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New oral anticoagulants for venous thromboembolism prophylaxis. A Bruyère Rapid Review

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Key messages

New oral anticoagulants (NOACs) also known as Direct-acting oral anticoagulants (DOACs) are cost-effective and easier to administer than low molecular weight heparins (LMWHs). Antidotes for reversing the anticoagulant effect in case of severe bleeding exist for LMWHs. Three antidotes for NOACs are under development and one (idarucizumab (PRAXBIND) has recently been approved for dabigatran. The guideline recommendations were based on studies conducted before the availability of an antidote.

- The decision and choice of venous thromboembolism (VTE) prophylaxis should be based on patient risk assessments of VTE risk and risk of bleeding.
- New oral anticoagulants are recommended for VTE prophylaxis in patients with hip or knee joint replacement surgery provided they have no contraindications.
- There was insufficient evidence to support the use of NOACs instead of LMWHs in other patient populations.
- Although NOACs are cost-effective, the choice of VTE prophylaxis should be patient-centred, considering each patient's needs, preferences, and values.

Executive summary

In this rapid review we sought to find evidence of the effectiveness, cost-effectiveness and safety of new oral anticoagulants (NOACs) versus low molecular weight heparins (LMWHs) for venous thromboembolic (VTE) prophylaxis in all patient populations across Bruyère Continuing Care (BCC) and whether the use of NOACs would achieve cost-savings for Bruyère over the use of dalteparin, a LMWH.

VTE is the formation of a blood clot in a vein. The clot may get detached and travel in the blood (embolism) to other parts of the body. Many cases of VTE are preventable with anticoagulants alone, or in combination with general methods (e.g. mobilization and leg exercises), and mechanical methods (e.g. graduated compression stockings). Dalteparin is currently the treatment of choice for VTE prophylaxis at BCC as recommended by clinical practice guidelines. The new oral anticoagulants are increasingly being used for VTE prophylaxis in patients with atrial fibrillation and to a lesser extent for VTE prevention after knee or hip replacement surgery in geriatric rehabilitation.

Dalteparin is administered parenterally and is more expensive per dose (considering prophylaxis-related drug costs) than NOACs. There is a risk of bleeding with anticoagulant prophylaxis which may be severe and life-threatening. Antidotes for LMWH exist and only one antidote to control bleeding with dabigatran exists. Antidotes for other NOACs, rivaroxaban and apixaban, are under development.

The choice of treatment therefore involves a trade-off between decreased risk of VTE vs increased bleeding risk and burden of treatment. Patient centered care requires consideration of patient preferences in treatment choices and Bruyère is committed to providing compassionate, excellent care according to the needs of each individual. It is therefore important for clinicians to discuss the complications of VTE, potential risks and benefits of VTE prophylaxis with the patients so that they can make informed choices and develop an adequate treatment plan, taking into account the patients' needs and preferences.

We searched for systematic reviews, health technology assessments or economic evaluations and guidelines and found and screened 2000 potentially relevant articles. Forty met our inclusion criteria: 22 reviews focused on the effectiveness and safety of NOACs versus LMWHs; 10 economic evaluations assessed the cost-effectiveness of NOACs versus LMWHs with three done in Canada; and eight guidelines addressed VTE prophylaxis with NOACs.

Based on our findings, we suggest the following:

1. Patient risk assessment for VTE risk and risk of bleeding should be done before deciding whether or not VTE prophylaxis should be used, and which type. For VTE risk assessment, additional risks such as the clinical condition or reason for hospitalization should also be taken into account. When assessing patients for risk of bleeding, a balance between actual and perceived risk should be considered as well as contraindications for prophylaxis.

2. Various guideline groups recommend thromboprophylaxis with either NOACs or LMWH in patients including elderly with hip or knee joint replacement surgery, provided patients have no contraindications.

3. For patients undergoing orthopedic surgery who refuse injections, NOACs is recommended.

4. NOACs are more cost-effective than LMWH for patients with hip or knee joint replacement even when risk of major bleeds is considered.

5. For the medically ill, there is higher risk of bleeds (4 per 1000, from 1-7 more per 1000; high certainty of evidence) with NOACs and guideline groups recommend LMWH or unfractionated heparin for this population.

6. For palliative care, we found no systematic reviews but two guidelines recommend the use of LMWH for thromboprophylaxis.

