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ORIGINAL RESEARCH ARTICLE

Safety of OnabotulinumtoxinA with Concomitant Antithrombotic Therapy in Patients with Muscle Spasticity: A Retrospective Pooled Analysis of Randomized Double-Blind Studies

Rozalina Dimitrova[1] · Lynn James[1] · Chengcheng Liu[2] · Amelia Orejudos[2] · Irina Yushmanova[1] · Mitchell F. Brin[1,3]

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Abstract

Background OnabotulinumtoxinA is approved as a treatment across multiple indications. For the treatment of spasticity, onabotulinumtoxinA is injected directly into affected muscles. Intramuscular injections may result in local bleeding and related complications, especially in patients receiving anticoagulant therapy. Despite anticoagulants being commonly used, there is limited information in the medical literature regarding the safety of intramuscular medications in patients receiving oral anticoagulants. This retrospective analysis included pooled safety data from Allergan-sponsored studies evaluating onabotulinumtoxinA for the treatment of patients with muscle spasticity.

Objective The objective of this study was to determine the risk of bleeding complications in patients with post-stroke spasticity receiving antithrombotic therapy and intramuscular onabotulinumtoxinA.

Methods We conducted a retrospective analysis of pooled safety data from 16 randomized, double-blind, placebo-controlled Allergan-sponsored studies of onabotulinumtoxinA for the treatment of post-stroke upper or lower limb muscle spasticity, including adult patients with at least moderate upper or lower limb spasticity and receiving at least one dose of the study drug. Bleeding-related adverse events starting within 4 weeks of study treatment were assessed. The incidence rates of bleeding complications were compared for patients receiving classes of antithrombotic therapy vs those not receiving antithrombotic therapy and for those receiving onabotulinumtoxinA vs placebo (with or without antithrombotic therapy).

Results Of 1877 patients, 1182 received antithrombotic therapy. The overall incidence of bleeding complications was < 2%. In those receiving any antithrombotic therapy, the incidence of bleeding was 1.0% vs 1.4% (no antithrombotic therapy); after onabotulinumtoxinA, it was 0.9% for those receiving antithrombotic therapy vs 1.4% (no antithrombotic therapy), and for placebo 1.2% vs 1.4%, respectively. Subgroup results were similar.

Conclusions No apparent increased risk of bleeding complications was observed following administration of onabotulinumtoxinA to patients receiving antithrombotic therapy. Nonetheless, patient education and careful observation of the injection site in patients receiving antithrombotic therapy remains warranted.

Key Points

In post-stroke patients receiving antithrombotic therapy, no increased risk for bleeding complications was observed following treatment with onabotulinumtoxinA

However, careful monitoring of the injection site immediately following onabotulinumtoxinA is warranted and patients also treated with antithrombotic therapies should be educated about the possibility for bleeding complications

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✉ Mitchell F. Brin
Brin_Mitchell@allergan.com

[1] Allergan plc, 2525 Dupont Drive; T1-1B, Irvine, CA 92623-9534, USA

[2] Allergan plc, Bridgewater, NJ, USA

[3] University of California, Irvine, CA, USA

1 Introduction

OnabotulinumtoxinA (BOTOX®; Allergan plc, Dublin, Ireland) was first approved by the US Food and Drug Administration in 1989 for the treatment of blepharospasm and strabismus [1, 2] and is now used in many more indications. The safety and tolerability profile of onabotulinumtoxinA is well established [3–8].

OnabotulinumtoxinA is approved by the Food and Drug Administration for the treatment of upper and lower limb spasticity in adult patients to reduce the severity of increased muscle tone in elbow, wrist, finger, thumb, ankle, and toe flexors [2]. According to the US labeling, it is recommended to inject onabotulinumtoxinA directly into the affected muscle using a 25- to 30-gauge needle for superficial muscles and a longer 22-gauge needle for deeper musculature [2]. It is also recommended that patients inform their physicians if they are receiving antiplatelet and/or anticoagulant therapy before receiving onabotulinumtoxinA [2].

Intramuscular injections may result in local bleeding, especially in patients receiving anticoagulant therapy [9, 10]. In particular, concerns have been raised about the potential for multiple intramuscular injections into deep compartmentalized muscles to cause acute compartment syndrome [11, 12]. Limited information is available regarding the safety of intramuscular medications in patients receiving oral anticoagulants even though anticoagulants are commonly used, for example, in stroke patients as a prophylaxis for recurrent stroke [13]. Further, a small number of studies have suggested that onabotulinumtoxinA may affect the coagulation cascade as both acetylcholine and norepinephrine contribute to antifibrinolytic activation. It has been proposed that by binding to peripheral cholinergic nerve endings and preventing acetylcholine and norepinephrine exocytosis, onabotulinumtoxinA may prevent the formation of fibrin. Although the majority of these reports have arisen in studies in which onabotulinumtoxinA has been used to treat detrusor overactivity where local tamponade is not possible [14], one case study has reported hematuria in a patient who received onabotulinumtoxin A for the treatment of upper limb spasticity [15].

Recent surveys of physicians in Korea and Canada revealed considerable variability in physician practices and preferences when injecting botulinum toxin in anticoagulant-treated patients with spasticity, especially with regard to their comfort level using international normalized ratio (INR) ranges [11, 12]. For example, in the Korean survey, 23% of the respondents indicated that they were uncertain whether they should inject patients with botulinum toxin without knowing the INR values, and 69% of the respondents reported that they did not have any standardized protocols for performing botulinum toxin injections in patients who were receiving anticoagulants [11]. The absence of clear information regarding bleeding risks and INR values associated with the injection of botulinum toxin in these patients contributes to physician uncertainty and to the wide range of approaches related to botulinum toxin injections in this population.

