The safety of continued oral anticoagulation therapy in joint injections and aspirations: a qualitative review of the current evidence

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- *Abstract (250 words, divided into Objectives, Methods, Results and Conclusion)*
- *Keywords (up to 10 - please note that the word count refers to individual words, not phrases)*
- *Key messages (up to 3, maximum 15 words each)*

Abstract:

Objectives: To quantify the safety of performing joint injections and aspirations in patients on long-term oral anticoagulants in terms of bleeding risk.
To identify, in those receiving vitamin K antagonists, what level of International Normalised Ratio (INR) is safest to perform joint procedures.

Methods: A systematic review of the medical literature was performed through electronic searches in Ovid (MEDLINE), EMBASE and the Cochrane Library.

English language publications within the last ten years, that were original reports of patients undergoing joint injections or aspirations performed on anticoagulant therapy, were included.

Results: Seven studies met inclusion criteria. Patients were taking a variety of anticoagulants: warfarin, acenocoumarol, and direct oral anticoagulants. Four cases of haemorrhage were reported following 5427 procedures, over a pooled 32-year period, across nine centres. INR values were available for three cases with bleeding complications: values were 1.9, 2.3 and 3.4.
The authors of all studies concluded that joint injection is safe in patients on anticoagulants. A variety of joints and approaches, reversal or withholding of anticoagulation and bridging with low molecular weight heparin did not appear to alter bleeding risk. Some studies included patients with renal or hepatic impairment, and those taking concomitant antiplatelets; nevertheless bleeding complications remained low.

Conclusion: Joint aspiration and injection are safe in patients taking anticoagulants. Anticoagulation should not be routinely discontinued in these patients, and decisions should be made on a case-by-case basis.
Due to low numbers of events, a recommended safe maximum INR value for joint procedures cannot be determined.

247 words

Keywords: joint injection, arthrocentesis, haemarthrosis, anticoagulation

Key messages:

1. The risk of haemarthrosis following joint procedures in patients on therapeutic anticoagulation is low.
2. Routine discontinuation of anticoagulants prior to joint procedures should be avoided.
3. Decisions regarding anticoagulants prior to joint procedures should be made on a case-by-case basis.

Introduction:

Joint injections and aspirations are common procedures carried out in hospital and community settings in both elective and emergency scenarios. The management of patients on long-term oral anticoagulation therapy poses a conundrum on how best to manage anticoagulation in the peri-procedural period.

The paucity of clinical trial data makes it difficult for clinicians to risk stratify bleeding risk, whereas the risk of thromboembolic events even on temporary discontinuation of anticoagulation is well-established (1). There is a growing body of evidence that the traditional practice of anticoagulation discontinuation, reversal with infusions of coagulation factors or bridging with heparin may no longer be necessary. Instead, ensuring that anticoagulation is within the therapeutic range for warfarin, and timing procedures during trough concentration periods for Direct Oral Anticoagulants (DOACs) may help minimise bleeding complications (2–4).

The ageing population, with increased requirement for oral anticoagulants including DOACs, makes this an important issue in today's approach to modern healthcare.

Objectives:

Primary outcome measure: To quantify the safety of performing joint injections and aspirations in patients on long-term oral anticoagulants in terms of bleeding risk.
Secondary outcome measures: To identify, in those receiving vitamin K antagonists, what level of International Normalised Ratio (INR) is safest to perform joint procedures.

Methods:

Search methodology: (See figure 1)

We performed a systematic review of the medical literature through electronic searches in Ovid (MEDLINE), EMBASE and the Cochrane Library. An independent search was performed by two assessors (RM) and (BG) based on the following search criteria:
Joint aspiration OR joint injection OR arthrocentesis OR joint tap OR synovial tap AND complications AND bleeding or coagulation OR INR OR coagulopathy.

A manual search of the referenced articles was also performed. Filters for inclusion were human only and English language papers.

Study selection:
To enable a balanced overview, all published literature within the last 10 years (January 2010-December 2020) was included.

Papers were selected for inclusion if they were original reports of patients undergoing joint injections or aspirations performed on anticoagulation therapy. There was 100% agreement with selection inclusion between the two authors.

