

RESEARCH

Open Access



Low risk of haematomas with intramuscular vaccines in anticoagulated patients: a systematic review with meta-analysis

Daniel Caldeira^{1,2,3,8*}, Bárbara Sucena Rodrigues⁴, Mariana Alves^{1,5,6}, Fausto J. Pinto^{2,3} and Joaquim J. Ferreira^{1,5,7}

Abstract

Introduction: The summary of product characteristics of vaccines administered intramuscularly, including the vaccine for coronavirus SARS-CoV-2 (COVID-19) and Influenza, warned for risks of bleeding in patients treated with oral anticoagulants. We aimed to estimate the incidence of major bleeding events in this setting and to compare these risks against other vaccination routes.

Methods: This systematic review included all prospective and retrospective studies enrolling anticoagulated patients that received intramuscular vaccination, published until December 2020 in CENTRAL, MEDLINE and EMBASE. The outcomes of interest were major bleeding and haematoma related with vaccination. The incidence of the outcomes was estimated through a random-effects meta-analysis using the Freeman-Turkey transformation. The results are expressed in percentages, with 95%-confidence intervals (95%CI), limited between 0 and 100%. When studies compared intramuscular vaccination vs. other route, the data were compared and pooled using random-effects meta-analysis. Risk ratios (RR) with 95%CI were reported.

Results: Overall 16 studies with 642 patients were included. No major bleeding event was reported. The pooled incidence of haematomas following vaccination (mostly against Influenza) in patients treated with oral anticoagulants (mostly warfarin; no data with DOACs / NOACs) was 0.46% (95%CI 0-1.53%). Three studies evaluated the intramuscular vs. subcutaneous route of vaccination. Intramuscular vaccines did not increase the risk of haematoma (RR 0.53, 95%CI 0.10-2.82) compared with subcutaneous route.

Conclusions: Intramuscular vaccination in anticoagulated patients is safe with very low incidence of haematomas and the best available evidence suggests that using the intramuscular route does not increase the risk of haematomas compared with the subcutaneous route.

Keywords: Bleeding, Haemorrhage, Vaccine, Flu, anticoagulation

Introduction

Oral anticoagulants are used to treat or prevent thromboembolic events. Atrial fibrillation, venous thromboembolism, and mechanical prosthesis are the

main indications for the use of these drugs. Despite the invasiveness of intramuscular injections, oral anticoagulation is not discontinued in vaccination contrary to what occurs before major surgeries due to the increased risk of bleeding.[1, 2] Nevertheless, the summary of product characteristics of vaccines administered intramuscularly recommend precaution in patients with coagulation disorders, due to potential risk of bleeding after intramuscular injection.[3] This

* Correspondence: dgcaldeira@hotmail.com

¹Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

²Centro Cardiovascular da Universidade de Lisboa - CCUL, CAML, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

Full list of author information is available at the end of the article



© The Author(s). 2022 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

issue has raised some doubts, particularly for the recent vaccine against coronavirus SARS-CoV-2 (COVID-19).[4].

To further elucidate all stakeholders about the risks of intramuscular vaccines in anticoagulated patients, we aimed to perform a systematic review to estimate the incidence of hemorrhagic complications in this setting and to compare the hemorrhagic risks of intramuscular vaccination against other routes, namely subcutaneous.

Methods

This systematic review has been developed based on the applicable aspects of Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines and Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) Checklist.[5, 6].

Types of studies included

This systematic review aimed to enrol all interventional or observational studies, including randomized controlled trials, quasi-randomized clinical trials, cohort/nested case-control studies, case-control studies, either prospective or retrospective. Studies had to include at least one arm with anticoagulated patients receiving vaccines deemed to be administered through intramuscular route. For eligibility we considered all types of oral anticoagulation, i.e. vitamin K antagonists (warfarin, acenocoumarol, phenprocoumon, fluindione) or direct oral anticoagulants (DOACs / NOACs: dabigatran, apixaban, edoxaban, rivaroxaban) or oral anticoagulation without specifying the used drugs. Case reports and case series of bleeding events were excluded.

Types of outcome measures

The primary outcomes were: (1) the incidence of major bleeding events; (2) the incidence of local haematoma. The secondary outcome was the increase of arm circumference as a surrogate of local complication, defined as an increase of at least 1 cm or swollen arm as defined by the investigators.

Search methods for identification of studies

We searched for studies in the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE; from inception until 18th December 2020. The full search strategy is presented in the [Table 1](#) of the Supplementary Data Appendix.

