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Use of tramadol and the risk of bleeding complications in patients on oral anticoagulants: A systematic review and meta-analysis

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Abstract

Purpose This systematic review and meta-analysis aimed to determine whether tramadol intake increases the risk of bleeding in patients receiving oral anticoagulants.

Methods This systematic review was registered on PROSPERO, CRD42022327230. We searched Pubmed and Embase up to 14 April 2022 and references and citations of included studies were screened. Comparative and non-comparative studies exploring bleeding complications among adult patients on oral anticoagulants and tramadol were included. Risk of bias was assessed using an adaptation of the Drug Interaction Probability Scale for case reports and case series, and the Newcastle-Ottawa Scale for comparative studies. A meta-analysis was performed for the risk of serious bleeding (leading to hospitalisation or death) associated with tramadol in patients on vitamin K antagonists.

Results A total of 17 studies were included: 1 case series, 12 case reports, 2 case-control studies, and 2 cohort studies. Most of the studies described tramadol-vitamin K antagonists concomitant use; one case-control study also assessed dabigatran and rivaroxaban; one case report involved dabigatran. Among case reports/series, a total of 33 patients had a bleeding complication while using tramadol and an oral anticoagulant. The 4 comparative studies reported an increased bleeding risk during tramadol and vitamin K antagonist intake which was statistically significant in one study. The pooled risk ratio of serious bleeding was 2.68 [95% CI: 1.45 to 4.96; $p < 0.001$].

Conclusion This systematic review confirms an association between tramadol use and risk of bleeding in patients on vitamin K antagonists. Evidence is too limited to assess whether this risk extends to patients on direct oral anticoagulants and further studies are needed.

Keywords Bleeding; Direct oral anticoagulants; Oral anticoagulants; Tramadol; Vitamin K antagonists

Introduction

Oral anticoagulants, including vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs), are antithrombotic drugs prescribed for several indications such as treatment of venous thromboembolism or prevention of stroke in patients with atrial fibrillation [1–3]. The main complication of anticoagulants is bleeding [4]. Since non-steroidal anti-inflammatory drugs (NSAIDs) potentiate the risk of gastrointestinal bleeding [5], tramadol is often prescribed to manage pain in patients on oral anticoagulants. The analgesic effect of tramadol comes from μ -opioid receptors binding and from norepinephrine and serotonin reuptake inhibition. Selective serotonin reuptake inhibitors (SSRIs) increase the risk of bleeding [6–8]. Tramadol could therefore increase the risk of bleeding complications among patients who receive oral anticoagulants.

A few case reports and pharmaco-epidemiological studies have been published but the clinical relevance of tramadol-oral anticoagulants interactions is still uncertain. We therefore undertook a systematic review and meta-analysis to synthesize available evidence on the risk of bleeding among patients receiving tramadol in association with oral anticoagulants.

Methods

We performed a systematic review, reported according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9, 10] and the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) statement [11]. The protocol was registered on the PROSPERO International prospective register of systematic reviews (registration number: CRD42022327230). We initially planned to perform a restricted review allowing data extraction and risk of bias assessment to be performed by one reviewer and checked by a second one but we managed to conduct a systematic review with two reviewers working independently. To better assess the methodological quality of case-control and cohort studies, we modified the initial risk of bias assessment tool described in the protocol. Due to the limitations of the available evidence, we decided to reduce the outcomes studied to any bleeding and serious bleeding (leading to death or hospitalisation).

Information sources and search strategy

We performed a literature search in Pubmed and Embase through their web user interface up to 14 April 2022 with no language restrictions. To be as inclusive as possible, our queries only included terms referring to the target population (such as vitamin K antagonists; anticoagulants; novel oral anticoagulants, direct oral anticoagulants; VKA; NOAC; and DOAC), exposure (tramadol), and outcome (bleeding). The full search strategy for each database is available in the **Supplementary Table 1**. No restrictions were placed on the time frame and method of outcome measurement. In addition, we hand-searched the reference lists of included publications and the full report of conference abstracts, and we screened the articles citing the included publications (using Web of Science and Google Scholar) to identify further eligible studies.

