or transient ischemic attack (TIA), and peripheral vascular disease and noncardiovascular comorbidities including chronic pulmonary disease, chronic kidney disease, and cancer.

As the main outcome, we extracted the reported incidence of all-cause hospital admissions. If available, we also extracted incidences on admissions for cardiovascular vs noncardiovascular causes. Extracted data were entered into a Microsoft Access database (Microsoft Corp, Redmond, Washington).

Assessment of study quality

The methodological quality of included studies was evaluated using a modified version of the Newcastle-Ottawa Scale.[17] We focused on the individual components of the Newcastle-Ottawa Scale and excluded the comparability component from the scale because it did not apply to this meta-analysis. The following quality components were evaluated: representativeness of the study population, methods of the outcome assessment, and adequacy of follow-up assessment. Studies were categorized as having a high study quality

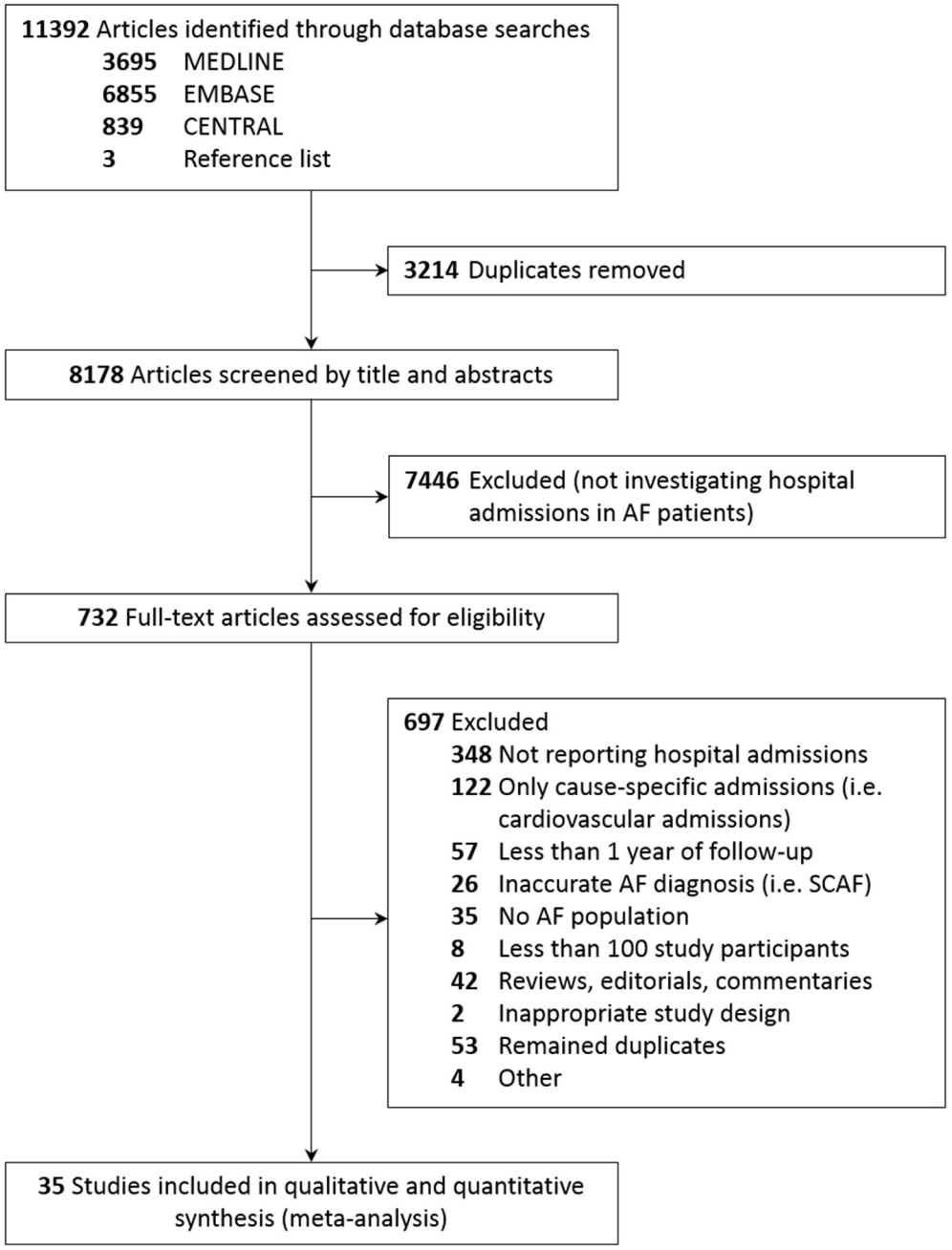

Figure 1. Flow diagram of literature search strategy. SCAF, subclinical atrial fibrillation.

(3 points), moderate study quality (2 points), or low study quality ($\leq$ 1 point).