Data extraction and risk of bias evaluation

Two reviewers (BSR and MA) screened the titles and abstracts yielded by the searches against the inclusion

criteria. In a second phase, the full text reports were assessed independently by the reviewers to determine whether these met the inclusion criteria. Disagreements were solved by consensus or recurring to a third party (DC). The reasons for exclusion at this stage were recorded and are detailed in [Table 2](#) of the Supplementary Data Appendix.

The data from the individual studies identified for inclusion was introduced into a pre-piloted form. This information included: authors, year of publication; sample size; participants' characteristics; anti-coagulant used; indication for oral anticoagulation; vaccines used, measures before and after vaccination.

The risk of bias evaluation of the included studies was performed using a scale adapted from Hoy and colleagues[7, 8]. This tool evaluates the representativeness of the sample, the sampling technique, the response rate, the data collection method, the measurement tools, the case definitions, and the statistical reporting. According to this score the risk of bias of the studies were categorised as "low risk" (7-9 points), "moderate risk" (4-6 points), or "high risk" (0-3 points).[8] For randomized controlled trial evaluating the intramuscular route against others, the Cochrane Risk of Bias Tool was applied.

Meta-analysis

STATA 12.0 and RevMan 4.3 were used to synthesize the results.

For incidence calculations we used the incidence of events in the numerator and the evaluated population in the denominator. The incidence of individual and pooled studies was estimated using the Freeman-Turkey transformation (double arcsine transformation) to adjust the limiting the CI among 0-100%.[9, 10] For the comparison of intramuscular route vs. others, we used a Mantel-Haenszel method to pool the data using risk ratios (RRs).

The random effects model was used by default. If studies reported to have zero events, we applied a correction factor of 0.5 to allow for the inclusion of those studies in the analysis.[11] Statistical heterogeneity was assessed using I^2 , which describes the percentage of the variability that is attributable to heterogeneity rather than chance.[12] Publication bias was assessed through the Egger test [13].

Results

The study search yielded 368 records, from which 16 fulfilled the inclusion criteria. All the 16 studies had data (including zero events) used for the estimation of bleeding events in patients anticoagulated submitted to vaccination[14–29], and 3 studies had comparative data

about the risks of intramuscular route vs. subcutaneous route [22, 24, 26] (Fig. 1). Influenza vaccination was the commonest vaccine in the included studies. Most of the studies included only patients treated with VKA. The main characteristics of the included studies are shown in Table 1.

Risk of bias

The risk of bias of all studies was classified as moderate with score ranging between 5 and 6 (Supplementary Table 3). The major sources of bias are related to the small sample sizes, and the definition of the exposure which as deemed to be intramuscular due to the type of vaccine used in the older studies. Regarding the 3 RCTs included, the most remarkable feature of risk of bias, in particular performance bias, was the

single-blinded nature of all trials (Supplementary Table 4).

Incidence of major bleeding or haematomas

Among the included studies, no major bleeding was reported. The pooled data of 16 studies enrolling 642 anticoagulated patients showed that the estimated incidence of haematomas was 0.46% (95%CI 0-1.53%) (Fig. 2). There was no significant heterogeneity ($I^2=0\%$).

Exploratory analyses showed that when only studies at lower risk bias were included the incidence was 0.44% (95%CI 0-1.60%). This incidence was lower but not significantly so than that estimated for higher risk of bias studies (1.80%, 95%CI 0-5.75) (Supplementary Fig. 1; Table 2). Also, different methods to handle zero events did not show

