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Effect of tramadol and DOACs with special attention to dabigatran on concomitant use, on the risk of mayor bleeding using BIFAP database in Spain

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Abstract

Background: Tramadol, a weak opioid, inhibits the reuptake of serotonin, a key feature on vascular homeostasis. A suspected interaction exists between dabigatran and tramadol, which might trigger an excess on risk of bleeding however, there is a gap in knowledge on this topic.

Purpose: To estimate the effects of tramadol, dabigatran and concomitant use on the risk of hospitalized major bleeds (Gastrointestinal bleeding and intra-extracranial bleeds).

Methods: Among a validated established cohort of new users of oral anticoagulants for non-valvular atrial fibrillation (NVAF) aged 18 years or older, we identified all hospitalized bleed episodes (GIB and extra/intracranial bleeds) within 2008–2015. A nested case–control analysis was conducted using conditional logistic regression. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were calculated for dabigatran, tramadol, and concomitant use. Several sensitivity analyses were carried out.

Results: aORs (95%CIs) for current use of only dabigatran, only tramadol and concomitant users were 1.73 (1.37–2.18) and 1.38 (1.13–1.67) and 2.04 (0.74–5.67) compared with non-users of both drugs (>365 days). aORs for current continuers and non-continuer users of dabigatran were 1.36 (1.00–1.86) and 2.19 (1.61–2.98), respectively. For the latter, non-continuer users with a short duration of dabigatran cumulated the highest risk (3.36 [1.88–5.99]). There also was an increased risk with concomitant use of tramadol and rivaroxaban (2.24 [1.19–4.21]), or antagonist of vitamin K (1.30 [1.00–1.69]).

Conclusion: There was a trend towards and increased risk of excess bleeds when using concomitantly with dabigatran. The effect decreases with a narrower definition of current use.

KEYWORDS
bleeds, drug safety, interaction, oral anticoagulants, tramadol

Key Points

- There is a suspected interaction between tramadol and dabigatran that may increase bleeding risk.
- A new user design of anticoagulants with a nested case control analysis was performed using BIFAP and there was a trend towards an increased risk with concomitant use of tramadol and dabigatran.
- Further studies would help the clinicians' decision making when prescribing these drugs.

Plain language summary

Tramadol is a weak opioid that can affect the vascular homeostasis. A suspected interaction exists between dabigatran and tramadol, which might trigger an excess on risk of bleeding, however, there is a gap of knowledge on this topic. We aimed to estimate the effects of tramadol, dabigatran, and concomitant use on the risk of hospitalized major bleedings. We used a validated cohort of new users of oral anticoagulants for non-valvular atrial fibrillation aged <18 years where we identified all hospitalized bleedings within 2008–2015. We conducted a nested case–control study and used conditional logistic regression for analysis. The adjusted odds-ratio (aORs) and 95% confidence intervals for currently using (<30 days) only dabigatran, only tramadol and both together were 1.71 (1.37–2.13), 1.22 (0.87–1.71) and 2.38 (0.72–13.30) compared with non-users of both drugs (>365 days). Also, there was not an increased risk with concomitant use of tramadol and other anticoagulants such as rivaroxaban (0.49 [0.11–2.27]), or antagonists of vitamin K (1.17 [0.77–1.78]). As a conclusion, although tramadol was not associated with an increased risk of bleeds, there was a trend towards and increased risk of excess bleeds when using concomitantly with dabigatran. More studies are needed to further explore this potential interaction.

1 | INTRODUCTION

Vitamin K antagonists (VKAs) have been the cornerstone and first line anticoagulant therapy for years. Over the past few years, a new pharmacological class, direct oral anticoagulants (DOACs), which includes dabigatran, apixaban, rivaroxaban, and edoxaban, has been introduced as an alternative to VKAs. In fact, they are now recommended in European clinical care guidelines,[1] among other countries, as an alternative or in preference to VKAs, in patients with non-valvular atrial fibrillation. Evidence coming from randomized clinical trials as well as meta-analyses have shown non-inferiority of DOACs compared to VKAs as well as similar or lower risk of bleeds.[2–5] This has helped to palliate some limitations traditionally associated to VKAs such as regular anticoagulation monitoring, dietary and drug–drug interactions, and the potential for serious bleeding.[6]