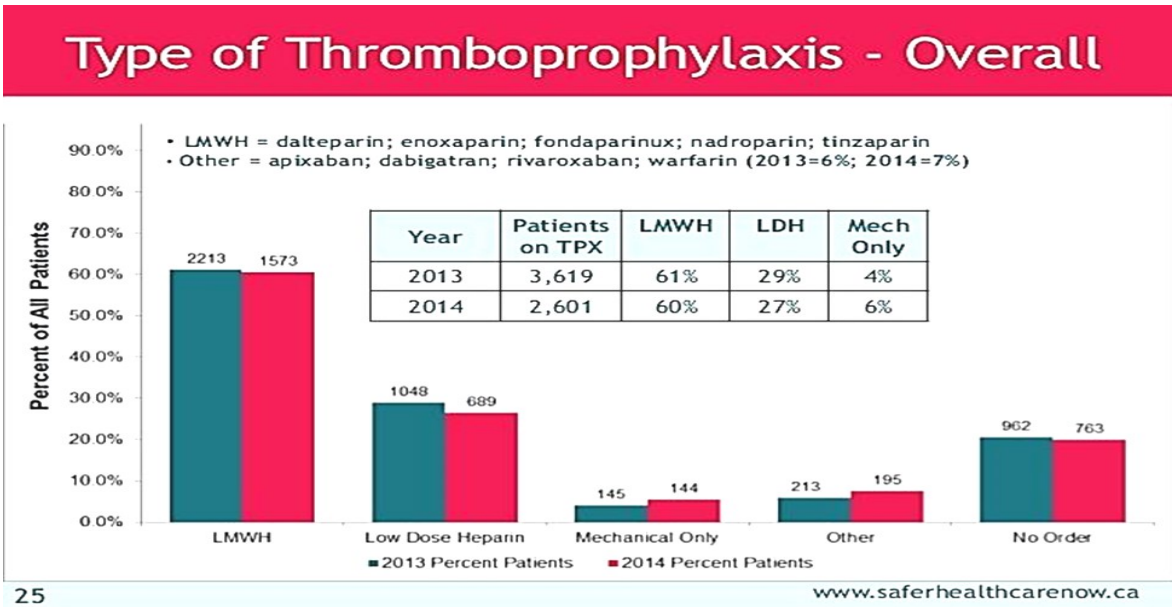
Background

The issue

Venous thromboembolism (VTE) is the formation of a blood clot in a vein. The clot may get detached and travel in the blood (embolism) to other parts of the body. The incidence for venous thromboembolism is 1 per 1000 person- years in the community (1-3) and 96 per 1000 person-years in hospitalized patients (2). Common risk factors are: increasing age, active or occult malignancy, some forms of cancer chemotherapy, previous VTE, varicose veins, obesity, prolonged severe immobility (prolonged bed rest, immobilization in a plaster cast or brace or prolonged travel resulting in limited movement and subsequent venous stasis), use of oestrogen-containing hormone replacement therapy or oral contraceptives in women, inherited or acquired thrombophilia, heart failure, myocardial infarction, stroke with immobility, acute inflammatory bowel disease, severe acute infection, nephrotic syndrome, pregnancy and the puerperium, trauma, anesthesia and surgery(17, 18).

Many cases of VTE are preventable with anticoagulants alone, or in combination with general methods (e.g. mobilization and leg exercises), and mechanical methods (e.g. graduated compression stockings). Anticoagulant prophylaxis is recommended in patients with no contraindications such as active bleeding, previous major bleeding, known untreated bleeding disorder, severe renal or hepatic disorder, and thrombocytopenia. The standard anticoagulant prophylaxis is with the indirect thrombin inhibitor: unfractionated heparin(17), and low molecular weight heparin (LMWH, such as dalteparin, enoxaparin, nadroparin, and tinzaparin)(3, 18), fondaparinux, or vitamin K antagonists (VKAs) such as warfarin (3, 19-21). Direct-acting oral anticoagulants (DOACs) also known as new oral anticoagulants (NOACs) have been approved in recent years for VTE prophylaxis in Canada(22). These new oral anticoagulants (NOACs) include the direct thrombin inhibitor dabigatran, and the direct factor Xa inhibitors rivaroxaban and apixaban(3, 22) and have been studied in certain patient populations only. They may have the advantage of easier administration, orally instead of injections and requiring no dose adjustment and monitoring, but reversing their anticoagulant effects in case of major bleeding is a concern(15, 16). Three antidotes are under development and one has recently been approved for dabigatran. LMWHs are the most often used type of VTE prophylaxis in Canada as shown in Figure 1(23). These data show a slight decrease in LMWH usage from 2013 to 2014, and this trend may continue with an increase in the usage of other anticoagulants (apixaban, rivaroxaban, dabigatran). They may cause major bleeding as well but their effects are generally reversible.

Figure 1: Types of VTE prophylaxis used in Canada: 2013-2014



Context

Dalteparin, a low molecular weight heparin, is currently the treatment of choice for venous thromboembolic prophylaxis at Bruyère Continuing Care (BCC) as recommended by clinical practice guidelines(4-11). The new oral anticoagulants are increasingly being used at BCC for VTE prophylaxis in patients with atrial fibrillation mostly, and also for VTE prevention after knee or hip replacement surgery in geriatric rehabilitation.

Dalteparin is administered parenterally and is more expensive per dose (considering prophylaxis-related drug costs) than new oral anticoagulants(12, 13). It is the drug with the highest expenditure across inpatient programs in BCC.

Serious bleeding may occur with anticoagulant prophylaxis. This side effect is considered reversible with traditional anticoagulants such as warfarin, unfractionated heparin, and low molecular weight heparin. An antidote has recently been approved for dabigatran but there is none yet for rivaroxaban or apixaban. However, all episodes of serious bleeding at BCC would need to be transferred to acute care for urgent management. SVH estimates that there are fewer than 5 cases per year transferred to acute care from SVH. It is unclear if new oral anticoagulants could be recommended for VTE prophylaxis in all patient populations at BCC.

Objective

By comparing the effectiveness (including cost-effectiveness) and safety of new oral anticoagulants versus low molecular weight heparins for preventing venous thromboembolism (VTE) in adult patients in subacute care, this review will address the following questions:

- Will the use of NOACs for VTE prophylaxis across all patient populations at BCC have a financial advantage over the use of dalteparin?
- Does the lack of antidotes to address the risk of serious bleeding risk with NOACs preclude their use across all patient populations at BCC?

Methods

Eligibility and selection criteria

We used the PICO (population, intervention, comparison, and outcome) framework to define the eligibility criteria.

Population: subacute care patients 18 years or older – palliative care, geriatric and stroke rehabilitation, and complex continuing care (mixed population)

Interventions: Direct-acting Oral Anticoagulants (DOACs) or New Oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban for prophylaxis of VTE.

Treatment with NOACs for stroke prevention was not included.

Comparison: Low molecular weight heparin such as dalteparin, enoxaparin, tinzaparin for prophylaxis of VTE.
We excluded articles that compared NOACs with other anticoagulants such as warfarin, antiplatelet drugs.

Outcomes: morbidity e.g. venous thromboembolism events (DVT, PE), bleeding events, mortality, cost-effectiveness (hospital perspective), patient preference related to inconvenience of injections.

Bleeding events include major bleeding as well as clinically -relevant non-major bleeding events (such as nose bleed, gastrointestinal bleed, bleeding gums, hematuria, spontaneous skin hematoma, bleeding leading to hospitalization or surgery).

