Article

Thromboembolic Events in Users of Warfarin Treated with Different Skeletal Muscle Relaxants

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Abstract: *Background and Objectives*: Warfarin and a skeletal muscle relaxant are co-treatments in nearly a quarter-million annual United States (US) office visits. Despite international calls to minimize patient harm arising from anticoagulant drug interactions, scant data exist on clinical outcomes in real-world populations. We examined effects of concomitant use of warfarin and individual muscle relaxants on rates of hospitalization for thromboembolism among economically disadvantaged persons. *Materials and Methods*: Using 1999–2012 administrative data of four US state Medicaid programs, we conducted 16 retrospective self-controlled case series studies: half included concomitant users of warfarin + one of eight muscle relaxants; half included concomitant users of an inhaled corticosteroid (ICS) + one of eight muscle relaxants. The ICS analyses served as negative control comparisons. In each study, we calculated incidence rate ratios (IRRs) comparing thromboembolism rates in the co-exposed versus warfarin/ICS-only exposed person-time, adjusting for time-varying confounders. *Results*: Among ~70 million persons, we identified 8693 warfarin-treated subjects who concomitantly used a muscle relaxant, were hospitalized for thromboembolism, and met all other inclusion criteria. Time-varying confounder-adjusted IRRs ranged from 0.31 (95% confidence interval: 0.13–0.77) for metaxalone to 3.44 (95% confidence interval: 1.53–7.78) for tizanidine. The tizanidine finding was robust after quantitatively adjusting for negative control ICS findings, and in numerous prespecified secondary analyses. *Conclusions*: We identified a potential >3-fold increase in the rate of hospitalized thromboembolism in concomitant users of warfarin + tizanidine vs. warfarin alone. Alternative explanations for this finding include confounding by indication, a native effect of tizanidine, or chance.

Keywords: central muscle relaxants; drug interactions; Medicaid; pharmacoepidemiology; thromboembolism; warfarin

1. Introduction

Minimizing patient harm associated with anticoagulants and their drug interactions is an international patient safety goal. To address knowledge gaps in anticoagulant safety, the United States (US) Department of Health and Human Services issued a call to generate real-world evidence on anticoagulant drug interactions [1]. Yet, the evidence base underlying many anticoagulant interactions is limited [2,3]. Most evidence arises from case reports and pharmacokinetic studies. Of the few population-based interaction studies of a clinical endpoint, most have investigated bleeding from over-anticoagulation. However, real-world evidence on anticoagulant interactions and thrombotic consequences of under-anticoagulation is limited.

Recent data suggest that warfarin and a skeletal muscle relaxant are co-treatments in 240,000 annual US office visits [4]. The scale of co-treatment is not surprising since warfarin use remains common and muscle relaxant use is increasing [5] as providers seek alternatives to opioids. The potential for drug interactions between warfarin and muscle relaxants has received little attention because most muscle relaxants are neither metabolized by nor inhibit cytochrome P450 (CYP) 2C9 [6], the isozyme primarily responsible for warfarin's hepatic metabolism; further, it has been 50 years since pharmacokinetic studies were conducted in concomitant users [7,8]. Yet, recent hypothesis-free screening for anticoagulant interactions generated potential signals of decreased international normalized ratios (INRs) among concomitant users of warfarin and some muscle relaxants [9]. In response, we conducted a series of hypothesis-testing pharmacoepidemiologic studies to generate real-world evidence on these drug interactions. We specifically examined the effects of concomitant use of warfarin and individual muscle relaxants on rates of thromboembolism, i.e., venous thromboembolism and ischemic stroke—consequences of under-anticoagulation—among economically disadvantaged persons, a population especially vulnerable to adverse drug events [1].