Despite the advantages towards the monitoring and management of DOACs in clinical practice, there are still uncertainties according to both pharmacodynamic and pharmacokinetic drug interactions that might result in an increased risk of bleed episodes. A recent meta-analysis reported interacting drugs to cause bleeding events associated to concomitant use with DOACs were amiodarone and ritonavir, and thrombotic events with phenytoin and carbamazepine, although data is limited.[7] Other studies have focused on pharmacodynamic consequences reporting an increased risk of bleeds associated with concomitant use of DOACS with selective serotonin reuptake inhibitors (SSRIs), Nonsteroidal anti-inflammatory drugs (NSAIDs) and antiplatelet.[8,9]

Similar to SSRIs, tramadol, a weak opioid analgesic,[10] also possesses a dual mechanism of action acting as an opioid agonist inhibiting the reuptake of noradrenaline and serotonin, which might result in a serotonin syndrome.[11] Therefore, a consequence of this syndrome is the excess risk of bleeding, already observed with SSRIs. In fact, it has been reported an increased risk of bleeding peptic ulcer associated with tramadol.[12] Prior epidemiological studies and case reports have studied the potential of increased bleeding between concurrent use of tramadol and VKAs leading to an excessive anticoagulation.[13–16] Specifically, both in vitro and in vivo, results that focused on the evaluation of the pharmacological interactions of DOACs (7), showed that among the most potent interactions was the increase in anticoagulation and antiprotease, observed in dabigatran with tacrolimus and dabigatran with tramadol with differences, not observed with either rivaroxaban or apixaban.

Due to lack of established evidence towards the potential drug interaction with DOACs, epidemiological studies are warranted in order to fill major gaps. This is of special importance as tramadol, currently recommended for the treatment of certain moderate to severe pain syndromes such as acute pain after surgery[17] or chronic back pain,[18] is widely used and prescribed to approximately 2% of the Spanish population.[19] Of note, tramadol has been considered an acceptable alternative as analgesic to NSAIDs due to the gastrointestinal and renal toxicity associated to NSAIDs and COXIBs[20] together with a less addictive perception. We aimed to examine the potential role of DOACs, with special focus on dabigatran, and tramadol in the

risk of major bleeds and its concomitant use taking advantages of the Spanish primary care database BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público, Pharmacoepidemiological Research Database for Public Health Systems).

2 | METHODS

2.1 | Data source

The current study used data from the Spanish population-based database BIFAP. BIFAP includes anonymized electronic medical records of primary care practitioners (PCPs) and pediatricians from nine participating Autonomous Regions (out of 17) in Spain. BIFAP's age and sex distribution are comparable to the Spanish population, covering 8.6% of the total Spanish population at the time this study was performed.[21,22] Data of BIFAP includes information of demographic factors, consultation visits, referrals, laboratory test results, diagnostic procedures, diagnoses (using two coding systems International Classification of Primary Care—Second Edition [ICPC-2] and ICD-9; the ICPC is the coding system for eight out of nine participant Autonomous Regions, and its granularity is limited when compared with ICD-9) and prescriptions. Prescriptions issued by the PCP are automatically recorded; prescriptions from specialists as well as those used during hospitalizations may not be fully captured. Prescriptions are entered using the ATC classification. From 2011 onwards, e-prescription was progressively implemented in primary care centers therefore, dispensation is also available. Information on product name, date, quantity, and dosage is included.

2.2 | Source population

The source population included all individuals registered in BIFAP aged ≥18 years within the study period Jan 2008–Dec 2015, who met the eligibility criteria of at least 1 years' registration with the PCP. We identified all new users of DOACs: dabigatran, rivaroxaban, apixaban for non-valvular atrial fibrillation (NVAF) indication. New users were defined as non-use of DOAC for at least 365 days prior to the date of study entry. The date of DOAC prescription was considered the start date of follow up.

2.3 | Follow-up to identify incident bleed episodes

Cohort of new users was followed from the start date until the earliest of the following events whichever came first: an entry code for major bleeding events defined as a composite of intracranial, gastrointestinal and other symptomatic bleeding in a critical area or organ, as agreed by the International Society on Thrombosis and Haemostasis,[23,24] death, end of the follow up period (31 December 2015) or transferred out from the database. Final number of major bleed episodes was 2419 cases. Further details on the cohort and the bleeding events are described elsewhere.[25]