Major bleeding is defined in some of the included articles (24-27) as a fall in hemoglobin of at least 20 g/L or transfusion of at least two units of red cells, or symptomatic bleeding into a critical area or organ, such as intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome, or bleeding leading to death(28).
Clinically-relevant non-major bleeding is defined as any sign or symptom of hemorrhage that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: requires medical intervention by a healthcare professional, or leads to hospitalization or increased level of care, or prompts a face to face evaluation(29)

We excluded systematic reviews and clinical guidelines if they focused on treatment of acute venous thromboembolism, acute settings (e.g. emergency), outpatients, children or pregnant women. We also excluded articles that compared NOACs with other anticoagulants such as warfarin, antiplatelet drugs.

Literature search

We searched the Trip Database on February 9 2016 and retrieved 383 articles. We also searched for relevant systematic reviews, health technology assessments, economic evaluations and clinical practice guidelines in PubMed, the Cochrane Library (DARE and HTA) up to March 14 2016 and retrieved 1617 articles (see Appendix 1 for the full search strategy).

Relevance assessment

We screened the search results and reference lists of eligible articles in duplicate. Disagreements were resolved by consensus. We only considered articles in English or French and identified 40 articles (32 systematic reviews, health technology assessments (HTAs) and economic evaluations, and eight guidelines) that met our inclusion criteria.

Quality assessment and grading of evidence

We assessed the quality of the included reviews and guidelines using AMSTAR and AGREE II respectively (see Appendix 2). The quality of the included reviews ranged from low to high with an AMSTAR score of 2 to 10 out of 11. The AGREE II score for the guidelines was good with scores ranging from 125 to 148 out of 168.
We also graded the quality of the evidence using GRADE (see Appendix 3). These ranged from low to high.

Evidence review

Evidence from systematic reviews and HTAs or economic evaluations

We identified 32 systematic reviews and HTAs or economic evaluations on new oral anticoagulants for the prevention of venous thromboembolism in hospitalized adult patients. We considered the three new anticoagulants approved in Canada (dabigatran, apixaban, and rivaroxaban) compared with low molecular weight heparins (LMWHs such as dalteparin, enoxaparin, or tinzaparin).

Of the 22 systematic reviews that focused on the effectiveness of NOACs, nine reviews assessed direct factor Xa inhibitors (rivaroxaban or apixaban)(30-38), two assessed direct thrombin inhibitor (dabigatran)(39, 40) and 11 assessed both types of NOACs(24, 25, 27, 41-48) compared with LMWHs. Four recent systematic reviews(25, 27, 46, 48) considered only the recommended prophylactic doses of the NOACs whereas others included studies assessing other doses as well. Clinical categories rather than hospital settings were considered. Seventeen were in patients who had orthopedic surgery (hip/knee joint replacement)(24, 25, 30, 31, 33-44, 46), two in elderly patients older than 65 years(27, 48), one in cancer patients(32), one in patients with renal impairment(45) and one in a mixed population (surgery and medically ill)(47).

Ten articles focused on cost-effectiveness of NOACs compared with LMWHs; three in Canada((13, 49, 50), two each in Norway(41, 51) and the UK(52, 53); and one each in Australia(54), Ireland(55), and the US(56). We decided to focus on the three cost-effectiveness analyses done in Canada. Two assessed the cost-effectiveness of rivaroxaban compared to enoxaparin or dalteparin based on Ontario data(13, 49) and the other assessed apixaban compared to enoxaparin based on Quebec data(50). Both were in patients who had hip/knee joint replacement surgery. Cost-effectiveness evaluations have not been done in other patient populations.

Evidence from clinical practice guidelines

We identified eight clinical practice guidelines on new oral anticoagulants for the prevention of venous thromboembolism in hospitalized adult patients. Three were from the US(4, 9, 10), two from Scotland(6, 7), and one each from Canada(11), Australia(8) and the UK (5). They all focused on clinical categories of patients (surgery and medically ill) rather than hospital settings. These guidelines were based on studies conducted before the availability of an antidote for NOACs.

Synthesis of findings

Clinical categories rather than hospital settings were considered. We focused on the findings from the reviews with the highest quality, the most recent search date, the recommended prophylactic doses (10 mg daily for rivaroxaban, 2.5 mg twice daily for apixaban, and 220 mg daily for dabigatran) and the outcomes of interest. Older systematic reviews included studies assessing other doses than the current recommended prophylactic doses.

No article assessed inconvenience of injections as an outcome. Bleeding events and VTE events were classified inconsistently across the articles. For example, most articles presented overall bleeding risk including both major bleeding and clinically relevant non-major bleeding events. Some articles also presented VTE events and mortality as a composite outcome. In all the included systematic reviews effectiveness was assessed by VTE events and all-cause mortality and safety by bleeding. One review also considered arterial thrombosis and assessed myocardial infarction and ischemic stroke as primary outcomes(57).

Findings from systematic reviews and HTAs or economic evaluations

Results are grouped by the type of patients: 1) orthopedic surgery patients, 2) elderly patients with hip or knee joint replacement surgery, 3) patients with cancer, 4) patients with renal impairment, 5) mixed population of patients (medically ill with infectious disease, cardiovascular disease and inflammatory disease).

ORTHOPEDIC SURGERY PATIENTS

For VTE events and all-cause mortality, there were no important differences between NOACs and LMWH (0 fewer events per 1000 patients, high certainty evidence). For bleeding (including major bleeding and clinically relevant non-major bleeding events), there were no important differences between NOACs and LMWH (1 more event with NOACs per 1000 patients, moderate certainty evidence).

There are no head-to-head direct comparisons of specific NOACs. However, a network meta-analysis used indirect evidence to compare different NOACs to each other and enoxaparin(46). These analyses showed that rivaroxaban is more effective at preventing VTE (56 fewer (70 fewer to 34 fewer) events per 1000 patients compared to enoxaparin) (See Appendix 4A for details).