Statistical analyses

If not available in the original publication, we calculated the incidence of all-cause, cardiovascular and noncardiovascular hospital admissions by dividing the number of admissions by the mean follow-up time in years multiplied with the total number of patients with AF. We calculated 95% confidence intervals (95% CI) approximating the Poisson distribution. Incidence rates were pooled using random-effect models according to the method described by DerSimonian and Liard.[18] The influence of each individual study on the overall incidence estimate was tested in a sensitivity analysis by sequentially excluding each study and subsequently repeating the meta-analysis. The between-study heterogeneity was assessed using the Cochran's Q statistic and quantified by the I^2 statistic. We considered I^2 values $\geq$ 50% to indicate substantial heterogeneity and values $\geq$ 75% considerable heterogeneity.[19]

To explore the between-study heterogeneity, we divided study results into subgroups according to predefined study-level characteristics (geographical region, sample size, study design, publication status [peer-reviewed article versus abstract], and study quality) and compared them using random-effects meta-regression.[20] Differences in incidence across

Table 1. Characteristics of included studies

Author, year	Study design	Country	No. of patients	Age, years	Male sex, no. (%)	Hypertension, no. (%)	Heart failure, no. (%)	Prior stroke/TIA, no. (%)	Follow-up, years	NOS*
Hohnloser et al.[23] 2000	Randomized controlled trial	Germany	252	Mean (SD), 60.5 (9.5)	184 (73)	123 (49)	0 (0)	N/R	Mean: 1	1
Inglis et al.[24] 2004	Randomized controlled trial	Australia	152	Mean (SD), 73.3 (8.8)	81 (53)	85 (56)	87 (57)	N/R	Mean: 5	3
Nieuwlaat et al.[25] 2008	Prospective cohort	Europe	3890	Mean (SD), 66.4 (12.1)	2199 (57)	N/R	N/R	N/R	Median (IQR), 1 (1-1.1)	2
Ahmed et al.[26] 2009	Randomized controlled trial	United States, Canada	487	Mean (SD), 63.2 (11.2)	417 (86)	286 (59)	487 (100)	N/R	Median (range), 1.8 (1-50)	2
Connolly et al.[27] 2009	Randomized controlled trial	International	18113	Mean (SD), 72 (8.7)	11514 (64)	14283 (79)	5793 (32)	3623 (20)	Median: 2.0	3
Reynolds et al.[28] 2010	Prospective cohort	United States, Canada	933	Mean (SD), 66 (14)	559 (60)	452 (48)	423 (45)	N/R	Mean (SD), 2.0 (0.8)	2
Yusuf et al.[29] 2011	Randomized controlled trial	International	9016	Mean (SD), 69.5 (9.7)	5475 (61)	7929 (88)	2881 (32)	1212 (13)	4.1	3
Linssen et al.[30] 2011	Randomized controlled trial	Netherlands	336	Mean (SD), 73 (9.5)	218 (65)	154 (46)	336 (100)	57 (17)	1.5	2
Torp-Pedersen et al.[31] 2011	Randomized controlled trial	International	4628	Mean (SD), 71.6 (9)	2459 (53)	3995 (86)	979 (21)	N/R	Mean (SD), 1.8 (0.4)	3
Amin et al.[32] 2012	Retrospective cohort	United States	3498	Mean (SD), 80 (7.6)	1484 (42)	3119 (89)	0 (0)	546 (16)	1	2
Naccarelli et al.[33] 2012	Retrospective cohort	United States	55774	Mean (SD), 77.7 (6.8)	29129 (52.2)	44877 (80)	0 (0)	4186 (8)	Mean (SD), 2.0 (0.7)	1
Piccini et al.[34] 2012	Retrospective cohort	United States	15423	Mean (SD), 72 (5.3)	9158 (59)	12072 (78)	3980 (26)	992 (6)	1	2
Vidal-Perez et al.[35] 2013	Prospective cohort	Spain	778	Mean (SD), 74.8 (9.2)	413 (53)	595 (76)	96 (12)	64 (8)	Mean (SD), 2.8 (0.7)	3
Hohnloser et al.[36] 2013	Randomized controlled trial	International	5599	Mean (SD), 70 (9.5)	3277 (59)	4837 (86)	2171 (39)	764 (14)	Mean: 1.1	2
Mohanty et al.[55] 2013	Randomized controlled trial†	Italy	360	Mean (SD), 61.5 (9.5)	273 (76)	N/R	N/R	N/R	Mean (SD), 1.7 (0.8)	0
LaPointe et al.[37] 2014	Retrospective cohort	United States	79232	Median (IQR), 57 (51-61)	50708 (64)	40408 (51)	9508 (12)	3962 (5)	Median (IQR), 1.1 (0.5-2.0)	2
Bengtson et al.[38] 2014	Prospective cohort	United States	932	Mean (SD), 73.5 (4.8)	519 (56)	559 (60)	98 (11)	N/R	Mean (SD), 4.1 (3.6)	2
Gallagher et al.[39] 2014	Retrospective cohort	United Kingdom	16513	Mean (SD), 74 (12)	8592 (52)	8113 (49)	1357 (8)	1844 (11)	Mean (SD), 1.9 (1.4)	2
Lip et al.[40] 2014	Prospective cohort	International	2589	Mean (SD), 68.7 (11.6)	1568 (61)	N/R	N/R	N/R	Mean (SD), 1 (0.1)	2
Ozin et al.[56] 2014	Prospective cohort†	Turkey	213	N/R	N/R	N/R	N/R	N/R	1	1
Steinberg et al.[9] 2014	Prospective cohort	United States	9484	Median (IQR), 75 (67-82)	5406 (57)	7872 (83)	3073 (32)	1423 (15)	1	3
Whitbeck et al.[41] 2014	Prospective cohort	United States, Canada	3804	Mean (SD), 69.7 (9)	61‡	N/R	N/R	N/R	Mean: 3.5	2
Khazanie et al.[42] 2014	Retrospective cohort	United States	11535	Mean (range), 81 (75-87)	54444 (47)	8406 (73)	11535 (100)	1911 (17)	3	2
Freeman et al.[43] 2015	Retrospective cohort	United States	14787	Mean (SD), 71.7 (11.3)	7714 (52)	11573 (78)	0 (0)	877 (6)	Median (IQR), 1.2 (0.5-2.0)	3
Wu et al.[44] 2015	Retrospective cohort	Canada	25284	Mean (SD), 70.4 (13.8)	14122 (56)	13270 (52)	4945 (20)	1631 (6)	1	1
DeVore et al.[45] 2016	Prospective cohort	International	14171	Median (IQR), 73 (65-78)	8566 (60)	12824 (90)	8851 (6)	7767 (55)	Median (IQR), 1.8 (1.3-2.3)	3

Continued

Table 1. Continued.