2.4 | Control selection

Controls were randomly selected from NVAF cohort by risk-set sampling and individually matched to cases (4:1) by age and sex. To do this, for each case, we identified all cohort members who were still at risk within follow-up and of the same age (+/−1 year) and sex (the case set). Within each case set, four controls were selected at random using an automated function in the software package. Matched controls were assigned the index date of their corresponding case. Cases were eligible to be controls for another case until the date of their bleed. By this design, the derived odds ratio (OR) is an unbiased estimate of the incidence rate ratio that would have emerged from a cohort study based on the source population.[26]

2.5 | Exposure to dabigatran, tramadol, and other concomitant medication

To collect the exposure of drugs of interest we used as time frame the start date and the index date based on the most recent episode of drug use before the index date. Drug exposure was categorized as follows: *current use*, when the prescription supply lasted until/over the index date or ended within the 30 previous days; *recent use*, when the prescription supply ended 31–90 days before the index date; *past*, when the prescription supply ended 91–365 days before the index date; and *non-use*, when the prescription supply ended >365 days or there was no recorded prescription within the time frame. A treatment episode comprised the length of consecutive prescriptions disregarding gaps between prescriptions of ≤30 days (grace period). Among current users, duration was classified using the following cut off points: duration <91 days, 90–180 days, and >180 days, respectively.

Current users were further subdivided according to continuous use throughout the follow up period (that is from start to index date). The time interval between their first prescription date and last day of therapy before the index date within the follow up period was computed, and the duration of treatment was calculated by summing the individual durations of consecutive prescriptions. To do so, gaps in treatment of >30 days were considered genuine breaks in treatment; (gaps in treatment of <30 days were disregarded and the patient was considered on continuous therapy). Each patient's total treatment duration was subtracted from their time interval, and those with a value greater than zero were deemed to be non-continuous users.

Finally, to evaluate the interaction between the drugs of interest A + B (e.g., tramadol & dabigatran) we created one variable with five mutually exclusive levels of exposure: *nonuse of either agent (No A No B)* (within the year prior to index date); current *use of both agents (A + B)*; *current use of only A (nonuse of B within the year prior)*; *current use of only B (nonuse of A within the year prior)*; and *remaining* (other combinations of both agents).

2.6 | Potential confounding factors

We deemed from the database the covariates known for being risk factors for bleeding: body mass index (BMI), smoking status, arterial

hypertension, renal and hepatic disorders, prior bleeds, gastrointestinal conditions (Supplemental Table 1). Moreover, we included other medications such as acid suppressing drugs, selective serotonin receptor inhibitors, VKAs, and other analgesics such as NSAIDs, codeine, and opioids using the same definition as the main exposure of interest. To collect this information, we looked any time prior to the index date, taking the most recent information that is closest to the index date.

2.7 | Statistical analysis

Descriptive statistics were used to assess characteristics of cases and controls. Means and standard deviations are shown for continuous variables and proportions for categorical variables. Nested case–control analyses were conducted using conditional logistic regression to calculate ORs as a measure of the relative risk of major bleeds associated with dabigatran and tramadol. We adjusted for risk factors mentioned above that showed significant association after applying the stepwise process. Several sensitivity analyses were performed: first, we aimed to evaluate the interaction of tramadol with remaining DOACs, and tramadol and VKAs, separately. Second, we evaluated the interaction between tramadol and other antagonists (SSRIs). Third, we evaluated if the risk of major bleeds associated with concomitant use of tramadol and dabigatran differed according to type of continuous use. Fourth, we changed the definition for current users, defining them as when the prescription supply lasted until/over the index date or ended within the 7 previous days. Finally, we looked for the concomitant effect of dabigatran and tramadol stratifying by obesity (i.e., BMI ≥ 30) Analyses were undertaken using Stata (StataCorp. 2017).

3 | RESULTS

3.1 | Main characteristics

There were a total of 2419 cases with a major bleed matched to 9671 controls. Frequency distributions of characteristics of the two study groups at the start of follow-up are shown in Table 1 for demographics, lifestyle factors, healthcare use and comorbidities and in Table 2 for other medications. Frequency of women were higher than men (54.9% vs. 45.1%) with a mean age of 77.8 (*SD*: 9.3) in cases and controls. The distribution of demographics, lifestyle factors, was, overall, very similar among cases and controls with the exception of health care utilization. Controls had a higher percentage of patients in categories less than 5 visits up to 15–19 visits and cases had a higher percentage of patients with 30 or more visits.

