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SYSTEMATIC REVIEW

Antipsychotic Drug Exposure and Risk of Venous Thromboembolism: A Systematic Review and Meta-Analysis of Observational Studies

Corrado Barbui · Valentino Conti · Andrea Cipriani

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Abstract

Background Venous thromboembolism (VTE) is a serious disorder that may be complicated by pulmonary embolism (PE). Case reports and observational studies published in the early 1950s suggested that antipsychotic (AP) drugs may represent a risk factor, while observational studies conducted in the last 3 decades have provided conflicting results.

Objective The aim was to investigate whether AP drugs increase the risk of VTE and PE, and to ascertain the risk associated with first- and second-generation AP drugs and with exposure to individual drugs.

Data Source Relevant studies were located by searching MEDLINE, PubMed, EMBASE, PsychINFO, CINAHL and Scopus up to March 2013. Reference lists of relevant papers and previous review articles were hand searched for other relevant studies.

Study Selection Based on the titles and abstracts of 1,386 citations, we identified 30 potentially relevant studies. Of these, 17 studies were eligible for inclusion and were included in the meta-analysis.

Main Outcomes and Measures The primary outcome measure of this meta-analysis was the occurrence of VTE or PE in individuals exposed to AP drugs in comparison with individuals unexposed or with past exposure to AP drugs.

Results Antipsychotic exposure was associated with a significant increase in risk of developing VTE [odds ratio (OR) 1.54, 95 % confidence interval (CI) 1.28–1.86, 11 studies]. Exposure to APs did not significantly increase the risk of PE (OR 4.90, 95 % CI 0.77–30.98, three studies), but the overall estimate was highly heterogeneous and the CI included the possibility of substantial harm. Random-effects meta-analysis on the risk of VTE associated with exposure to first- (OR 1.74, 95 % CI 1.28–2.37, six studies) and second-generation (OR 2.07, 95 % CI 1.74–2.52, five studies) APs revealed an increased risk. Only a few studies provided data on individual drugs, and estimates of effect were very uncertain.

Conclusions Antipsychotic exposure in unselected patient populations may be associated with a 50 % increase in the risk of developing VTE. However, between-study heterogeneity limits the confidence in this estimate. This increased risk similarly applies to first- and second-generation AP drugs.

1 Background

Venous thromboembolism (VTE) is a serious disorder affecting up to one in 1,000/2,000 adults annually [1]. It may be complicated by pulmonary embolism (PE) and is associated with significant morbidity and mortality. Advanced age, pregnancy, surgery, malignancies and other inherited and acquired characteristics are known risk factors [2–4]. VTE and PE may additionally be associated with use of medicines, and several case reports and observational studies published in the early 1950s and 1960s suggested that antipsychotic (AP) drugs may represent a risk factor [5–12].

In 1997, Walker et al. [13] conducted an epidemiological study suggesting that exposure to clozapine, an agent

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C. Barbui (✉) · A. Cipriani
Section of Psychiatry, Department of Public Health and Community Medicine, University of Verona, Policlinico GB Rossi, Piazzale Scuro 10, 37134 Verona, Italy
e-mail: corrado.barbui@univr.it
URL: http://www.psychiatry.univr.it

V. Conti
Regional Centre for Pharmacovigilance, Lombardy Region, Milan, Italy

belonging to the group of the so-called second-generation AP drugs (SGAs), significantly increased the risk of PE mortality. Since then, other epidemiological cohort and case–control studies have provided additional data on this association, but still unclear is the magnitude of effect and whether all AP drugs bear the same risk [12]. In 2011, a review of case–control studies concluded that AP exposure was associated with a more than doubled risk of VTE [14]. This finding raised concerns among clinicians, and criticism among researchers, as cohort studies were not included and crude instead of adjusted data were pooled, possibly inflating the relative estimate of the association [15].

Therefore, we planned a systematic review and meta-analysis of epidemiological cohort and case–control studies to investigate if AP drugs increase the risk of VTE and PE and to ascertain the risk associated with first-generation AP drugs (FGAs) and SGAs and with exposure to individual drugs.

2 Materials and Methods

2.1 Registration of Review Protocol

The protocol for this review was registered in advance with PROSPERO (International Prospective Register of Systematic Reviews) [16].

2.2 Type of Studies

Studies were included if they were observational cohort or case–control studies that reported all VTE or PE only outcomes in individuals exposed to AP drugs (N05A group excluding lithium of the Anatomical Therapeutic Chemical Classification System) as compared with individuals unexposed or with past exposure to AP drugs. Study participants were of either sex and any age, with no restrictions in terms of diagnostic categories.

Included and excluded studies were collected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Additionally, because included studies were observational in design, we followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines for the meta-analysis of observational studies.