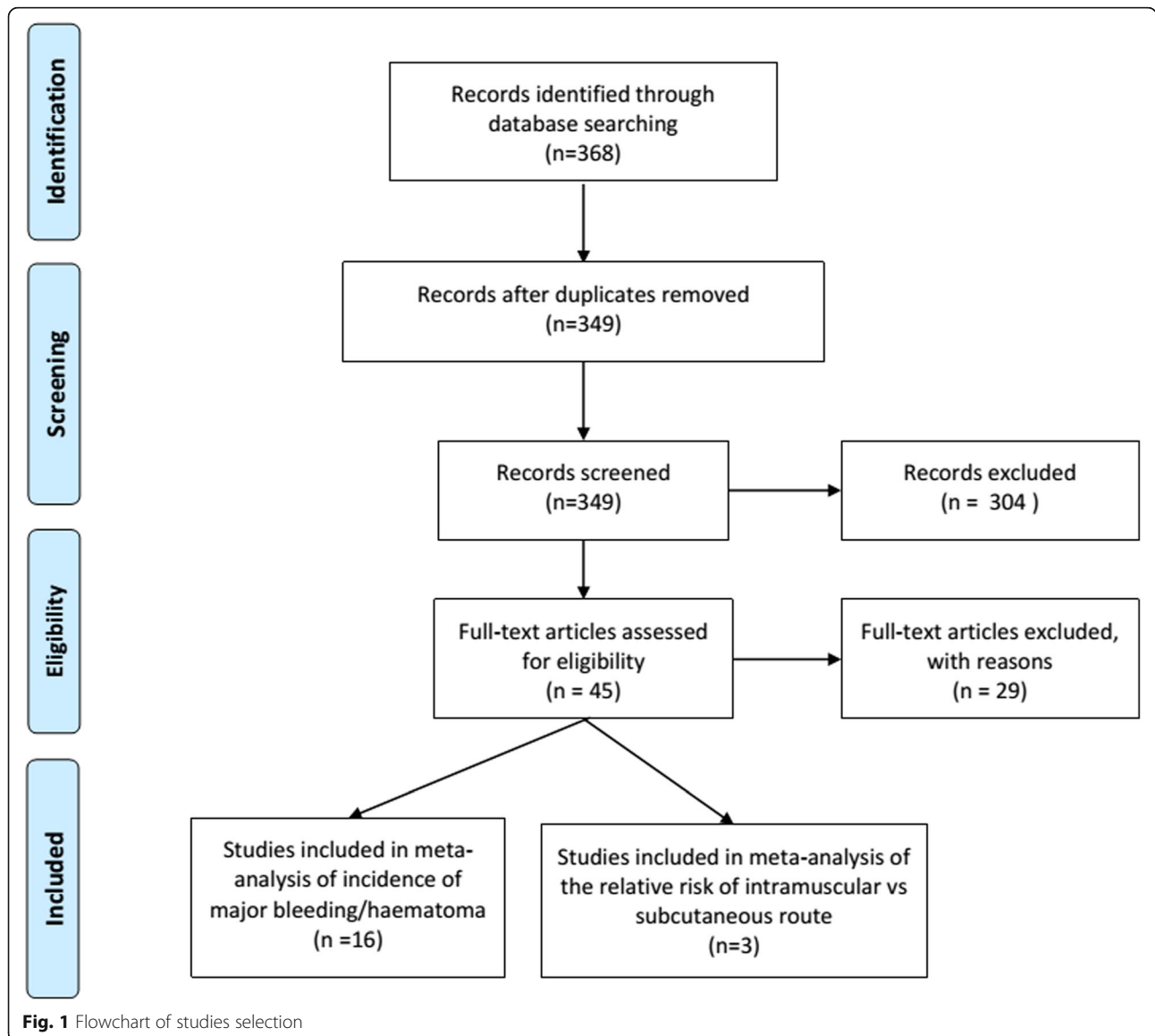
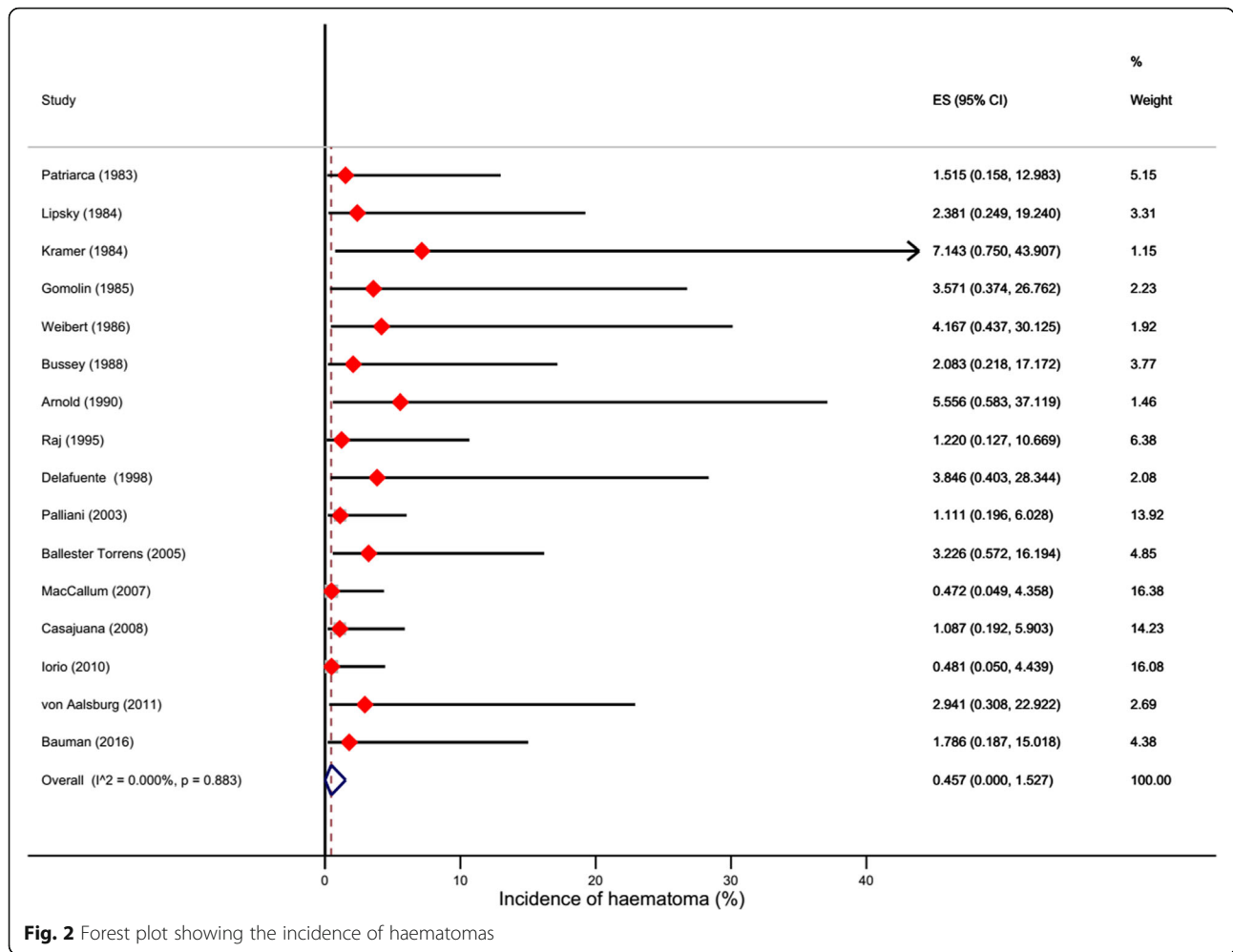