3.2 | DOACs and analgesics and risk of major bleeds

Figure 1 shows the risk of major bleeds associated with DOACs, VKAs, and analgesics, separately. We present the results of current

TABLE 1 Baseline characteristics among cases and controls

	Controls *N* = 9671		Cases *N* = 2419	
Sex				
Men	4368	45.2	1092	45.1
Women	5303	54.8	1327	54.9
Age				
<70 years	1704	17.6	425	17.6
70–74 years	1304	13.5	325	13.4
75–79 years	2056	21.3	511	21.1
80–84 years	2185	22.6	548	22.7
≥85 years	2422	25.0	610	25.2
Smoking				
Non-smoker	4236	43.8	1088	45.0
Current	1018	10.5	288	11.9
Former	989	10.2	265	11.0
Unknown	3428	35.4	778	32.2
BMI				
15–19 kg/m^2	98	1.0	26	1.1
20–24 kg/m^2	1193	12.3	352	14.6
25–29 kg/m^2	3228	33.4	824	34.1
30 and more kg/m^2	3422	35.4	847	35.0
Unknown	1730	17.9	370	15.3
GP visits				
0–5 visits	344	3.6	23	1.0
5–9 visits	515	5.3	62	2.6
10–14 visits	887	9.2	156	6.4
15–19 visits	1383	14.3	310	12.8
20–25 visits	1534	15.9	374	15.5
≥30 visits	5008	51.8	1494	61.8
Comorbidities				
Cardiovascular diseases	8245	85.3	2114	87.4
IHD	1464	15.1	429	17.7
Any ICB	23	0.2	11	0.5
IS	841	8.7	258	10.7
HTA	7209	74.5	1844	76.2
Heart Failure	1660	17.2	471	19.5
Diabetes	2681	27.7	713	29.5
Dyslipidemia	5564	57.5	1418	58.6
Respiratory diseases	6142	63.5	1662	68.7
Digestive diseases	2787	28.8	901	37.3
Cholecystitis	1143	11.8	346	14.3
Hiatus hernia	747	7.7	234	9.7
GIB	492	5.1	256	10.6
Renal diseases	826	8.5	280	11.6
Cancer	1617	16.7	490	20.3

Abbreviations: AHT, arterial hypertension; BMI, body mass index; GIB, Gastrointestinal Bleeding; GP, general practitioner; ICB, intracranial bleeding; IHD, ischemic heart diseases.

TABLE 2 Use of other medications among cases and controls and risk of major bleeds

	Controls, $N = 9671$		Cases $N = 2419$	
SSRIs				
Non-users (>365 days)	8628	89.2	2121	87.7
Current users (hasta 30 days)	718	7.4	214	8.8
Recent users (31–90 days)	101	1.0	19	0.8
Past users (91–365 days)	224	2.3	65	2.7
COXIBs				
Non-users (>365 days)	9217	95.3	2306	95.3
Current users (hasta 30 days)	143	1.5	32	1.3
Recent users (31–90 days)	50	0.5	13	0.5
Past users (91–365 days)	261	2.7	68	2.8
NSAIDs				
Non-users (>365 days)	7093	73.3	1703	70.4
Current users (hasta 30 days)	603	6.2	236	9.8
Recent users (31–90 days)	486	5.0	107	4.4
Past users (91–365 days)	1489	15.4	373	15.4
Corticosteroids				
Non-users (>365 days)	8687	89.8	2080	86.0
Current users (hasta 30 days)	321	3.3	118	4.9
Recent users (31–90 days)	151	1.6	57	2.4
Past users (91–365 days)	512	5.3	164	6.8
Antiplatelets				
Non-users (>365 days)	7123	73.7	1690	69.9
Current users (hasta 30 days)	1158	12.0	371	15.3
Recent users (31–90 days)	315	3.3	108	4.5
Past users (91–365 days)	1075	11.1	250	10.3
PPIs				
Non-users (>365 days)	3769	39.0	829	34.3
Current users (hasta 30 days)	4647	48.1	1311	54.2
Recent users (31–90 days)	448	4.6	128	5.3
Past users (91–365 days)	807	8.3	151	6.2
H_2RA				
Non-users (>365 days)	9351	96.7	2307	95.4
Current users (hasta 30 days)	216	2.2	84	3.5
Recent users (31–90 days)	27	0.3	6	0.2
Past users (91–365 days)	77	0.8	22	0.9
Benzodiazepines-Hypnotics				
Non-users (>365 days)	6032	62.4	1415	58.5
Current users (hasta 30 days)	2463	25.5	685	28.3
Recent users (31–90 days)	369	3.8	125	5.2
Past users (91–365 days)	807	8.3	194	8.0
Statins				
Non-users (>365 days)	5318	55.0	1314	54.3
Current users (hasta 30 days)	3621	37.4	928	38.4
Recent users (31–90 days)	294	3.0	75	3.1
Past users (91–365 days)	438	4.5	102	4.2

Abbreviations: H_2RA, histamine H_2 receptor antagonists; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors.

