Antidepressant Use and Risk of Venous Thromboembolism: A Systematic Review and Meta-Analysis

Ying Wang, Zhikang Ye, Lihong Liu, Xiangli Cui

Department of Pharmacy, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China.

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ABSTRACT - Purpose. Studies provided conflicting results on whether antidepressant use increased the risk of venous thromboembolism (VTE). Our aim was to examine the association between antidepressant use and the risk of VTE. **Methods.** Pubmed, Embase, and the Cochrane Library were searched up to March 13, 2018. Case-control studies and cohort studies that examined the association between antidepressant use and the risk of VTE, deep vein thrombosis or pulmonary embolism were included. Several subgroup analyses and sensitivity analyses were conducted. GRADE approach was used to assess the quality of evidence. **Results.** Nine studies (six case-control studies and three cohort studies) were included. Overall, antidepressant use may be associated with an increased risk of VTE (OR 1.27, 95% CI 1.09 to 1.49); however, no association was observed in studies with low risk of bias (OR 1.27, 95% CI 0.84 to 1.92). No association between selective serotonin reuptake inhibitor use and VTE risk was detected in the overall analysis (OR 1.10, 95% CI 0.90 to 1.34) and in subgroup analysis of studies with low risk of bias. Tricyclic antidepressant may be associated with an increased VTE risk (OR 1.26, 95% CI 1.02 to 1.57), and the quality of evidence was rated as very low by GRADE approach; however, no association was observed when we only included studies with low risk of bias. **Conclusions.** There was no association between selective serotonin reuptake inhibitor use and VTE risk. Tricyclic antidepressant may be associated with an increased VTE risk, but the quality of evidence was very low.

INTRODUCTION

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) (1). VTE may be fatal in the acute phase, and may lead to many long-term complications (2-4). Many risk factors for VTE have been identified, such as pregnancy, surgery, cancer and so on (1). VTE may also be associated with some drugs.

As the incidence of psychiatric disorders increases, the use of psychotropic drugs (antipsychotic drugs and antidepressant drugs) has increased dramatically (5-7). Two meta-analyses showed that antipsychotic drugs may be associated with an increased risk of VTE (without examine the relationship between antidepressant use and VTE risk) (8,9); however, whether a relationship exists between antidepressant exposure and VTE is unclear. Some cases report the occurrence of VTE in patients with antidepressant use have been published in the past decade (10-12).

Some observational studies have been designed to evaluate the association between antidepressant and VTE; however, their results are controversial. Some of them found an association between antidepressant use and VTE risk (13,14), whereas others not (15,16). In addition, several studies indicated that different classes of antidepressant may be associated with different risk of VTE (14,15).

The objective of this systematic review and meta-analysis was to examine the association between antidepressant use and the risk of VTE, and to ascertain the VTE risk associated with different type of antidepressant.

METHODS

Search strategy

A systematic search of Pubmed, Embase, and the Cochrane Library was conducted from inception to March 13, 2018, using the following combined Medical Subject Headings (MeSH) and free text words: (antidepressant or antidepressive or "monoamine oxidase inhibitors" or "serotonin reuptake inhibitors" or tricyclic or amitriptyline or clomipramine or dosulepin or dothiepin or doxepin or imipramine or maprotiline or amoxapine or desipramine or nortriptyline or protriptyline or trimipramine or lofepramine or moclobemide or

Corresponding Authors: Xiangli Cui (1484043795@qq.com) and Lihong Liu (liulihong@bjcyh.com), Department of Pharmacy, Beijing Chao-Yang Hospital, 8 Gongren Tiyuchang Nanlu, Chaoyang District, Beijing, China

isocarboxazid or phenelzine or tranylcypromine or iproniazid or citalopram or escitalopram or fluoxetine or paroxetine or fluvoxamine or sertraline or venlafaxine or desvenlafaxine or duloxetine or milnacipran or levomilnacipran or trazodone or mirtazapine or nefazodone or vilazodone or bupropion or mianserin or tianeptine or viloxazine or maprotiline or agomelatine or vortioxetine or reboxetine) and (thromboembolism or "venous thromboembolism" or "venous thrombosis" or "pulmonary embolism" or "pulmonary thromboembolism" or "deep vein thrombosis"). In addition, the reference lists of included studies and review articles were screened for potential eligible studies. Included and excluded studies were collected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17).

Study selection

Two reviewers independently performed the study selection, including screening titles and abstracts, and retrieving full texts of studies for details. Disagreements were resolved by discussion or through consultation with other authors. Case-control studies and cohort studies that examined the association between antidepressant use and the risk of VTE, DVT or PE were included. Only studies provided odds ratio (OR), risk ratio (RR), or hazard ratio (HR) with 95% confidence intervals (CI), or provided data allowing the calculation of the estimate (OR, RR, or HR) and 95% CI were included. No language restriction was applied.

Data extraction and quality assessment

Following information were extracted from the included studies: author name, year of publication, study design, data source, population, number of patients, definition of antidepressant exposure, outcomes, and adjusted/matched factors. Two reviewers independently assessed the risk of bias of included case-control studies and cohort studies using the Newcastle-Ottawa Scale (NOS) (18). Any discrepancies were addressed by consensus. NOS assess the quality of studies in three domains: selection, comparability, and exposure for case-control studies; and selection, comparability, and outcome for cohort studies. A maximum of nine stars can be received. Studies with nine stars on the NOS were judged to be at low risk of bias.