Study Quality:
Observational studies are inherently heterogeneous in terms of trial design and outcome measures. Study quality was therefore assessed using the strengthening the reporting of observational studies in epidemiology (STROBE) criteria. This is an established qualitative methodology for assessing observational studies (5).

Data extraction and synthesis:
Data including number of patients, type of procedure (inclusive of joint type and approach), anticoagulant therapy, comorbidities, additional antiplatelet medication and complications were collated from each study by one author and cross-checked for accuracy by another.

Results:

Seven studies met our criteria, covering 5427 procedures, including 2971 in patients receiving oral anticoagulation. Of these, 1280 procedures were performed in patients on a DOAC (apixaban, dabigatran or rivaroxaban), 901 in patients on acenocoumarol and 790 in patients on warfarin. Four bleeding complications were observed in total over a pooled 32-year period, across nine centres. Table 1 summarises the studies, which are described in more detail below.

Qualitative summary of studies:

Nord *et al.* 2019 (6)**:**
This was a retrospective observational study over four years (2013-2017) of 571 procedures in 445 inpatients receiving joint or soft tissue corticosteroid injections at a single centre in Ontario, Canada. Adverse events were compared for patients taking Direct Oral Anticoagulants (DOACs) versus those not. DOACs included rivaroxaban (n=42 patients), dabigatran (n=12) or apixaban (n=36). Information about any concomitant antiplatelet medications was not documented. INR values were not assessed.

Injection sites were the knee (n=203 patients, 56 on DOACs), shoulder (n=131; 27 on DOACs), greater trochanter (n=36; 5 on DOACs) and other sites (n=75; 2 on DOACs).

The cohort taking DOACs were significantly older (mean age 80.1 versus 75.5 years, $p<0.001$) than the cohort not taking DOACs. There were otherwise no significant differences in demographics.

All injections were performed using landmark-based technique only. Data collection was via review of discharge summaries and progress notes from the time of injection to the day of discharge: note was made of bleeding events or other documented complications. All patients were assessed daily by the injecting physician and/or a nurse.

Outcome: No complications were documented for any patients, regardless of whether the patient was taking a DOAC. The authors concluded that joint and soft tissue injections are safe in patients taking DOACs.

Study quality: There is no specific statement declaring conflicts of interest. The study otherwise met STROBE criteria.

Noteworthy points: This was the only study of inpatients: daily assessment of all patients would likely increase detection rates of bleeding complications, compared to other studies assessing re-attendance to health services. It also provides a useful comparison between patients on DOACs versus those not on DOACs.

Bleeding risk generally increases with age (7); the fact that there were no bleeding complications in an older group of patients taking DOACs is further reassuring for the safety of joint injections in this context.

31% of the patients taking DOACs were taking prophylactic rivaroxaban (10 or 15mg daily) rather than a therapeutic dose of anticoagulation. The number of procedures in each sub-group of DOAC patients was not given, therefore we are unable to determine how many procedures were performed in patients taking a therapeutic DOAC dose.

Guillen Astete *et al.* 2017 (8)**:**
This study presents data of 117 procedures in 117 patients receiving joint injections over a four-year period (2019-2016) at a single centre in Madrid, Spain. It is not stated whether the study was prospective or retrospective. All patients had been taking dabigatran for at least one month. INR values were not given. No information was provided regarding any concurrent antiplatelet therapy. The mean patient age was 71 years.

Injections were given either to the knee (68 patients) or shoulder (49 patients). Ultrasound guidance was used for 23.5% of knee injections and 34.6% of shoulder injections. Arthrocentesis as well as injection was carried out for 71% of knee and 24% of shoulder injections.

The method used for identifying patients suitable for the study is not detailed. Complications were identified by assessing follow-up charts of the rheumatological and musculoskeletal unit of the Emergency Department of the hospital, as well as the registry of visits to the Emergency Department (exact follow-up duration is not specified).