2. Materials and Methods

We conducted 16 retrospective self-controlled case series (SCCS) studies: half included concomitant users of warfarin + one of eight muscle relaxants; half included concomitant users of an inhaled corticosteroid (ICS) + one of eight muscle relaxants. The ICS analyses served as negative control comparisons [10]. We defined exposure by the presence/absence of muscle relaxant therapy, based on prescription dispensing dates and days' supplied, on each eligible observation day. We defined the outcome as hospitalization for thromboembolism (i.e., venous thromboembolism, ischemic stroke). We adjusted for numerous time-varying covariates, assessed on each observation day. Time-invariant factors are inherently accounted for by the self-controlled nature of the SCCS design. This substantial benefit is accompanied by reliance on the following assumptions: outcomes are independent or rare; outcomes do not appreciably affect observation time or subsequent exposure; and exposures do not affect outcome ascertainment. We conducted analyses within 1999–2012 Medicaid data from California, Florida, New York, and Pennsylvania, linked to Medicare data for dual-eligibles and the Social Security Administration Death Master File (Supplemental Table S1), which does not include laboratory results such as the international normalized ratio (INR). We calculated incidence rate ratios (IRRs), in which thromboembolism rates in co-exposed and warfarin-only exposed persons were in the numerator and denominator, respectively. We conducted analyses using SAS version 9.4 (SAS Institute Inc.: Cary, NC, USA). The University of Pennsylvania's institutional review board approved this research via expedited procedure set forth in 45 CFR 46.110. See Supplemental Methods for further detail on the study design.

3. Results

Among ~70 million Medicaid beneficiaries in states contributing data, we identified 8693 warfarin-treated subjects who concomitantly used a muscle relaxant, experienced ≥1 thromboembolism event, and met all other inclusion criteria. Subjects were predom-

inantly female (67.4%), white (45.6%), with a median age of 67.4 years, and contributed 1,005,246 observation days. The mean per-subject observation period was 116 days. Table 1 further describes subjects. We did not examine chlorzoxazone or orphenadrine, as these samples contained <10 persons.

Table 1. Characteristics of persons under study who, by nature of the self-controlled study design, experienced at least one thromboembolic outcome during treatment with the object drug.

	Object Drug	
	Warfarin	**Inhaled Corticosteroid (Negative Control)**
Persons, person-days, and outcome occurrence		
Persons, total	8693	4582
Person-days of observation time, median per individual (Q1–Q3)	67.0 (36.0–134.0)	53.0 (36.0–109.0)
Person-days of observation time, total	1,005,246	521,722
Exposed to a skeletal muscle relaxant	42,572 (4.2%)	38,351 (7.4%)
Unexposed to a skeletal muscle relaxant	962,674 (95.8%)	483,371 (92.6%)
Thromboembolism outcomes during observation time	9396	4662
Exposed to a skeletal muscle relaxant	474 (5.0%)	318 (6.8%)
Unexposed to a skeletal muscle relaxant	8922 (95.0%)	4344 (93.2%)
Thromboembolism outcomes during observation time that were venous thromboembolisms, vs. ischemic strokes (% of total thromboembolism outcomes)	6569 (69.9%)	2381 (51.1%)
Demographics and other baseline clinical characteristics, at start of observation time		
Age, in years, median (Q1–Q3)	67.4 (51.3–78.3)	69.9 (57.4–79.4)
Female	5598 (64.4%)	3052 (66.6%)
Race		
White	3966 (45.6%)	2153 (47.0%)
Black	1877 (21.6%)	915 (20.0%)
Hispanic/Latino	1357 (15.6%)	675 (14.7%)
Other/unknown	1493 (17.2%)	839 (18.3%)
State of residence		
CA	3835 (44.1%)	1885 (41.1%)
FL	1528 (17.6%)	864 (18.9%)
NY	2606 (30.0%)	1369 (29.9%)
PA	724 (8.3%)	464 (10.1%)
Calendar year (see Supplemental Figure S1)		
1999	287 (3.3%)	43 (0.9%)
2000	512 (5.9%)	79 (1.7%)
2001	564 (6.5%)	127 (2.8%)
2002	602 (6.9%)	187 (4.1%)
2003	625 (7.2%)	251 (5.5%)
2004	531 (6.1%)	260 (5.7%)
2005	613 (7.1%)	295 (6.4%)
2006	728 (8.4%)	406 (8.9%)
2007	663 (7.6%)	355 (7.7%)
2008	653 (7.5%)	423 (9.2%)
2009	799 (9.2%)	524 (11.4%)
2010	774 (8.9%)	547 (11.9%)
2011	683 (7.9%)	599 (13.1%)
2012	659 (7.6%)	486 (10.6%)
Nursing home residence (Yes)	124 (1.4%)	70 (1.5%)
CHA_2DS_2-VASc score, median (Q1–Q3)	3.0 (1.0–4.0)	3.0 (1.0–4.0)
Exposure to skeletal muscle relaxant, during observation time (day level)		
Antispastic Agent Baclofen	11,794 (1.2%)	10,007 (1.9%)