Data synthesis and analysis

The primary outcome was VTE. VTE comprises DVT and PE. For studies that reported only DVT or PE, data on DVT or PE was regarded as VTE for analysis. We also conducted analysis on PE. In order to explore the sources of heterogeneity, we conducted several subgroup analyses according to type of antidepressant (selective serotonin reuptake inhibitor (SSRI) vs. tricyclic antidepressant (TCA)), quality of study methodology (low risk of bias vs. high risk of bias) and type of study design (case-control studies vs. cohort studies). Sensitivity analyses were conducted by limiting meta-analysis to studies that only included depressed patients or studies that only included female patients. Sensitivity analysis that only included studies that have eliminated the effect of antipsychotics was also conducted.

When possible, adjusted estimates were used; otherwise, unadjusted estimates were calculated with raw data. Random effects model was used, as this takes into account any differences between studies even if there is no statistically significant heterogeneity. We assumed similarity between OR, RR, and HR because VTE and PE were rare events. Publication bias was assessed using Begg's funnel plot and Egger's test (19,20). All statistical analyses were conducted using Stata 12.0.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the quality of evidence (21).

RESULTS

Literature search

Of a total of 1,531 records that were retrieved, 46 were duplicate records. After screening of the titles and abstracts, 1,428 records were excluded. After full text review of the remaining 57 records, 9 studies, including 6 case-control studies involving 40,831 patients (14,15,22-25), and 3 cohort studies involving 900,562 patients (13,16,26), were included in the final analysis (Figure 1).

Characteristics of included studies

Table 1 shows the characteristics of all the included studies. Of the 6 case-control studies, 2 were nested case-control studies, 2 were population based case-control studies, 1 was national case-control study and 1 was hospital based case-control study.

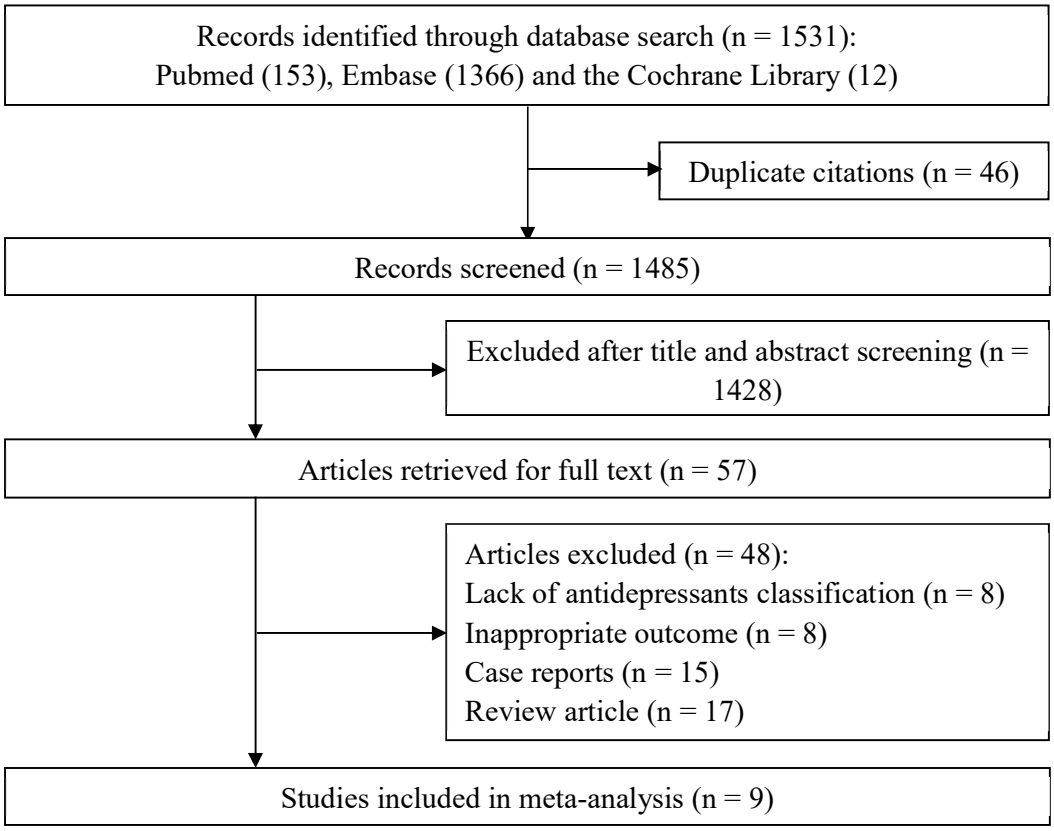

Figure 1. Flow chart depicting the selection process of studies included in the meta-analysis

Of the 3 cohort studies, 2 were retrospective cohort studies and 1 was prospective cohort study. Of these 9 included studies, 1 case-control study was designed to examine the relationship between corticosteroids exposure and VTE, while data on antidepressant use was also reported (24). One study which aimed to investigate the relationship between depression and VTE, evaluated the association between antidepressant and VTE in depressed patients (depressed patients with antidepressant vs. depressed patients without antidepressant) (16). One study only included female patients (13). The outcome measures were different among studies. Six studies reported data on VTE (13-16,22,26), 3 studies reported data on DVT (13,25,26), and 3 studies reported data on PE (in 1 of these 3 studies, the outcome measure was fatal PE) (13,23,24). All the 9 studies reported adjusted estimate.

