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

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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
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 hematoma. 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; anticoagulant 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

![Flowchart of studies selection](Fig. 1)
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                        | 30 days   |
| Lipsky 1984   | 21          | 62.5 years      | Warfarin      | Not reported                     | Influenza vaccine                           | 28-30 days|
| Kramer 1984   | 8           | Not reported    | Warfarin      | Not reported                     | Influenza vaccine                           | 21 days   |
| Gomolin 1985  | 15          | Not specified (geriatric) | Warfarin | Not reported                     | Influenza vaccine                           | 21 days   |
| Weibert 1986  | 13          | N/R             | Warfarin      | Not reported                     | Influenza vaccine                           | 14 days   |
| Bussey 1988   | 24          | 60.3 years      | Warfarin      | Not reported                     | Influenza vaccine                           | 4 months  |
| Arnold 1990   | 9           | 68 years        | Warfarin      | Not reported                     | Influenza vaccine                           | 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 Torres 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      | Atenocoumarol (98%), warfarin (2%) | Atrial fibrillation (70%), valvular heart disease (17%), ischemic heart disease (12%) | Influenza vaccine. Route: im vs. sc | 10 days   |
| Iorio 2010    | 104         | 71.3 years      | Warfarin      | Atrial fibrillation (54%), venous tromboembolism (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 haematoma 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

| Study | Incidence (%) | 95% Confidence interval | I² |
|-------|---------------|-------------------------|----|
| Patriarca (1983) | 0.44 | 0.00-1.60 | 0% |
| Lipsky (1984) | 1.515 (0.158, 12.983) | 5.15 |
| Kramer (1984) | 7.143 (0.750, 43.907) | 1.15 |
| Gomolin (1985) | 3.571 (0.374, 26.762) | 2.23 |
| Weibert (1986) | 4.167 (0.437, 30.125) | 1.92 |
| Bussey (1988) | 2.083 (0.218, 17.172) | 3.77 |
| Arnold (1990) | 5.556 (0.583, 37.119) | 1.46 |
| Raj (1995) | 1.220 (0.127, 10.669) | 6.38 |
| Delahunty (1998) | 3.846 (0.403, 28.344) | 2.08 |
| Pallini (2003) | 1.111 (0.196, 6.028) | 13.92 |
| Ballestor Torrens (2005) | 3.226 (0.572, 16.194) | 4.85 |
| MacCallum (2007) | 0.472 (0.049, 4.358) | 16.38 |
| Casajuana (2008) | 1.087 (0.192, 5.903) | 14.23 |
| Iorio (2010) | 0.481 (0.050, 4.439) | 16.08 |
| von Aslaburg (2011) | 2.941 (0.308, 22.923) | 2.69 |
| Baumann (2016) | 1.786 (0.187, 15.018) | 4.38 |
| Overall (I² = 0.00%, p = 0.883) | 0.457 (0.000, 1.527) | 100.00 |

Fig. 2 Forest plot showing the incidence of haematoma.
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/benefit ascertainments were recommended[30]. However, vaccines seem 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 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 regarding patients on stable anticoagulation therapy, supratherapeutic treatment should be avoided (by confirming non-supratherapeutic 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 that 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.

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Authors’ contributions
Conception and design: DC, FP, JF; 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.

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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 Daichi 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, Technimede, Merck Sharp & Dohme. FJP had consultant and speaker fees with AstraZeneca, Bayer, BMS, Boehringer Ingelheim and Daichi Sankyo. JF is a consultant for Ipsen, GlaxoSmithKline, Novartis, Teva, Lundbeck, Solvay, AbbV, BIAL, Merck-Serono, and Merz; received grants from GlaxoSmithKline, Grunenthal, Teva, and Fundação MSD.

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