Eligibility criteria

Reports were eligible for inclusion if they referred to any bleeding complication among adult patients (aged 18 or older) on oral anticoagulant therapy and using tramadol. Any type of study may provide some evidence to our review question. As a consequence, comparative studies (controlled trials, cohort studies, case-control studies, cross-sectional studies, case-crossover studies, and self-controlled case series) and non-comparative studies (case series and case reports) were eligible. Review articles, laboratory, and animal studies were excluded.

Study selection

Each step of the study selection was performed independently by two reviewers (OS and CL) and disagreements were resolved through discussion. First, titles and abstracts of all the references retrieved using the search strategy were screened for potential eligibility. Then, the full text of potentially eligible reports was assessed for inclusion. Several full-text reports were not available through our institutional library and were provided by the authors or the journal office. Articles published in other languages than English or French were translated using Google Translate for the full-text evaluation.

Data extraction

Data from included studies were extracted by two independent reviewers (OS and CL) as well. Reviewers were not blinded to titles and authors of reports. Case reports and case series describe the characteristics of individual patients whereas comparative studies provide group data and include risk estimates. Consequently, we used two different standardized pre-piloted forms to extract the relevant data: one for case reports and case series, and one for case-control and cohort studies. From each case report and case series, we extracted data on the study characteristics (first author's name, study design and number of cases); patient characteristics (age, sex, comorbidities); condition leading to tramadol intake; anticoagulant and tramadol regimen; concomitant medications; time to bleeding event; bleeding complications; and INR values. The following data were extracted from each case-control and cohort study: study characteristics (first author's name, study design, study period, country, sample size, study population, and studied bleeding complication); patient characteristics (age and sex); incidence rate of bleeding under anticoagulants alone; statistical method used; and outcome measures (odds ratios (OR), relative risks (RR), and adjustments).

Risk of bias assessment

The risk of bias in case reports and case series was evaluated with an adaptation of the Drug Interaction Probability Scale (DIPS) [12]. The template used consists of 6 questions listed in the **Supplementary File 1**. We considered that the methodological quality of each

study increased with the number of items fulfilled. Case-control and cohort studies were assessed for risk of bias using the Newcastle-Ottawa Scale (NOS) adapted for both studies [13]. This tool described in the **Supplementary Files 2 and 3** gives a maximum score of 9 stars. The higher number of stars indicates the highest methodological quality. The risk of bias of each included study was assessed independently by two raters (OS and CL) and discrepancies were resolved through discussion. Raters were not blinded to titles and authors of reports.

Data synthesis

Methodological and clinical data from all included studies were abstracted in description and risk of bias tables. Case reports/series and comparative studies were tabulated separately. Risk ratios were reported for cohort studies and OR for case-control studies to quantify the association between tramadol exposure and bleeding complication in patients taking anticoagulants. A case-control study used a prevalence ratio to quantify the association but reported numbers allowed the calculation of the OR [14].

When more than one study was available, we combined the estimates of the risk of bleeding associated with tramadol in patients under a given class of anticoagulants compared to patients under the same class of anticoagulants alone. OR were transformed into risk ratios using the baseline rate of bleeding in patients taking anticoagulants in cohort studies [15].

We used Stata 17.2 (StataCorp, College Station, TX) to perform a random-effects meta-analysis of log-transformed risk ratios and their 95% confidence intervals (restricted maximum likelihood method). Heterogeneity was assessed using the Cochran statistic (Chi^2 test) and quantified using the I^2 and the Tau^2 heterogeneity indices. We considered an I^2 value greater than 50% indicative of substantial statistical heterogeneity. The number of studies was too low to draw funnel plots or perform Egger's test to look for publication bias.

Certainty assessment

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence [16]. To rate the evidence regarding a given outcome, we considered: the number of studies analysing this outcome, their design and risk of bias; the consistency of their results and the precision of their risk estimate; the applicability of their results (directness); and the suspicion of publication bias.