2.3 Search Strategy and Data Extraction

Relevant studies were located by searching MEDLINE, PubMed, EMBASE, PsychINFO, CINAHL and Scopus up to March 2013 using the terms 'antipsychotic agents', 'antipsychotic drugs', 'antipsychotics' AND 'venous thromboembolism', 'pulmonary embolism', 'deep venous thrombosis', 'thrombosis' (full search strategies reported in Electronic Supplementary Material 1). No language restriction was applied. Reference lists of relevant papers and previous review articles were hand searched for other relevant studies. Two investigators (CB and AC) independently examined all titles and abstracts, and obtained full texts of potentially relevant papers. Working independently and in duplicate, we read the papers and determined whether they met inclusion criteria. We resolved disagreement by consensus, and extracted data independently using an electronic spreadsheet. For all studies, we extracted information on study design, source of data, population characteristics, outcomes of interests, matching and confounding factors.

2.4 Assessment of Risk of Bias

Two authors (CB and VC) assessed the risk of bias independently. Since all the included studies were nonrandomized and had a cohort or case–control design, the Newcastle–Ottawa Scale (NOS) was used to judge study quality, as recommended by the Cochrane Collaboration [17]. This scale uses a star system to assess the quality of a study in three domains: selection, comparability, and outcome (cohort studies) or exposure (case–control studies). The NOS assigns a maximum of four stars for selection, two stars for comparability, and three stars for exposure/outcome. Therefore, nine stars reflects the highest quality. Any discrepancies were addressed by a joint revaluation of the original article with a third author. We recorded the review authors' judgments about the three NOS domains (selection, comparability and exposure or outcome) in the Risk of Bias tool of the Review Manager software of the Cochrane Collaboration. This tool allowed us to keep a record of the background reasons for each judgment, and was additionally used to produce a graphical representation of quality ratings similar to that produced by Cochrane reviews for randomized studies, as suggested by Wells et al. [18].

2.5 Data Synthesis

The outcome measure of this meta-analysis was the occurrence of VTE or PE in individuals exposed to AP drugs in comparison with individuals unexposed or with past exposure to AP drugs. The summary odds ratio (OR) for exposure to AP drugs was the primary measure of interest. Secondary measures of interest were exposure to SGAs versus no exposure, exposure to FGAs versus no exposure, and exposure to individual AP drugs versus no exposure. When possible, we pooled adjusted relative risks or ORs or hazard ratios, with their 95 % confidence interval (CI), with the assumption that these are comparable measures of association given that VTE and PE are

relatively rare events [19]; otherwise we used raw data to compute unadjusted ORs [20, 21]. Visual inspection of graphs was used to investigate the possibility of statistical heterogeneity. This was supplemented using, primarily, the I-squared (I^2) statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. According to Higgins and Thompson [22], a rough guide to interpretation is as follows: I^2 around 25 % represents low heterogeneity; I^2 around 50 % represents medium heterogeneity; I^2 around 75 % represents high heterogeneity.

The results of studies were pooled and an overall estimate of OR was obtained from a random effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity [23]. Publication bias was evaluated using funnel plot and Egger's regression test [24].

A summary of findings table was produced following the methodology described by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group [25] and the coding instructions suggested by the World Health Organization [26].

2.6 Primary and Secondary Analyses and Meta-Regression

The primary analysis included all VTE or PE studies meeting the review inclusion criteria. Secondary analyses were carried out to examine effect sizes when limiting the analysis to the following subgroups of studies: elderly participants; studies with nine stars on the NOS (high-quality studies); studies that included only incident cases and excluded patients at risk of VTE; studies without autopsy design; studies employing a cohort design. Additionally, given the limited number of included studies, we tested for possibly excessive influence of individual studies using a meta-analysis influence test that eliminated each of the included studies one at a time.

Unrestricted maximum likelihood random effects meta-regression was used to find whether there was a relationship between age and risk of VTE. All calculations were done with Comprehensive Meta-Analysis version 2.

3 Results

3.1 Characteristics of Included Studies

Based on the titles and abstracts of 1,386 citations, we identified 30 potentially relevant studies. Of these, we excluded 13 studies for the reasons reported in the PRISMA diagram (Fig. 1). Thus, 17 studies were eligible for inclusion and were assessed for quality (Fig. 1) [13, 27–42]. Of the included studies, 11 were case–control studies [28, 30–34, 36–38, 40, 42] and six had a cohort design [13, 27, 29, 35, 39, 41]. Fourteen of the studies identified patients from administrative databases, two used records of autopsies and one used data from a previously performed cohort study, the Leiden Thrombophilia Study (Table 1). All studies included heterogeneous patient populations without restrictions in terms of diagnostic categories, with a focus on elderly subjects in three studies [33, 35, 39]. While the majority of studies employed VTE and PE diagnostic codes as an outcome measure, in five studies, only PE diagnostic codes were used (Table 1). In two of these five studies, the outcome measure was fatal PE [13, 38]. Five studies included only incident cases and excluded patients at VTE risk (Table 1).