Outcome: 11 of the 68 patients (16%) who had received injections to the knee re-presented to the Emergency Department within 15 days of their procedure: nine because of persistence of symptoms and two because of increased pain. Both patients with increased pain underwent ultrasound evaluation: one was found to have a haemarthrosis (managed conservatively). Seven of the 49 patients (14%) who had received shoulder injections re-presented to the Emergency Department within 15 days of their procedure, all due to persistence of symptoms. None of the patients who re-presented required hospitalisation, and there were no presentations due to complications beyond a period of 15 days after the procedure. None of the patients in whom ultrasound guidance had been used re-presented to the hospital. The authors concluded that joint injection was safe in patients taking dabigatran.

Study quality: The method of recruitment to the study and the exact duration of follow-up was not specified. There was no specific statement declaring conflicts of interest. The study otherwise met STROBE criteria.

Noteworthy points: Whilst this is a small study, there was a follow-up period of at least 15 days.
Whilst in this study ultrasound guidance was associated with lower re-presentation rates, none of the other studies found a difference in complication or re-presentation rates according to the use of ultrasound guidance.

Yui *et al.* 2017 (9)**:**

This study presents data of 1050 procedures in 483 patients at a single centre: The Mayo Clinic, Minnesota, USA. A retrospective review of arthrocentesis and joint injections took place of all patients attending for these procedures over a six-year period (2010-2016) in the outpatient or Emergency Department setting. Suitable patients were identified using the electronic coding system. Patients were all taking DOACs (rivaroxaban, apixaban or dabigatran); some were taking concomitant aspirin (21.5%) or clopidogrel (1%). Patients were excluded if later manual review of the clinical notes revealed that anticoagulation therapy was withheld before the procedure. INR was measured for 303 patients within 90 days prior to the procedure. Mean patient age was 75 years.

Injection was directed by the treating physician using either landmark technique (48.4%), ultrasound (48.2%) or fluoroscopic visualization (3.4%).

Outcomes of bleeding complications were defined as clinically important bleeding leading to outpatient clinic or emergency department visits, or hospitalisation within 14 days after the procedure.

52% of injections took place in patients on rivaroxaban, 31% in patients on apixaban and 17% in patients on dabigatran. The mean INR in this study was 1.2 (range 0.5–3.6; the reasons for raised INR values were not detailed).

The commonest sites of injection were the knee (442), shoulder (142), hip joint or bursa (207) and hand or wrist (103).

Outcome: No bleeding complications occurred. The authors concluded that DOACs can be safely continued for patients undergoing joint or bursa aspirations and injections.

Study Quality: There is no specific statement declaring conflicts of interest, but the study otherwise met STROBE quality criteria.

Noteworthy points:
This was a relatively large study compared to others in this review. A proportion of patients had renal (4.7%) or hepatic (0.4%) dysfunction, or were taking concurrent antiplatelets; nevertheless there were no bleeding complications.

INR was not assessed for all patients, however of those with INR measured, there were no bleeding complications even with INR>3.

Bashir *et al.* 2015 (10)**:**

This study presents data of 2084 procedures in 1714 individuals from a single centre: Guy's & St Thomas' NHS Foundation Trust, London, UK. It was a retrospective analysis of all patients undergoing joint injection over a five-year period (2008-2013). Suitable patients for inclusion were identified from electronic coding of outpatient records. 41 patients were taking warfarin (86 injections); for these patients INR was checked within two weeks prior to the injection. No information was given about any concurrent antiplatelet therapy. The mean age for the cohort taking warfarin was 71 years; the mean age for those not on warfarin was not provided.

Patients were reviewed for any evidence of bleeding by clinical examination (for landmark-guided injections) or ultrasound 15 minutes post-procedure (for ultrasound-guided injections). Complications (bleeding, infection or acute injection-related pain) occurring up to four weeks post-procedure were assessed through Primary Care and Emergency Department records (including imaging results).

Both landmark- and ultrasound-guided procedures were performed (however the numbers in these groups were not stated). The mean INR was 2.77 (range 1.7 – 5.5; there was no explanation for the raised INR values). 1142 injections were given to the shoulder and 942 to the knee.