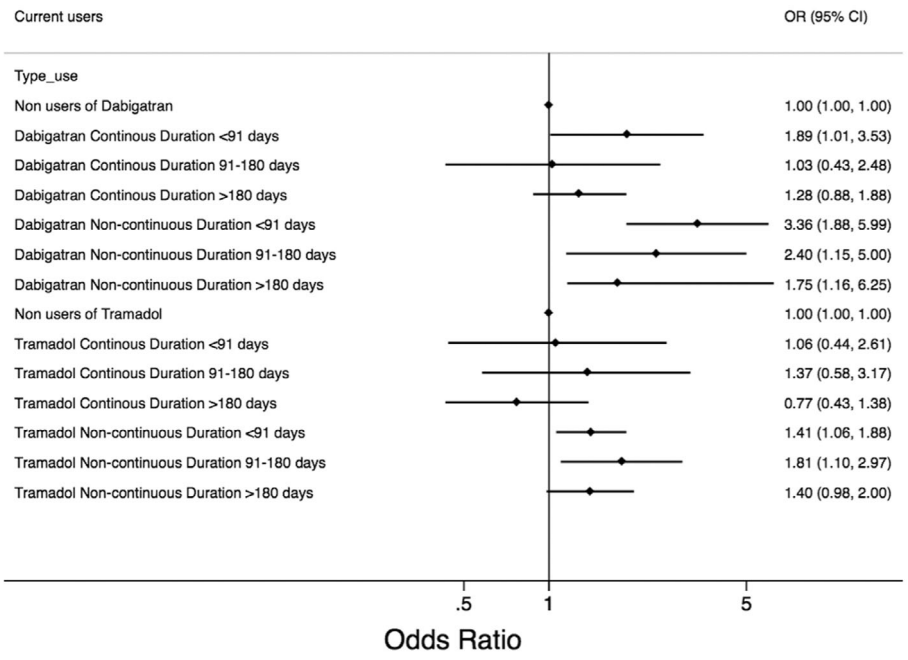

FIGURE 1 Associations between use of OACs and dabigatran and the risk of major bleeding according to type of current use

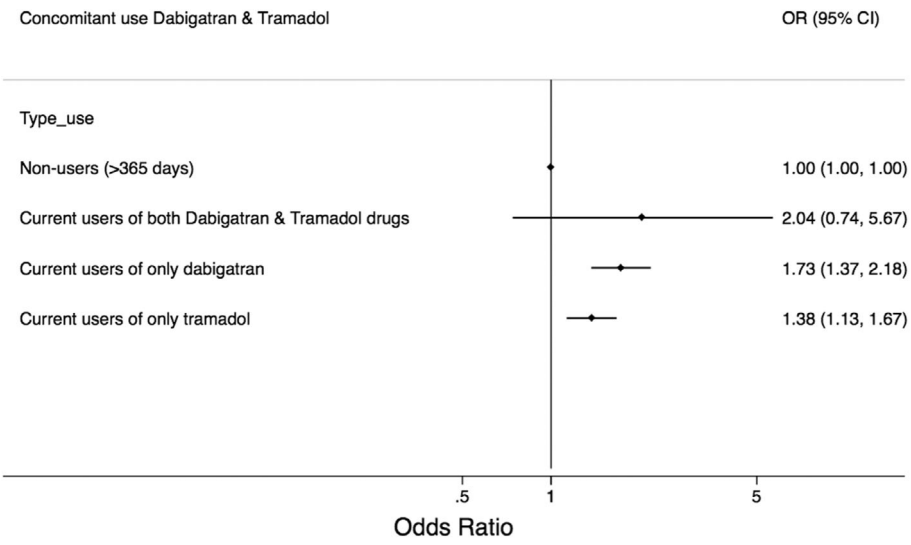

FIGURE 2 Associations between use of tramadol and dabigatran and the risk of major bleeding according to type of current use and duration