An audit of a small number of patients receiving stable long-term anticoagulation with warfarin ($n = 14$) who also received intramuscular botulinum toxin for spasticity showed no significant pain, tenderness, or swelling at the injection site and no major or minor bleeding after injection or during follow-up [10]. However, the safety of using onabotulinumtoxinA with concomitant antiplatelet and/or anticoagulant (antithrombotic) therapy has not been reported in detail. To determine the risk of potential bleeding complications, pooled safety data from Allergan-sponsored muscle spasticity studies in which patients who were receiving concomitant antithrombotic therapy and received at least a single intramuscular injection of study drug (onabotulinumtoxinA or placebo) were analyzed. A comparison of onabotulinumtoxinA vs placebo was included in this analysis to provide context, as in the studies included in this analysis, injection paradigms for onabotulinumtoxinA and placebo groups were matched and also to delineate any effect of onabotulinumtoxinA, per se, on thrombosis. The objective of the analysis was to compare the safety of onabotulinumtoxinA vs placebo between the overall analysis population receiving antithrombotic therapy relative to those who did not.

2 Methods

This retrospective analysis included pooled safety data from Allergan-sponsored studies evaluating onabotulinumtoxinA for the treatment of patients with muscle spasticity. The analysis was further divided among those receiving intramuscular injections of either onabotulinumtoxinA or placebo with or without antithrombotic medication. The individual studies included in this analysis had appropriate ethics committee approval. The pooled data for this analysis were de-identified, thus further approval was not needed.

To be considered for this analysis, studies had to be Allergan-sponsored studies evaluating onabotulinumtoxinA in adult patients post-stroke with at least moderate upper or lower limb spasticity ($N = 29$ studies). Allergan-sponsored studies were chosen because patient-level data were available, which was not possible from non-Allergan studies. Furthermore, Allergan has access to a robust safety database based on the numerous clinical trials that have been conducted on onabotulinumtoxinA. In contrast, published studies typically report sparse information on adverse events,

providing insufficient details on the use of anticoagulants in the small population of interest.

Included studies were placebo controlled in design. Studies were excluded if they were open label ($n=8$) or if patients did not receive concomitant medication or the concomitant medication was not coded per World Health Organization terminology ($n=5$). The remaining 16 randomized double-blind studies assessed lower limb spasticity ($n=9$), upper limb spasticity ($n=5$), or upper limb and/or lower limb spasticity ($n=2$). Ten were single-cycle studies and six had at least two double-blind cycles (Study #9/10 had up to three cycles). Upper limb muscles that were injected included wrist flexors (flexor carpi radialis and flexor carpi ulnaris), elbow flexors (biceps), and finger flexors (flexor digitorum superficialis, flexor digitorum profundus). Lower limb muscles that were injected included ankle flexors (gastrocnemius, soleus, tibialis posterior), toes (flexor digitorum longus, flexor digitorum brevis, flexor hallucis longus, extensor hallucis), and rectus femoris. Injections were delivered with appropriately sized needles depending on the depth of the musculature, with doses divided among one or more injection sites per muscle. Deep muscles were tibialis posterior, flexor digitorum longus, and flexor digitorum profundus. International normalized ratio values were not used to guide the onabotulinumtoxinA dose, and neither INR nor partial thromboplastin time data were collected. Further details of these studies, and their associated publications can be found in Table 1.

The pooled analysis comprised all patients in the safety population, which included all who had received at least a single intramuscular injection of the study drug (onabotulinumtoxinA or placebo) during the double-blind periods. Three subgroup analyses were conducted based on the category of antithrombotic medications. In the overall antithrombotic analysis, all patients who had received concomitant treatment that may be associated with an increased risk of bleeding (based on the World Health Organization dictionary) were included. The medications selected in this antithrombotic category included: platelet aggregation inhibitors, except heparins [$n=948$ (80.2%)], vitamin K antagonists [$n=250$ (21.2%)], heparins [$n=70$ (5.9%)], direct factor Xa inhibitors [$n=4$ (0.3%)], direct thrombin inhibitors [$n=3$ (0.3%)], other antithrombotic agents [$n=0$ (0.0%)], and thrombolytic agents [$n=0$ (0.0%); Table 2]. Because platelet aggregation inhibitors (e.g., aspirin) may have a mild anticoagulant effect, a separate analysis was conducted excluding those patients who received platelet aggregation inhibitors. A third subanalysis included only heparins and vitamin K antagonists because these medications are commonly associated with bleeding complications.

Treatment-emergent adverse events (TEAEs) of interest were defined as those directly or indirectly indicating a bleeding complication and starting within 4 weeks of the first injection in the double-blind period. Injection-site reactions (bruising, discoloration, extravasation hematoma, hemorrhage, edema, or swelling), purpura, and compartment syndrome were the TEAEs of interest for this analysis.

The incidence rates for bleeding-related TEAEs across all studies were pooled to determine the overall incidence rate for bleeding-related TEAEs. Estimated pooled risk differences with 95% confidence intervals (95% CIs) were obtained using the Cochran–Mantel–Haenszel test assuming a fixed-effect model with continuity correction for zero TEAEs. Incidence rates for bleeding-related TEAEs were determined and the risk difference was calculated for patients receiving antithrombotic therapy (ATT) vs no ATT and for patients receiving intramuscular injections of onabotulinumtoxinA vs intramuscular injections of placebo (with or without ATT). Incidence rates and risk differences were also determined for all studies, upper limb, lower limb, and upper/lower limb studies.

3 Results

The analysis included 16 studies and 1877 patients, of whom 1182 received antithrombotic therapy in one of the seven overall categories. The subgroup that excluded platelet aggregation inhibitors (except heparins, six categories) included 308 patients, and the subgroup that included only vitamin K antagonists and heparins totaled 302 patients.

Demographic characteristics were generally similar in patients receiving antithrombotic therapies compared with those not receiving antithrombotic therapies, except that a greater proportion of patients receiving antithrombotic therapies were ≥65 years of age and Caucasian (Table 3). Among patients receiving antithrombotic therapies, aspirin was the most common (59%) followed by warfarin (18%) and clopidogrel (11%; Table 2).