Results

Selection process and study characteristics

The database search identified 163 references. After the removal of 32 duplicates, 131 titles and abstracts were screened, resulting in the exclusion of 103 references. Then, the full-text of the 28 remaining reports was analysed and 15 were included. Seven additional reports were identified from references of included studies, publications citing included reports, and searching the full-length report of included abstracts.

Eventually, we included 22 reports of 17 different studies. The search process and reasons for exclusion are depicted in the PRISMA flow diagram (**Figure 1**). Of the 17 included studies, 1 was a case series [17], 12 were case reports [18–29], 1 was a case-control study nested in a cohort study [30], 1 was a case-control study [14], and 2 were cohort studies [31, 32].

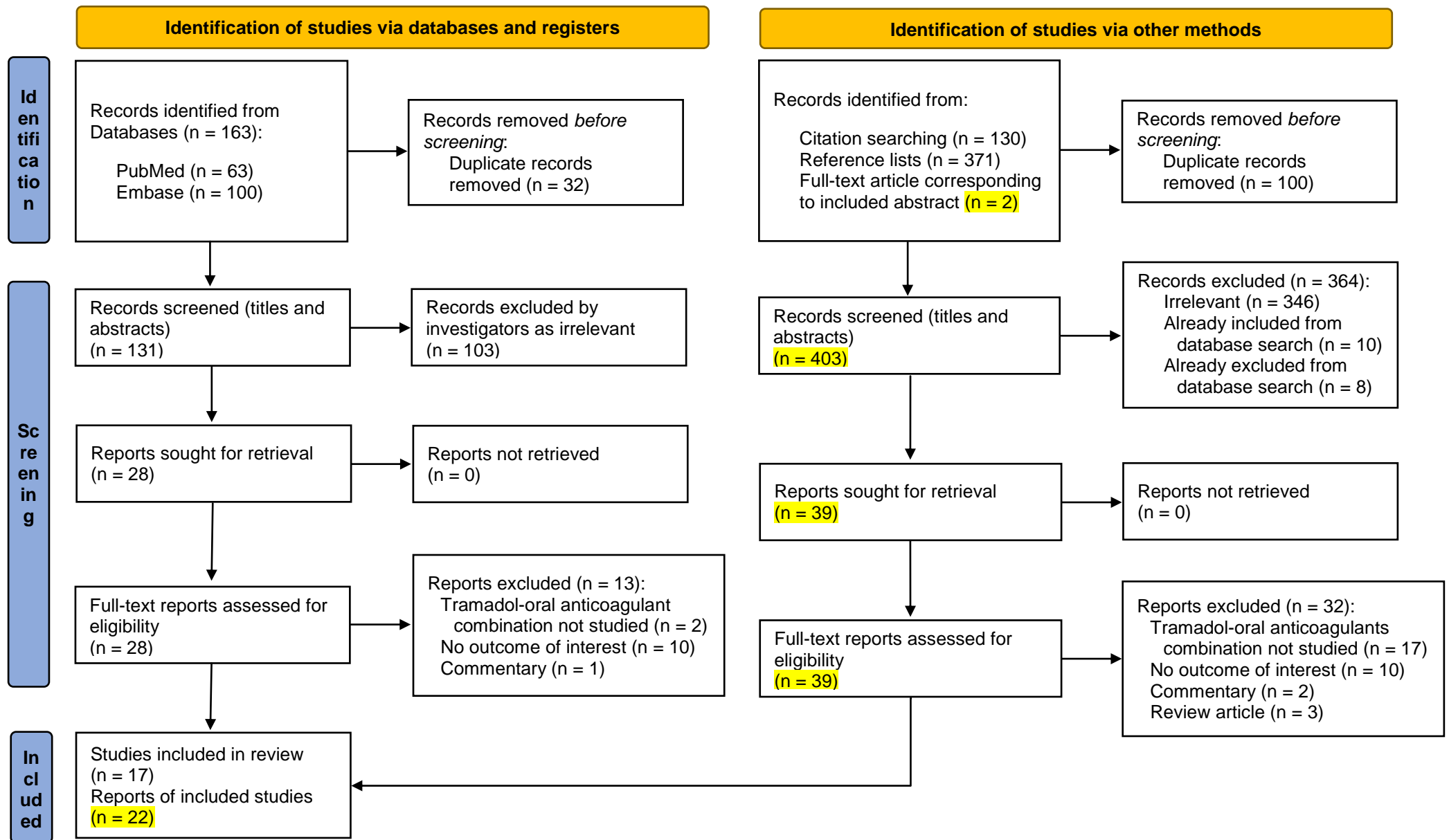


Figure 1. PRISMA flow diagram of the study selection

Table 1. Characteristics of included case-control and cohort studies

Author (year)	Study design	Study period	Country	Sample size	Population with oral anticoagulant therapy	Bleeding complications
Burgos-Gonzalez et al (2022) [30]	Case-control analysis nested in a prospective cohort	2008-2015	Spain	Not reported	New users of oral anticoagulants for atrial fibrillation, age 18 years or more, with at least a 1-year follow up in the BIFAP database	Bleeding-related hospital admission, recorded by primary care physicians in the BIFAP database using ICD and ICPC codes
Launiainen et al (2010) [14]	Case-control study	1 February 2007 to 31 January 2008	Finland	Cases 31 Controls 197	Deceased subjects who had detectable blood concentrations of warfarin at the time of death, with an autopsy performed at the Department of Forensic Medicine, University of Helsinki	Bleeding recognized as the cause of death by the autopsy
Penning-van Beest et al (2005) [31]	Retrospective cohort study	1992–2000	Netherlands	19,935	New users of phenprocoumon (5%) or acenocoumarol (95%) aged 40 to 80 years with a registration in the PHARMO database of at least 1 year	Bleeding-related hospital admission (ICD 9 diagnostic code) more than 15 days after VKA onset