Table 1: Summary of findings for NOACs vs LMWH in orthopedic surgery patients

Population	Outcome	# participants, # studies	Risk with LMWH	Absolute difference (95% CI) (Risk with NOACs)	Relative effect	NNT	Quality (GRADE)
NOACs vs enoxaparin							
Patients with hip/knee joint replacement surgery	VTE events	26055 (8 studies)	5 per 1000 patients	0 fewer (2 fewer to 2 more) events per 1000 patients	**RR 0.97** [0.69, 1.36]	NA	High
Patients with hip/knee joint replacement surgery	Overall bleeding risk (including major bleeding and clinically relevant non-major bleeding events)	34056 (11 studies)	39 per 1000	1 more (3 fewer to 5 more) events per 1000 patients	**RR 1.03** [0.92, 1.14]	93 (66 to 278)	Moderate
Patients with hip/knee joint replacement surgery	Mortality	29357 (11 studies)	1 per 1000	0 fewer (0 fewer to 1 more) event per 1000 patients	**RR 1.00** [0.56 to 1.77]	NA	High

Data from Cui 2014 and Squizzato 2015. Control event rate from LMWH group.

Cost-effectiveness in the Ontario setting was assessed in two studies using data from the provincial government and hospital perspective. Rivaroxaban was more cost-effective compared to enoxaparin after hip and knee joint replacement surgery(49)(44). Rivaroxaban was associated with an overall cost savings of C$296.95 per patient who had hip replacement surgery, compared with enoxaparin (Table 2a). The cost savings per patient who had knee replacement surgery was up to C$150.44 (Table 2b). Factors contributing to the cost-effectiveness include fewer symptomatic VTE events with rivaroxaban leading to a higher number of QALYs gained; the reduction of treatment-related monitoring needs and the reduction in long term complications that would impact upon healthcare resources.
When rivaroxaban was compared to dalteparin in a sensitivity analysis, similar results were found with cost savings of C$374.17 in patients who had hip replacement surgery and C$180.83 in patients who had knee replacement surgery.

Table 2a: Costs and cost-effectiveness of rivaroxaban vs enoxaparin following total hip replacement surgery in the Ontario setting

	Rivaroxaban 35 days vs enoxaparin 35 days			**Rivaroxaban 35 days vs enoxaparin 14 days**		
	Rivaroxaban	**Enoxaparin**	**Incremental**	**Rivaroxaban**	**Enoxaparin**	**Incremental**
Total cost, C$ (Medication + direct costs)	437.80	734.75	-296.95	418.6	383.25	35.35
Medical costs (C$)	334.63	310.05	24.57	334.62	120.21	214.41
Direct costs (C$)	103.18	424.70	-321.52	83.98	263.04	-179.06
QALY	4.1858	4.1825	0.0033	4.1857	4.1805	0.0052
Symptomatic VTE	0.0052	0.0132	-0.0081	0.0069	0.0332	-0.0263
Incremental cost per QALY			Rivaroxaban dominates			6741.96
Incremental cost per VTE event averted			Rivaroxaban dominates			1342.21

THR, total hip replacement; QALY, quality-adjusted life year; VTE, venous thromboembolism. Data from McDonald 2012.

Diamantopoulos found similar results comparing rivaroxaban to enoxaparin and dalteparin(22). For rivaroxaban versus enoxaparin, cost savings of C$300 per patient who had hip replacement surgery and C$129 per patient who had total knee replacement surgery were found. When rivaroxaban was compared to dalteparin in a sensitivity analysis, similar results were found with cost savings of C$360 in patients who had hip replacement surgery and C$153 in patients who had knee replacement surgery.

In the Quebec setting, apixaban was equally found to be more cost-effective compared to enoxaparin with cost savings of C$277 in patients who had hip joint replacement surgery and C$181 in patients who had knee joint replacement surgery(45). See Appendix 4.

Table 2b: Costs and cost-effectiveness of rivaroxaban vs enoxaparin following total knee replacement surgery in the Ontario setting

	Rivaroxaban 14 days	Enoxaparin 14 days	Incremental
Total cost, C$ (Medication + direct costs)	279.68	430.12	-150.44
Medical costs (C$)	134.71	125.04	9.67
Direct costs (C$)	144.97	205.08	-160.11
QALY	4.1870	4.1851	0.0019
Symptomatic VTE	0.0125	0.0319	-0.0194
Cost per QALY			Rivaroxaban dominates
Incremental cost per VTE event averted			Rivaroxaban dominates

TKR, total knee replacement; QALY, quality-adjusted life year; VTE, venous thromboembolism. Data from McDonald 2012.

ELDERLY PATIENTS

In elderly patients, >65 years, who had hip/knee joint replacement surgery, there were no important differences between NOACs and LMWH for VTE events including VTE-related deaths (6 fewer events per 1000 patients on NOACs, moderate certainty evidence), and risk of major bleeding (4 more events per 1000 patients on NOACs, moderate certainty evidence).

Table 3: Summary of findings for NOACs vs LMWH in elderly patients

Population	Outcome	# participants, # studies	Risk with LMWH	Absolute difference (95% CI) (Risk with NOACs)	Relative effect	NNT	Quality (GRADE)
NOACs vs enoxaparin							
Elderly patients, >65 yrs	VTE events including VTE-related death	21652 (9 studies)	16 per 1000	6 fewer (11 fewer to 4 more) events per 1000 patients	**RR** 0.60 [0.29, 1.26]	NA	Moderate
Elderly patients, > 65 yrs	Major or clinically relevant bleeding	24462 (9 studies)	26 per 1000	4 more (4 fewer to 13 more) events per 1000 patients	**RR** 1.14 [0.86, 1.50]	NA	Moderate

Data from Pathak 2015 (<75 years old). RR: relative risk. NNT: number needed to treat

In elderly patients, ≥75 years old, VTE events including VTE-related deaths were similar but major bleeding was significantly lower in NOACs compared with LMWH (See Appendix 4B for details).

PATIENTS WITH CANCER

In a subgroup of 405 hospitalized patients with cancer, there was no difference between rivaroxaban compared to enoxaparin on VTE and VTE-related deaths (RR 1.34, 0.71-2.54; with 25 more events per 1000 patients, moderate certainty evidence), but rivaroxaban was associated with a higher risk of major bleeding (37 more per 1000). No studies assessed apixaban or dabigatran in cancer patients.