Table 1. *Cont.*

		Object Drug	
		Warfarin	**Inhaled Corticosteroid (Negative Control)**
Antispasmodic Agents	Carisoprodol	11,070 (1.1%)	9611 (1.8%)
	Chlorzoxazone	551 (0.1%)	42 (0.0%)
	Cyclobenzaprine	12,502 (1.2%)	13,382 (2.6%)
	Metaxalone	1739 (0.2%)	1273 (0.2%)
	Methocarbamol	2515 (0.3%)	2102 (0.4%)
	Orphenadrine	176 (0.0%)	239 (0.0%)
Antispastic-Antispasmodic	Tizanidine	2225 (0.2%)	1695 (0.3%)

Time-varying covariates, on the current observation day or in the prior 30 days (unless otherwise noted)

	Warfarin	Inhaled Corticosteroid (Negative Control)
Major non-chronic risk factors for venous thromboembolism		
Hospital discharge	359,313 (35.7%)	150,271 (28.8%)
Venous thromboembolism in the prior 90 days	327,187 (32.5%)	74,466 (14.3%)
Major non-chronic risk factor for ischemic stroke		
Ischemic stroke in the prior 90 days	101,368 (10.1%)	61,226 (11.7%)
Drug exposures that increase risk of venous thromboembolism and ischemic stroke		
Oral contraceptive/hormone replacement therapy	15,777 (1.6%)	11,813 (2.3%)
Nonsteroidal anti-inflammatory drug	89,310 (8.9%)	95,203 (18.2%)
Tamoxifen	1475 (0.1%)	522 (0.1%)
Nicotine	5082 (0.5%)	5017 (1.0%)
Recombinant factor VIIa	0 (0.0%)	‡
Cisplatin	1405 (0.1%)	346 (0.1%)
Drug exposures that increase risk of venous thromboembolism, but not ischemic stroke		
Testosterone	3661 (0.4%)	3591 (0.7%)
Dexamethasone	9104 (0.9%)	2561 (0.5%)
Methylprednisolone	5900 (0.6%)	8747 (1.7%)
Epoetin alpha/darbepoetin alpha	19,233 (1.9%)	8218 (1.6%)
Filgrastim/sargramostim	4400 (0.4%)	931 (0.2%)
Flutamide	223 (0.0%)	0 (0.0%)
Goserelin	647 (0.1%)	147 (0.0%)
Leuprolide	1153 (0.1%)	407 (0.1%)
Raloxifene	6539 (0.7%)	7082 (1.4%)
Anastrozole	3539 (0.4%)	826 (0.2%)
Megestrol	20,602 (2.0%)	14,633 (2.8%)
Cyclosporine	1279 (0.1%)	360 (0.1%)
Infliximab	385 (0.0%)	316 (0.1%)
Immune globulin	980 (0.1%)	527 (0.1%)
Interferon gamma-1b	24 (0.0%)	0 (0.0%)
Sirolimus/tacrolimus	4173 (0.4%)	1394 (0.3%)
Aldesleukin	52 (0.0%)	0 (0.0%)
Bevacizumab	1159 (0.1%)	342 (0.1%)
Bleomycin	108 (0.0%)	0 (0.0%)
Carboplatin	4359 (0.4%)	1414 (0.3%)
Denileukin	126 (0.0%)	33 (0.0%)
Docetaxel	940 (0.1%)	326 (0.1%)
Estramustine	80 (0.0%)	155 (0.0%)
Fluorouracil	3095 (0.3%)	806 (0.2%)
Imatinib	224 (0.0%)	66 (0.0%)
Irinotecan	1247 (0.1%)	232 (0.0%)
Lenalidomide	699 (0.1%)	66 (0.0%)
Paclitaxel	3611 (0.4%)	1002 (0.2%)
Thalidomide	1970 (0.2%)	0 (0.0%)
Heparin (including low molecular weight heparin)	89,942 (8.9%)	24,034 (4.6%)
Pentosan	60 (0.0%)	64 (0.0%)
Chlorpromazine	2116 (0.2%)	276 (0.1%)
Clozapine	1198 (0.1%)	891 (0.2%)