users split by type of use (i.e., continuous/non-continuous) compared with non-users. Current users of dabigatran had an increased risk of major bleeds (1.71 [95% CI: 1.37–2.13]), which was cumulated among non-continuous users (corresponding aOR estimates were 2.19 [95% CI: 1.61–2.98] vs. 1.36 [95% CI: 1.00–1.86] for continuous users). Neither current users of rivaroxaban or VKAs showed an increased risk of major bleed (Figure 1). Among current users of tramadol (aOR of 1.35 [95% CI: 1.11–1.63]), the risk was also pronounced among those with non-continuous use (aOR of 1.47 [95% CI: 1.19–1.81]). Paracetamol and codeine were not associated with a significant change in risk of bleeds. Of note, there were no cases with current continuous use of codeine (Supplemental Figure 1).

We also looked at the effect of treatment duration among continuous and non-continuous current users (Figure 2). For dabigatran, the risk of major bleeds for continuous current users was only observed for those with a duration <91 days (aOR of 1.89 [95% CI: 1.01–3.53]), but for non-continuous users it was observed for any treatment duration (aOR of 3.36 [95% CI: 1.88–5.99] for <91 days, 2.4 [95% CI: 1.15–5.00] for 91–180 days, 1.75 [95% CI: 1.16–2.65] for >180 days). Among continuous current users of tramadol, the risk was more heterogeneous, for example among continuer users, the risk was observed among those with duration between 91–180 days (95% CI:1.37 [0.58–3.17]) while there was an increased risk for all types of duration among non-continuous users.

3.3 | Concomitant use of dabigatran/tramadol and risk of major bleeds

Compared with non-use of both dabigatran and tramadol, current users of only dabigatran showed an aOR of 1.73 (95% CI: 1.37–2.18) and 1.38 (95% CI: 1.13–1.67) for current users of only tramadol. Users

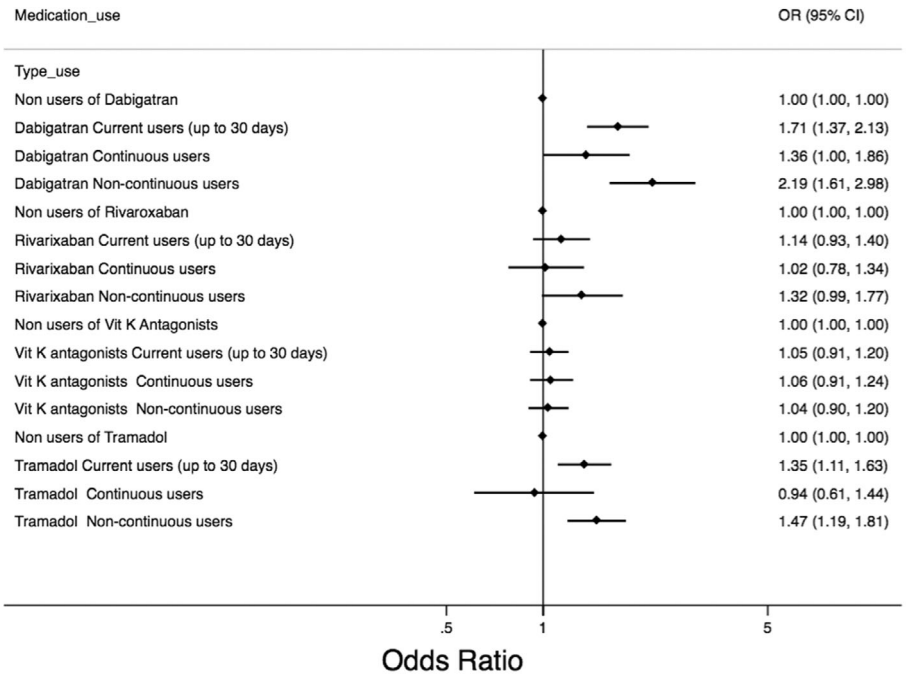

FIGURE 3 Associations between the concomitant use of tramadol and dabigatran and the risk of major bleeding according to type of current use

of both drugs concomitantly had an increased risk of 2.04 (95% CI: 0.74–5.67) (Figure 3). As a sensitivity analysis, when using 7 days as definition of current users, the corresponding estimates were 1.63 (95% CI: 1.28–2.08) for current users of only dabigatran and 1.38 (95% CI: 1.13–1.68) for current users of only tramadol. Users of both drugs concomitantly had an increased risk of 1.35 (95% CI: 0.42–4.36) although these results should be interpreted with caution due to low numbers of current users of both dabigatran and tramadol (<15 patients) (data not shown). We did not observe any effect modification by obesity, users of both drugs concomitantly had an increased risk of 2.05 (95% CI: 0.25–16.75) for obese patients and 2.24 (95% CI: 0.46–10.90) for non-obese patients (data not shown).