3.1 Subanalysis of All Antithrombotic Agents

In the cohort of patients who received an antithrombotic agent in at least one of the seven categories, the overall incidence of TEAEs that indicated a bleeding complication was <2% and rates were similar between those patients who received antithrombotic therapy (1.0%) and those who did not (1.4%; Table 4). The risk difference (95% CI) for having a bleeding event was −0.0042 (−0.0148 to 0.0063) among patients who received antithrombotic therapy vs those who did not (Table 5). In patients receiving antithrombotic therapy, the TEAEs that indicated a bleeding complication were injection-site bruising (0.8% overall; 0.7% in patients receiving onabotulinumtoxinA), injection-site hemorrhage (0.1% overall; none in patients receiving onabotulinumtoxinA), and purpura (0.1% overall and in patients receiving

Table 1 Description of studies included in analysis

Study ID	ClinicalTrials.gov ID	Location (number of centers)	Study design	Treatment	Duration	*N* entered/*N* completed	Publication
Lower limb							
Study #6	NCT01575054	North America, Europe, and Asia (60)	Part 1: Phase III, double-blind, randomized, placebo-controlled Part 2: Open-label	Part 1: OnabotA 300–400 U Placebo Part 2: OnabotA ≤400 U IM injection; ankle, plantar flexors, toe flexors/extensors, and knee flexors	Part 1: 1 treatment with 12-wk follow-up Part 2: up to 3 treatments ≥ 12-wk follow-up	Part 1: OnabotA 300–400 U: 233/223 Placebo: 235/227 Part 2: 447/413	[26, 27]
Study #7		Europe (29)	Phase II, double-blind, randomized, placebo-controlled	OnabotA ~4 or ~2 U/kg ± 1 U/kg Placebo IM injection; medial and lateral gastrocnemius ± anterior or posterior tibialis	One treatment; 12-wk follow-up	4 U/kg: 45/43 2 U/kg: 45/44 Placebo: 41/41	Data included in pooled analysis: [28]
Study #11/Study #12		North America (18)	Phase II, double-blind, randomized, placebo-controlled	Onabot ~4 or ~2 U/kg Placebo IM injection; medial and lateral gastrocnemius	One treatment; 24-wk follow-up	4 U/kg: 33/29 2 U/kg: 36/33 Placebo: 27/26	Data included in pooled analysis: [28]
Study #15		Australia (7)	Part 1: Phase II, double-blind, randomized, placebo-controlled Part 2: Open-label	Part 1: OnabotA 200 or 300 U Placebo Part 2: OnabotA/OnabotA or placebo/OnabotA	Part 1: 1 treatment; 12- to 32-wk follow-up Part 2: 1 treatment; ≥12-wk follow-up	Part 1: 200 U: 28/24 300 U: 28/25 Placebo: 29/28 Part 2: OnabotA/OnabotA: 44/38 Placebo/OnabotA: 26/24	[29] Data included in pooled analysis: [28]
Upper limb							
Study #1		North America (19)	Phase III, double-blind, randomized, placebo-controlled	OnabotA 200–240 U Placebo IM injections; wrist, finger flexor, and/or thumb	One treatment; 12-wk follow-up	200–240 U: 64/64 Placebo: 62/58	[30] Data included in pooled analysis: [28]
Study #3		North America (4)	Phase II, double-blind, randomized, placebo-controlled	OnabotA 200, 220, or 240 U Placebo IM injections: wrist, finger flexors, and thumbs	Two treatments at wks 2 and 14 (30-wk follow-up)	200, 220, or 240 U: 22/19 Placebo: 8/7	Data included in pooled analysis: [28]

Table 1 (continued)

Study ID	ClinicalTrials.gov ID	Location (number of centers)	Study design	Treatment	Duration	*N* entered/*N* completed	Publication
Study #4	NCT00076687	North America and Europe (58)	Phase II, double-blind, randomized, placebo-controlled	OnabotA 240 or 360 U Placebo IM injection upper limbs	Up to two treatments over 12 or 18 wks; 1-wk follow-up after second injection	240 U: 52/47 360 U: 55/51 Placebo: 48/42	
Study #5	NCT00651690	North America (13)	Phase II, double-blind, randomized, placebo-controlled (first treatment); open-label (second treatment)	OnabotA 200–360 U Placebo IM injections into wrist, fingers, thumb, hand, and forearm muscles	Two treatments (day 0 and either wk 2 or wk 18) over 24 wks	200–360 U: 41/39 Placebo: 21/20 Open-label: OnabotA/OnabotA: 33/33 Placebo/OnabotA: 18/15	Data included in pooled analysis: [28]
Study #9/Study #10		North America (19)	Phase II, double-blind, randomized, dose–response, placebo-controlled	OnabotA 90, 180, or 360 U Placebo IM injection: wrist, fingers, and elbow	Two or three treatments over 24 or 36 wks, ≥ 12 wks between treatments	90 U: 21/19 180 U: 23/15 360 U: 21/21 Placebo: 26/22	[31] Data included in pooled analysis: [28]
Study #13/Study #14		Europe (10)	Phase II/III, double-blind, randomized, placebo-controlled	OnabotA 90, 180, or 360 U Placebo IM injection: wrist, fingers, and elbow muscle	One treatment; 12-wk follow-up	90 U: 23/22 180 U: 23/20 360 U: 23/23 Placebo: 20/18	[32] Data included in pooled analysis: [28]
Study #16		Asia (14)	Phase III, double-blind, randomized, placebo-controlled	OnabotA 200 or 240 U (thumb) Placebo IM injection: wrist, fingers, and thumb	One treatment; 12-wk follow-up	200 or 240 U: 87/82 Placebo: 83/74	
Upper/lower limb							
Study #2		North America (12)	Phase II, double-blind, randomized, placebo-controlled	OnabotA 240 or 360 U Placebo IM injections into the upper and/or lower limb muscles	Up to two treatments over 18 wks, ≥ 12 wks between treatments	240 U: 36/34 360 U: 37/36 Placebo: 36/31	Data included in pooled analysis: [28]
Study #8		North America and Europe (34)	Phase IIIb, double-blind, randomized, placebo-controlled followed by open-label extension	OnabotA + SOC Placebo + SOC IM injections into the upper and/or lower limb muscles	Up to two treatments; 34-wk follow-up Open-label: up to four treatments	OnabotA: 139/131 Placebo: 135/122 Open-label: 225/204	[33] [34]