Outcome: There were no cases of haemarthrosis. The authors concluded that their practice would be to continue warfarin to maintain a therapeutic INR when performing joint injections.

Study Quality: There is no specific statement declaring conflicts of interest, but the study otherwise met STROBE criteria.

Noteworthy points: This was the largest study included in our review, although only a small proportion of procedures (4%) were in patients taking warfarin. The study included post-procedure ultrasound for all ultrasound-guided procedures, which would likely increase the detection rate of haemarthrosis in these patients. Follow-up was via Primary Care and Emergency Department records, which would also likely increase the detection rate of complications compared to other studies looking at re-presentation to the Emergency Department only.

Guillen Astete *et al.* 2015 (11)**:**

This was a retrospective analysis of 901 procedures in 760 patients undergoing arthrocentesis or joint injections over a four-year period (2009-2013) at three different centres in Madrid, Spain. The majority of the procedures (804) were performed in the Emergency Department of the Hospital Universitario Ramón y Cajal. All patients were anti-coagulated with Acenocoumarol. INR was recorded within 24 hours prior to the procedure being performed.

It is not specified how the patients were identified for study inclusion. Patient analysis was grouped into an INR cohort <2.0 and >2.0. 51% of the cohort with INR <2.0 were taking concurrent antiplatelet therapy, compared with 55% of the cohort with INR >2.0. Mean age of the cohort with INR <2.0 was 68 years, compared with 71 years for the cohort with INR >2.0.

Clinically significant pain or bleeding were noted following the procedure. Clinically significant bleeding was defined as “bleeding during the period immediately following the procedure that required reversal of anti-coagulation, hospitalization or surgery”. It was defined as “early” (within 24 hours of procedure) or “late” (between 24 hours and 30 days following the procedure).

Procedures included standard landmark techniques and ultrasound-guided procedures (12%).

268 (29.7%) of patients had INR <2.0 and 633 (70.3%) had INR >2.0. The median INR for >2.0 cohort was 2.9 (range 2.0-8.1). No reason was given for cases of raised INR. 58% of injections were performed on the knee, 40% on the shoulder and 2% on other joints. 14% of procedures were aspiration only, 72% of procedures infiltrations only, and 14% aspiration and infiltration.

Outcome: Two cases of haemarthrosis were identified. One was due to a knee arthrocentesis (INR 3.4) occurring within 72 hours of the procedure, and the second was due to a shoulder injection (INR 1.9) occurring within 24 hours of the procedure. There was no statistically significant difference in complications between the two cohorts. The authors therefore concluded that INR>2 does not increase the risk of bleeding in joint procedures in those on Acenocoumarol.

Study Quality: The method for identifying patients for study inclusion was not stated, but the study otherwise met STROBE criteria.

Noteworthy points: This is the only study to assess the vitamin K antagonist Acenocoumarol. (The half-life of acenocoumarol is 10 hours versus 48 hours for warfarin.)

Conway *et al.* 2013 (12)**:**

This was a study of 64 procedures in 39 patients over a one-year period at a single centre: St James's Hospital, Dublin, Ireland. There was six months of retrospective (18 patients, 32 procedures) and six months of prospective (21 patients, 32 procedures) data collection. All patients were taking warfarin.

The initial six-month retrospective review regarded review of the existing practice: to discontinue warfarin five days prior to an elective joint or soft tissue injection and bridge with low molecular weight heparin (which was omitted on the day of the procedure). Warfarin was then restarted the day following the procedure, with bridging with low molecular weight heparin until therapeutic INR was achieved.

The subsequent six-month prospective study was conducted following introduction of a new anticoagulation protocol allowing the procedure to go ahead on warfarin with an INR <3.0.

For both cohorts, complications within four weeks of the procedure were noted by assessing medical records and telephone calls to the helpline number.

Baseline characteristics were comparable between the two groups: mean age was 77 years in the retrospective cohort compared with 74 years in the prospective cohort. Any concurrent antiplatelets or non-steroidal anti-inflammatory drugs (NSAIDs) were continued in both cohorts. Three patients

from the retrospective cohort were taking aspirin and two were taking NSAIDs; one from the prospective cohort was taking aspirin and one NSAIDs. No patients were taking concomitant clopidogrel.