Fig. 1 Flowchart of studies selection

Table 1 Studies included in the review

Study	Sample size	Mean/median age	Anticoagulant	Indication for anticoagulation	Vaccine used and route(s) of administration	Follow-up
Patriarca 1983	33	Not reported	Warfarin	Not reported	Influenza vaccination Route not reported	30 days
Lipsky 1984	21	62.5 years	Warfarin	Not reported	Influenza vaccine Route not reported	28-30 days
Kramer 1984	8	Not reported	Warfarin	Not reported	Influenza vaccine Route not reported	21 days
Gomolin 1985	15	Not specified (geriatric)	Warfarin	Not reported	Influenza vaccine Route not reported	21 days
Weibert 1986	13	N/R	Warfarin	Not reported	Influenza vaccine Route not reported	14 days
Bussey 1988	24	60.3 years	Warfarin	Not reported	Influenza vaccine Route not reported	, 4 months
Arnold 1990	9	68 years	Warfarin	Not reported	Influenza vaccine Route not reported	30 days
Raj 1995	41	65.7 years	Warfarin	Not reported	Influenza vaccine Route: im	14 days
Delafuente 1998	36	68 years	Warfarin	Not reported	Influenza vaccine Route: im vs. sc	4 months
Paliani 2003	90	74 years	Warfarin (98%), acenocoumarol (2%)	Not reported	Influenza vaccine Route: im	7-10 days
Ballester Torrens 2005	59	72.4 years	Not specified	Atrial fibrillation (majority), valvular prosthesis (10%)	Influenza vaccine Route: im vs. sc	7 months
MacCallum 2007	106 (INR analysis only 78)	73.7 years	Warfarin	Not reported	Influenza vaccination Route not known, possibly im	3 months
Casajuana 2008	229	73.6 years	Acenocoumarol (98%), warfarin (2%)	Atrial fibrillation (70%), valvular heart disease (17%), ischemic heart disease (12%)	Influenza vaccine. Route: im vs. sc	10 days
lorio 2010	104	71.3 years	Warfarin	Atrial fibrillation (54%), venous thromboembolism (14%), aortic valve prosthesis (12%), dilated cardiomyopathy (12%), mitral valve prosthesis (6%), mitral and aortic valve prosthesis (2%)	Influenza vaccine Route: im	28 days
Van Aalsburg 2011	19 (im) 9 (sc)	65 years (im) 57 years (sc)	89% oral anticoagulants, 11% combination platelet anti-aggregate therapy	Not reported	DTP, HepA, Hib, typhoid fever vaccine, combination of HepA and HepB Route: im HepA Route: sc	3 days
Bauman 2016	28	5 years	Warfarin	Congenital heart disease (86%), Kawasaki syndrome (7%), others	Influenza vaccine (82%), combinations of PCV, DTaP-IPV, MMR, MMRV, MenC, Hib, HepA, HepB, palivizumab Route: im, sc	6 days (1-14 days)