ID identification, *IM* intramuscular, *OnabotA* onabotulinumtoxinA, *SOC* standard of care, *wk* week

Table 2 Concomitant antithrombotic medications by category

Category/medication	*n* (%)
Any antithrombotic medication	1182 (100)
Platelet aggregation inhibitors (except heparins)	948 (80.2)
Aspirin	692 (58.5)
Clopidogrel	130 (11.0)
Dipyridamole	46 (3.9)
Asasantin	44 (3.7)
Ticlopidine hydrochloride	44 (3.7)
Acetylsalicylate lysine	37 (3.1)
Magnyl	23 (1.9)
Ticlopidine	11 (0.9)
Cilostazol	6 (0.5)
Paynocil	6 (0.5)
Triflusal	2 (0.2)
Carbasalate	1 (0.1)
Vitamin K antagonists	250 (21.2)
Warfarin	213 (18.0)
Phenprocoumon	13 (1.1)
Acenocoumarol	12 (1.0)
Fluindione	12 (1.0)
Heparin group	70 (5.9)
Heparin	37 (3.1)
Enoxaparin/enoxaparin sodium	20 (1.7)
Nadroparin calcium	4 (0.3)
Certoparin sodium	3 (0.3)
Dalteparin sodium	2 (0.2)
Heparinoid	2 (0.2)
Nadroparin	2 (0.2)
Pentosan polysulfate/pentosan polysulfate sodium	2 (0.2)
Tinzaparin sodium	1 (0.1)
Direct factor Xa inhibitors	4 (0.3)
Rivaroxaban	4 (0.3)
Direct thrombin inhibitors	3 (0.3)
Dabigatran etexilate mesylate	3 (0.3)
Other antithrombotic agents	0 (0.0)
Thrombolytic agents	0 (0.0)

onabotulinumtoxinA). All TEAEs resolved (except one instance of injection-site bruising in a placebo recipient who was ongoing at the conclusion of the study) and none were considered serious; there were no reports of compartment syndrome.

Across all studies, the incidence of TEAEs indicating a bleeding complication in patients receiving onabotulinumtoxinA plus antithrombotic therapy was 0.9%, compared with 1.4% in patients receiving onabotulinumtoxinA and no antithrombotic therapy. Treatment-emergent adverse events indicating a bleeding complication were reported in 1.2% of patients receiving placebo plus antithrombotic therapy, and 1.4% in patients receiving placebo and no antithrombotic therapy (Table 4). Among patients who received antithrombotic therapies, the risk difference (95% CI) was −0.0036 (−0.0156 to 0.0083; Table 5) for those receiving onabotulinumtoxinA vs placebo. The incidence of TEAEs of interest by study type and also by individual study is also shown in Table 5. Only patients enrolled in the upper limb studies had a higher incidence of bleeding when receiving antithrombotic therapy vs no antithrombotic therapy; the risk difference (95% CI) was 0.0191 (0.0035–0.0346). Bleeding-related TEAEs were more likely to occur in patients receiving antithrombotic therapy and receiving onabotulinumtoxinA in upper limb sites (1.9%) than those injected in lower limb sites (0.0%; Fig. 1a); similar results were reported for patients receiving antithrombotic therapy and patients receiving placebo (2.2% and 0.8%, respectively).

3.2 Subanalysis of Antithrombotic Medications Excluding Platelet Aggregation Inhibitors

In the subanalysis of patients who received antithrombotic therapy but excluding platelet aggregation inhibitors (referred to herein collectively as anticoagulants), the overall incidence of TEAEs that indicated a bleeding complication was <2%, and rates were lower in patients who received an anticoagulant (0.6%) than in those who did not (1.3%; Table 4). The risk difference (95% CI) was −0.0063 (−0.0168 to −0.0043) among patients who received anticoagulant therapy vs those who did not (Table 4). In patients receiving anticoagulant therapy, the only TEAE indicating a bleeding complication was injection-site bruising (0.6% overall; 0% in patients receiving onabotulinumtoxinA). All TEAEs resolved and none were deemed serious.

Across all studies, the incidence of TEAEs indicating a bleeding complication in patients receiving onabotulinumtoxinA plus anticoagulant therapy was 0%, compared with 1.3% in patients receiving onabotulinumtoxinA and no anticoagulant therapy, 1.7% in patients receiving placebo plus anticoagulant therapy, and 1.2% in patients receiving placebo and no anticoagulant therapy (Table 4; Fig. 1b). Among patients who took anticoagulant therapies, the risk difference (95% CI) was −0.0168 (−0.0399 to 0.0063; Table 5).

Only patients enrolled in the lower limb studies had a higher incidence of bleeding when receiving anticoagulant therapy vs no anticoagulant therapy (Table 5). In patients receiving anticoagulant therapy, bleeding-related TEAEs were similar whether patients received onabotulinumtoxinA injections in the upper or lower limbs (0.7% vs 0.8%, respectively). Patient numbers for those being treated in the upper and lower limbs were relatively low and no bleeding-related TEAEs were reported.