Author, year	Study design	Country	No. of patients	Age, years	Male sex, no. (%)	Hypertension, no. (%)	Heart failure, no. (%)	Prior stroke/TIA, no. (%)	Follow-up, years	NOS*
Kuck et al.[46] 2016	Randomized controlled trial	Europe	750	Mean (SD), 60 (9.5)	457 (61)	436 (58)	209 (28)	30 (4)	Mean (SD), 1.5 (0.8)	2
Steinberg et al.[47] 2016	Prospective cohort	United States	5738	Median (IQR), 71 (64-79)	3339 (58)	N/R	1187 (21)	683 (12)	Median: 1	2
Wen et al.[57] 2016	Retrospective cohort†	China	992	Mean (SD), 73.8 (11.7)	N/R	387 (39)	99 (10)	992 (100)	Mean (SD), 1.3 (0.4)	1
Cadrin-Tourigny et al.[48] 2017	Randomized controlled trial	International	655	Mean (SD), 69.8 (10.4)	530 (81)	N/R	655 (100)	49 (7)	Mean (SD), 3.1 (1.6)	2
Chamberlain et al.[49] 2017	Prospective cohort	United States	1430	Mean (SD), 73.6 (13.8)	695 (49)	1016 (71)	260 (18)	208 (15)	Mean (SD), 6.3 (3.9)	2
Ferguson et al.[50] 2017	Prospective cohort	Australia	133	Mean (SD), 72 (16)	87 (65)	85 (64)	133 (100)	29 (22)	1	2
Gibson et al.[51] 2017	Randomized controlled trial	International	2124	Mean (SD), 70.1 (8.9)	1581 (74)	1571 (74)	542 (26)	N/R	1	3
Vora et al.[52] 2017	Prospective cohort	India	1537	Mean (SD), 54.7 (15.9)	746 (49)	482 (31)	288 (19)	141 (9)	1	2
Zweiker et al.[53] 2017	Retrospective cohort	Austria	172	Median (IQR), 82 (78-85)	107 (62)	143 (83)	25 (15)	N/R	1	1

IQR, interquartile range; NOS, Newcastle Ottawa Scale; N/R, not reported; Ref., reference; SD, standard deviation TIA, transient ischemic attack.
* 3 points indicate high quality, 2 points moderate, and ≤ 1 point low quality.
† Abstract from conferences.
‡ This information was extracted from the baseline characteristics reported in the main study.

predefined characteristics (age, sex, duration of follow-up, hypertension, diabetes, coronary artery disease, previous stroke or TIA, heart failure, peripheral vascular disease, chronic pulmonary disease, chronic kidney disease, and cancer) were explored using meta-regression analysis. The R^2 value was used to indicate the proportion of between-study variability explained by the model. As most characteristics were available only in a minority of studies, we did not perform multivariable analyses.

Specific causes for hospital admissions were extracted if available and classified into the following categories: AF-related, heart failure, bleeding, stroke, myocardial infarction, systemic embolism, bacterial and viral infections, gastrointestinal, respiratory, renal, neurological, cancer, endocrine and metabolic, hematological, skin and soft tissue, and psychiatric. Proportions for each cause category and corresponding 95% CIs were calculated and subsequently pooled using random-effects meta-analysis.

Publication bias was examined by visual inspection of funnel plots and using Egger's tests.[21,22] All analyses were performed using Stata, version 13.0 (StataCorp LLC, College Station, Texas). Statistical tests were 2-tailed, and a $P < 0.05$ was considered to indicate statistical significance.

Results

Characteristics of included studies

A total of 35 studies including 311,314 patients with AF were included, 32 full-text articles,[9,23-54] and 3 abstracts (Fig. 1, Table 1).[55-57] Twenty-five articles were prospective studies (13 prospective cohorts and 12 randomized controlled trials) (n = 88,104), and 10 were retrospective cohort studies (n = 223,210). Fourteen studies were conducted in North America, 10 in Europe, 2 in Australia, 1 in China, 1 in India, and 7 were international studies. The median number of participants per study was 3498 (interquartile range [IQR], 750-9,484). The average age in each study ranged from 55 to 82 years, and 42% to 86% of the participants were men. The average duration of follow-up was 1.5 (range: 1 to 6.3) years. From the assessment of study quality using the Newcastle-Ottawa Scale, 9 studies received 3 points, 19 studies received 2 points, 6 studies received 1 point, and 1 abstract received 0 points (Table 1) (see full study quality assessment in the Supplemental Table S1).

Incidence of all-cause hospital admissions

The pooled incidence of all-cause hospital admissions was 43.7 (95% CI, 38.5-48.9) per 100 person-years. The individual incidence rates ranged from 8.9 to 88.0 per 100 person-years, indicating considerable between-study heterogeneity ($I^2 = 99.9\%$, $P < 0.001$) (Fig. 2). None of the individual studies strongly influenced the pooled estimate, as shown in Supplemental Table S2. There was no statistically significant difference in the incidence of hospital admission across different geographic regions, sample size, study design, publication status, or total Newcastle Ottawa Scale (all P for difference > 0.05), as shown in Figure 3.