Of the included studies, seven received nine stars on the NOS, indicating low risk of bias (Electronic Supplementary

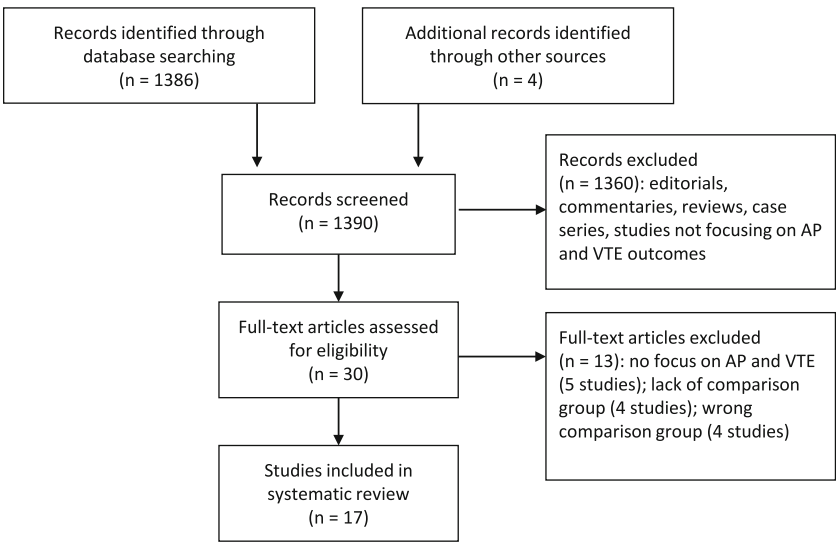

Fig. 1 Included and excluded studies with reasons: PRISMA flow-diagram. *AP* antipsychotic, *VTE* venous thromboembolism

Table 1 Characteristics of observational studies assessing the risk of VTE or PE associated with exposure to AP drugs

Study	Data source	Design	Population characteristics	Out-come	Total population	Participants with VTE risk factors excluded	Participants with previous VTE excluded	Definition of AP exposure	Case or outcome definition	Controlled variables	High-quality study
Allenet et al. (2012) [27]	US database from 500 hospitals	Retrospective cohort study	Men and women over 18 years of age attending a hospital consultation or who had been hospitalized at least once during the year 2006	PE	450,951 AP users and 28,272,820 non-AP users; 76,814 PE events	No	No	Any AP prescription during 2006	ICD codes	Age, sex and the individual components of the Charlson Comorbidity Index	No
Hamanaka et al. (2004) [28]	Records of autopsies in Japan from 1998 to 2002	Case–control study	Autopsies in men and women performed for investigation of the cause of sudden unexpected death; cases of massive thrombus that filled the lumen of the major pulmonary vessels were identified	PE	1,125 forensic autopsies; 34 PE events	Autopsies were excluded if findings related to the cause of death were identified	No	Unclear	Unclear	Age, gender, body mass index	No
Hippisley-Cox and Coupland (2011) [29]	Primary care patients from the QResearch database (England and Wales)	Prospective cohort study	Patients aged 25–84 followed until diagnosis of VTE, death, deregistration with the practice, last upload of computerized data, 5 years after study entry	VTE	2,314,701 patients; 14,756 cases of VTE	History of VTE, use of oral anticoagulation drugs, pregnancy	Yes, incident cases only	Current use (previous 30 days)	ICD codes	Age, body mass index, smoking status, medical history, current medication	Yes
Ishiguro et al. (2011) [30]	UK General Practice Research Database	Nested case–control study	From a base population of recipients of first- and second-generation AP drugs, incident cases of VTE aged 25–59 and matched controls were identified from 1998 to 2009	VTE	112 cases and 375 controls	Unclear	Yes, incident cases only	Current use (unclear definition)	Unclear	Age, gender, index date and general practice	No
Jonsson et al. (2008) [31]	Records of autopsies in Sweden from 1992 to 2005	Case–control study	Autopsies in men and women aged 18–65 were included; injuries and intoxications were excluded; participants in whom PE was the cause of death were identified	PE	14,439 forensic autopsies; 279 PE events	No	No	Unclear	ICD codes	Age and sex	No
Jonsson et al. (2009) [32]	Medical databases in Denmark	Nested case–control study	Patients with a first-time diagnosis of VTE and ten population controls for each case, matched on age, sex and county	VTE	5,999 cases and 59,990 controls	Surgery, major trauma, fractures, pregnancy within the prior 3 months, cancer	Yes, incident cases only	Current use (previous 90 days)	ICD codes	Medical history, current medication, pregnancy	No