Vitry et al (2011) [32]	Retrospective cohort study	1 July 2002 to 30 June 2006	Australia	17,661	Veterans aged 65 years and over on 1 July 2001, eligible for all health services subsidised by the department of veteran's affairs, and who were new users of warfarin (not having had a prescription for warfarin dispensed in the previous 6 months)	Bleeding-related hospital admission (ICD 10 primary diagnostic code)

BIFAP, Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria; *ICD-9-CM*, International Classification of Diseases, Ninth Revision, Clinical Modification; *ICD-10*, International Classification of Diseases, 10th Revision; *ICPC*, International Classification of Primary Care; *VKA*, vitamin K antagonist

Table 2. Results of included case-control and cohort studies

Author (year)	Mean age in years	Women (%)	Incidence rate of bleeding under anticoagulants alone	Statistical method used	Risk Calculation		
					OR (95% CI)	RR (95% CI)	Adjusted OR and RR (95% CI)
Burgos-Gonzalez et al (2022) [30]	Not reported	Not reported	Not reported	Conditional logistic regression	Not reported	Not applicable	Dabigatran + tramadol vs neither of both 2.04 (0.74 to 5.67) ^a Rivaroxaban + tramadol vs neither of both 2.24 (1.19 to 4.21) ^a VKAs + tramadol vs neither of both 1.30 (1.00 to 1.79) ^a
Launiainen et al (2010) [14]	69.1	19.5%	Not applicable	Unadjusted OR calculation from reported figures	Exposure to tramadol in cases compared to controls 2.77 (0.81 to 9.46)	Not applicable	Not reported
Penning-van Beest et al (2005) [31]	40–50: 2,677 (13.4%) 51–60: 3,790 (19.0%) 61–70: 6,281 (31.5%) 71–80: 7,187 (36.1%)	52%	1.02 (0.88 to 1.18) per 100 patient-year	Incidence rates ratios for unadjusted estimates Poisson regression for adjusted estimates	Not applicable	VKA+tramadol/ VKA alone 3.4 (1.1 to 10.8)	VKA+tramadol/ VKA alone 3.3 (1.1 to 10.4) ^b
Vitry et al (2011) [32]	81.8	36%	4.1 (3.7 to 4.6) per 100 patient-year	Poisson generalised estimating equations for adjusted estimates	Not applicable	warfarin+tramadol/ warfarin alone 2.28 (0.90 to 5.78)	warfarin+tramadol/ warfarin alone 2.37 (0.93 to 6.01) ^c