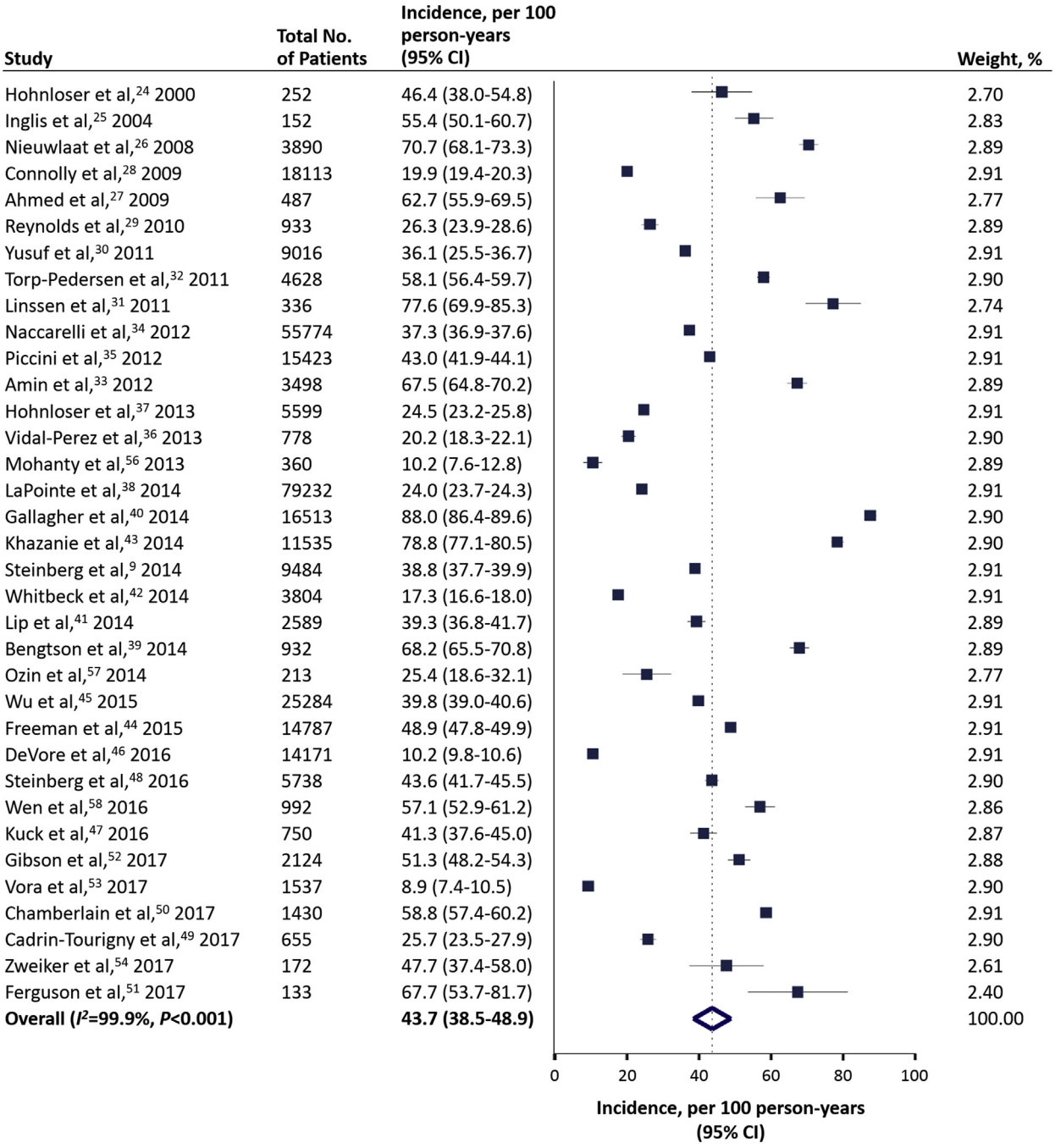

Figure 2. Cumulative incidence of all-cause hospital admissions. **Small black squares** represent the individual study incidence estimates with corresponding 95% confidence interval denoted by **black lines**. The **blue diamond** represents the pooled incidence estimate. Meta-anaylsis is done with random-effects model.

Cardiovascular vs noncardiovascular hospital admissions

Twenty-four studies including 234,028 patients provided separate data on the rates of cardiovascular and noncardiovascular admissions. In these studies, the pooled incidence of cardiovascular and noncardiovascular hospital admissions was 26.3 (95% CI, 22.7-29.9; I^2 = 99.9%, P < 0.001) and 15.7 (95% CI, 12.5-18.9; I^2 = 99.8%, P < 0.001) per 100 person-years, respectively (Figs. 4 and 5). None of the individual studies significantly affected the summary estimates of either cardiovascular or noncardiovascular admissions (Supplemental Tables S3 and S4). No statistically significant variations in cardiovascular hospital admission rates were observed by geographic region, sample size, study design, and total Newcastle-Ottawa Scale (all P for difference > 0.05) (Supplemental Fig. S2). There were significant differences in incidence estimates of