Of the included studies, only 2 studies (1 case-control study (14) and 1 cohort study (26)) received nine stars on the NOS, indicating low risk of bias (Table 2 and Table 3). For case-control studies, stars were lost in comparability (n = 4), selection of controls (n = 3), definition of the cases (n = 1), ascertainment of exposure (n = 1) (Table 2). For cohort studies, stars were lost in comparability (n = 1) and ascertainment of exposure (n = 1) (Table 3).

Antidepressant use and risk of VTE

Figure 2 shows the association between antidepressant use and the risk of VTE of all included studies. Overall, the use of antidepressant significantly increased the risk of VTE (9 studies; OR 1.27, 95% CI 1.09 to 1.49; I^2 = 77.1%). When we only included studies reported PE risk in the meta-analysis, the results shows that antidepressant use was associated with an increased risk of PE (3 studies; OR 1.50, 95% CI 1.33 to 1.69; I^2 = 15.9%; Figure 3). In the subgroup analysis by quality of study methodology, a significant increased VTE risk with antidepressant use was observed in studies with high risk of bias (7 studies; OR 1.30, 95% CI 1.12 to 1.51; I^2 = 54.9%; Figure 2), while no association observed in studies with low risk of bias (2 studies; OR 1.27, 95% CI 0.84 to 1.92; I^2 = 91.1%; Figure 2). 1 study reported the relationship between antidepressant use and VTE in depressed patients. The study showed there was no significant

difference in the VTE risk between depressed patients with and without antidepressant use (OR 0.72, 95% CI 0.39 to 1.31; Table 4). On the contrary, other studies showed that antidepressant use was associated with an increased VTE risk (8 studies; OR 1.31, 95% CI 1.12 to 1.53; I^2 = 77.9%). Table 4 summarizes the results of subgroup analyses and sensitivity analyses. There was no publication bias (Begg's test P = 1.000, Egger's test P = 0.576). With GRADE approach, the quality of evidence was rated as very low because of risk of bias and inconsistency (Table 5).

SSRI and risk of VTE

Five studies evaluated the association between SSRI use and the risk of VTE. The results showed there was no significant difference in the VTE risk between patients with and without SSRI use (OR 1.10, 95% CI 0.90 to 1.34; I^2 = 62.3%; Figure 4). Subgroup analysis by quality of study methodology did not change the results (studies with low risk of bias: OR 1.05, 95% CI 0.94 to 1.18; I^2 = 0.0%; studies with high risk of bias: OR 1.05, 95% CI 0.71 to 1.55; I^2 = 73.5%; Figure 4). No significant difference in the VTE risk between patients with and without SSRI was observed when we excluded the study with depressed patients (4 studies; OR 1.14, 95% CI 0.93 to 1.40; I^2 = 66.8%). The study with depressed patients reported similar result (OR 0.75, 95% CI 0.40 to 1.38; Table 4). There was no publication bias (Begg's test P = 1.000, Egger's test P = 0.799). With GRADE approach, the quality of evidence was rated as very low because of risk of bias and inconsistency (Table 5).