BCR British Corrected Ratio, *DOACs* direct oral anticoagulants, *DTP* diphtheria, tetanus and polio virus vaccine, *DTaP-IPV* diphtheria, tetanus, acellular pertussis, inactivated polio virus combination vaccine, *Hib* Hemophilus influenzae type B vaccine, *HepA* hepatitis A vaccine, *HepB* hepatitis B vaccine, *im* intramuscular, *INR* International Normalized Ratio, *MenC* conjugate meningococcal type C vaccine, *MMR* measles, mumps and rubella vaccine, *MMRV* measles, mumps rubella and varicella vaccine, *PCV* pneumococcal conjugate vaccine, *sc* subcutaneous



substantial changes in the estimates (Table 2; Supplementary Figs. 2 and 3).

The Egger test was performed to raw data (i.e. without continuity correction) and it did not suggest publication bias (Supplementary Fig. 4).

Intramuscular vs. subcutaneous route for vaccination

There were 3 studies reporting data about haematomas for intramuscular and subcutaneous route. Intramuscular route did not increase the risk of haematoma (RR 0.53, 95%CI 0.10-2.82; I²=0%; 2 studies, 266 patients)

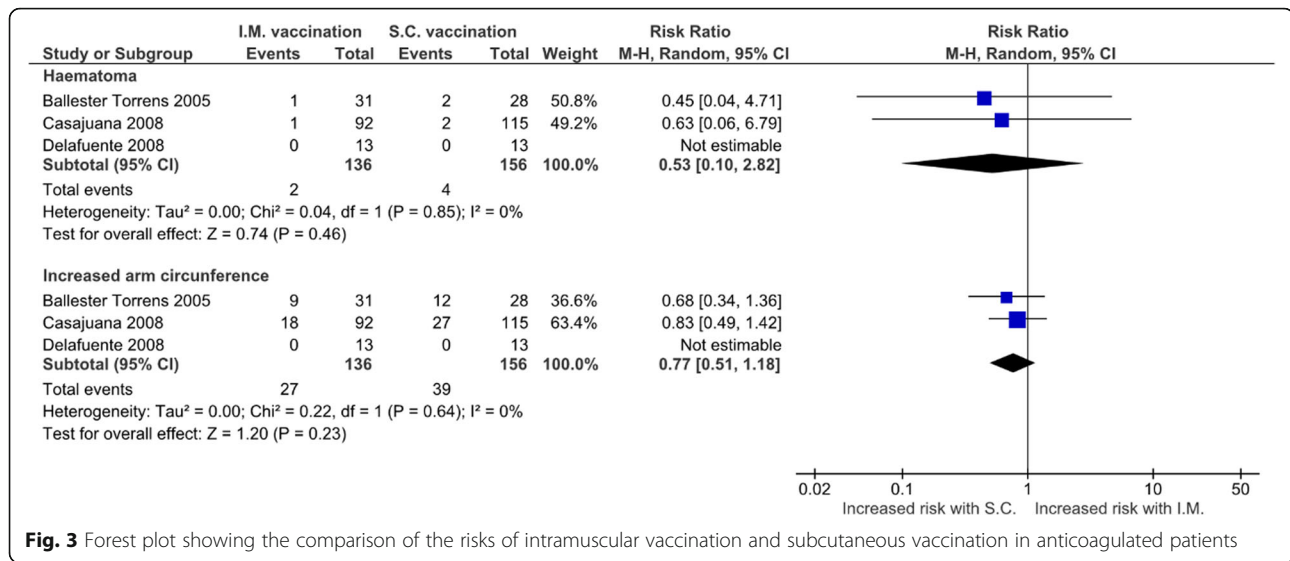
nor the risk of increased arm circumference (RR 0.77, 95%CI 0.51-1.18; I²=0%; 2 studies, 266 patients) (Fig. 3). Publication bias was not formally evaluated due to the small number of studies (Supplementary Fig. 5).