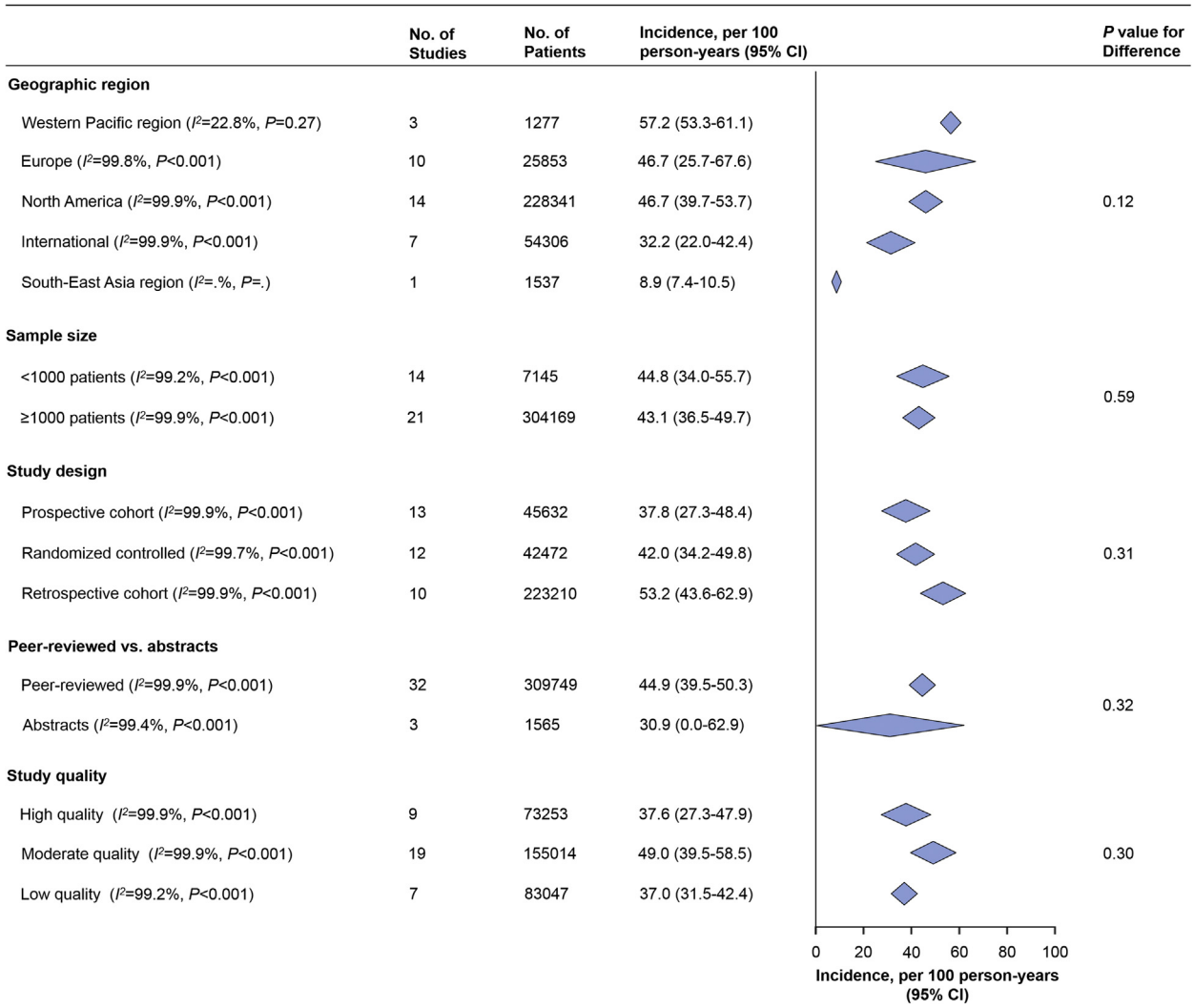

Figure 3. Cumulative incidence of all-cause hospital admissions stratified by study-level characteristics. **Blue diamonds** represent the pooled incidence estimate for each subgroup computed by random-effects models. Pooled estimates are weighted according to number of studies within the subgroups. *P* for difference between subgroups was calculated using random-effects meta-regression.

noncardiovascular admissions across different geographic regions (P for difference = 0.04). Further significant differences in incidence estimates of noncardiovascular admissions by sample size, study design and total Newcastle-Ottawa Scale were not observed, as presented in the Supplemental Fig. S3 (all P for difference > 0.05).

Specific causes for cardiovascular hospital admissions were reported in all 24 studies. AF-related admissions (22.0% [95% CI, 16.7%-27.2%]; $I^2 = 99.8\%$, $P < 0.001$) and admissions due to heart failure (16.6% [95% CI, 13.1%-20.2%]; $I^2 = 99.8\%$, $P < 0.001$) were the most common causes for cardiovascular admissions, followed by bleedings (5.9% [95% CI, 4.4%-7.5%]; $I^2 = 98.8\%$, $P < 0.001$), stroke (4.5% [95% CI, 4.4%-7.5%]; $I^2 = 97.9\%$, $P < 0.001$), and myocardial infarction (4.4% [95% CI, 3.4%-5.3%]; $I^2 = 97.2\%$, $P < 0.001$) (Supplemental Fig. S4). Four studies [24,36,45,51] including 22,046 patients provided specific causes for noncardiovascular hospital admissions, with the most common being bacterial infections (6.9% [95% CI, 0.0%-15.4%]; $I^2 = 99.2\%$, $P < 0.001$), gastrointestinal disorders (6.5% [95% CI, 4.3%-8.6%]; $I^2 = 88.5\%$, $P < 0.001$), and respiratory diseases (6.1% [95% CI, 3.2%-8.9%]; $I^2 = 94.5\%$, $P < 0.001$) (Supplemental Fig. S5).