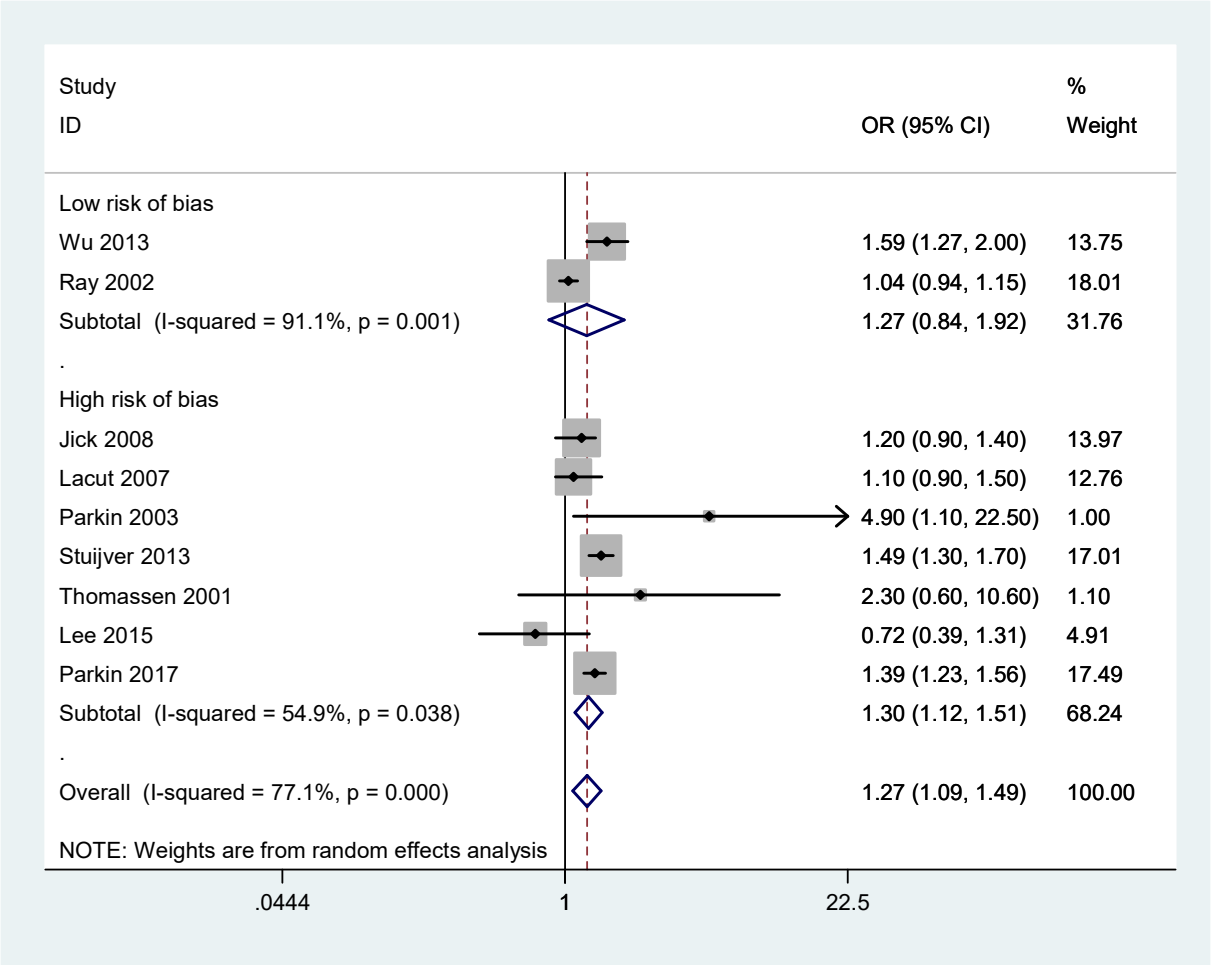

Figure 2. Association between antidepressant use and risk of VTE

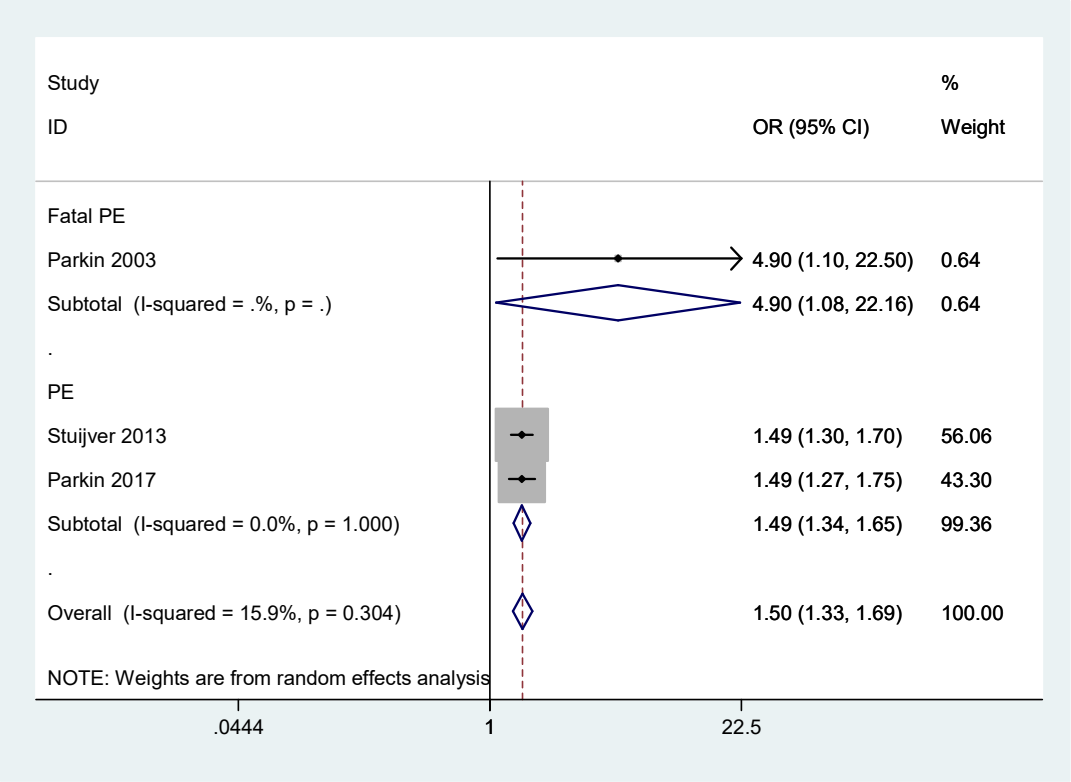

Figure 3. Association between antidepressant use and risk of PE

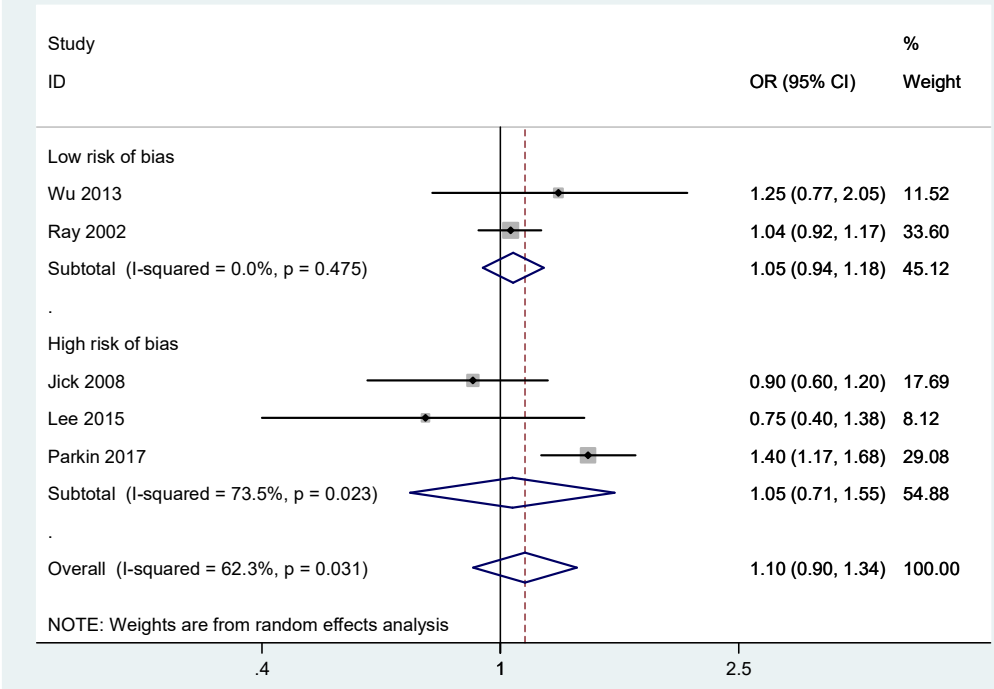

Figure 4. Association between SSRI use and risk of VTE

TCA and risk of VTE

Four studies evaluated the association between TCA use and the risk of VTE. The results showed that use of TCA was associated with an increased VTE risk (OR 1.26, 95% CI 1.02 to 1.57; I^2 = 79.1%; Figure 5). In the subgroup analysis, a significant increased VTE risk with TCA exposure was observed in studies with high risk of bias (2 studies; OR 1.34, 95% CI 1.17 to 1.54; I^2 = 0.0%; Figure 5), while no association observed in studies with low risk of bias (2 studies; OR 1.20, 95% CI 0.77 to 1.89; I^2 = 84.3%; Figure 5). The study with depressed patients did not report the association between TCA use and VTE. There was no publication bias (Begg's test P = 0.734, Egger's test P = 0.175). With GRADE approach, the quality of evidence was rated as very low because of risk of bias and inconsistency (Table 5).

DISCUSSION

Our meta-analysis indicated that antidepressant use may be associated with an increased risk of VTE; however, no association was observed when we only included studies with low risk of bias and when we only included study with depressed patients. No association between SSRI use and VTE risk was detected in the overall analysis and in the subgroup analysis by quality of study methodology. A significant increased VTE risk with TCA use was observed, and the quality of evidence was rated as very low. However, no association between TCA use and VTE risk was observed when we only included studies with low risk of bias and when we only included studies that have eliminate the effect of antipsychotics.

A significant increased VTE risk was detected with antidepressant use, and the quality of evidence was rated as very low by GRADE approach. However, no association was detected when we only included studies with low risk of bias. Such phenomenon was also observed in the TCA group. Only 2 studies were judged to be at low risk of bias. When we pooled the data from these 2 studies with low risk of bias, high heterogeneity was detected (antidepressant: I^2 = 91.1%; TCA: I^2 = 84.3%), which lead the quality of evidence was rated down by GRADE approach. The heterogeneity can be partly explained by the different type of study design. Of these 2 studies with low risk of bias, 1 was case-control study and 1 was cohort study. Compared with cohort studies, case-control studies may reflect relatively short-term effects of antidepressant exposure (27). In addition, the duration of antidepressant use may also different between case-control studies and cohort studies.