Table 4: Summary of evidence of effects of processes of care or interventions to create a pleasant stimulating environment on health and psychosocial outcomes in people with dementia

Population	Outcome	# participants, # studies	Risk with LMWH	Absolute difference (95% CI) (Risk with NOACs)	Relative effect	NNT	Quality (GRADE)
Rivaroxaban vs enoxaparin							
Cancer patients	Composite of asymptomatic proximal DVT or symptomatic VTE, including VTE-related death	405 (1 study)	74 per 1000	25 more (21 fewer to 114 more) events per 1000 patients	**RR 1.34** (0.71 to 2.54)	NA	Moderate
Cancer patients	Major bleeding	584 (1 study)	17 per 1000	37 more (3 more to 128 more) events per 1000 patients	**RR 3.16** (1.17 to 8.50)	28 (8 to 347)	Moderate

Data from Franchini 2015. RR=relative risk; NA=not applicable

PATIENTS WITH RENAL IMPAIRMENT

Patients hospitalized for renal impairment, were assessed in one review. Dabigatran was compared to enoxaparin in 159 hospitalized patients who had moderate renal dysfunction (defined as creatinine clearance between 30 and 49 mL/min). The rates of VTE events were not significantly different for dabigatran and enoxaparin (43 per 1000 compared to 90 per 1000) but enoxaparin had higher rates of major bleeding than dabigatran (47 compared to 5 per 1000). Rivaroxaban and apixaban have not been studies in this patient population.

Table 5: Summary of findings for NOACs vs LMWH in patients with renal impairment

Population	Outcome	# participants, # studies	Risk with LMWH	Absolute difference (95% CI) (Risk with NOACs)	Relative effect	NNT	Quality (GRADE)
Dabigatran vs enoxaparin							
Patients with moderate renal impairment	Major VTE events	159 (1 study)	90 per 1000	47 fewer (78 fewer to 66 more) events per 1000 patients	**RR 0.48,** (0.13-1.73)	NA	Low
Patients with moderate renal impairment	Major bleeding	224 (1 study)	47 per 1000	42 fewer (47 fewer to 37 more) events per 1000 patients	**RR 0.10** (0.01 to 1.79)	NA	Low

Data from Sardar 2014

MIXED POPULATION (MEDICALLY ILL)

In a mixed population of patients with infectious disease (excluding septic shock), congestive heart failure, respiratory failure, ischemic stroke, acute rheumatic disorder, inflammatory bowel disease, there was a higher rate of major bleeding with NOACs than with enoxaparin (4 more events per 1000 patients). Other outcomes were not assessed in the systematic review. See Appendix 4C for additional details.

Table 6: Summary of findings for NOACs vs LMWH in a mixed population of patients

Population	Outcome	# participants, # studies	Risk with LMWH	Absolute difference (95% CI) (Risk with NOACs)	Relative effect	NNT	Quality (GRADE)
NOACs vs enoxaparin							
Medically ill	Major bleeding	14,399 (2 studies)	2 per 1000	4 more (1 more to 7 more) events per 1000 patients	**RR 2.77** [1.68, 4.56]	283 (141 to 736)	High

Data from Sardar 2014

Recommendations from clinical practice guidelines

Dabigatran, rivaroxaban, apixaban or LMWH were all recommended as first line preventive therapy for thromboembolism in patients with hip/knee joint replacement surgery in four guidelines(5, 6, 8, 58) although one preferred LMWH over NOACs(58). The ACCP guidelines(58) recommended the use of dabigatran in patients undergoing major surgery (hip or knee replacement surgery or hip fracture surgery) who decline injections. Rivaroxaban and apixaban could be used if dabigatran was unavailable. In the ACCP guidelines(59), dabigatran alone is recommended in patients with a history of ischemic stroke or TIA and atrial fibrillation, including paroxysmal atrial fibrillation. However, it is contraindicated in patients with severe renal impairment. UFH is the preferred anticoagulant for VTE prophylaxis in patients with renal impairment and LMWHs in all other patient populations with no contraindications.

Cost effectiveness analyses were done in four guidelines(4, 5, 8, 10).

See Table 7 and Appendix 4D for additional details.

Patient preferences

We did not find any systematic reviews comparing NOACs to LMWHs which reported patient experience or preferences related to injections required by LMWH. We did not search for patient values about the outcomes of VTE or bleeding.

NICE guidelines(5) reported about patient adherence to LMWH injections. In a study comparing dalteparin and enoxaparin in patients with spinal cord injury, adherence for subcutaneous LMWH injection during hospitalisation reached more than 99%, both for once and twice daily injections. In another study of LMWHs in out-patients with a knee plaster cast, 12% of 148 participants discontinued treatment due to discomfort or refusal to self-inject.

All the included guidelines except one(11) recommended that the choice of thromboprophylactic agents should be based on availability, and individual patients' risk characteristics and preferences. Three guidelines also considered cost(5, 8, 9) and one, compliance(6). The ACCP clinical practice guideline group (4) found that patient values and preferences for treatment choices vary widely, and made a recommendation that NOACs could be considered for patients who disliked or refused daily injections of LMWH.

VTE can result in complications such as post-thrombotic limb syndrome, pulmonary hypertension, stroke, heart failure and even death. VTE prophylaxis also carries some known risks e.g. bleeding which can be extremely frightening and uncomfortable for patients, and the consequences will depend on the site (e.g. intracranial bleeding) and severity particularly if the bleeding is difficult to stop due to anticoagulation effect. It is therefore important for clinicians to discuss potential risks and benefits of VTE prophylaxis with the patient so that they can make informed choices and develop an adequate treatment plan, taking into account the patient's needs and preferences.