CI, confidence interval; OR, odds ratio; RR, relative risk; VKA, vitamin K antagonist

^a Adjusted for age, sex, body mass index, smoking status, arterial hypertension, renal and hepatic disorders, prior bleeds, gastrointestinal conditions, other medications (such as acid suppressing drugs, selective serotonin receptor inhibitors, VKAs, and other analgesics such as NSAIDs, codeine, and opioids)

^b Adjusted for age, sex, hypertension and history of GI bleeding

^c Adjusted for age, sex, socio-economic index of disadvantage for postcode of residence, number of comorbidities, number of prescribers (annually), number of different pharmacies used (annually), previous bleeding related hospitalisations during the 1-year period before first warfarin prescription, number of different medicines prescribed during the study period (annually), residential status (annually) and if bleeding occurred in the first 2 weeks of warfarin initiation

Case reports and case series

Characteristics of case reports/series are provided in the **Supplementary Table 2**. Across case reports and case series, a total of 33 patients had a bleeding complication while using tramadol and an oral anticoagulant. Anticoagulants prescribed concurrently with tramadol were mainly VKAs: warfarin (n=13, 39%) [18, 21–23, 25, 26, 29], fluindione (n=3, 9%) [20, 28], acenocoumarol (n=2, 6%) [19], phenprocoumon (n=1, 3%) [24], and unspecified VKAs (n=13, 39%) [17]. Only one case report described the concomitant use of tramadol and a DOAC: dabigatran (n=1, 3%) [27]. When specified, ages ranged from 54 to 88 years old and most cases involved women. All reported international normalized ratio (INR) values at admission were above the therapeutic level, ranging from 4 to 10.6. Time between tramadol prescription and bleeding event was specified in 7 case reports, ranging from 2 to 24 days [19–21, 24–26, 28]. Amidst all concomitant medications, 4 were known to increase the risk of bleeding: carbasalate calcium (antiplatelet) [19], sertraline (SSRI) [19], diclofenac and naproxen (NSAIDs) [27]. Among case reports/series, only two studies fulfilled the 6 items of the modified DIPS tool for risk of bias assessment [25, 26]. 5 out of 13 case reports/series fulfilled 2 or fewer items [17, 18, 20, 22, 28] (**Supplementary Table 3**). The main reasons for quality downgrading were that other possible causes of bleeding were not explicitly excluded (8/13, 62%) and the lack of information regarding the previous uneventful history of oral anticoagulants intake (7/13, 53%).

Cohort studies and case-control studies

Characteristics of case-control and cohort studies are presented in **Table 1** and their results in **Table 2**. Anticoagulants prescribed concurrently with tramadol were warfarin in one cohort study and the case-control study [14, 32], phenprocoumon or acenocoumarol in the other cohort study [31], and dabigatran, rivaroxaban or VKAs in the nested case-control study [30]. The nested case-control study found no statistically significant increase in the risk of bleeding in patients with atrial fibrillation taking tramadol + dabigatran (aOR: 2.04 [95% CI: 0.74 to 5.67]), compared to patients with atrial fibrillation taking neither tramadol nor dabigatran, but possibly taking another anticoagulant [30]. In the same study, associations with bleeding were also not statistically significant for tramadol + rivaroxaban (aOR: 2.24 [95% CI: 1.19 to 4.21]) and tramadol + VKAs (aOR: 1.30 [95% CI: 1.00 to 1.79]). The other case-control study found no statistically significant increase in the risk of fatal bleeding during warfarin-tramadol combination compared to warfarin alone (OR: 2.77 [95% CI: 0.81 to 9.46]; calculated from the data presented in the article) [14]. The concurrent use of tramadol and VKA was associated with a significantly higher risk of hospitalisation for bleeding compared to VKA alone in one of the two cohort studies: aRR 3.3 [95% CI: 1.1 to 10.4]) [31]. The other cohort study had an aRR of 2.37 [95% CI: 0.93 to 6.01] [32]. The 2 case-control studies reached a NOS score of 9 stars [30] and 6 stars [14] and the 2 cohort studies a score of 9 stars [31] and 8 stars [32] (**Supplementary Tables 4 and 5**).