Table 1. *Cont.*

	Object Drug	
	Warfarin	**Inhaled Corticosteroid (Negative Control)**
Olanzapine	20,842 (2.1%)	19,714 (3.8%)
Quetiapine	25,349 (2.5%)	26,212 (5.0%)
Risperidone	20,212 (2.0%)	18,860 (3.6%)
Thioridazine	898 (0.1%)	648 (0.1%)
Celecoxib	26,992 (2.7%)	27,321 (5.2%)
Botulinum toxin	309 (0.0%)	178 (0.0%)
Papaverine	159 (0.0%)	12 (0.0%)
Topiramate	9856 (1.0%)	6773 (1.3%)
Drug exposures that increase risk of ischemic stroke, but not venous thromboembolism		
Selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitor	161,503 (16.1%)	125,524 (24.1%)
Disease influencing anticoagulation		
Acute infection on current day or in prior 14 days	106,105 (10.6%)	67,681 (13.0%)
Other drug exposures influencing anticoagulation		
Oral anticoagulant (non-warfarin)	20 (0.0%)	NA
Oral anticoagulant	NA	118,230 (22.7%)
Oral antiplatelet	57,492 (5.7%)	115,997 (22.2%)
Aspirin	50,928 (5.1%)	74,362 (14.3%)
Injectable/subcutaneous anticoagulant	81,923 (8.1%)	20,656 (4.0%)
Drug exposures related to drug interactions *		
Oral agents that can interact with warfarin **	219,787 (21.9%)	NA
Oral agents that can interact with muscle relaxants **	28,078 (2.8%)	18,172 (3.5%)
CYP2C9 inhibitors †	85,801 (8.5%)	53,407 (10.2%)
CYP2C9 inducers †	24,174 (2.4%)	8229 (1.6%)
CYP1A2 inhibitors †	68,810 (6.8%)	44,959 (8.6%)
CYP1A2 inducers †	12,822 (1.3%)	4905 (0.9%)
CYP2C19 inhibitors †	282,004 (28.1%)	225,690 (43.3%)
CYP2C19 inducers †	8379 (0.8%)	8823 (1.7%)
CYP2D6 inhibitors †	135,687 (13.5%)	97,209 (18.6%)
CYP2E1 inhibitors †	41 (0.0%)	0 (0.0%)
CYP2E1 inducers †	1170 (0.1%)	843 (0.2%)
CYP3A4 inhibitors †	110,361 (11.0%)	71,567 (13.7%)
CYP3A4 inducers †	80,359 (8.0%)	57,269 (11.0%)
CYP2C8 inhibitors †	34,548 (3.4%)	102,645 (19.7%)
CYP2B6 inhibitors †	50,283 (5.0%)	101,917 (19.5%)
CYP2B6 inducers †	61,987 (6.2%)	26,819 (5.1%)
Other non-chronic factors potentially related to muscle relaxant exposure		
Diseases of the esophagus (including GERD)	48,237 (4.8%)	33,696 (6.5%)
Disorders of musculoskeletal system and connective tissue	379,091 (37.7%)	205,783 (39.4%)
Central nervous system diseases	50,622 (5.0%)	29,657 (5.7%)
Injury	135,122 (13.4%)	54,539 (10.5%)
Jaw pain	31 (0.0%)	54 (0.0%)
General pain	4458 (0.4%)	1699 (0.3%)
Symptoms involving nervous and musculoskeletal system	43,312 (4.3%)	30,105 (5.8%)
Temporomandibular joint disorders	562 (0.1%)	336 (0.1%)
Warfarin monitoring		
Warfarin monitoring on current day or in prior 7 days	291,833 (29.0%)	NA