Characteristics associated with hospital admissions

In meta-regression analyses, average age (R^2 across 34 studies 15.7%) and prevalence of chronic pulmonary disease (R^2 across 13 studies 49.8%) were significantly associated with the incidence of all-cause hospital admissions (Table 2). No significant associations were observed for sex; duration of follow-up; prevalence of hypertension, diabetes, coronary artery disease, history of stroke/TIA, heart failure, or chronic kidney disease (meta-regression plots of statistically significant associations are presented in Supplemental Fig. S6). No significant predictor for cardiovascular hospital admissions was identified (Table 2). Mean duration of follow-up, prevalence of chronic pulmonary disease, and prevalence of cancer were associated with a higher incidence of noncardiovascular

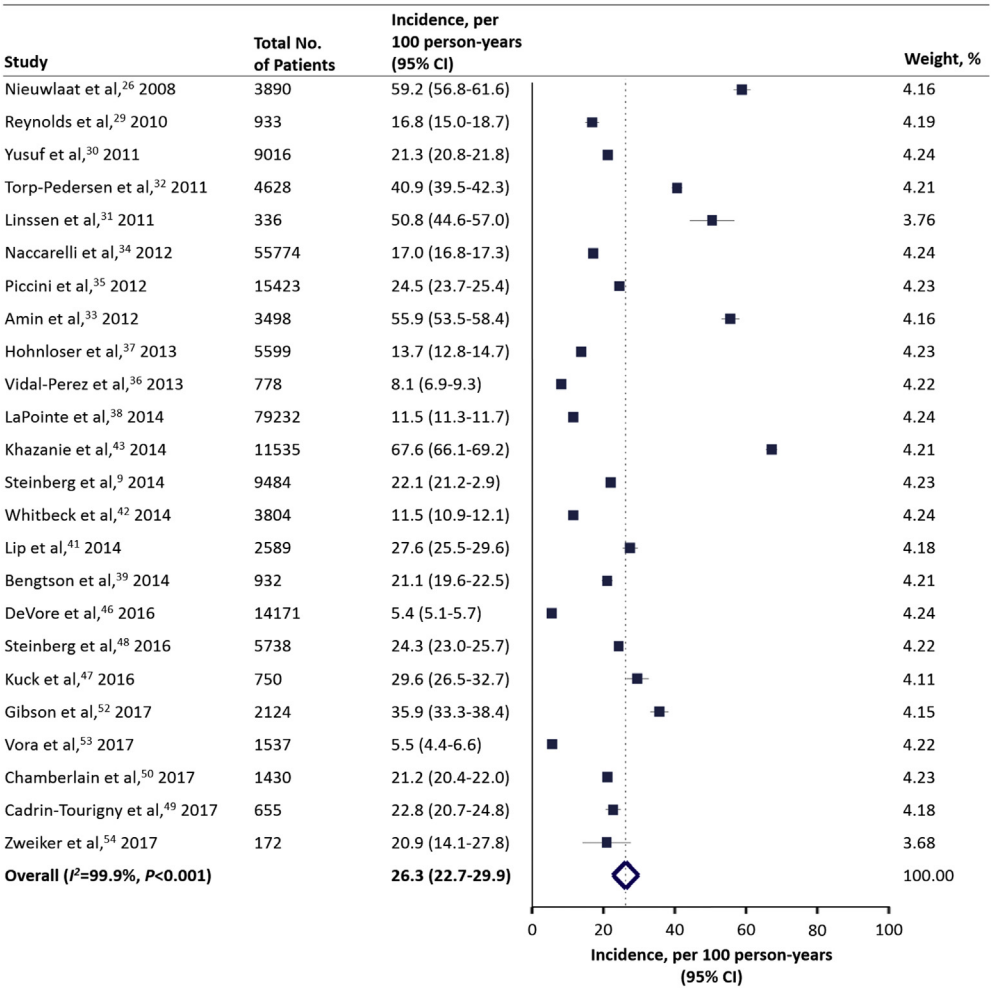

Figure 4. Cumulative incidence of cardiovascular hospital admissions. **Small black squares** represent the individual study incidence estimates with corresponding 95% confidence interval denoted by **black lines**. The **blue diamond** represents the pooled incidence estimate. Meta-anaylsis is done with random-effects model.

hospital admissions. Prevalence of chronic pulmonary disease explained 52.4% of the observed between-study heterogeneity across 9 studies, longer duration of follow-up explained 15.2% of the observed heterogeneity across 24 studies, and prevalence of cancer explained 99.9% of the observed heterogeneity across 3 studies.

Publication bias

Visual inspection of the funnel plot of studies reporting on cardiovascular hospitalizations showed some asymmetry (Supplemental Fig. S7) and the Egger's test indicated some evidence for publication bias suggesting that smaller studies present more extreme incidence rates ($P = 0.05$). No evidence of publication bias was observed for studies reporting on all-cause hospitalizations ($P = 0.06$), and noncardiovascular hospitalizations ($P = 0.87$), as shown in Supplemental Figs. S8 and S9.

Discussion

In this systematic review and meta-analysis of 35 studies including 311,314 patients with AF, we found a very high risk of hospital admissions, with a pooled incidence of 43.7 per 100 person-years. Patients with AF were more often admitted for cardiovascular causes (26.3 per 100 person-years) but also had substantial risk of admissions for noncardiovascular causes (15.7 per 100 person-years). Main risk factors for hospital admissions were older age, duration of follow-up, and major comorbidities such as chronic pulmonary disease and cancer.