All procedures were landmark-based. In the retrospective cohort, there were 30 joint injections (80% knee, 16.7% shoulder, 3.3% elbow) and 2 soft tissue injections. In the prospective cohort, there were 27 joint injections (88.9% knee, 3.7% each: shoulder, elbow and metatarsophalangeal joint) and 5 soft tissue injections.

Outcome: There was no reported haemarthrosis in either group. The authors concluded that it is safe for patients taking warfarin who have a therapeutic INR to undergo joint and soft tissue injections.

Study Quality: Met STROBE quality criteria.

Noteworthy points: Although this was a small study, it is the only study to compare retrospective and prospective data following a change in practice.

Ahmed and Gertner 2012 (13)**:**

This was a retrospective chart review of 640 arthrocentesis and joint injection procedures performed in 514 consecutive patients anticoagulated with warfarin over an eight-year period (2001-2009) at a single centre: HealthPartners Medical Group and Regions Hospital, Minneapolis, USA. Data from charts was assessed by three individuals independently. The HealthPartners Research Foundation Grant funded the study.

Two cohorts of patients were reviewed: group A (n = 456 procedures) with continuation of warfarin and group B (n=184) where procedures were only carried out if INR was <2.0. In group B warfarin was either discontinued 3-5 days prior to procedure, or INR was normalized prior to the procedure with coagulation factors or vitamin K. No bridging therapy was used and warfarin was restarted on the evening of the procedure. Any antiplatelet therapy was continued in both groups.

Baseline characteristics were comparable between both groups: mean age was 73 years in group A compared with 72 years in group B. 43 individuals in group A were taking concurrent aspirin and seven concurrent clopidogrel; for group B these figures were 53 and 11 individuals respectively.

INR values were reported within 24 – 48 hours prior to the procedure. Arthrocentesis and joint injection were performed by standard landmark techniques with local anesthesia.

Clinically significant bleeding was defined as bleeding during the periprocedural period requiring reversal of the anticoagulation, prolonged

haemostasis to stop bleeding, a need for hospital admission or surgical evacuation of the joint, or resulting in a delay in discharge. Complications were defined as “early” (within 24 hours following the procedure) or “late” (between 24 hours and 30 days following the procedure).

The mean INR in group A was 2.7 (range 2.0 – 7.8), and 103 (22.5%) of procedures in this group had an INR >3.0. No reason was given for high INR values. 13 injections were given to the hip; the remainder were given to the knee or shoulder. 90% of procedures involved injection only, 4.4% aspiration only, and 5.6% both injection and aspiration.

Outcome: One procedure in group A resulted in a clinically significant bleed, presenting with pain within 24 hours of procedure (INR 2.3). There were no bleeding complications in group B. The difference in bleeding complication rates between the two groups was not significant (p=0.708). The authors concluded that arthrocentesis and joint injections in patients on warfarin with therapeutic INR are safe procedures.

Study Quality: All STROBE criteria were met.

Noteworthy points: Along with the study by Conway et al. (12), this was the only other study to assess outcomes in patients whose anticoagulation had been held (or INR normalized). The cohort with INR>2.0 was over twice the size of the cohort with INR<2.0; nevertheless there was only one bleeding complication in the former group, which was not statistically significant.

Discussion:

Practice regarding continuation of anticoagulant therapy and monitoring of INR prior to joint procedures varies considerably. Discontinuation of anticoagulant therapy increases the risk of significant thromboembolic complications and therefore should be approached with careful thought (1,14,15)**.**

There is no level 1 evidence data available for joint procedures and anticoagulation. This review discusses the evidence published in cohort studies within the last decade, to facilitate clinical practice, based on the best evidence available. Quality assessment of each study was performed using the STROBE criteria.