Discussion

The main results of our systematic review were: (1) There was no report of major bleeding events related with intramuscular vaccination; (2) The incidence of haematomas was very low among these patients treated with oral anticoagulants; (3) The comparative risk of

Table 2 Results of subgroup/exploratory analyses

Subgroup/Method	Incidence (%)	95% Confidence interval	I ²
Moderate-Low risk of bias	0.44	0.00-1.60	0%
Moderate-High risk of bias	1.80	0.01-5.75	0%
Adding 0.5 to zero cells (primary approach)	0.46	0.00-1.53	0%
Adding 0.1 to zero cells	0.03	0.00-0.65	0%
No addition	<0.001	0.00-0.25	0%



haematomas through intramuscular vaccination is not higher than the subcutaneous route in patients treated with oral anticoagulants.

These results are particularly relevant for patients treated with oral anticoagulants because they are usually at high risk of cardiovascular events due to their baseline diagnosis. This high-risk group can be considered also to be at high risk of bleeding complications, and caution with previous risk/benefits ascertainment was recommended[30]. However, vaccines seem to trend towards the disease prevention supporting the benefit[31–33], and our results support the absence of substantial bleeding risk. In fact, Influenza vaccination is recommended for patients with coronary disease and heart failure[34], important risk factors for atrial fibrillation, which is the most prevalent cause for needing chronic oral anticoagulation. The relevance of this topic increases with the vaccination for COVID-19 because patients with atrial fibrillation are at high-risk of mortality[35], and most of these patients are at high-risk for complications for COVID-19 and belong to priority groups.

The “COVID-19: the green book” is a British document that has guidance for vaccination in anticoagulated patients.[36] It is important to mention that this book states that there are very few individuals who cannot receive the vaccines. As for care regarding patients on stable anticoagulation therapy, suprathreshold treatment should be avoided (by confirming non-suprathreshold International Normalised Ratio – INR in the last measure) and a fine needle (23 or 25 gauge) should be used for the vaccination, followed by firm pressure applied to the site without rubbing for at least 2 min.

These precautions are overall shared in intramuscular procedures such as the administration of botulinum

toxin in neurological conditions,[37] without any safety warning. In other conditions requiring intramuscular injections, such as the administration of penicillin in patients treated with oral anticoagulants, data has shown to be safe with a low incidence of haematomas.[38].

The subcutaneous route has been considered as a possible strategy to avoid bleeding complications of vaccination in anticoagulated patients. Besides the potential problems of inadequate immunoreactivity/vaccine efficacy[39], this route did not show increased safety. In fact, in one study the subcutaneous route showed increased risk of cutaneous lesions and higher values in pain scales at 24 h.[26].

Our results are limited by the small sample sizes of the studies included. Larger population-based studies would be necessary to determine the prevalence of major bleeding events and haematomas related to intramuscular vaccination, which seems to be a rare event. The safety concerns and strict monitoring of COVID-19 vaccination could be an interesting opportunity to collect and report those data. Some studies were included deeming that the vaccination was intramuscular, however this option showed to be conservative because the studies at lower risk of bias had lower incidences of haematoma. Vitamin K antagonist are still recommended for few clinical entities, such as mechanical prosthetic heart valve or significant mitral stenosis but, nowadays, an important share of anticoagulated patients is treated with DOACs [40, 41], which were not represented in our review. Nevertheless, DOACs seem to be safer than warfarin in terms of bleeding,[42] and we cannot exclude some interaction between the vaccine and the INR in patients receiving warfarin despite many studies stating against it[25, 27, 43]. Overall, these limitations suggest that our results can be less frequent than

our estimates, stressing the safety of intramuscular vaccination in this population.

Conclusions

Intramuscular vaccination in anticoagulated patients is safe, with a very low incidence of haematomas. The best available evidence suggests that using the intramuscular route does not increase the risk of haematomas compared with the subcutaneous route. Anticoagulated patients and healthcare personnel involved in vaccination should be reassured regarding intramuscular vaccinations.

Supplementary information

The online version contains supplementary material available at <https://doi.org/10.1186/s12959-022-00367-1>.

Additional file 1

Acknowledgements

None.

Authors' contributions

Conception and design: DC, FP, JFF; Acquisition of data: BSR and MA; Analysis and interpretation: DC, BSR, MA; Drafting main manuscript: DC. All authors reviewed the manuscript. The author(s) read and approved the final manuscript.

Funding

None. This is an academic project without any governmental or non-governmental grant.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Due to methodology of systematic review and meta-analysis, ethical approval and participants consent was not needed.

Consent for publication

All authors have seen and approved the final version of the manuscript.