Meta-analysis

Meta-analysis was only possible for the risk of serious bleeding (resulting in hospitalisation or death) associated with tramadol exposure in patients taking a VKA. The nested case-control study did not report the OR of bleeding in users of tramadol and anticoagulants compared to users of anticoagulants alone, but compared to non-users of both drugs [30]. The estimates from this study could not be included in the meta-analysis.

The OR quantifying the association of tramadol and fatal bleeding in patients under anticoagulants in the case-control study was converted to a risk ratio. To this end, we hypothesized that the risk of hospitalisation for bleeding was higher than the risk of fatal bleeding and we used the upper bound of the 95% confidence interval of the highest reported risk of hospitalisation for bleeding under anticoagulants alone (4.6 per 100 patients-year, **Table 2**). These choices lead to the most conservative estimate of the RR, 2.59 [95% IC: 0.78 to 8.60]. The meta-analysis did not detect significant heterogeneity across studies (**Figure 2**). The pooled risk ratio of bleeding requiring hospitalisation was 2.71 [95% CI: 1.32 to 5.56; $p = 0.01$] and the pooled risk ratio of overall serious bleeding was 2.68 [95% CI: 1.45 to 4.96; $p < 0.001$] (**Figure 2**). The resulting absolute risk of bleeding requiring hospitalisation associated with tramadol was + 1.74 events per 100 patient-year of tramadol exposure [95% CI: 0.33 to 4.74] when using the lowest baseline risk of bleeding in patients taking a VKA (1.02 par 100 patient-year), and + 7.01 events per 100 patient-year [95% CI: 1.31 to 18.7] when using the highest baseline risk (4.1 par 100 patient-year).