Table 1 continued

Study	Data source	Design	Population characteristics	Out-come	Total population	Participants with VTE risk factors excluded	Participants with previous VTE excluded	Definition of AP exposure	Case or outcome definition	Controlled variables	High-quality study
Kleijer et al. (2010) [33]	PHARMO database covering 950,000 residents in the Netherlands	Nested case–control study	In a cohort aged 60 years or older with at least one AP prescription, cases were those patients with a primary hospital diagnosis of VTE; for each case, four controls were randomly selected from the exposure cohort (matched on age, sex, and duration of registration in the database)	VTE	1,032 cases and 4,125 controls	No	No	Current use (previous 7 days)	ICD codes	Comorbidity and drug use	Yes
Lacut et al. (2007) [34]	Medical records of hospital admissions in France	Case–control study	Adult patients hospitalized with a well-documented symptomatic VTE; for each case, one control was selected from the roster of patients hospitalized in the same ward (matched on age and gender)	VTE	677 cases and 677 controls	Surgery in the past 3 months, plaster cast in the past 3 months, pregnancy or delivery in the past 3 months, and active malignancy	No	Current use of drugs at the time of admission	Clinical diagnosis + objective tests	Body mass index, factor V Leiden and prothrombin G20210A gene variation	Yes
Liperoti et al. (2005) [35]	Database of nursing home residents in five US States	Retrospective cohort study	Nursing home residents 65 years or older who were new users of AP drugs or nonusers; follow-up: 6 months	VTE	19,940 exposed and 112,078 unexposed residents; 539 VTE cases	Hip fracture, cancer, treatment with anticoagulant agents or estrogens	Yes, incident cases only	Current use (previous 7 days)	ICD codes	Body mass index, functional and cognitive status, comorbidity and drug use	Yes
Masopust et al. (2007) [36]	Records of hospital admissions in the Czech Republic	Case–control study	Patients aged 18–60 years hospitalized with deep-vein thrombosis or PE (case group), or arterial hypertension (control group)	VTE	266 cases and 274 controls	No	Yes, incident cases only	Current use (4 weeks)	Hospital's electronic information system	No	No
Parker et al. (2010) [37]	UK QResearch primary care database	Nested case–control study	Patients (cases) with a first ever record of VTE between January 1996 and July 2007; each case was matched with up to four controls by age, calendar time, sex, and practice	VTE	25,532 cases and 89,491 controls	Use of warfarin, previous cancer, coronary heart disease, stroke, congestive cardiac failure, hip surgery, hip or lower limb fracture, or pregnancy within the previous 6 months	Yes, incident cases only	Current use (previous 90 days)	QResearch electronic information system	Socioeconomic status, mental health indication, months of data, comorbidity and drug use	Yes

Table 1 continued

Study	Data source	Design	Population characteristics	Out-come	Total population	Participants with VTE risk factors excluded	Participants with previous VTE excluded	Definition of AP exposure	Case or outcome definition	Controlled variables	High-quality study
Parkin et al. (2003) [38]	Coroners' and police records, death certificates and hospital records in New Zealand	Case–control study	Cases were New Zealand men and women aged 15–59 years who died between January 1990 and December 1998 with a diagnosis of fatal PE; for each case, four controls, matched for sex and year of birth, were selected	Fatal PE	75 cases and 300 controls	No	No	Current use (previous 90 days)	ICD codes and validation with necropsy, ventilation-perfusion scans or angiography	Weight, combined oral contraceptive use and hormone replacement therapy	No
Ray et al. (2002) [39]	Administrative databases in Ontario, Canada	Retrospective cohort study	Individuals aged 65 years and over exclusively prescribed either AP drugs or thyroid replacement hormones, the referent control group	VTE	22,514 individuals exposed to AP and 33,033 not exposed	Cancer, use of warfarin	New cases (no VTE within 36 months prior to study entry)	Current use (previous 180 days)	ICD codes	Age, sex, living in residential facility, recent prior hospitalization, comorbidity and drug use	Yes
Thomassen et al. (2001) [40]	Data from the Leiden Thrombophilia Study	Case–control study	Incident cases of outpatients with a first episode of VTE (cases) and controls matched on age and sex	VTE	474 cases and 474 controls	Cancer and individuals over 70	Yes, incident cases only	Current use (unclear definition)	VTE validated with objective tests	Unclear	No
Walker et al. (1997) [13]	US Clozaril National Registry	Retrospective cohort study	Fatal PE was compared in current and recent clozapine exposure with rates in past exposure (age group 10–54)	Fatal PE	67,072 eligible patients	Individuals over 54	No	Current use (14 days)	ICD codes	Ethnicity, sex and age	No
Wolstein et al. (2000) [41]	Databases in Germany and Switzerland	Prospective cohort study	Inpatients of 35 psychiatric hospitals monitored for severe adverse drug reactions	VTE	13,081 inpatients exposed to clozapine and 30,282 unexposed controls	No	No	Current use (unclear definition)	Unclear	No	No
Zornberg and Jick (2000) [42]	UK General Practice Research Database	Nested case–control study	Men and women <60 years exposed to AP; from this population, cases were individuals with a first-time diagnosis of VTE, and controls were selected matched on age, sex, general practice attended, and index date	VTE	42 cases and 168 controls	Individuals over 60, trauma, pregnancy, surgery, coagulopathies, congestive heart failure, myocardial infarction, cancer, renal failure, epilepsy, diabetes mellitus, cystic fibrosis, multiple sclerosis, psychotic episode, alcohol and substance use disorders	Yes, incident cases only	Current use (60 days)	ICD codes validated with objective tests	Age, sex, smoking status, body mass index, comorbidity and drug use	Yes

AP antipsychotic, *ICD* International Classification of Diseases, *PE* pulmonary embolism, *VTE* venous thromboembolism

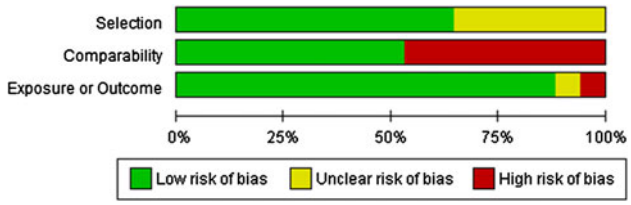

Fig. 2 Risk of bias graph: review authors' judgments about each domain of the Newcastle–Ottawa Scale presented as percentages across all included studies

Material 2). Comparability of cohorts, or comparability of cases and controls, was judged to be at high risk of bias in eight studies, and in one study, it was unclear if the outcome of interest was present at the start of the study (Fig. 2 and Electronic Supplementary Material 3).