In 2013, the estimated AF-related health care spending in the United States reached $27.7 billion, of which 41% was directly attributable to inpatient care.[58] Annual hospital admission rates in the general United States population were 10.4 per 100 person-years in 45 to 64 year old individuals, and 26.4 per 100 person-years in 65 to 84 year olds.[59] Our meta-analysis suggests that this risk is 1.6 times higher among patients with AF, underscoring the enormous burden these hospitalizations represent, both from a health and an economical perspective.

Most admissions for patients with AF are due to cardiovascular causes, with a pooled incidence of 26.3 per 100 person-years. Not surprisingly, the most common individual causes were due to AF-related conditions, heart failure, and stroke. Although lower, the risk of admissions for noncardiovascular causes was also considerable, with a pooled incidence of 15.7 per

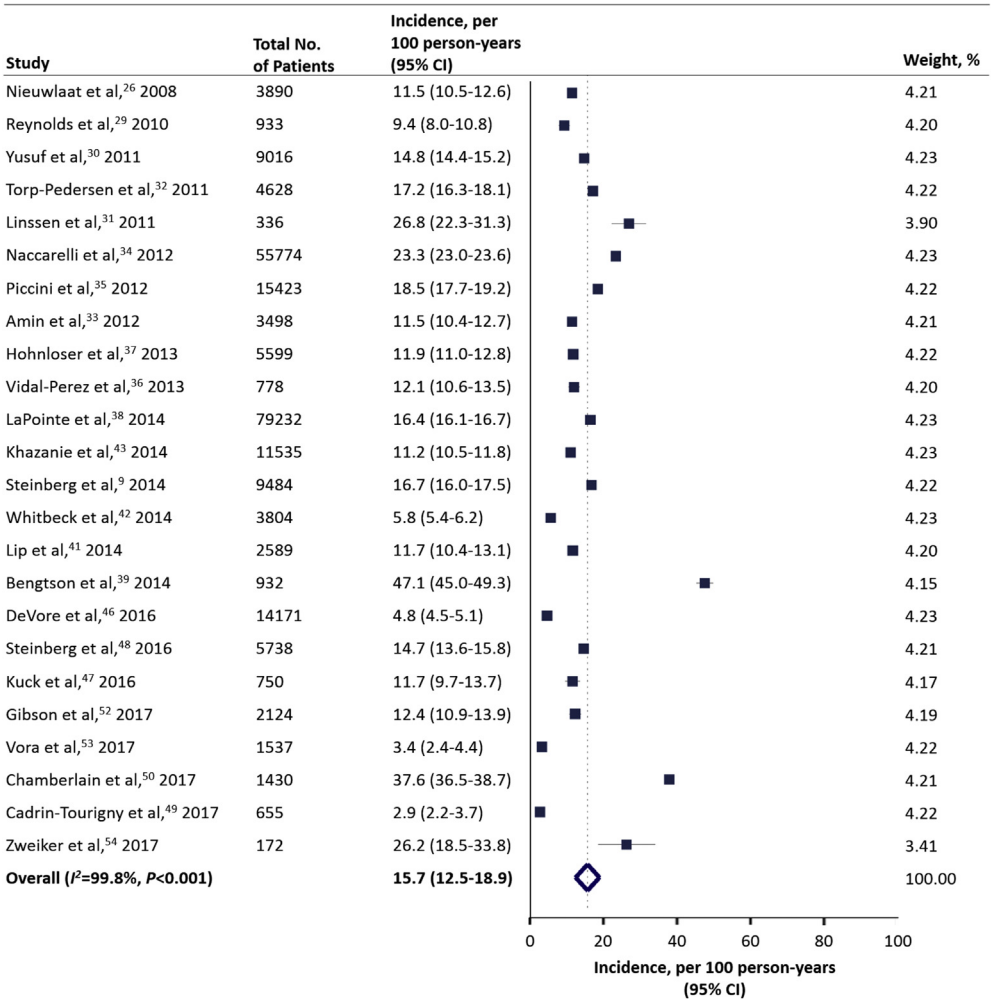

Figure 5. Cumulative incidence of noncardiovascular hospital admissions. **Small black squares** represent the individual study incidence estimates with corresponding 95% confidence intervals denoted by **black lines**. The blue diamond represents the pooled incidence estimate. Meta-anaylsis is done with random-effects model.

100 person-years. Unfortunately, information on specific admission causes was unavailable in most studies. Getting a better understanding on causes for noncardiovascular admissions will be crucial to develop effective prevention strategies.

Several patient characteristics significantly contributed to the observed between-study heterogeneity. Studies including older patients or patients who had a higher prevalence of chronic pulmonary disease or cancer had a higher incidence for all-cause or noncardiovascular admissions. None of the assessed characteristics explained the heterogeneity for cardiovascular admissions. Studies with longer follow-up duration resulted in higher incidence rates for noncardiovascular admissions, and there was some evidence of publication bias for all-cause and cardiovascular admissions. Regional differences in hospital admission did not significantly explain the observed heterogeneity in our study. Given the small number of studies in the subgroups and the potential associated decrease in statistical power, we cannot exclude the possibility that significant variations in admission rates exist across different subgroups. These data indicate that large long-term studies with more complete reporting of comorbidities are needed to get a better understanding in this area.