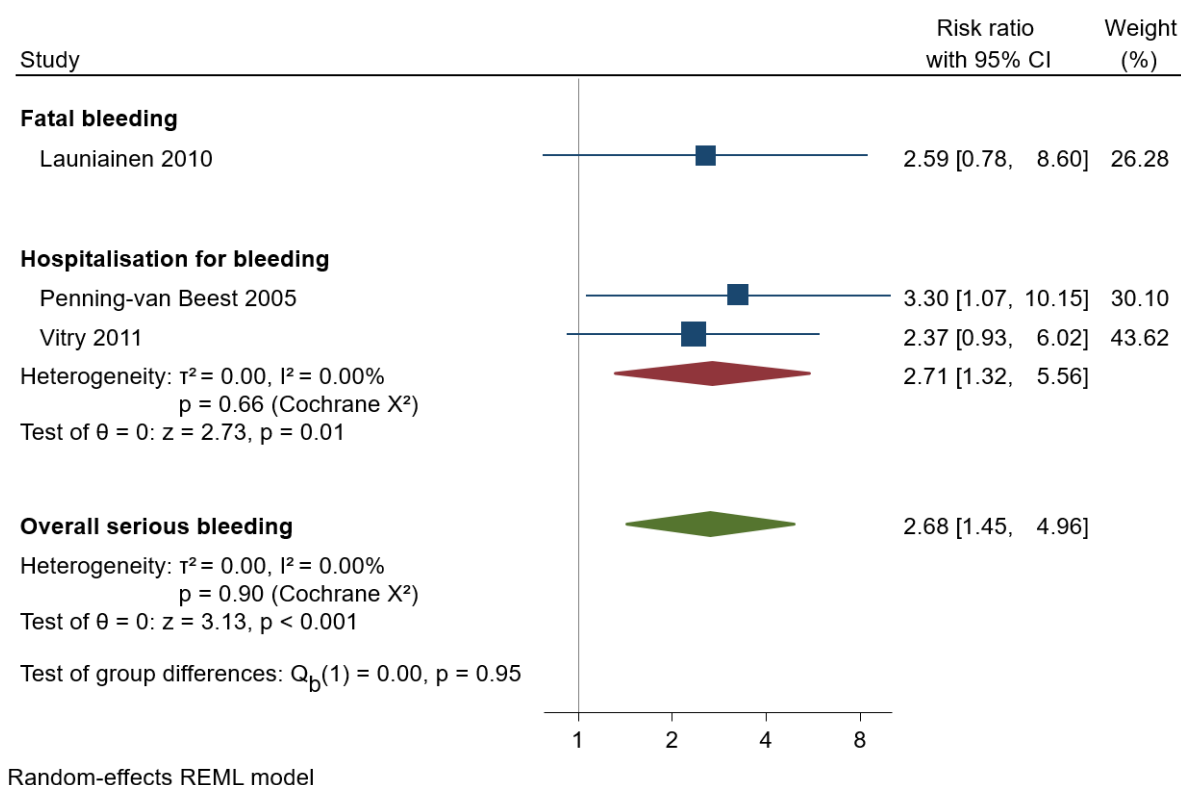


Figure 2. Forest plot of the studies reporting the risk of serious bleeding in patients on tramadol and VKA compared to patients on VKA alone. Horizontal lines represent 95% confidence intervals (CI). Squares represent study-specific risk ratio. Diamonds represent pooled risk ratio from random-effects meta-analysis, regarding hospitalisation for bleeding (upper diamond, 2 studies) and overall serious bleeding (lower diamond, 3 studies).

Certainty assessment

Three comparative observational studies assessed the risk of serious bleeding associated with tramadol in patients taking a VKA: bleeding requiring hospitalisation for two studies [31, 32] and fatal bleeding for one study [14]. The risk of bias is low for the two cohort studies on bleeding requiring hospitalisation [31, 32] but high for the case-control study on fatal bleeding [14]. Publication bias is unlikely for bleeding requiring hospitalisation (large studies) but possible for fatal bleeding (small study). Risk estimates were consistent across these studies. The pooled RR is > 2 but its 95% confidence interval is large. The evidence for fatal bleeding is indirect (derived from an autopsy study) but the evidence for bleeding requiring hospitalisation is direct. The resulting certainty of evidence is very low for fatal bleeding (starting at moderate, downgraded for risk of bias, imprecision and indirectness) and moderate for bleeding requiring hospitalisation (starting at moderate, downgraded for imprecision and upgraded for the large magnitude of effect).

Discussion

Comparative studies show that exposure to tramadol more than double the risk of serious bleeding in patients already taking a VKA. Case reports and case series suggest that bleedings mainly occur during the first month of tramadol exposure. Published evidence is too limited to draw any conclusion about the risk of bleeding complication associated with tramadol in patients on DOACs.

Limitations

This review has several limitations. First, our review included a small number of studies, most of them being case reports. The absence of a control group in case reports/series makes it difficult to ascertain the causal role of a drug interaction. The included case reports often lacked the information needed to support a causal role, as assessed with the DIPS tool. Several patients were taking drugs increasing the bleeding risk besides tramadol and oral anticoagulants.

Case-control and cohort studies can be subjected to indication bias: the bleeding risk increase could be due to the painful conditions treated by tramadol rather than tramadol itself. Moreover, several studies used diagnostic codes to identify bleeding-related hospitalisations. Misclassification is possible if secondary diagnostic codes were considered, because they may refer to non-serious bleeding occurring during hospitalisation for another reason. Concomitant and potentially confounding medications were not adjusted for in the studies included in the meta-analysis. Notably, many patients treated with tramadol may have comedicated with paracetamol, which is associated with an increased INR [33]. More generally, included studies did not investigate the risk factors of serious bleeding in patients taking both tramadol and an anticoagulant. Studies on INR changes with tramadol suggest that patients with defective CYP2D6 alleles are at higher risk of pharmacokinetic interaction with VKAs [22].

Among the four comparative studies, only one demonstrated a statistically significant increased risk of bleeding during tramadol and VKA intake compared to VKA intake alone [31]. However, the other studies reported consistent figures even if not statistically significant and the meta-analysis was conclusive.

The number of studies exploring the bleeding risk associated with tramadol and DOAC concomitant use was limited and we were unable to draw any evidence-based conclusion in this case.