3.4 | Sensitivity analysis

When we evaluated the effect of concomitant use of tramadol with other oral anticoagulants such as rivaroxaban or VKAs, we also found an increased risk of major bleeds (aORs of 2.24 [95% CI: 1.19–4.21] and 1.30 [95% CI: 1.00–1.69]) (Supplemental Figure 2). Of note, we also estimated the risk of bleeding associated with concomitant use of dabigatran with SSRIs (1.14 [95% CI: 0.68–1.90]) (data not shown).

4 | DISCUSSION

This study aimed to evaluate the potential pharmacodynamical interaction between concomitant use of dabigatran and tramadol. We found a trend towards an increased risk of major bleed episodes when these drugs are used concomitantly (aOR 2.04). Although previous studies have showed and increased risk between dabigatran and other drugs such as SSRIs and NSAIDs[8] and between tramadol and other anticoagulant drugs (i.e., Vit K antagonists),[13–16] there are no studies focusing on the concomitant use of both drugs of interest. Our study suggests a potential interaction on the risk of major bleeds associated with concomitant use of tramadol and dabigatran, although it should be noted that numbers are quite small so further studies are warranted in order to answer this unresolved question. We performed several sensitivity analyses to discard a spurious association. To start with, we conducted several negative controls, first one was focusing on VKAs as well as other DOACs (i.e., rivaroxaban), where we found an increased risk of bleeds when using each drug solely, and we also found a potential interaction between Rivaroxaban and tramadol, which might suggest a class effect; second one was using another compounds different to tramadol (i.e., concomitant dabigatran and SSRI use) as negative controls, where we also did not observe any potential interaction (aOR of 1.14). These results support our findings, even more when these analyses included more patients than the main comparison between current users of tramadol and dabigatran. In addition, to better assess the potential interaction we deepened into treatment episodes construction, such as continuous or non-continuous use, and to the duration of the treatment to further evaluate their potential bleeding risk. This information is often lacking in other interaction studies[8] and it helps to better understand how treatment episode characteristics influence the risk associated to the drug. Interestingly, we found how the increased risk is accumulated among non-continuous users for both drugs while, for those with continuous use, the increased risk was concentrated with short durations. These findings may suggest that the irregular use and the initial treatment period of drugs with potential for bleeding could increase the risk for bleeding. This agrees with other studies that have found that the risk of bleeding is highest during the initial period of anticoagulation.[27]

This study fills major gaps on the drug patterns of concomitant use of anticoagulants in addition to the existing ones. NSAIDs have

been reported to increase risk of bleeds when using concomitantly with DOACs[28] and although there has been a decreased in the last years, the proportion of subjects receiving concomitantly DOACs with NSAIDs, it remains high ranging from 11.3% to 9.7%.[29] In parallel to this trend, there has been a worldwide increase of prescribing opioids being tramadol the most preferred option[30–32] among the general population. A study has reported how between 2006 and 2017 there was a 7-fold increase in tramadol prescriptions in general population using a primary care setting in the UK.[33] Current recommendations on pain[34] urge to start with non-opioids, the second step includes the combination of tramadol with paracetamol +/−NSAIDs. These recommendations together with the great proportion of subjects suffering chronic pain (ranging 12%–30%)[35] might contribute to explain the risen trend. In view of the current trends, it is reasonable to think there will be an increase of concomitant use of dabigatran and tramadol, thus further studies are warranted to evaluate the potential interaction between its concomitant use and the safety profile.