3.2 Antipsychotics and Risk of PE and VTE

The distribution of studies by estimate of the association between AP exposure and risk of PE or VTE outcome is plotted in Fig. 3. Three studies provided data suitable for analysis of PE outcomes, and 11 studies (12 comparisons) provided data suitable for analysis of VTE outcomes. Significant heterogeneity was detected among studies belonging to both groups (Fig. 3).

Table 2 presents the results of meta-analyses carried out under different assumptions. Three studies provided data suitable for analysis of the risk of PE outcomes. Exposure to APs did not significantly increased the risk of PE (random effect OR 4.90, 95 % CI 0.77–30.98, $I^2 = 92$ %), but the overall estimate was highly heterogeneous and the CI included the possibility of substantial harm. However, eliminating each of the three PE studies from the analysis affected the overall treatment estimate: after removing Allenet et al. [27], the two remaining studies showed a statistically significant increased risk (two studies, random effect OR 11.09, 95 % CI 4.73–26.03, $I^2 = 0.0$ % indicating no evidence of heterogeneity) (Table 2).

Eleven studies (12 comparisons) provided data suitable for analysis of the risk of VTE outcomes. Exposure to APs significantly increased the risk of VTE (random effect OR 1.54, 95 % CI 1.28–1.86, $I^2 = 84$ % suggesting high heterogeneity) (Table 2). Although Egger's regression test did not show statistically significant asymmetry, visual inspection of the funnel plot suggested that there might be a lack of small studies that failed to show an excess risk associated with AP exposure (Electronic Supplementary Material 4). The sensitivity analysis that included studies with only elderly participants failed to detect an association between AP exposure and VTE outcomes (Table 2). By contrast, limiting the analysis of VTE outcomes to high-quality studies, or to studies that included only incident cases and excluded patients at VTE risk, did not substantially affect the primary analysis (Table 2). Similarly, excluding autopsies studies and excluding case–control studies provided overall treatment estimates consistent with the primary analysis. Additionally, eliminating each of the included studies from the analysis had no effect on the overall risk of VTE.

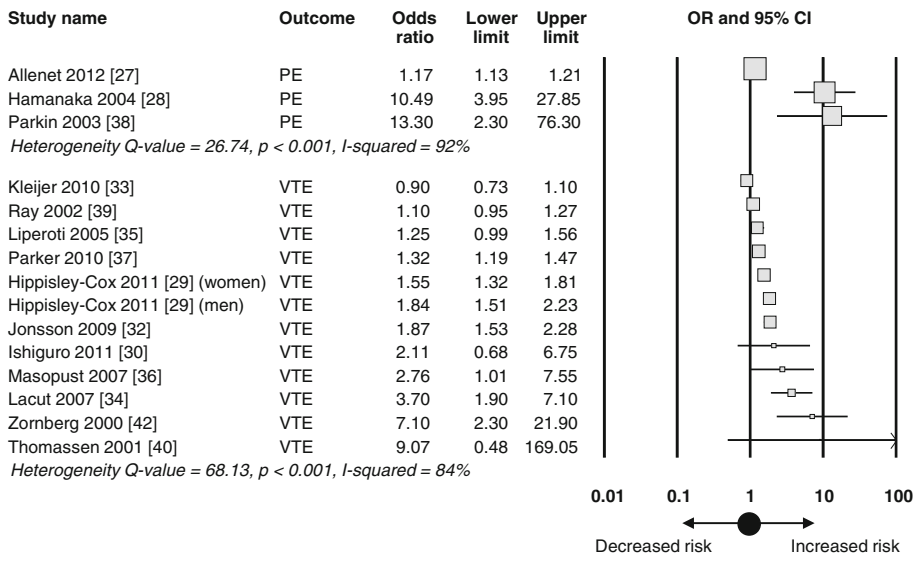

Fig. 3 Forest plot on the risk of venous thromboembolism (VTE) or pulmonary embolism (PE) associated with exposure to antipsychotics versus no exposure to any antipsychotic. *CI* confidence interval, *OR* odds ratio

Table 2 Random-effects meta-analyses on the risk of VTE or PE associated with exposure to AP drugs