CYP = cytochrome P450; GERD = gastroesophageal reflux disease; NA = not applicable; Q = quartile. Note that the CHA2DS2-VASc score was calculated using demographic (i.e., age, sex) and healthcare claims diagnoses (e.g., hypertension, diabetes). * drugs in these subcategories with acute indications were assessed on current day or in prior 14 days. ** per Truven Health Analytics Micromedex Solutions, limited to those with "major" or "contraindicated" severity and with "good" or "excellent" documentation. † limited to clinically relevant entries in The Flockhart Table™ (Flockhart DA, Thacker D, McDonald C, Desta Z. The Flockhart Cytochrome P450 Drug-Drug Interaction Table. Division of Clinical Pharmacology, Indiana University School of Medicine (Updated 2021). https://drug-interactions.medicine.iu.edu/ (accessed on 1 March2019). ‡ cell was suppressed to maintain compliance with the Centers for Medicare and Medicaid Services cell size suppression policy (HHS-0938-2020-F-7420).

Confounder-adjusted IRRs for thromboembolism ranged from 0.31 (95% confidence interval 0.13–0.77) for *warfarin + metaxalone* to 3.44 (1.53–7.78) for *warfarin + tizanidine*. Negative control findings ranged from 0.39 (0.10–1.49) for *ICS + tizanidine* to 1.99 (1.04–3.83) for *ICS + carisoprodol*. See Supplemental Table S2 and Figure 1. Findings from secondary analyses (Supplemental Table S3) were consistent with primary analyses.
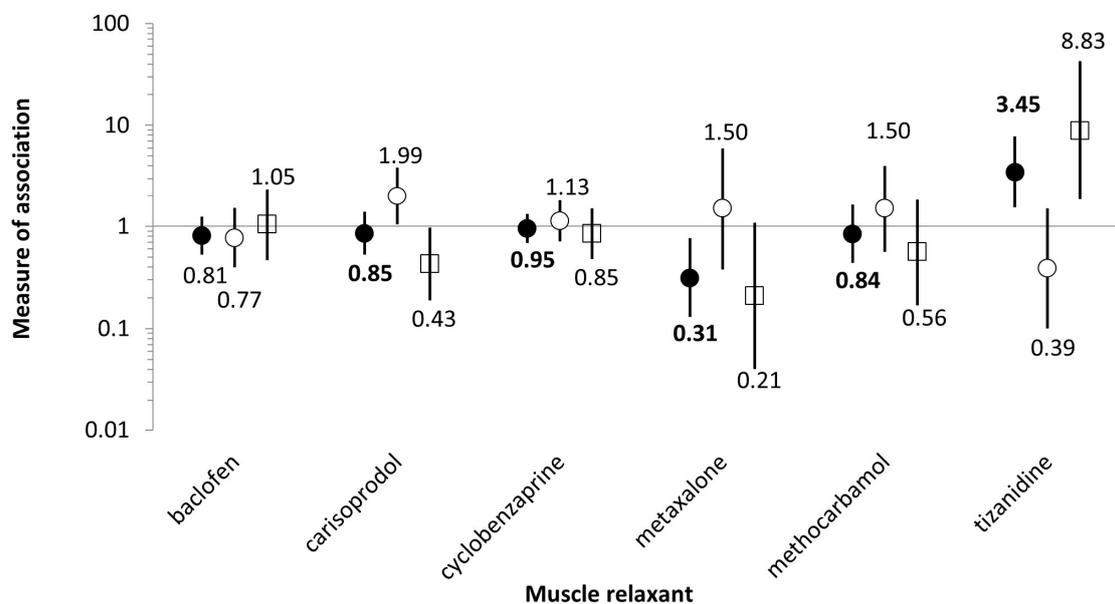

Figure 1. Confounder-adjusted incidence rate ratios (IRRs, circles) and ratios of adjusted incidence rate ratios (rIRRs, squares) with 95% confidence intervals for thromboembolism, for primary analyses, by muscle relaxant precipitant drug. *Legend*: Black circles: confounder-adjusted incidence rate ratios (IRRs) for warfarin (bolded since effect estimates of primary interest); White circles: confounder adjusted IRRs for inhaled corticosteroids (negative control); White squares: ratios of IRRs, i.e., ([adjusted incidence rate ratios for use of warfarin + muscle relaxant vs. warfarin alone]/[adjusted incidence rate ratios for use of inhaled corticosteroid + muscle relaxant vs. inhaled corticosteroid alone]).