Some of the preventive strategies against bleeding due to use of oral anticoagulants include improvement of appropriate prescription, tailoring DOAC doses, identifying drug interactions and identifying modifiable risk factors. For the latter, it has been proposed to screen conditions that may lead to major bleeding events before initiating the NOAC therapy such as history of gastrointestinal bleeding, esophageal varices, and so forth.[36] Several studies have evaluated the protective effect of acid suppressants on anticoagulant-related gastrointestinal bleeding (GIB) which represented 82.6% of all our major bleed cases in our study. The results from a meta-analysis showed how proton pump inhibitors (PPIs) showed a protective effect against GIB episodes, but there was no evidence towards dabigatran related GIB.[37] Another study did evaluate the impact of PPI cotherapy and the risk of hospitalized UGIB and found lower rates compared with those not related with PPIs.[38] Keeping in mind the great proportion that GIB cases represent among major bleeds, further strategies are needed to approach when co-prescribing tramadol and dabigatran in order to reinforce appropriate decision-making and implement risk minimization strategies.

Our current research has some strengths and limitations that deserve comment. The main strength of our study was the true population-based approach when using a well-established and validated database like BIFAP, which makes our results highly generalizable and reflects the real-world practices. The nested case–control analysis allowed to accurately assess the drug exposure and its changes over time. In addition, we evaluated adherence to treatment by subdividing current users according to having continuous use since treatment initiation and non-continuous use, where substantial differences by type of use were observed in the risk estimates. In Spain, both tramadol and dabigatran require medical prescription, so, although we cannot discard some misclassification effect, this should be minimal and would be non-differential among cases and controls. The study cases correspond to a cohort from 2008 to 2015 when the use of DOACs for NVAF was not that widespread because their indications were still limited, so it could be of interest to repeat the analysis with up-to-date data. We identified and explored multiple confounders associated with an increased risk of bleeding with adjustments made accordingly in our analyses, which helped to minimize confounding although some residual confounding is possible since we did not capture major bleeding predictors as HASBLED, CHADS2 score, or creatinine clearance. For the latter, at the time of the study, there was no algorithm to completely extract the serum creatinine value, therefore, we adjusted by renal disease as a proxy. We performed a stratified analysis by BMI, however, it was not possible to evaluate and perform stratified analyses according to site of bleeding, age and other potential risk factors due to the limited sample size. Our case definition of major bleeding event includes hemorrhagic stroke/intracranial bleeding, GI bleeding, other extracranial or unclassified bleeding, and traumatic intracranial bleeding based on the definition by the International Society on Thrombosis and Haemostasis.[39] An exact replication of the mentioned definition was difficult and limited as BIFAP is not automatically and systematically linked to hospital admissions and some specific information as data on blood transfusions and blood loss is not systematically registered in electronic healthcare records. As a result, some major bleed episodes might be overlooked if information from secondary care was not recorded. Likewise, although DOACs and tramadol are not available as over the counter (OTC) at the pharmacies it is possible we might miss the first prescription issued either in hospitals or at secondary care, however, the impact should be minor as the PCPs also monitor these patients in their daily basis continuing prescribing at their surgery. Since we used prescription or dispensing, we do not have complete information on actual drug intake, and there might have been certain degree of drug use misclassification, which is quite common in epidemiological studies. Finally, drugs prescribed by physicians other than PCPs of the public sector are missing, as this database has only primary care prescriptions.

In conclusion, the current study shows a trend towards an increased risk of major bleeds when using concomitantly tramadol and dabigatran. Yet, when narrow the definition of current use the effect was slightly diluted. A more comprehensive evaluation with larger sample size will help to elucidate the pharmacodynamical interaction as well as the maximum peak of bleeding risk following the treatment initiation in order to help physicians to better decision making when prescribing both drugs.

AUTHOR CONTRIBUTIONS

Consuelo Huerta is the guarantor of the article. Consuelo Huerta, María José Peñalver, and Lucía Cea Soriano originated and designed the study. Airam de Burgos, Luis Sordo, José Pulido, Lucía Cea Soriano contributed to the analysis of the data and to the drafting of the paper. Airam de Burgos, Consuelo Huerta, María José Peñalver, Luis Sordo, José Pulido, and Lucía Cea Soriano collected data of the study and contributed to the interpretation of the results and to the drafting of the paper. Airam de Burgos and Lucía Cea Soriano contributed to the analysis of the data and to the drafting of the paper. All authors contributed to and approved the final version of the article and the authorship list.

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FUNDING STATEMENT

Authors have no funding to declare for this study.

CONFLICT OF INTEREST

All the authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and the code for data management and analysis used during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The study protocol was approved by the BIFAP Scientific Committee (09_2019) and Ethical Committee on Clinical Research of the Hospital Clínico San Carlos of Madrid (19/458-E).

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