Reducing hospital admissions should be a major public health priority, not only from an economic perspective. Hospitalized patients with AF have a substantially higher risk of stroke and all-cause death compared with outpatients.[60,61] For example, an analysis of the **A**pixaban **Ver**sus Acetylsalicylic Acid (ASA) to P**r**event Str**o**k**e**s in Atrial Fibrillation Patient**s** Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial showed that, compared with patients who did not need hospital admission, those admitted had an almost 4-fold higher risk of death after discharge.[36] This observation may also account for some of the variability in reported outcome rates in the literature. However, it is important to note that hospital admissions should be seen as a marker for patients who may have a worse prognosis because it is patient illness severity rather than hospital admission that increases the risk of death and other complications among admitted patients. Consequently, preventive interventions to reduce unplanned hospital admissions may also reduce other adverse events in this patient population.

Given the multiple cardiovascular and noncardiovascular causes associated with admissions for patients with AF,

Table 2. Meta-regression analyses

Characteristic	All-cause hospital admission				Cardiovascular hospital admission				Noncardiovascular hospital admission			
	No. of studies	β coefficient (95% CI)	*P* value	R^2, %*	No. of studies	β coefficient (95% CI)	*P* value	R^2, %*	No. of studies	β coefficient (95% CI)	*P* value	R^2, %*
Mean age, years	34/35	1.43 (0.33-2.53)	0.012	15.73	24/24	0.87 (−0.19 to 1.92)	0.10	-	24/24	0.51 (−0.13 to 1.16)	0.11	-
Male sex, %	33/35	−0.47 (−1.27 to 0.34)	0.25	-	24/24	−0.39 (−1.29 to 0.50)	0.37	-	24/24	−0.25 (−0.80 to 0.29)	0.34	-
Follow-up duration, years	35/35	1.48 (−4.24 to 7.21)	0.60	-	24/24	−1.62 (−7.06 to 3.81)	0.54	-	24/24	3.20 (0.20-6.21)	0.038	15.23
History of hypertension, %	29/35	−0.10 (−0.59 to 0.39)	0.69	-	20/24	0.16 (−0.32 to 0.64)	0.50	-	20/24	0.02 (−0.29 to 0.33)	0.90	-
History of diabetes mellitus, %	26/35	0.59 (−0.51 to 1.70)	0.28	-	18/24	0.42 (−0.69 to 1.52)	0.44	-	18/24	0.14 (−0.58 to 0.86)	0.68	-
History of coronary artery disease, %	28/35	0.23 (−0.13 to 0.59)	0.20	-	19/24	0.28 (−0.07 to 0.63)	0.11	-	19/24	−0.01 (−0.26 to 0.24)	0.93	-
Prior stroke/TIA, %	22/35	0.06 (−0.43 to 0.56)	0.79	-	16/24	−0.11 (−0.99 to 0.77)	0.79	-	16/24	−0.14 (−0.56 to 0.28)	0.48	-
History of heart failure, %	31/35	0.11 (−0.13 to 0.35)	0.36	-	22/24	0.20 (−0.03 to 0.43)	0.09	-	22/24	−0.10 (−0.26 to 0.06)	0.22	-
History of peripheral vascular disease, %	14/35	1.25 (−0.65 to 3.15)	0.18	-	12/24	0.83 (−1.27 to 2.92)	0.40	-	12/24	0.57 (−0.06 to 1.21)	0.07	-
History of chronic pulmonary disease, %	13/35	1.51 (0.57-2.45)	0.005	49.76	9/24	1.36 (−0.27 to 3.00)	0.09	-	9/24	0.91 (0.19-1.64)	0.021	52.40
History of chronic kidney disease, %	10/35	0.35 (−1.15 to 1.86)	0.60	-	7/24	−0.11 (−1.85 to 1.63)	0.88	-	7/24	0.14 (−0.73 to 1.01)	0.70	-
History of cancer, %	5/35	0.64 (−0.68 to 1.96)	0.22	-	3/24	0.14 (−4.73 to 5.00)	0.78	-	3/24	0.71 (0.47-0.95)	0.017	99.99

* R^2 value is only displayed if *P* value was < 0.05.

multidisciplinary approaches are needed to have a significant effect.[62] Previous studies suggested that providing access to health care to patients with chronic conditions reduces their need for future hospital readmissions.[63] As for the high burden of comorbidities, specific treatment should be optimized to reduce admission risk.[64] Self-management programs for patients with heart failure have shown to substantially reduce all-cause readmissions and readmissions due to heart failure; however, these effects remain to be determined in patients with AF.[65,66]

Limitations

There are some limitations that should be considered when interpreting the findings of this meta-analysis. First, this current study is based on aggregated published data from studies with different methodologies and patient characteristics and not from individual patient-level data. The lack of standardized definitions for variables could have led to misclassification, particularly in retrospective studies that used administrative databases to collect data. However, there was no significant difference in incidence rates for admission across subgroups. Accordingly, the risk of misclassification bias seems low. Second, a substantial amount of the observed between-study heterogeneity remained largely unexplained by the variables examined. Third, some of the included studies did not report the incidence rate or person-years of follow-up. Both variables had to be calculated from the information available and might therefore slightly differ from the true results. Finally, data on cause specific hospital admissions were incomplete, particularly for studies related to noncardiovascular admissions.

Conclusions

Patients with AF have a very high risk of being admitted to the hospital, both for cardiovascular and noncardiovascular causes. Further research is needed to determine interdisciplinary strategies for reducing unplanned hospital admissions and subsequently preventing adverse events in this population. Successful strategies to prevent hospital admissions may have a large impact not only on individual patients but also on the overall health care system, as hospital admissions constitute more than 50% of the estimated health care spending in AF patients.

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Supplementary Material

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