Analysis	Number of comparisons	Outcome	OR with 95 % CI	*P* value	I^2	Studies
All PE studies (primary analysis)	3	PE	4.90 (0.77–30.98)	0.091	92 %	Allenet et al. (2012) [27], Hamanaka et al. (2004) [28], Parkin et al. (2003) [38]
Excluding Allenet et al. (2012) from PE studies	2	PE	11.09 (4.73–26.03)	<0.001	0.0 %	Hamanaka et al. (2004) [28], Parkin et al. (2003) [38]
All VTE studies (primary analysis)	12	VTE	1.54 (1.28–1.86)	<0.001	84 %	Hippisley-Cox and Coupland (2011) (two comparisons) [29], Ishiguro et al. (2011) [30], Jonsson et al. (2009) [32], Kleijer et al. 2010 [33], Lacut et al. (2007) [34], Liperoti et al. (2005) [35], Masopust et al. (2007) [36], Parker et al. (2010) [37], Ray et al. (2002) [39], Thomassen et al. (2001) [40], Zornberg and Jick (2000) [42]
Studies including only elderly participants	3	VTE	1.07 (0.90–1.26)	0.429	58 %	Kleijer et al. (2010) [33], Liperoti et al. (2005) [35], Ray et al. (2002) [39]
High-quality studies at the NOS	8	VTE	1.44 (1.18–1.76)	<0.001	87 %	Hippisley-Cox and Coupland (2011) (two comparisons) [29], Kleijer et al. (2010) [33], Lacut et al. (2007) [34], Liperoti et al. (2005) [35], Parker et al. (2010) [37], Ray et al. (2002) [39], Zornberg and Jick (2000) [42]
Studies including only incident cases and excluding patients at VTE risk	6	VTE	1.44 (1.19–1.73)	<0.001	83 %	Hippisley-Cox and Coupland (2011) (two comparisons) [29], Liperoti et al. (2005) [35], Parker et al. (2010) [37], Ray et al. (2002) [39], Zornberg and Jick (2000) [42]
Autopsies studies excluded	14	PE and VTE	1.48 (1.27–1.72)	<0.001	86 %	Allenet et al. (2012) [27], Hippisley-Cox and Coupland (2011) (two comparisons) [29], Ishiguro et al. (2011) [30], Jonsson et al. (2009) [32], Kleijer et al. (2010) [33], Lacut et al. (2007) [34], Liperoti et al. (2005) [35], Masopust et al. (2007) [36], Parker et al. (2010) [37], Parkin et al. (2003) [38], Ray et al. (2002) [39], Thomassen et al. (2001) [40], Zornberg and Jick (2000) [42]
Case–control studies excluded	5	PE and VTE	1.34 (1.13–1.58)	0.001	87 %	Allenet et al. (2012) [27], Hippisley-Cox and Coupland (2011) (two comparisons) [29], Liperoti et al. (2005) [35], Ray et al. (2002) [39]

AP antipsychotic, *CI* confidence interval, *NOS* Newcastle–Ottawa Scale, *OR* odds ratio, *PE* pulmonary embolism, *VTE* venous thromboembolism

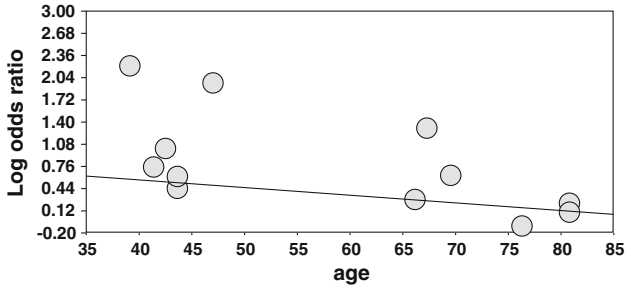

Fig. 4 Meta-regression on the effect of age on the Log odds ratio for the risk of venous thromboembolism associated with exposure to antipsychotic drugs. Each *circle* represents a study. Slope $= -0.0129$, $Q = 68.13$, $df = 11$, $p < 0.001$

The meta-regression with average age as a moderator and the risk of VTE as a dependent variable suggested a higher effect of AP exposure on the risk of VTE among adults and a decreased effect among elderly individuals (Fig. 4).

3.3 First- and Second-Generation Antipsychotics and Risk of PE and VTE

Random-effect meta-analysis on the risk of VTE associated with exposure to SGAs revealed an increased risk (five studies, random effect OR 2.07, 95 % CI 1.74–2.52, $I^2 = 0.0$ % indicating no evidence of heterogeneity) (Fig. 5). Similarly, random-effect meta-analysis on the risk of VTE associated with exposure to FGAs revealed an increased risk (six studies, eight comparisons, random effect OR 1.74, 95 % CI 1.28–2.37, $I^2 = 78$ % indicating high heterogeneity) (Fig. 6).

Table 3 presents the results of random-effects meta-analyses on the risk of VTE or PE associated with exposure to individual AP drug. Only a few studies provided data on individual drugs, and substantial heterogeneity was observed for most of these analyses (Table 3).

Using GRADE methodology, the overall quality of evidence was rated as very low, meaning that estimates of effect were very uncertain, with the exception of the evidence on the risk of VTE associated with SGAs, which was rated as low, meaning that further research may have an important impact on our confidence in the estimate (Electronic Supplementary Material 5).

4 Discussion

Current epidemiological evidence suggests that AP exposure in unselected patient populations may be associated with a 50 % increase in risk of developing VTE. However, between-study heterogeneity and concerns about comparability at baseline for some of the included studies limit the confidence in this estimate. In addition, AP exposure may substantially increase the risk of PE, as suggested by a high overall estimate, but high heterogeneity and low statistical power accounted for a wide and nonsignificant CI.