Competing interests

DC has participated in educational meetings and/or attended a conferences or symposia (including travel, accommodation) with Daiichi Sankyo, Menarini, Merck Serono and Roche, in the last 3 years. MA reported participation in conferences with Boehringer-Ingelheim, AstraZeneca, Bayer, Bristol-Myers-Squibb, Grünenthal, Tecnimed, Merck Sharp & Dohme. FJP had consultant and speaker fees with Astra Zeneca, Bayer, BMS, Boehringer Ingelheim and Daiichi Sankyo. JFF is a consultant for Ipsen, GlaxoSmithKline, Novartis, Teva, Lundbeck, Solvay, Abbott, BIAL, Merck-Serono, and Merz; received grants from GlaxoSmithKline, Grünenthal, Teva, and Fundação MSD.

Author details

¹Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal. ²Centro Cardiovascular da Universidade de Lisboa - CCUL, CAML, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal. ³Cardiology Department, Hospital Universitário de Santa Maria - CHULN, Santa Maria, Portugal. ⁴Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal. ⁵Instituto de Medicina Molecular João Lobo Antunes, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal. ⁶Serviço de Medicina III, Hospital Pulido Valente, CHLN, Lisboa, Portugal. ⁷CNS - Campus Neurológico Sénior, Torres Vedras, Portugal. ⁸Laboratório de Farmacologia Clínica e Terapêutica - CCUL, Faculdade de

Medicina, Universidade de Lisboa, Av. Prof. Egas Moniz, 1649-028 Lisboa, Portugal.

Received: 21 December 2021 Accepted: 26 January 2022

Published online: 16 February 2022

References

- Steffel J, Verhamme P, Potpara TS et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J*, 39(16), 1330–1393 (2018).
- Tafur A, Douketis J. Perioperative management of anticoagulant and antiplatelet therapy. *Heart*, 104(17), 1461–1467 (2018).
- compendium eem. Influvac Tetra - Summary of Product Characteristics. (Ed. ^)(Eds) (2020)
- Agency EM. Cominarty - Summary of Product Characteristics. (Ed. ^)(Eds) (2021)
- Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj*, 339, b2700 (2009).
- Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*, 283(15), 2008–2012 (2000).
- Hoy D, Brooks P, Woolf A et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol*, 65(9), 934–939 (2012).
- Nguyen KA, Peer N, Mills EJ, Kengne AP. A Meta-Analysis of the Metabolic Syndrome Prevalence in the Global HIV-Infected Population. *PLoS One*, 11(3), e0150970 (2016).
- Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health*, 72(1), 39 (2014).
- Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *J Epidemiol Community Health*, 67(11), 974–978 (2013).
- Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med*, 26(1), 53–77 (2007).
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*, 21(11), 1539–1558 (2002).
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj*, 315(7109), 629–634 (1997).
- Patriarca PA, Kendal AP, Stricof RL, Weber JA, Meissner MK, Dateno B. Influenza vaccination and warfarin or theophylline toxicity in nursing-home residents. *N Engl J Med*, 308(26), 1601–1602 (1983).
- Lipsky BA, Pecoraro RE, Roben NJ, de Blaquiere P, Delaney CJ. Influenza vaccination and warfarin anticoagulation. *Ann Intern Med*, 100(6), 835–837 (1984).
- Kramer P, Tsuru M, Cook CE, McClain CJ, Holtzman JL. Effect of influenza vaccine on warfarin anticoagulation. *Clin Pharmacol Ther*, 35(3), 416–418 (1984).
- Gomolin IH, Chapron DJ, Luhan PA. Lack of effect of influenza vaccine on theophylline levels and warfarin anticoagulation in the elderly. *J Am Geriatr Soc*, 33(4), 269–272 (1985).
- Weibert RT, Lorentz SM, Norcross WA, Klauber MR, Jagger PI. Effect of influenza vaccine in patients receiving long-term warfarin therapy. *Clin Pharm*, 5(6), 499–503 (1986).
- Bussey HI, Saklad JJ. Effect of influenza vaccine on chronic warfarin therapy. *Drug Intell Clin Pharm*, 22(3), 198–201 (1988).
- Arnold WS, Mehta MK, Roberts JS. Influenza vaccine and anticoagulation control in patients receiving warfarin. *Br J Clin Pract*, 44(4), 136–139 (1990).
- Raj G, Kumar R, McKinney WP. Safety of intramuscular influenza immunization among patients receiving long-term warfarin anticoagulation therapy. *Arch Intern Med*, 155(14), 1529–1531 (1995).
- Delafuente JC, Davis JA, Meuleman JR, Jones RA. Influenza vaccination and warfarin anticoagulation: a comparison of subcutaneous and intramuscular routes of administration in elderly men. *Pharmacotherapy*, 18(3), 631–636 (1998).
- Paliani U, Filippucci E, Gresele P. Significant potentiation of anticoagulation by flu-vaccine during the season 2001-2002. *Haematologica*, 88(5), 599–600 (2003).
- Ballester Torrens Mdel M, Aballí Acosta M, Maudos Pérez MT et al. [Intramuscular route for the administration of the anti-flu vaccine in patients