Table 3 Patient demographic characteristics (safety population)

Characteristic	Patients receiving any antithrombotic[a]		Patients receiving any antithrombotic excluding platelet aggregation inhibitors[b]	
	Yes ($n=1182$)	No ($n=695$)	Yes ($n=308$)	No[c] ($n=1569$)
Mean age, years (SD)	59.4 (11.7)	54.8 (13.7)	59.4 (12.4)	57.3 (12.7)
Age ≥ 65 years, *n* (%)	433 (36.6)	167 (24.0)	123 (39.9)	477 (30.4)
Male, *n* (%)	746 (63.1)	436 (62.7)	191 (62.0)	991 (63.2)
Race, *n* (%)				
Caucasian	972 (82.2)	467 (67.2)	266 (86.4)	1173 (74.8)
Black	74 (6.3)	53 (7.6)	24 (7.8)	103 (6.6)
Asian	110 (9.3)	148 (21.3)	11 (3.6)	247 (15.7)
Hispanic	20 (1.7)	22 (3.2)	4 (1.3)	38 (2.4)
Other	6 (0.5)	5 (0.7)	3 (1.0)	8 (0.5)
Mean weight, kg (SD)	77.5 (15.5)	75.5 (15.9)	79.4 (16.8)	76.3 (15.4)

SD standard deviation

[a]All antithrombotic agent analysis included direct factor Xa inhibitors, direct thrombin inhibitors, heparin group, other antithrombotic agents, platelet aggregation inhibitors, thrombolytic agents, and vitamin K antagonists

[b]Antithrombotic agents excluding platelet aggregation inhibitors analysis included direct factor Xa inhibitors, direct thrombin inhibitors, heparin group, other antithrombotic agents, thrombolytic agents, and vitamin K antagonists

[c]Patients received none of the listed antithrombotic medications in footnote b, but may have received platelet aggregation inhibitors

3.3 Subanalysis of Heparins and Vitamin K Antagonists

In patients who received heparins or vitamin K antagonists ($n=302$), the incidence of TEAEs indicating a bleeding complication was 0.3% compared with 1.3% in patients who did not receive heparin or vitamin K antagonist therapy ($n=1575$; Table 6). The incidence of TEAEs indicating a bleeding complication in patients receiving onabotulinumtoxinA plus heparins or a vitamin K antagonist therapy ($n=188$) was 0%, compared with 1.3% in patients receiving onabotulinumtoxinA and no heparin or vitamin K antagonist therapy ($n=922$), 0.9% in patients receiving placebo plus heparin or a vitamin K antagonist ($n=114$), and 1.4% in patients receiving placebo and no heparin or vitamin K antagonist therapy ($n=653$).

4 Discussion

Results of this retrospective pooled safety analysis showed no increased risk of bleeding complications in patients receiving intramuscular onabotulinumtoxinA with vs without concomitant antithrombotic therapy. In all three analyses, no significant differences in the incidence of bleeding complications were observed in patients receiving onabotulinumtoxinA and concomitant antithrombotic therapy compared to those for patients receiving placebo and concomitant antithrombotic therapy, which may reflect the fact that both agents were administered in the same manner. No bleeding-related TEAEs were reported in patients receiving onabotulinumtoxinA for both upper and lower limb spasticity, but patient numbers were relatively low.

The most common bleeding complications observed overall were injection-site bruising and injection-site hemorrhage. These events were not serious and all resolved. Similar results were found in a separate analysis of patients who were receiving concomitant therapy with heparin or vitamin K antagonists (e.g., warfarin), with no increased risk of bleeding complications observed. Notably, there were no cases of compartment syndrome reported in this study. Compartment syndrome is a rare but life-threatening complication associated with minor trauma in patients receiving antithrombotic therapy [16], including after a simple percutaneous needle puncture [17]. Examination of the Allergan safety database revealed one post-marketing case of compartment syndrome after treatment with onabotulinumtoxinA. The case was reported in 2014; a male patient who received treatment between 2008 and 2009 experienced compartment syndrome in the calf following administration of onabotulinumtoxinA for leg spasticity. There was limited information provided, preventing further meaningful assessment. In one additional case reported in 2018, compartment syndrome was recorded in a lower limb of a patient, but the patient had received onabotulinumtoxinA for right arm spasticity, and was therefore excluded from the assessment.

Table 4 Pooled incidence of treatment-emergent adverse events of interest

Adverse event, *n* (%)	Analysis of all antithrombotic medications,[a] *n* (%)					
	Antithrombotic medication (*n* = 1182)	No antithrombotic medication (*n* = 695)	OnabotulinumtoxinA/antithrombotic medication (*n* = 694)	OnabotulinumtoxinA/no antithrombotic medication (*n* = 416)	Placebo/antithrombotic medication (*n* = 488)	Placebo/no antithrombotic medication (*n* = 279)
Any adverse event	12 (1.0)	10 (1.4)	6 (0.9)	6 (1.4)	6 (1.2)	4 (1.4)
Injection-site bruising	10 (0.8)	8 (1.2)	5 (0.7)	4 (1.0)	5 (1.0)	4 (1.4)
Injection-site discoloration	0	0	0	0	0	0
Injection-site extravasation	0	0	0	0	0	0
Injection-site hematoma	0	1 (0.1)	0	1 (0.2)	0	0
Injection-site hemorrhage	1 (0.1)	2 (0.3)	0	1 (0.2)	1 (0.2)	1 (0.4)
Injection-site edema	0	0	0	0	0	0
Injection-site swelling	0	1 (0.1)	0	1 (0.2)	0	0
Purpura	1 (0.1)	0	1 (0.1)	0	0	0
Compartment syndrome	0	0	0	0	0	0
	Analysis of any antithrombotic except platelet aggregation inhibitors,[b] *n* (%)					
	Antithrombotic medication (*n* = 308)	No antithrombotic medication (*n* = 1569)	OnabotulinumtoxinA/antithrombotic medication (*n* = 189)	OnabotulinumtoxinA/no antithrombotic medication (*n* = 921)	Placebo/antithrombotic medication (*n* = 119)	Placebo/no antithrombotic medication (*n* = 648)
Any adverse event	2 (0.6)	20 (1.3)	0	12 (1.3)	2 (1.7)	8 (1.2)
Injection-site bruising	2 (0.6)	16 (1.0)	0	9 (1.0)	2 (1.7)	7 (1.1)
Injection-site discoloration	0	0	0	0	0	0
Injection-site extravasation	0	0	0	0	0	0
Injection-site hematoma	0	1 (0.1)	0	1 (0.1)	0	0
Injection-site hemorrhage	0	3 (0.2)	0	1 (0.1)	0	2 (0.3)
Injection-site edema	0	0	0	0	0	0
Injection-site swelling	0	1 (0.1)	0	1 (0.1)	0	0
Purpura	0	1 (0.1)	0	1 (0.1)	0	0
Compartment syndrome	0	0	0	0	0	0