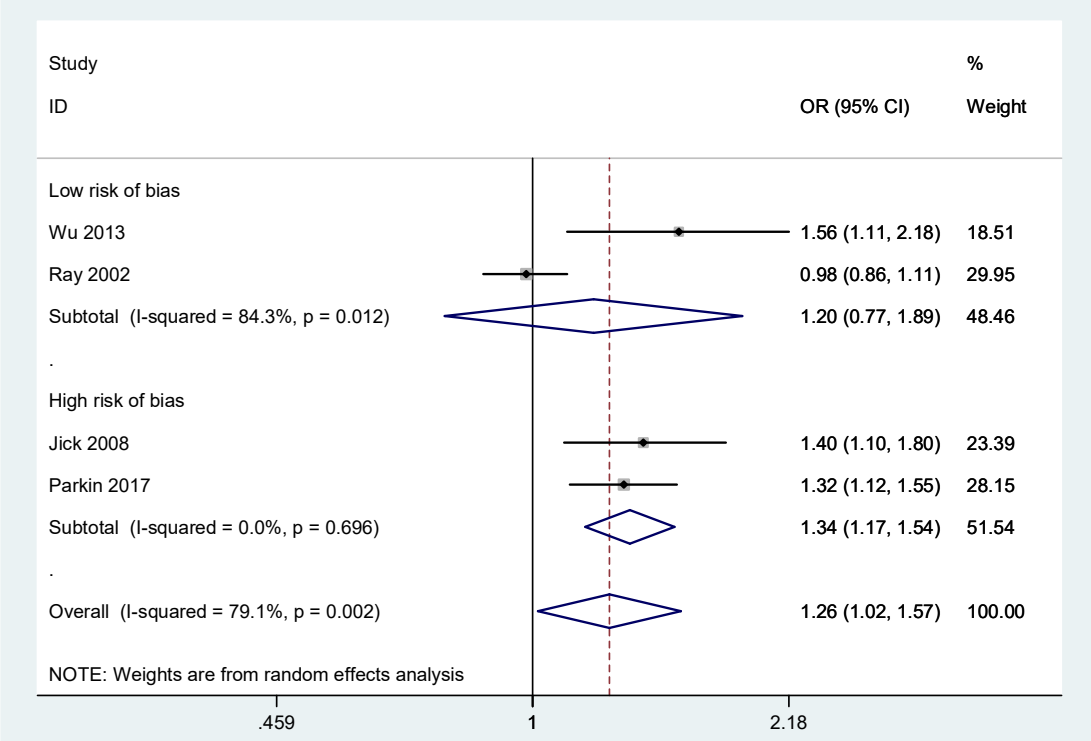

Figure 5. Association between TCA use and risk of VTE

Several previous studies observed a significant increased risk of VTE in depressed patients (28-30); however, it is unclear whether depression, antidepressant use or even another related factor drove the increased VTE risk (31). In our meta-analysis, an increased VTE risk with antidepressant use was detected; whereas, sensitivity analysis that only included study with depressed patients failed to detect an association between antidepressant use and VTE risk. Because most of the antidepressant drugs were prescribed for depression treatment and most patients without antidepressant use were non-depressed patients, these data seem to indicate that increased VTE risk may actually be associated with the depression itself but not the antidepressant use.

Interestingly, in the subgroup analyses of our study, we found that the relationship between antidepressant use and VTE risk varied according to the type of antidepressant exposure. Increased VTE risk was detected in TCA use group, but not in SSRI use group. The data did not support the previous hypothesis that depression lead to the increased VTE risk. If it is the depression drove the increased VTE risk, the VTE risk would not be changed according to the type of antidepressant. Serotonin is a weak platelet agonist and serotonin potentiates platelet stimulation induced by adenosine diphosphate or thrombin (32). SSRI decrease serotonin level in platelets by inhibiting serotonin reuptake; therefore, SSRI may relate to decreased platelet activation and prolongation of bleeding time (32). This view may explain why SSRI use did not associate with an increased VTE risk. In fact, a systematic review suggested that SSRI may be associated with increased perioperative bleeding events (33). Systematic reviews showed that antipsychotic drugs may be associated with an increased risk of VTE (8,9). As for the first-generation antipsychotics, the OR was 1.74, 95 % CI 1.28–2.37 (8) and 1.72, 95 % CI 1.31–2.24 (9) in these two systematic reviews, respectively. The chemical structure of the TCA is similar to that of the phenothiazines, one kind of the first-generation antipsychotics (14). This view may explain why TCA use increased VTE risk.

Although another meta-analysis examined the association between antidepressant use and the risk of VTE has been published (34), the findings from our manuscript differ from that paper. The previous meta-analysis showed that both TCA and SSRI were associated with an increased VTE risk, however no association between SSRI use and VTE risk was detected in our manuscript. The previous meta-analysis only included 6 studies compared patients with antidepressant versus individuals without antidepressant, so 1 study with data about SSRI was not included into analysis. In addition, fix effects model was used in the previous meta-analysis, although high heterogeneity was found.

The strengths of this study included the comprehensive literature search, critical appraisal of the included studies, planned subgroup analyses and sensitivity analyses, and the use of GRADE approach. However, our meta-analysis has several limitations. First, only observational studies were included in our meta-analysis. No randomized control trial addressing antidepressant use and its effect on VTE have been published. VTE is associated with a lot of risk factors. Although the included studies attempted to minimize the effect of other risk factors, possibly none of them could fully adjust for all these risk factors. This is the reason why we did not conducted sensitivity analysis on idiopathic VTE. Second, the heterogeneity is relatively high in our meta-analysis. There are many differences between the included studies, such as the definition of antidepressant exposure, age and gender of the patients, and so on. We largely divided antidepressants into TCA and SSRI; however, some studies had different categories (14,15). Third, only 9 studies were included and only 2 studies were judged to be at low risk of bias. The number of studies on this topic limited the possibility of further analysis. More high-quality studies examining the relationship between antidepressant use and VTE risk are needed.

CONCLUSIONS

In conclusion, our meta-analysis suggested that there was no association between selective serotonin reuptake inhibitor use and venous thromboembolism risk in the overall analysis and in subgroup analysis of studies with low risk of bias. Tricyclic antidepressant may be associated with an increased venous thromboembolism risk, but the quality of evidence was rated as very low. However, no association between tricyclic antidepressant use and venous thromboembolism risk was observed when we only included studies with low risk of bias.

CONFLICTS OF INTEREST

The author(s) declared no conflicts of interest.

ACKNOWLEDGEMENTS

Not applicable.

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Table 1. Characteristics of included observational studies