All the studies in our review found a low risk of haemorrhage with joint injection procedures (four cases of haemorrhage in 5427 procedures). The authors of each study concluded that joint injection is safe in patients on anticoagulation. A variety of joints, landmark approaches, ultrasound and fluoroscopic guidance, prior infiltration with local anaesthetic and bridging with low molecular weight heparin did not appear to alter the risk of bleeding complications. Some authors demonstrated safety of joint procedures with

renal and hepatic impairment and continuation of antiplatelet medication, although the number of patients for whom this data was available was small.

Whilst INR was not measured for all patients in all studies in this review, the value of the INR in isolation does not appear to be associated with bleeding risk. Indeed, haemorrhagic complications were also demonstrated in patients with INR <2. Furthermore, the studies comparing outcomes in patients receiving joint injections who continued warfarin with those whose warfarin was discontinued, failed to demonstrate any difference in outcomes between these cohorts. Due to the low incidence of these events, it is not possible to make definitive recommendations on INR values below which joint procedures would be deemed safe. Particularly with the increased use of DOACs, in which INR variations are difficult to interpret (16,17), measuring INR would not seem useful in informing safety of joint injections.

Interestingly a wider review of the literature demonstrated that arthrograms (4), hand and wrist surgery (18) for Dupuytren's contracture and carpal tunnel decompression can all be safely carried out without alteration to the anticoagulation regimen (19).

Conclusion:

The risk of haemarthrosis in joint procedures in patients on anticoagulation appears to remain low regardless of INR value, technique or site injected. The routine discontinuation of anticoagulation should therefore be avoided and decisions should be taken on a case-by-case basis, dependent on overall risk factors for bleeding.

Future work should look more closely at additional risk factors such as antiplatelets, platelet function and hepatic function, to enable a better understanding of those at risk of haemarthrosis.

3499 words (word limit 3500 words)

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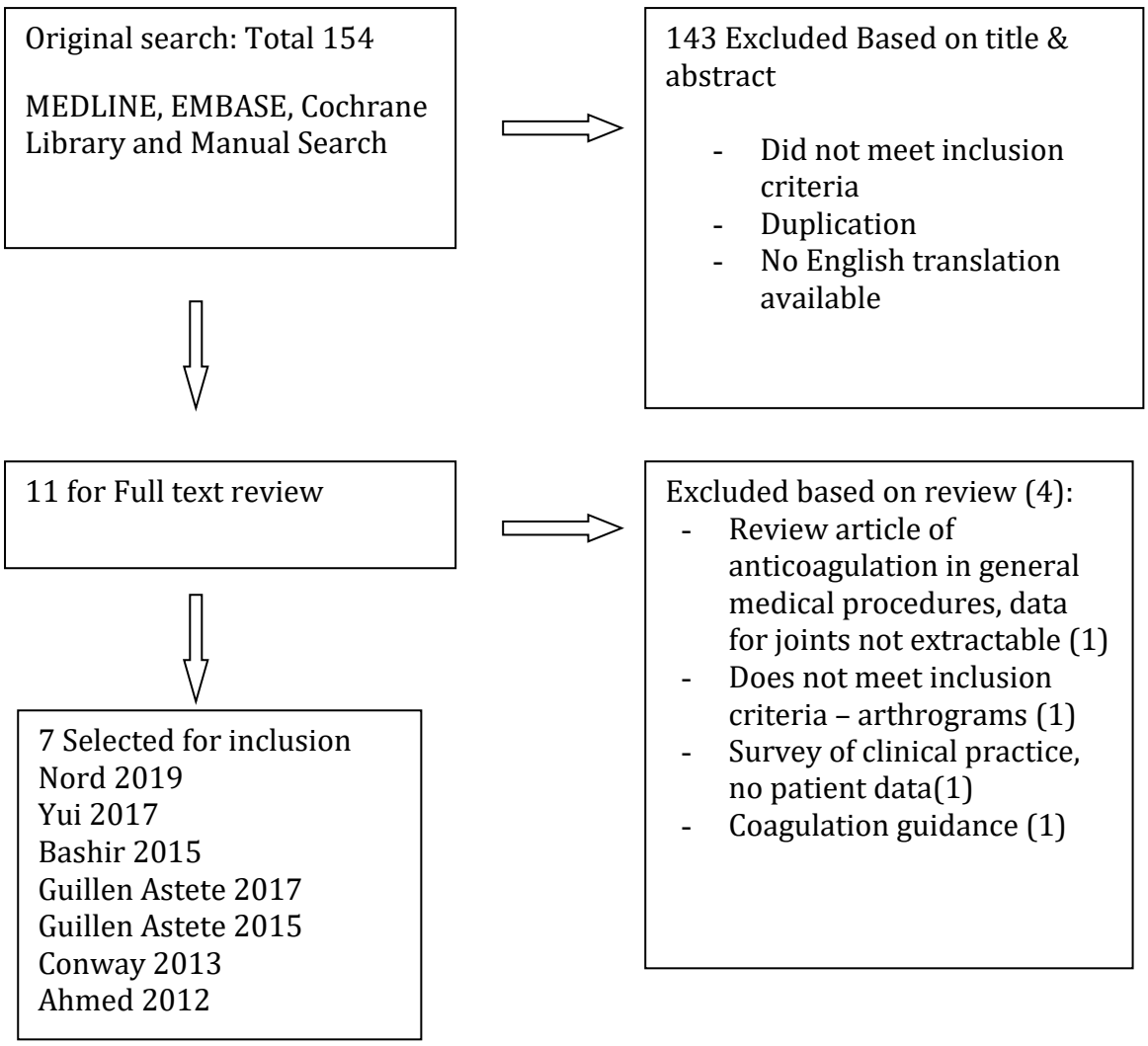
Figure 1 : Diagrammatic representation of search methodology