[a]All antithrombotic agent analysis included direct factor Xa inhibitors, direct thrombin inhibitors, heparin group, other antithrombotic agents, platelet aggregation inhibitors, thrombolytic agents, and vitamin K antagonists

[b]Antithrombotic medications excluding platelet aggregation inhibitors included direct factor Xa inhibitors, direct thrombin inhibitors, heparin group, other antithrombotic agents, thrombolytic agents, and vitamin K antagonists

Table 5 Incidence of treatment-emergent adverse events of interest by study type and individual study

Study	Antithrombotic medication, *n/N* (%)	No antithrombotic medication, *n/N* (%)	Risk difference (95% CI)	Patients who took antithrombotic medications		
				Onabotulinum-toxinA, *n/N* (%)	Placebo, *n/N* (%)	Risk difference (95% CI)
Analysis of all antithrombotic agents,[a] *n* (%)						
All studies	12/1182 (1.0)	10/695 (1.4)	−0.0042 (−0.0148 to 0.0063)	6/694 (0.9)	6/488 (1.2)	−0.0036 (−0.0156 to 0.0083)
Lower limb studies	1/532 (0.2)	1/242 (0.4)	−0.0023 (−0.0111 to 0.0066)	0/304 (0)	1/228 (0.4)	−0.0044 (−0.0130 to 0.0042)
Upper limb studies	10/442 (2.3)	1/280 (0.4)	0.0191 (0.0035 to 0.0346)	6/287 (2.1)	4/155 (2.6)	−0.0049 (−0.0349 to 0.0251)
Lower/upper limb studies	1/208 (0.5)	8/173 (4.6)	−0.414 (−0.0741 to −0.0088)	0/103 (0)	1/105 (1.0)	−0.0095 (−0.0281 to 0.0091)
Study #1	4/89 (4.5)	1/37 (2.7)	0.0179 (−0.0498, 0.0856)	2/50 (4.0)	2/39 (5.1)	−0.0113 (−0.0993, 0.0767)
Study #2	0/0 (0.0)	8/108 (7.4)	−0.0741	–	–	–
Study #3	0/21 (0.0)	0/9 (0.0)	0.0000	0/15 (0.0)	0/6 (0.0)	0.0000
Study #4	5/94 (5.3)	0/61 (0.0)	0.0532 (0.0078, 0.0986)	3/66 (4.5)	2/28 (7.1)	−0.0260 (−0.1338, 0.0818)
Study #5	0/43 (0.0)	0/19 (0.0)	0.0000	0/27 (0.0)	0/16 (0.0)	0.0000
Study #6	1/347 (0.3)	1/117 (0.9)	−0.0057 (−0.0233, 0.0119)	0/175 (0.0)	1/172 (0.6)	−0.0058 (−0.0172, 0.0055)
Study #7	0/92 (0.0)	0/39 (0.0)	0.0000	0/61 (0.0)	0/31 (0.0)	0.0000
Study #8	1/208 (0.5)	0/65 (0.0)	0.0048 (−0.0046, 0.0142)	0/103 (0.0)	1/105 (1.0)	−0.0095 (−0.0281, 0.0091)
Study #9	0/24 (0.0)	0/8 (0.0)	0.0000	0/19 (0.0)	0/5 (0.0)	0.0000
Study #10	0/46 (0.0)	0/13 (0.0)	0.0000	0/30 (0.0)	0/16 (0.0)	0.0000
Study #11	0/42 (0.0)	0/19 (0.0)	0.0000	0/33 (0.0)	0/9 (0.0)	0.0000
Study #12	0/24 (0.0)	0/11 (0.0)	0.0000	0/15 (0.0)	0/9 (0.0)	0.0000
Study #13	1/9 (11.1)	0/2 (0.0)	0.1111 (−0.0942, 0.3164)	1/9 (11.1)	0/0 (0.0)	0.1111
Study #14	0/50 (0.0)	0/27 (0.0)	0.0000	0/37 (0.0)	0/13 (0.0)	0.0000
Study #15	0/27 (0.0)	0/56 (0.0)	0.0000	0/20 (0.0)	0/7 (0.0)	0.0000
Study #16	0/66 (0.0)	0/104 (0.0)	0.0000	0/34 (0.0)	0/32 (0.0)	0.0000
Analysis of any antithrombotic medication except platelet aggregation inhibitors,[b] *n* (%)						
All studies	2/308 (0.6)	20/1569 (1.3)	−0.0063 (−0.0168 to 0.0043)	0/189 (0)	2/119 (1.7)	−0.0168 (−0.0399 to 0.0063)
Lower limb studies	1/121(0.8)	1/653 (0.2)	0.0067 (−0.0097 to 0.0231)	0/77 (0)	1/44 (2.3)	−0.0227 (−0.0668 to 0.0213)
Upper limb studies	1/129 (0.8)	10/593 (1.7)	−0.0091 (−0.0275 to 0.0092)	0/83 (0)	1/46 (2.2)	−0.0217 (−0.0639 to 0.0204)
Lower/upper limb studies	0/58 (0)	9/323 (2.8)	−0.0279 (-0.0458 to −0.0099)	0/29 (0)	0/29 (0)	0.0000
Study #1	1/34 (2.9)	4/92 (4.3)	−0.0141 (−0.0845 to 0.0564)	0/19 (0)	1/15 (6.7)	−0.0667 (−0.1929 to 0.0596)
Study #2	0/0 (0.0)	8/108 (7.4)	−0.0741	–	–	–
Study #3	0/9 (0.0)	0/21 (0.0)	0.0000	0/7 (0)	0/2 (0)	0.0000
Study #4	0/30 (0.0)	5/125 (4.0)	−0.0400 (−0.0744 to −0.0056)	0/19 (0)	0/11 (0)	0.0000
Study #5	0/16 (0.0)	0/46 (0.0)	0.0000	0/7 (0)	0/9 (0)	0.0000
Study #6	1/53 (1.9)	1/411 (0.2)	0.0164 (−0.0205 to 0.0534)	0/31 (0)	1/22 (4.5)	−0.0455 (−0.1325 to 0.0416)
Study #7	0/23 (0.0)	0/108 (0.0)	0.0000	0/14 (0)	0/9 (0)	0.0000