Study	Design, years	Data Sources, country	Population	Category	Definition of antidepressant exposure	Outcomes, follow up	Controlled variables
Jick 2008 (15)	Nested case-control study, from January 1, 1990 to December 31, 2005	United Kingdom General Practice Research Database, the United Kingdom	Inclusion criteria: patients aged 70 years or younger. Exclusion criteria: patients with a history of trauma, surgery, or pregnancy within the 3 months before the index date; patients with stroke, MI or angina, cerebrovascular disease, epilepsy, RF, insulin-dependent DM, cancer, drug abuse or alcohol abuse any time before the index date; patients with a history of anticoagulation therapy more than 60 days before the index date.	Total: 3867 Case: 782 (current use of antidepressant: 141, recent use of antidepressant: 23) Control: 3085 (current use of antidepressant: 497, recent use of antidepressant: 67)	Computerized data. Current use of antidepressant is defined as having the last prescription issued within the 60 days before the index date. Recent use of antidepressant is defined as having last prescription issued within 61–90 days before the index date.	Idiopathic VTE	Controls were matched according to age, sex, practice attended, index date, and duration of computerized medical record. No association between antipsychotic use and VTE. Case patients had the higher BMI than control patients, however, only data for amitriptyline adjusted for BMI using conditional logistic regression analysis.
Lacut 2007 (22)	Hospital based case-control study, from May 2000 to December 2004	The EDITH study, Brest University Hospital, France	Inclusion criteria: aged over 18 years hospitalized patients without major acquired risk factor for VTE. Exclusion criteria: patients with active malignancy, surgery or plaster cast in the past 3 months, pregnancy or delivery in the past 3 months.	Total: 1354 Case: 677 (antidepressant: 135) Control: 677 (antidepressant: 123)	One-to-one interview. If available, charts and medical records were reviewed. For outpatients, exposure was defined as current use of drugs at admission. All drugs recorded had to be taken at admission for more than 1 week. Drugs taken prior to admission but discontinued more than 1 week before admission were not recorded. For inpatients, all drugs taken at the time of inclusion were recorded, including drugs prescribed in hospital.	VTE	Controls were matched according to age and sex. However, without adjusted for BMI, factor V Leiden and prothrombin G20210A gene variation.
Parkin 2003 (23)	National case-control study, from January 1,	Coroners' and police records, death	Inclusion criteria: New Zealand patients aged 15-59 years without major risk factors for VTE.	Total: 263 Case: 54 (antidepressant: 6)	Records of general practitioners, family planning clinics and psychiatric services.	Fatal PE	Controls were matched according to age and sex. Conditional logistic

	1990 to December 31, 1998	certificates and hospital records, New Zealand	Exclusion criteria: patients with history of VTE or of prolonged immobility, severe injury, major surgery or pregnancy during the 2 months before the index date were excluded.	Control: 209 (antidepressant: 7)	Users of psychotropic drugs were defined as those who had been prescribed medication for at least 1 month. Current use was defined as prescribed use at any time during the 3 months before the index date.		regression adjusted for weight, combined oral contraceptive use and hormone replacement therapy during the 3 months before the index date. Current users of antipsychotics are excluded.
Stuijver 2013 (24)	Population based case-control study, from 1998 to 2008	PHARMO Record Linkage System, Netherlands	Inclusion criteria: patients aged 18 years or older. Exclusion criteria: patients with history of PE.	Total: 21297 Case: 4495 (antidepressant: 328) Control: 16802 (antidepressant: 844)	Database. Use of antidepressant is defined as having the prescription issued within 3 months period prior to the index date.	PE	Controls were matched according to age, sex and index date.
Thomassen 2001 (25)	Population based case-control study, from 1990 to 1993	Leiden Thrombophilia Study, Netherlands	Exclusion criteria: patients aged 70 years or older; patients with malignancies; psychiatric in-patients or general hospital in-patients; patients with a history of VTE.	Total: 948 Case: 474 (antidepressant: 8) Control: 474 (antidepressant: 3)	Records. Use of antidepressants prior to the first thrombosis.	DVT	Controls were matched according to age and sex.
Wu 2013 (14)	Nested case-control study, from 2001 to 2009	Longitudinal Health Insurance Database 2005, Taiwan	Inclusion criteria: patients aged 18 years or older. Exclusion criteria: patients who already had a prior diagnosis of VTE.	Total: 13102 Case: 1880 (antidepressant: 162) Control: 11222 (antidepressant: 397)	Prescription claim data. Current users were defined as those who had been prescribed at least 1 day of antidepressant drug supply during the month before the index date.	VTE	Controls were matched according to age and sex. Conditional logistic regressions adjusted for disease risk score (comorbid medical and psychiatric illnesses, medications, and health care use).
Lee 2015 (16)	Retrospective cohort study, from 2000 to 2011	Longitudinal Health Insurance Database 2010, Taiwan	Inclusion criteria: newly diagnosed depressed patients. Exclusion criteria: patients with VTE before index date, aged 20 years or younger and missing information about	Depressed patients: 35274 SSRI: 18177 (VTE: 68) Non-SSRI: 7634 (VTE: 30)	Prescription claim data.	VTE; Follow-up until diagnosis of VTE or the	Multivariate Cox proportional hazards regression. Adjusted with age, sex, and the comorbidities, namely, AF,

			age or sex.	Atypical antipsychotics: 7133 (VTE: 30) Without antidepressant: 2330 (VTE:12)		end of 2011	hypertension, diabetes, CVA, HF. Not adjusted with lower leg fracture or operations, and cancers.
Parkin 2017 (13)	Prospective cohort study, from 1996 to 2001	The Million Women Study, the National Health Service Breast Screening Programme, England and Scotland	Inclusion criteria: women included in the National Health Service Breast Screening Programme. Exclusion criteria: women who have prior VTE, cancer, or recent surgery.	Total: 734092 Antidepressant: 50354 (VTE: 313) Other psychotropic drugs: 19468 (VTE: 137) Treatment/no drugs: 13563 (VTE: 79) No treatment/no drugs (referent): 650707 (VTE: 3393)	Questionnaire, medications used during most of the last 4 weeks. Women were classified as antidepressant users if they ticked the amitriptyline or Prozac boxes, or if they recorded the names of other antidepressants.	VTE, PE, DVT; average of 7.3 y	Cox regression analyses. Adjusted with age, BMI, smoking, alcohol consumption, frequency of strenuous physical activity, hormone therapy, DM, high BP, and socioeconomic status, and stratified by recruitment region.
Ray 2002 (26)	Retrospective cohort study, from January 1, 1994 to March 31, 2000	Linked health care administrative databases of Ontario, Canada	Inclusion criteria: patients aged 65 years or older. Exclusion criteria: patients with a diagnosis of cancer, DVT, PE within 36 months prior to study entry, or patients had been prescribed warfarin within 12 months prior to study entry.	Total: 131196 Antidepressant: 75649 (DVT: 11.6 per 1000 person-years) Antipsychotics: 22514 (DVT: 16.5 per 1000 person-years) Thyroid replacement hormones (referent): 33033 (DVT: 10.1 per 1000 person-years)	Database. Had a prescription for a study drug between January 1, 1994 through January 31, 2000; had not filled a prescription for another study drug within 365 days of the current study drug; and had filled at least two prescriptions for the current study drug within 180 days of its initiation	DVT, VTE; follow-up until March 31, 2000	Cox proportional hazards regression model. Adjusted with age, sex, current residing within a long-term care facility, recent prior hospitalization, newly diagnosed cancer or concurrent prescription of lithium, estrogen, aspirin or warfarin.