Interpretation

Several mechanisms of tramadol-oral anticoagulants interaction have been considered. First, a pharmacokinetic interaction between tramadol and warfarin in patients with reduced CYP2D6-activity has been suggested. Tramadol is metabolized by CYP2D6 and by CYP3A4, also involved in warfarin metabolism. In patients with defective CYP2D6 alleles, tramadol metabolism could be transferred from CYP2D6 to CYP3A4. The resulting competition for CYP3A4 metabolism could lead to a decreased warfarin elimination, increase of the INR, and hence increase in the bleeding risk [22]. The prevalence of defective CYP2D6 alleles depends on the population [34]: 0–5 % in Asia, 2-7% in Hispanics, 7-10% in Caucasians (7–10 %), and 0–19% in Africa.

Several studies have documented an elevation of the INR consecutively to tramadol intake in patients on VKA [35–37]. For example, a large Danish study found that the risk of hospitalisation for excessive anticoagulation (high INR with or without bleeding) was increased in patients taking a VKA when they concomitantly took tramadol, with an adjusted OR of 3.1 [95% CI: 1.9 to 5.2] [36]. Although these studies could not be included in our review because data on bleeding events was not provided, they support an increased bleeding risk due to a pharmacokinetic interaction between VKAs and tramadol. Consistent with this hypothesis, all reported INR values in case reports/series of bleeding associated with tramadol were above the therapeutic range.

A pharmacodynamic interaction related to the inhibition of serotonin reuptake by tramadol has been considered [29, 38]. Platelets use a reuptake transporter to accumulate serotonin and its release stimulates platelet aggregation. Consequently, the inhibition of serotonin reuptake might trigger serotonin depletion in platelets, alter platelet aggregation, and increase the bleeding risk. This hypothesis is not supported by the findings of our review: as already mentioned, the INR was always elevated when tramadol was involved in bleeding events with VKAs. Moreover, in a nationwide Swedish study, tramadol use was associated with an increased risk of hospitalisation for bleeding peptic ulcer (adjusted odds ratio 2.1 [95% confidence interval: 2.0–2.3]) but so was codeine as well, despite no known interaction with haemostasis or peptic ulcer risk [39]. The authors suggest an indication bias: the association with bleeding would not be due to the pharmacologic properties of tramadol or codeine but to the painful undiagnosed ulcers for which they were eventually prescribed.

Implications

Clinicians and patients should be aware of the potential bleeding risk associated with the combination of tramadol and VKAs, pharmacokinetics drug interaction in susceptible patients. We recommend monitoring the INR in patients on VKA a few days after tramadol is introduced.

The bleeding risk is increased by various drugs in patients taking DOACs [40]. Further studies are required to ascertain and quantify the association between tramadol use and bleeding risk in patients on DOACs, which are now much more prescribed than VKAs. Real-world data could be used to investigate this risk efficiently. A first step may involve adverse drug registries, which probably include unpublished reports of serious bleeding with a causality evaluation of the potential interaction between tramadol and a direct oral anticoagulant. Further steps could involve the pharmaco-epidemiological analysis of large-scale real-world databases. These studies should control for comedications (including paracetamol) and investigate risk factors of serious bleeding in patients taking both tramadol and an anticoagulant.

Conclusion

This systematic review shows that tramadol increases the risk of bleeding in patients on VKAs, due to an interaction occurring within the first days of co-exposure in susceptible patients. Further pharmaco-epidemiological research is needed to investigate the bleeding risk in patients taking tramadol and DOACs.

Declarations

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to Publish

Not applicable.

Competing interests

The authors declare no conflict of interest.

Authors' contribution

Conceptualization, OS; data curation, CL; formal analysis, OS; investigation, OS and CL; methodology, OS; project administration, OS; supervision, OS; validation, OS; visualization, OS and CL; writing – original draft, CL; writing – review & editing, OS, CL, AV and LG.

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Availability of data and material

All data generated and analysed are available in this article and its Supplemental material. Stata files (meta-analysis dataset and code) are available from the authors, by request

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