Study	Duration of study (years)	No. of procedures (no. of patients)	Injection sites	Anticoagulants prescribed and any concomitant antiplatelets	Anticoagulant therapy held pre-procedure?	INR values assessed?	INR values (if assessed)	Follow-up period	No. of bleeding complications
Nord et al. 2019	4	571 (445)	Knee, shoulder, greater trochanter	90 patients on DOACs (113 procedures): Rivaroxaban (prophylactic/therapeutic), Dabigatran, Apixaban.	No	No	N/A	Duration of inpatient stay (no details of average/ range of duration)	0
Guillen Astete et al. 2017	4	117 (117)	Knee, shoulder	Dabigatran (all patients)	No	No	N/A	At least 15 days, but exact duration not specified	1
Yui et al. 2017	6	1050 (483)	Knee, shoulder, hip joint or bursa, hand or wrist	All patients on DOACS: Rivaroxaban, Apixaban, Dabigatran. 21.5% concomitant aspirin, 1% concomitant clopidogrel	No	Yes - for 303 of 483 pts	Mean = 1.2 (range 0.5 – 3.6)	14 days	0
Bashir et al. 2015	5	2084 (1714)	Knee, shoulder	Warfarin: 41 patients (86 procedures)	No	Yes: pts on warfarin	Mean = 2.77 (range 1.7 - 5.5)	4 weeks	0
Guillen Astete et al. 2015	4	901 (760)	Knee, shoulder	Acenocoumarol (all patients)	No	Yes	268 pts: INR <2.0 633 pts: INR >2.0 (median 2.9 (range 2.0-8.1)).	30 days	2: knee arthrocentesis (INR 3.4) within 72 hours, shoulder injection (INR 1.9) within 24 hours
Conway et al. 2013	1	64 (39)	Knee, shoulder, elbow, metatarsophalangeal, soft tissue	Warfarin (all patients). 8% also taking aspirin	Yes: retrospective cohort (50% of total procedures)	Yes	Retrospective cohort: mean INR 1.2 (range 1.1 - 1.5). Prospective cohort: mean INR 2.4 (range 2.1 - 2.6).	4 weeks	0
Ahmed and Gertner 2012	8	640 (514)	Knee, shoulder, hip	Warfarin (all patients). 19% concomitant aspirin, 3.5% concomitant clopidogrel	Yes, for one cohort – group A (29% of total procedures)	Yes	Mean INR in group A (warfarin not held): 2.7 (range 2.0 – 7.8)	30 days	1: INR 2.3 (in cohort where warfarin not held)

Table 1: Summary of studies