These results, generated by pooling adjusted risk estimates from cohort and case–control studies, mitigate the findings from a previous meta-analysis of crude estimates from case–control studies, which showed a considerable increase in the risk of VTE associated with AP exposure [14]. VTE is associated with a number of different risk factors, and possibly none of the included studies was able to fully adjust for the presence of all these factors in the statistical analysis [15]. Therefore, we cannot rule out the possibility that the small increase in risk that we observed in this review might be explained by residual confounding.

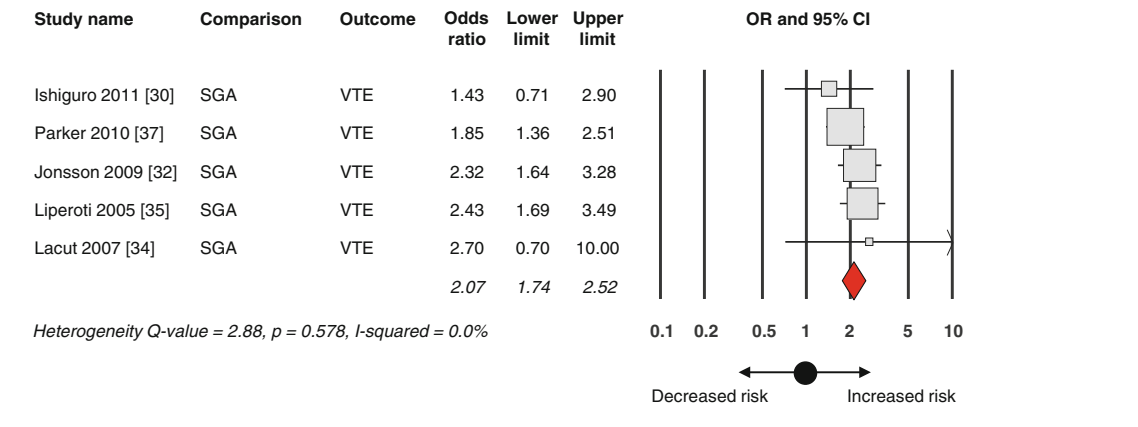

Fig. 5 Random-effect meta-analysis on the risk of venous thromboembolism (VTE) associated with exposure to second-generation antipsychotics (SGAs) versus no exposure to any antipsychotic. *CI* confidence interval, *OR* odds ratio

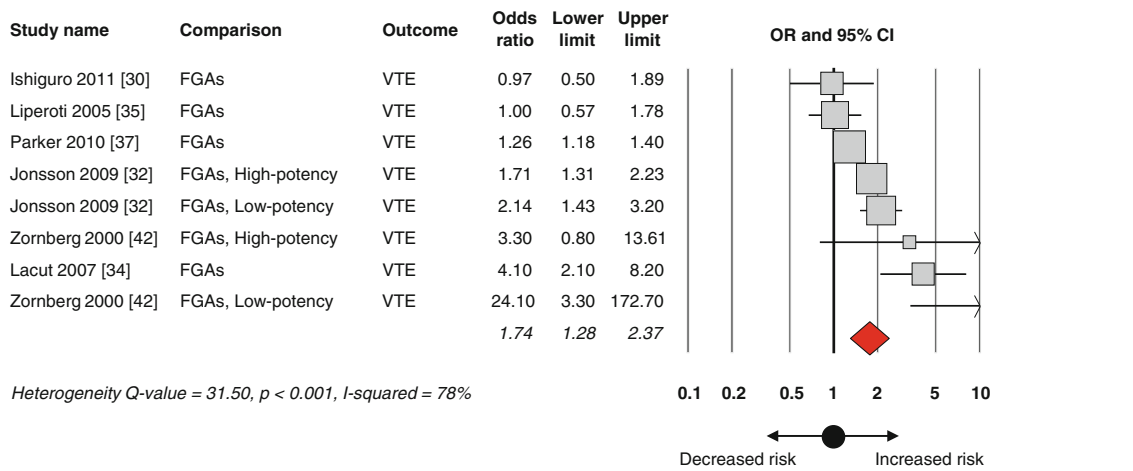

Fig. 6 Random-effect meta-analysis on the risk of venous thromboembolism (VTE) associated with exposure to first-generation antipsychotics (FGAs) versus no exposure to any antipsychotic. *CI* confidence interval, *OR* odds ratio

Table 3 Random-effects meta-analyses on the risk of VTE or PE associated with exposure to individual AP drugs