Table 7: Recommendations for venous thromboprophylaxis with NOACs

Population or clinical category	ACCP guide-lines	Australi-an guide-lines	NICE guide-lines	SIGN guide-lines	AAOS guidelines	APTP guide-lines	ASCO guide-lines	comments
Patients with hip/ knee joint replace-ment sur-gery	✓	✓	✓	✓	?	NA	NA	Compared to enoxapa-rin
Patients undergoing major sur-gery who decline injections	✓	NA	NA	NA	NA	NA	NA	Based on patient preferences
Patients with atrial fibrillation and risk factors for stroke	NA	NA	NA	?	NA	NA	NA	Compared to warfarin
Patients with is-chemic stroke	✓±	NA	NA	NA	NA	NA	NA	Compared to no an-tiplatelet drugs
Elderly populations with …	NA	X	X	NA	NA	X	X	
Cancer patients undergoing general surgery	?	?	NA	NA	NA	NA	X	
Non-surgical cancer pa-tients	?	?	NA	NA	NA	NA	X	
Patients with renal impairment	X	X	X	X	NA	X	X	
Medically ill patients	X	?	NA	NA	NA	NA	NA	

ACCP=American College of Chest Physicians; NICE=National Institute for Health and Care Excellence; SIGN= Scottish Intercollegiate Guidelines Network; AAOS= American Academy of Orthopaedic Surgeons clinical; APTP= Alberta Provincial Tumour Program; ASCO= American Society of Clinical Oncology

✓ = all three NOACs (dabigatran, rivaroxaban, apixaban) recommended;

✓± = Dabigatran alone recommended

? = no conclusive evidence to recommend or not;

NA = not assessed

Discussion

Applicability of evidence/ implementation

LMWHs have been the treatment of choice for VTE prophylaxis in adult patients in subacute care at BCC. With the recently approved NOACs we sought to find out whether NOACs could be used in place of LMWHs. We compared the effectiveness and safety of NOACs versus LMWHs. Different outcomes were assessed in different patient populations. VTE events and mortality were assessed separately in some reviews and combined as a composite outcome in others. Some reviews focused on one outcome e.g. major bleeding. No review assessed patient values or preference related to the inconvenience of injections. We found three economic evaluations comparing rivaroxaban or apixaban with LMWHs in patients with hip and knee replacement surgery in Canada. NOACs have been assessed mostly in patients with hip and knee joint replacement surgery.

All 19 reviews that assessed NOACs versus enoxaparin in patients (including the elderly) with hip or knee replacement surgery found that NOACs had a marginal or superior effect in preventing VTE events and had similar or increased risk of bleeding than enoxaparin. Four of these reviews considered only the approved doses and found that NOACs prevented more VTE events and mortality (0 to 6 fewer VTE/deaths per 1000 patients) and had an increased risk of bleeding than enoxaparin (1 to 4 more bleeds per 1000 patients).

NOACs are easier to administer and more cost-effective than LMWH for hip or knee surgery patient population, however, LMWHs remain the preferred anticoagulant prophylactic drugs as recommended by seven international guideline groups. These guidelines were developed before the approval of an antidote for dabigatran therefore the reversal of bleeding risk of NOACs was still a challenge. Antidotes for rivaroxaban and apixaban are still under development.Data in other patient populations such as cancer, renal impairment and mixed population of medically ill are limited (few studies with few participants for quite a rare outcome).

Guideline recommendations have been limited to the patient populations in whom NOACs have been studied. Four guidelines(4-6, 8) out of eight recommended NOACs in patients with hip and knee joint replacement surgery. The recommendations are in line with the findings of the included reviews that assessed NOACs in patients with joint replacement surgery. The AAOS guidelines(9) suggest that NOACs should be considered only in patients who are not at elevated risk beyond that of the surgery itself for venous thromboembolism or bleeding. The ACCP guidelines (4) recommend NOACs in patients undergoing major surgery who decline injections. Other guidelines(5, 6, 8-10) suggest that patient values and preferences should be considered in the choice of venous thromboprophylaxis but no clear recommendations were made based on patient's preferences and values as in the ACCP guidelines.

NOACs are recommended in patients with atrial fibrillation and risk of stroke based on studies comparing NOACs with warfarin, the most common thromboprophylactic treatment in this patient population. These were excluded from our synthesis. Also, the recommendation for dabigatran in patients with ischemic stroke is based on studies comparing it to antiplatelet drugs (also excluded from our synthesis).

NOACs were more cost-effective than LMWHs for hip or knee surgery patient population. Similar trends of effectiveness and safety effects were found in the systematic reviews and HTAs that assessed NOACs versus LMWHs. The inconvenience of injections was not assessed in any review or HTA but the administration cost of injections of LMWHs compared to oral administration of NOACs was considered in cost-effectiveness evaluations.

Guideline recommendations were limited to patient populations that have been studied and were based on effectiveness and safety data. Guidelines also recommended that patient preferences and values should be considered in the choice of treatment.

Recommendations

Overall, hospitals should consider approaches that will likely increase provider compliance and patient adherence as well as improve patient outcomes.

Based on our findings, we suggest the following:

1. Patient risk assessment for VTE risk and risk of bleeding should be done before deciding whether or not VTE prophylaxis should be used, and which type. For VTE risk assessment, additional risks such as the clinical condition or reason for hospitalization should also be taken into account. When assessing patients for risk of bleeding, a balance between actual and perceived risk should be considered as well as contraindications for prophylaxis.

2. Various guideline groups recommend thromboprophylaxis with either NOACs or LMWH in patients including elderly with hip or knee joint replacement surgery, provided patients have no contraindications.

3. For patients undergoing orthopedic surgery who refuse injections, NOACs is recommended.

4. NOACs are more cost-effective than LMWH for patients with hip or knee joint replacement even when risk of major bleeds is considered.

5. For the medically ill, there is higher risk of bleeds (4 per 1000, from 1-7 more per 1000; high certainty of evidence) and guideline groups recommend LMWH or or unfractionated heparin or unfractionated heparin for this population.

6. For palliative care, we found no systematic reviews but two guidelines recommend the use of LMWH for thromboprophylaxis.

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Appendices

Appendix 1: Search methods

We did a PICO search in Trip Database following our eligibility criteria described above.

P – patients in hospital

I – new acting oral anticoagulants

C – low molecular weight heparin

O – prevention of venous thromboembolism and/or cost-effectiveness

We used the following search strategy in PubMed and adapted it for the Cochrane Library.