- receiving oral anticoagulation therapy]. *Med Clin (Barc)*, 124(8), 291–294 (2005).
25. MacCallum P, Madhani M, Mt-Isa S, Ashby D. Lack of effect of influenza immunisation on anticoagulant control in patients on long-term warfarin. *Pharmacoepidemiol Drug Saf*, 16(7), 786–789 (2007).
 26. Casajuana J, Iglesias B, Fàbregas M et al. Safety of intramuscular influenza vaccine in patients receiving oral anticoagulation therapy: a single blinded multi-centre randomized controlled clinical trial. *BMC Blood Disord*, 8, 1 (2008).
 27. Iorio A, Basileo M, Marcucci M et al. Influenza vaccination and vitamin K antagonist treatment: a placebo-controlled, randomized, double-blind crossover study. *Arch Intern Med*, 170(7), 609–616 (2010).
 28. van Aalsburg R, van Genderen PJ. Vaccination in patients on anticoagulants. *Travel Med Infect Dis*, 9(6), 310–311 (2011).
 29. Bauman ME, Hawkes M, Bruce A, Siddons S, Massicotte P. Immunizations in Children Requiring Warfarin Therapy. *J Pediatr Hematol Oncol*, 38(8), e329–e332 (2016).
 30. Ringwald J, Strobel J, Eckstein R. Travel and oral anticoagulation. *J Travel Med*, 16(4), 276–283 (2009).
 31. Caldeira D, Ferreira JJ, Costa J. Influenza vaccination and prevention of cardiovascular disease mortality. *Lancet*, 391(10119), 426–427 (2018).
 32. Marques Antunes M, Duarte GS, Brito D et al. Pneumococcal vaccination in adults at very high risk or with established cardiovascular disease: systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes*, 7(1), 97–106 (2021).
 33. Rodrigues BS, David C, Costa J, Ferreira JJ, Pinto FJ, Caldeira D. Influenza vaccination in patients with heart failure: a systematic review and meta-analysis of observational studies. *Heart*, 106(5), 350–357 (2020).
 34. Rodrigues BS, Alves M, Duarte GS, Costa J, Pinto FJ, Caldeira D. The impact of influenza vaccination in patients with cardiovascular disease: An overview of systematic reviews. *Trends Cardiovasc Med*, (2020).
 35. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Atrial fibrillation and the risk of 30-day incident thromboembolic events, and mortality in adults \geq 50 years with COVID-19. *Journal of Arrhythmia*, n/a(n/a)).
 36. England PH. COVID-19: The green book, chapter 14a. (Ed.^(Eds) (2020)
 37. Boulias C, Ismail F, Phadke CP et al. A Delphi-Based Consensus Statement on the Management of Anticoagulated Patients With Botulinum Toxin for Limb Spasticity. *Arch Phys Med Rehabil*, 99(11), 2183–2189 (2018).
 38. Fox E, Misko J, Rawlins M, Manning L. The risk of intramuscular haematoma is low following injection of benzathine penicillin G in patients receiving concomitant anticoagulant therapy. *J Thromb Thrombolysis*, 50(1), 237–238 (2020).
 39. Ruben FL, Jackson GG. A new subunit influenza vaccine: acceptability compared with standard vaccines and effect of dose on antigenicity. *J Infect Dis*, 125(6), 656–664 (1972).
 40. Caldeira D, Ferreira JJ, Pinto FJ. The era of the novel oral anticoagulants in Portugal. *Rev Port Cardiol*, 36(7-8), 577–578 (2017).
 41. Zhu J, Alexander GC, Nazarian S, Segal JB, Wu AW. Trends and Variation in Oral Anticoagulant Choice in Patients with Atrial Fibrillation, 2010-2017. *Pharmacotherapy*, 38(9), 907–920 (2018).
 42. Caldeira D, Rodrigues FB, Barra M et al. Non-vitamin K antagonist oral anticoagulants and major bleeding-related fatality in patients with atrial fibrillation and venous thromboembolism: a systematic review and meta-analysis. *Heart*, 101(15), 1204–1211 (2015).
 43. Jackson ML, Nelson JC, Chen RT, Davis RL, Jackson LA. Vaccines and changes in coagulation parameters in adults on chronic warfarin therapy: a cohort study. *Pharmacoepidemiol Drug Saf*, 16(7), 790–796 (2007).

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