Individual AP drug	Number of studies	Outcome	OR with 95 % CI	*P* value	I^2	Study
Aripiprazole	1	PE	0.98 (0.83–1.15)	0.808	–	Allenet et al. (2012) [27]
Chlorpromazine	2	PE and VTE	1.52 (0.87–2.66)	0.135	84 %	Allenet et al. (2012) [27], Parker et al. (2010) [37]
Clozapine	3	PE and VTE	1.53 (0.94–2.52)	0.086	14 %	Allenet et al. (2012) [27], Walker et al. (1997) [13], Wolstein et al. (2000) [41]
Clozapine-quetiapine	1	VTE	4.88 (2.03–11.72)	<0.001	–	Liperoti et al. (2005) [35]
Haloperidol	2	PE and VTE	1.35 (0.90–2.02)	0.142	66 %	Allenet et al. (2012) [27], Parker et al. (2010) [37]
Olanzapine	3	PE and VTE	1.35 (0.97–1.89)	0.073	59 %	Allenet et al. (2012) [27], Liperoti et al. (2005) [35], Parker et al. 2010 [37]
Quetiapine	2	PE and VTE	1.79 (0.49–6.52)	0.374	93 %	Allenet et al. (2012) [27], Parker et al. (2010) [37]
Risperidone	3	PE and VTE	1.51 (0.96–2.36)	0.071	91 %	Allenet et al. (2012) [27], Liperoti et al. (2005) [35], Parker et al. (2010) [37]
Ziprasidone	1	PE	1.21 (1.06–1.34)	0.003	–	Allenet et al. (2012) [27]
AP polypharmacy	2	VTE	2.50 (0.68–9.10)	0.165	86 %	Liperoti et al. (2005) [35], Parker et al. (2010) [37]

AP antipsychotic, *CI* confidence interval, *OR* odds ratio, *PE* pulmonary embolism, *VTE* venous thromboembolism

We note, however, that it is also possible that the true effect might be higher than that estimate here, as differential case definition, i.e. inclusion/exclusion of participants with VTE risk factors, inclusion/exclusion of incident cases, and differential definitions of AP exposure, might have mitigated the harmful effect of drug exposure.

The increased risk associated with AP drugs was higher in studies carried out in younger populations as compared with studies carried out in older populations. This is a challenging finding, as the epidemiology of VTE in the population shows a progressive rise in incidence with increasing age [37], possibly because older people have more comorbidities, risk factors, and other proximate causes for VTE. Since many of these studies did not strictly restrict themselves to idiopathic cases regardless of age, case definition might be an explanation for the difference in results; it is possible that in late life, when the absolute baseline risk is high, AP exposure adds little relative risk; by contrast, in younger age, with lower absolute baseline risk, AP exposure may become a more evident risk factor. Additionally, it may be of interest to check if the biological mechanisms potentially involved in the pathogenesis of this adverse reaction act differently in different age groups. So far several mechanisms have been suggested, including drug-induced sedation, obesity, increased levels of anti-phospholipid antibodies, enhanced platelet aggregation,

hyperhomocysteinaemia and hyperprolactinaemia [12, 43, 44], but the exact mechanism has not been clarified yet.

Some limitations of this analysis should be acknowledged. Studies were quite heterogeneous in terms of design, criteria to define exposed and non-exposed cohorts, definition of cases and controls, comparability at baseline and outcome assessment. Patient populations were similarly heterogeneous, as studies did not select specific diagnostic groups, and this affected the exposed cohorts as well as the unexposed groups. In some cohort studies, for example, the unexposed group included individuals who had never been exposed to AP drugs, while in other cohort studies the unexposed group included individuals who had been exposed to AP drugs in the past. Clearly, this difference may have a relevant impact in terms of the overall risk estimate, as in the latter case all study individuals shared the key characteristic of being exposed to AP drugs.

These considerations would suggest the need for additional observational studies with enough statistical power to allow stratification by age and individual AP drugs, and with careful consideration given to adjustment and group comparability. For example, limiting the study only to individuals who were exposed to AP drugs would make the sample of included individuals more homogeneous. With such a design, it might be possible to ascertain if different levels of AP exposure, say, for example, occasional use, frequent use and long-term/chronic use, predict the outcome of interest. The reference group would this way include individuals who have been exposed to AP in the past rather than individuals who have never been exposed.

This systematic review has implications for practice and policy. Physicians should consider that current best evidence shows a small but statistically significant increased risk of VTE in individuals exposed to AP drugs, and this risk similarly applies to FGAs and SGAs. Policymakers and guideline developers should consider that for many tolerability questions evidence in the form of randomized trials is not available, and that epidemiological studies cannot easily be described using the templates suggested by guideline developers, such as, for example, GRADE tables [26, 45]. A risk therefore exists of omitting the contribution of nonrandomized research in the development of clinical recommendations, which would represent a major source of bias. In the present study, we showed that it is feasible to summarize the evidence base into GRADE tables following the same logic that is applied to the production of GRADE tables for randomized evidence. This may be a useful tool for synthesizing and presenting observational evidence on the harmful effects of interventions, to be used as supporting material by policymakers and guideline developers when making policy decisions or drafting clinical recommendations.

5 Conclusions

Our findings suggest that AP exposure may be associated with a 50 % increase in the risk of developing VTE. This increased risk seems to similarly apply to FGAs and SGAs, with sparse and inconclusive data on individual AP drugs. We note that statistical heterogeneity, overall study quality and concerns about comparability at baseline limit the confidence in these estimates. Future studies investigating this compelling association should carefully consider group comparability, adjustment for confounders and statistical power, focusing on risk estimates associated with individual AP drugs and on outcome measures that consider VTE but also PE outcomes.

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