PUBMED:

#3	Add	Search (#1 AND #2)	1462
#2	Add	Search ((((“Review”[Publication Type] OR “Review Literature as Topic”[Mesh]) OR (“Meta-Analysis as Topic”[Mesh] OR “Meta-Analysis”[Publication Type]) OR systematic[sb] OR Cost-Benefit Analysis[Mesh])))	2283021
#1	Add	Search (Dabigatran[tiab] OR desirudin[tiab] OR edoxaban[tiab] OR rivaroxaban [tiab] OR apixaban[tiab] OR betrixaban[tiab] OR YM150[tiab] OR razaxaban [tiab] OR “dabigatran etexilate”[Supplementary Concept] OR “desirudin”[Supplementary Concept] OR “edoxaban”[Supplementary Concept] OR “rivaroxaban”[Supplementary Concept] OR “apixaban”[Supplementary Concept] OR “betrixaban”[Supplementary Concept] OR “razaxaban hydrochloride”[Supplementary Concept] OR “factor Xa, Glu-Gly-Arg-”[Supplementary Concept] OR “KFA1411”[Supplementary Concept])	4531

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dabigatran or desirudin or edoxaban or rivaroxaban or apixaban or betrixaban or YM150 or razaxaban or "factor Xa inhibitors" or "factor Xa inhibitor" or "fxa inhibitors" or "fxa inhibitor" or "direct thrombin inhibitor" or "direct thrombin inhibitors" or DTIs or "novel anticoagulants" or "new anticoagulants" or "novel anticoagulant" or "new anticoagulant"

Limited to Reviews, Other Reviews and Economic Evaluations-205

We also examined reference lists of relevant articles.

We identified 1617 articles from PubMed and the Cochrane Library and 383 articles from Trip Database. The articles were screened in duplicate and 32 systematic reviews and eight guidelines met our inclusion criteria.

Appendix 2: Quality assessment

We assessed the quality of systematic reviews using AMSTAR score and used AGREE score for assessing the quality of guidelines.

Quality assessment of the systematic reviews

The AMSTAR instrument uses the following assessment criteria:

1. Was an a priori design provided?

2. Was there duplicate study selection and data extraction?

3. Was a comprehensive literature search performed?

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

5. Was a list of studies (included and excluded) provided?

6. Were the characteristics of the included studies provided?

7. Was the scientific quality of the included studies assessed and documented?

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

9. Were the methods used to combine the findings of studies appropriate?

10. Was the likelihood of publication bias assessed?

11. Was the conflict of interest stated?

The quality assessment of the reviews that provided data presented in tables are summarized in the table below.

AMSTAR criteria/score	Cui 2014	Squizzato 2015	Pathak 2015	Franchini 2015	Singh 2013	Sardar 2014
Was an a priori design provided?	can't	can't	yes	no	yes	can't
Was there duplicate study selection and data extraction?	yes	yes	yes	can't	yes	yes
Was a comprehensive literature search performed?	yes	yes	yes	no	yes	yes
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	no	yes	yes	can't	yes	can't

AMSTAR criteria/ score	Cui 2014	Squizzato 2015	Pathak 2015	Franchini 2015	Singh 2013	Sardar 2014
Was a list of studies (included and excluded) provided?	no	no	no	no	yes	no
Were the characteristics of the included studies provided?	yes	yes	yes	yes	yes	yes
Was the scientific quality of the included studies assessed and documented?	yes	yes	yes	no	yes	yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	yes	can't	yes	no	yes	can't
Were the methods used to combine the findings of studies appropriate?	yes	yes	yes	yes	yes	yes
Was the likelihood of publication bias assessed?	yes	yes	yes	no	yes	yes
Was the conflict of interest stated?	no	no	no	no	no	no
Score	**7/11**	**7/11**	**9/11**	**2/11**	**10/11**	**6/11**

Quality assessment of the guidelines

The AGREE II consists of 23 key items organized within 6 domains followed by 2 global rating items. Each domain captures a unique dimension of guideline quality. Each item (items 1-24) is rated a maximum of 7 and the last item is rated yes/no.

Domain 1. Scope and Purpose is concerned with the overall aim of the guideline, the specific health questions, and the target population (items 1-3).

Domain 2. Stakeholder Involvement focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users (items 4-6).

Domain 3. Rigour of Development relates to the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them (items 7-14).

Domain 4. Clarity of Presentation deals with the language, structure, and format of the guideline (items 15-17).

Domain 5. Applicability pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline (items 18-21).

Domain 6. Editorial Independence is concerned with the formulation of recommendations not being unduly biased with competing interests (items 22-23).

Overall assessment includes the rating of the overall quality of the guideline (item 24) and whether the guideline would be recommended for use in practice (item 25).

The quality assessments for the guidelines are summarized in the table below.

AGREE domain	**ACCP guidelines**	**Aussie guidelines**	**NICE guidelines**	**SIGN guidelines**	**AAOS guidelines**	**APTP guidelines**	**ASCO guidelines**
Domain 1 – scope and purpose (items 1-3)	21	21	21	21	21	21	21
Domain 2 – stakeholder involvement (items 4-6)	14	14	18	19	14	9	18
Domain 3 – Rigour of Development (items 7-14)	47	47	52	41	53	34	41
Domain 4 – Clarity of Presentation (items 15-17)	21	21	21	21	21	21	21
Domain 5 – Applicability (items 18-21)	19	11	22	25	17	13	8
Domain 6 – Editorial Independence (items 22-23)	14	12	8	5	9	14	11
Overall assessment (items 24-25)	6/yes	6/yes	6/yes	6/yes	6/yes	5/yes	5/yes
Score	**142/168**	**132/168**	**148/168**	**138/168**	**141/168**	**117/168**	**125/168**

Appendix 3: Grading of the quality of the evidence

We used the GRADE approach to assess the quality of the evidence(60). There are four categories: high, moderate, low and very low.