Table 5 (continued)

Study	Antithrombotic medication, *n/N* (%)	No antithrombotic medication, *n/N* (%)	Risk difference (95% CI)	Patients who took antithrombotic medications		
				Onabotulinum-toxinA, *n/N* (%)	Placebo, *n/N* (%)	Risk difference (95% CI)
Study #8	0/58 (0.0)	1/215 (0.5)	−0.0047 (−0.0137 to 0.0044)	0/29 (0)	0/29 (0)	0.0000
Study #9	0/10 (0.0)	0/22 (0.0)	0.0000	0/8 (0)	0/2 (0)	0.0000
Study #10	0/10 (0.0)	0/49 (0.0)	0.0000	0/7 (0)	0/3 (0)	0.0000
Study #11	0/12 (0.0)	0/49 (0.0)	0.0000	0/9 (0)	0/3 (0)	0.0000
Study #12	0/11 (0.0)	0/24 (0.0)	0.0000	0/6 (0)	0/5 (0)	0.0000
Study #13	0/5 (0.0)	1/6 (16.7)	−0.1667 (−0.4649 to 0.1315)	0/5 (0)	0/0 (0)	0.0000
Study #14	0/11 (0.0)	0/66 (0.0)	0.0000	0/9 (0)	0/2 (0)	0.0000
Study #15	0/22 (0.0)	0/61 (0.0)	0.0000	0/17 (0)	0/5 (0)	0.0000
Study #16	0/4 (0.0)	0/166 (0.0)	0.0000	0/2 (0)	0/2 (0)	0.0000

CI confidence interval

[a]All antithrombotic agent analysis included direct factor Xa inhibitors, direct thrombin inhibitors, heparin group, other antithrombotic agents, platelet aggregation inhibitors, thrombolytic agents, and vitamin K antagonists

[b]Antithrombotic agents excluding platelet aggregation inhibitors analysis included direct factor Xa inhibitors, direct thrombin inhibitors, heparin group, other antithrombotic agents, thrombolytic agents, and vitamin K antagonists

Patients and clinicians should be alert for any signs of swelling, paresthesia, or pain [17], particularly pain with passive stretching of the muscles [18]. If any such signs are noticed, patients should be advised to seek immediate medical attention, as the time between diagnosis and treatment influences outcome [18].

Limited data exist regarding the safety of administering intramuscular injections in patients receiving antithrombotic therapy. In this analysis, the incidence of bleeding complications was 1.2% in patients receiving intramuscular placebo and concomitant antithrombotic therapy, similar to that of patients receiving placebo injection without antithrombotic therapy (1.4%).

Several studies have evaluated the safety of other treatments and procedures involving the insertion of needles or pins into muscle tissues of patients receiving antithrombotic therapies. In a small retrospective chart review of Korean patients receiving warfarin ($n=42$) or oral antiplatelet agents ($n=100$) undergoing acupuncture, no significant adverse effects were observed compared with controls not receiving anticoagulant therapy ($n=100$) [19]. A chart review of 229 patients receiving warfarin therapy who underwent acupuncture showed that only minimal bleeding occurred at the puncture sites, with no differences observed based on INRs [20]. A study of 158 patients receiving antiplatelet therapies or warfarin who underwent needle electromyography showed no greater risk of hematoma formation compared with controls [21]. Likewise, in a pooled analysis of multiple studies of patients receiving anticoagulants undergoing electromyography, it was observed that the absolute risk of hematoma formation was approximately 1% [22]. Overall, the results of these studies suggest no increased risk of needle muscle procedures involving piercing of muscle tissues in patients receiving oral antithrombotic therapies.

The large size of this pooled analysis (16 studies; 1877 patients, including 1182 receiving antithrombotic therapy) provided high sensitivity for detecting less common bleeding complications in patients undergoing intramuscular therapy with onabotulinumtoxinA. However, because bleeding complications are rare, the Cochran–Mantel–Haenszel test with continuity corrections to a study with zero event(s) was used. However, as has been discussed by Sweeting et al. [23], this approach may be less optimal and they would suggest removing the ten zero event studies from the analyses [23]. Two additional limitations of this analysis are worthy of discussion. In this study, a greater proportion of patients receiving antithrombotic therapy was ≥65 years of age and Caucasian, compared with those not receiving antithrombotic therapy. Whereas advanced age is a known risk for anticoagulant-associated bleeding, race has not been identified as a risk factor [24, 25]. Therefore, despite our population being at a relatively high risk for anticoagulant-associated bleeding compared with the population not receiving antithrombotic therapy, no difference in bleeding risk was observed. Second, while comparison of onabotulinumtoxinA to a placebo group was of interest in examining whether the injection of onabotulinumtoxinA increased the risk of bleeding complications, it should be noted that the intramuscular injection itself as well as administration of