MI = myocardial infarction; RF = renal failure; DM = diabetes mellitus; VTE = venous thromboembolism; BMI = body mass index; EDITH = Etude des De´terminants et Interaction de la THrombose veineuse; PE = pulmonary embolism; SSRI = selective serotonin reuptake inhibitor; AF = atrial fibrillation; CVA = cerebral vascular accident; HF = heart failure; DVT = deep vein thrombosis; BP = blood pressure.

Table 2. Risk of bias of included case-control studies

Study	Selection				Comparability	Exposure		
	Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate
Jick 2008 (15)	*	*	*	*	*	*	*	*
Lacut 2007 (22)	*	*		*	*		*	*
Parkin 2003 (23)	*	*		*	**	*	*	*
Stuijver 2013 (24)		*	*	*	*	*	*	*
Thomassen 2001 (25)	*	*		*	*	*	*	*
Wu 2013 (14)	*	*	*	*	**	*	*	*

A study can receive a maximum of one star for each item within the Selection and Exposure categories and two stars for Comparability.

Table 3. Risk of bias of included cohort studies

Study	Selection				Comparability	Outcome		
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start		Assessment of outcome	Adequate follow-up length	Adequacy of follow-up
Lee 2015 (16)	*	*	*	*	*	*	*	*
Parkin 2017 (13)	*	*		*	**	*	*	*
Ray 2002 (26)	*	*	*	*	**	*	*	*

A study can receive a maximum of one star for each item within the Selection and Outcome categories and two stars for Comparability.

Table 4. Subgroup analyses and sensitivity analyses

Category	No. of studies	OR (95% CI)	Heterogeneity, I^2 (%)
Antidepressant			
Total	9 (13-16,22-26)	1.27 (1.09, 1.49)	77.1
Low risk of bias	2 (14,26)	1.27 (0.84, 1.92)	91.1
High risk of bias	7 (13,15,16,22-25)	1.30 (1.12, 1.51)	54.9
Case-control studies	6 (14,15,22-25)	1.38 (1.17, 1.63)	52.1
Cohort studies	3 (13,16,26)	1.12 (0.85, 1.47)	87.3
Depressed patients	1 (16)	0.72 (0.39, 1.31)	/
Eliminate the effect of antipsychotics	6 (13-16,23,26)	1.23 (1.02, 1.48)	75.9
Female	1 (13)	1.39 (1.23, 1.56)	/
SSRI			
Total	5 (13-16,26)	1.10 (0.90, 1.34)	62.3
Low risk of bias, SSRI	2 (14,26)	1.05 (0.94, 1.18)	0.0
High risk of bias, SSRI	3 (13,15,16)	1.05 (0.71, 1.55)	73.5
Case-control studies, SSRI	2 (14,15)	1.01 (0.74, 1.38)	13.2
Cohort studies, SSRI	3 (13,16,26)	1.12 (0.85, 1.47)	77.5
Depressed patients, SSRI	1 (16)	0.75 (0.40, 1.38)	/
Eliminate the effect of antipsychotics, SSRI	4 (14-16,26)	1.02 (0.92, 1.14)	0.0
Female, SSRI	1 (13)	1.40 (1.17, 1.68)	/
TCA			
Total	4 (13-15,26)	1.26 (1.02, 1.57)	79.1
Low risk of bias, TCA	2 (14,26)	1.20 (0.77, 1.89)	84.3
High risk of bias, TCA	2 (13,15)	1.34 (1.17, 1.54)	0.0
Case-control studies, TCA	2 (14,15)	1.45 (1.19, 1.77)	0.0
Cohort studies, TCA	2 (13,26)	1.13 (0.85, 1.52)	87.5
Eliminate the effect of antipsychotics, TCA	3 (14,15,26)	1.26 (0.92, 1.71)	81.7
Female, TCA	1 (13)	1.32 (1.12, 1.55)	/

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Table 5. GRADE evidence

Quality assessment							Summary of findings	
No. of studies (participants)	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Reporting bias**	**Upgrading**	**Relative risk (95% CI)**	**Quality of evidence**
Antidepressant 9 studies (13-16,22-26)	Serious limitations	Serious limitations	No serious limitations	No serious limitations	Undetected	None	1.27 (1.09, 1.49)	Very low
SSRI 5 studies (13-16,26)	Serious limitations	Serious limitations	No serious limitations	No serious limitations	Undetected	None	1.10 (0.90, 1.34)	Very low
TCA 4 studies (13-15,26)	Serious limitations	Serious limitations	No serious limitations	No serious limitations	Undetected	None	1.26 (1.02, 1.57)	Very low

SSRI selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.