4. Discussion

Warfarin users are commonly co-treated with a muscle relaxant [4], and tizanidine prescribing is specifically on the rise [11]. Further, a previous hypothesis-free screening study suggested that *warfarin + tizanidine* use may result in a modest, delayed INR reduction (−0.4 units during the third and fourth months of concomitant use) [9]. We therefore used population-based data to examine the association between concomitant use of warfarin with different muscle relaxants and thromboembolism—principally finding a >3-fold increase in the rate of hospitalization for thromboembolism among concomitant users of *warfarin + tizanidine* vs. warfarin alone. This finding, if causal, may represent a clinically relevant drug interaction, yet could also be explained by: confounding by indication for tizanidine; a native pharmacodynamic effect of tizanidine; the failure of an assumption underlying the statistical (i.e., SCCS) model; and/or chance. We subsequently discuss the possibilities of causation, systematic error, and chance.

A plausible pharmacokinetic mechanism would help support a case for causality. While *R*-warfarin and tizanidine are CYP1A2 substrates, we are unaware of evidence that tizanidine induces CYP1A2, which would enhance *R*-warfarin inactivation. We therefore must consider potential non-causal explanations, such as confounding. As an example, initiation of tizanidine to treat spasticity may portend a multiple sclerosis (MS) flare, and MS is associated with thromboembolism [12,13]. However, this explanation seems unlikely since our finding for baclofen, also used in MS, was null (IRR: 0.81, 0.53–1.25). That said, tizanidine may be used in settings of more severe MS-associated spasticity [14], and immobility accompanying more severe MS may portend a high thromboembolism risk

period [15]. Another example of confounding would be the common co-occurrence of muscle relaxant use and smoking [16]. Smoking, poorly measured in our data, may induce CYP1A2 resulting in enhanced *R*-warfarin inactivation. This explanation is unlikely since: within-subject smoking status is unlikely to change over the relatively short observation time; and our finding for cyclobenzaprine, also a CYP1A2 substrate, was null (IRR: 0.95, 0.69–1.32). Another potential non-causal explanation is a native pharmacodynamic effect of tizanidine. This is unlikely since: tizanidine's alpha-2 agonist effects do not affect stroke [17]; and our negative control analysis of *ICS + tizanidine* was inconsistent with a large positive association (upper 95% confidence limit: 1.49). It is additionally important to note that prior screening findings [9] identified: similar INR reductions for tizanidine and for carisoprodol, yet our thromboembolism finding for carisoprodol was consistent with the null; and an INR increase for metaxalone, consistent with our protective thromboembolism finding. Further, prior screening [9] did not produce a thromboembolism signal for tizanidine.

We must also consider the potential for systematic error introduced by violations of assumptions underlying the SCCS method. *First*, recurrent outcomes must be independent. This assumption may be violated if different within-patient factors cause a subsequent vs. initial thromboembolic event. Yet, our tizanidine finding held in a secondary analysis limited to persons with one thromboembolic event (IRR: 3.07, 1.24–7.60). *Second*, outcomes must not affect observation time or subsequent exposure. The former may be violated given thromboembolism-related mortality; yet, our tizanidine finding held in a secondary analysis limited to persons surviving during observation (IRR: 3.42, 1.51–7.74). The latter may be violated since muscle relaxants may be initiated after a stroke to treat spasticity; yet, this would explain a protective (not elevated) finding, as such stroke events would occur during warfarin-only exposed observation days and thereby artificially inflate the IRR's denominator. *Third*, exposures must not affect outcome ascertainment. We cannot think of a mechanism by which tizanidine could influence the diagnosis of or billing for thromboembolism. An additional limitation includes our lack of access to INR results. Finally, we cannot rule out the possibility of chance findings.

5. Conclusions

Using an epidemiologic design that inherently controls for measured and unmeasured static confounders, adjusting for critical time-varying confounders, and using a negative control, we identified a potential >3-fold increase in the rate of thromboembolism in concomitant users of *warfarin + tizanidine* vs. warfarin alone. While this finding may represent a clinically relevant drug interaction, alternative explanations include confounding, bias, and chance. Future work using a different data source (especially one with access to INR values) and/or alternative study design should seek to replicate this finding.

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