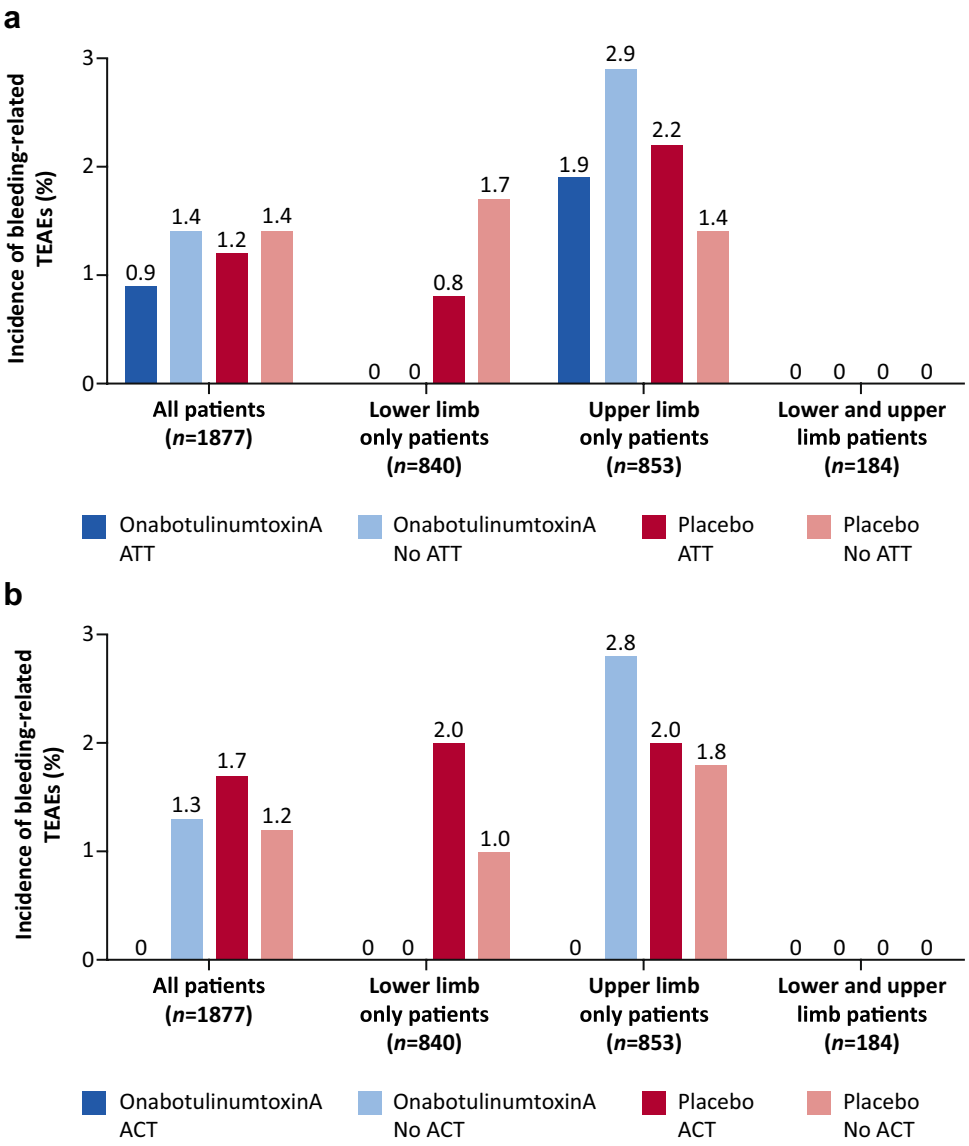

Fig. 1 Incidence of bleeding-related treatment-emergent adverse events (TEAEs) stratified by site of injection in patients receiving **a** antithrombotic treatment (ATT) and **b** anticoagulant treatment (ACT)

placebo (vehicle or normal saline) may potentially cause bleeding associated with mechanical trauma. Thus, the lack of comparison to a 'no intramuscular administration' group or even a 'dry needling' group could be considered a limitation of the analysis. Another limitation is that this analysis did not include non-Allergan sponsored trials and real-world studies. As the investigators of clinical trials are typically highly experienced clinicians, it is possible that the incidence of events may be higher in real-world studies that do not have the controlled environment of the clinical trial. A final limitation is that these conclusions are drawn based on data where tamponade is used as part of normal clinical practice and may not apply to situations in which tamponade cannot be applied (e.g., bladder injections, where the label provides explicit instructions regarding antiplatelet and anticoagulant therapy).

5 Conclusions

No apparent increased risk of bleeding complications was found with the administration of intramuscular onabotulinumtoxinA in a post-stroke population receiving antithrombotic therapies compared with those not receiving antithrombotic therapies. These results should be interpreted with caution as this was a retrospective pooled analysis. Careful observation of the injection site immediately following onabotulinumtoxinA and patient education regarding the potential for bleeding complications, including the signs and symptoms of compartment syndrome, when used with concomitant antithrombotic therapies are warranted.

Table 6 Pooled incidence of treatment-emergent adverse events of interest in patients receiving medications in heparin group or vitamin K antagonists

Adverse event, *n* (%)	Antithrombotic medication (*n* = 302)	No antithrombotic medication (*n* = 1575)	OnabotulinumtoxinA/antithrombotic medication (*n* = 188)	OnabotulinumtoxinA/no antithrombotic medication (*n* = 922)	Placebo/antithrombotic medication (*n* = 114)	Placebo/no antithrombotic medication (*n* = 653)
Any adverse event	1 (0.3)	21 (1.3)	0	12 (1.3)	1 (0.9)	9 (1.4)
Injection-site bruising	1 (0.3)	17 (1.1)	0	9 (1.0)	1 (0.9)	8 (1.2)
Injection-site discoloration	0	0	0	0	0	0
Injection-site extravasation	0	0	0	0	0	0
Injection-site hematoma	0	1 (0.1)	0	1 (0.1)	0	0
Injection-site hemorrhage	0	3 (0.2)	0	1 (0.1)	0	2 (0.3)
Injection-site edema	0	0	0	0	0	0
Injection-site swelling	0	1 (0.1)	0	1 (0.1)	0	0
Purpura	0	1 (0.1)	0	1 (0.1)	0	0
Compartment syndrome	0	0	0	0	0	0

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Compliance with Ethical Standards

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Conflict of interest Chengcheng Liu and Amelia Orejudos are employees of Allergan plc. Rozalina Dimitrova, Lynn James, Irina Yushmanova, and Mitchell F. Brin are employees of Allergan plc and own stock in the company. All authors met the International Committee of Medical Journal Editors authorship criteria. Neither honoraria nor payments were made for authorship.

Ethics approval For this type of study, formal consent is not required.

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