Quality level	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Factors that may decrease the quality level of a body of evidence

1. Limitations in the design and implementation of available studies suggesting high likelihood of bias.

2. Indirectness of evidence (indirect population, intervention, control, outcomes).

3. Unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses).

4. Imprecision of results (wide confidence intervals).

5. High probability of publication bias.

Appendices

Appendix 4: Additional findings

A. Orthopedic surgery patients

Table A1: Summary of findings for NOACs vs LMWH in orthopedic surgery patients

Population	Out-come	# partici-pants, # studies	Control event rate in LMWH	Absolute dif-ference (95% CI) (Risk with NO-ACs)	Relative effect	NNT	Quality (GRADE)
Apixaban vs enoxaparin							
Patients with hip/knee joint replacement surgery	VTE events	8126 (3 studies)	103 per 1000	38 fewer (63 fewer to 1 more) events per 1000 pa-tients	**RR 0.63** (0.39 to 1.01)	NA	Moderate
Patients with hip/knee joint replacement surgery	Major bleeding	9273 (3 studies)	47 per 1000	9 fewer (16 fewer to 0 more) events per 1000 pa-tients	**RR 0.80** (0.65 to 1.00)	NA	Moderate
Patients with hip/knee joint replacement surgery	Mortality	11569 (4 studies)	7 per 10,000	0 fewer (1 fewer to 3 more) events per 1000 pa-tients	**RR 1.89** [0.60, 5.91]	NA	High
Rivaroxaban vs enoxaparin							
Patients with hip/knee joint replacement surgery	VTE events	8512 (4 studies)	94 per 1000	56 fewer (70 fewer to 34 fewer) events per 1000 pa-tients	**RR** 0.40 [0.25, 0.64]	18 (15 to 30)	Moderate
Patients with hip/knee joint replacement surgery	Major bleeding	9131 (4 studies)	35 per 1000	10 more (1 more to 20 more) events per 100 pa-tients	**RR 1.28** [1.04, 1.57]	103 (51 to 715)	Moderate
Patients with hip/knee joint replacement surgery	Mortality	10388 (4 studies)	3 per 1000	1 fewer (2 fewer to 1 more) event per 1000 patients	**RR 0.54** [0.24, 1.26]	NA	High

Population	Out-come	# partici-pants, # studies	Control event rate in LMWH	Absolute differ-ence (95% CI) (Risk with NO-ACs)	Relative effect	NNT	Quality (GRADE)
Dabigatran vs enoxaparin							
Patients with hip/knee joint replacement surgery	VTE events	7665 (4 studies)	171 per 1000	15 more (12 fewer to 46 more) events per 1000 patients	**RR 1.09** [0.93, 1.27]	NA	Moderate
Patients with hip/knee joint replacement surgery	Major bleeding	10148 (4 studies)	44 per 1000	1 more (8 fewer to 12 more) events per 1000 patients	**RR 1.02** [0.82, 1.27]	NA	Moderate
Patients with hip/knee joint replacement surgery	Mortality	7360 (4 studies)	5 per 10,000	4 more (2 fewer to 29 more) events per 1000 pa-tients	**RR 1.87** [0.51, 6.83]	NA	High
NOACs vs enoxaparin							
Patients with hip/knee joint replacement surgery	VTE events	26055 (8 studies)	5 per 1000	0 fewer (2 fewer to 2 more) event per 1000 pa-tients	**RR 0.97** [0.69, 1.36]	NA	High
Patients with hip/knee joint replacement surgery	Major bleeding	26223 (11 studies)	39 per 1000	1 more (3 fewer to 5 more) events per 1000 patients	**RR 1.03** [0.92, 1.14]	NA	Moderate
Patients with hip/knee joint replacement surgery	Mortality	29357 (11 studies)	1 per 1000	0 fewer (0 fewer to 1 more) event per 1000 patients	**RR 1.00 (0.56 to 1.77)**	NA	High

Table A2: Costs and cost-effectiveness of rivaroxaban vs enoxaparin following total hip or knee replacement surgery

	Total hip replacement			**Total knne replacement**		
	Rivaroxaban	**Enoxaparin**	**Incremental**	**Rivaroxaban**	**Enoxaparin**	**Incremental**
Total cost, C$ (Medication + direct costs)	429.42	729.26	-299.83	268.03	397.00	-128.97
Medical costs (C$)	334.63	310.05	24.50	134.71	125.04	9.67
Direct costs (C$)	94.79	419.21	-324.41	133.32	271.96	-138.64
QALY	4.1858	4.1852	0.0006	4.1870	4.1852	0.0018
Symptomatic VTE	0.0052	0.0113	-0.0061	0.0125	0.0318	-0.0192
Incremental cost per QALY			Rivaroxaban dominates			Rivaroxaban dominates
Incremental cost per symptomatic VTE event averted			Rivaroxaban dominates			Rivaroxaban dominates

QALY, quality-adjusted life year; VTE, venous thromboembolism. Data from Diamantopoulos 2010.

Table A3: Costs and cost-effectiveness of apixaban vs enoxaparin following total hip or knee replacement surgery

	Total hip replacement			**Total knee replacement**		
	Apixaban	**Enoxaparin**	**Incremental**	**Apixaban**	**Enoxaparin**	**Incremental**
Total VTE	14	39	-25	124	160	-36
Total bleeding events	87	84	3	56	71	-15
Mortality (VTE or bleeding event)	0.6	1.6	-1.0	5.6	7.2	-1.6
Repeat VTE	4.4	12.0	-7.6	37.9	48.9	-11
PTS	4.0	10.9	-6.9	34.5	44.5	-10
Summary cost, discounted	265.98	540.71	-274.73	336.09	517.31	-181.22
Total QALY, discounted	3.50751	3.50305	0.00446	3.49940	3.49226	0.00714
Total life-years, discounted	4.36210	4.35773	0.00437	4.34640	4.33926	0.00714
Cost/VTE event avoided, discounted	Dominant	-		Dominant	-	
Cost/bleeding event avoided, discounted (C$)	Dominant	-		$88 480 (fewer bleeding events with enoxaparin blend)	-	
Cost/repeat VTE event avoided, discounted	Dominant	-		Dominant	-	
Cost/PTS event avoided, discounted	Dominant	-		Dominant	-	
Cost/QALY, discounted	Dominant	-		Dominant	-	
Cost/life-year, discounted	Dominant	-		Dominant	-	

QALY, quality-adjusted life year; VTE, venous thromboembolism; PTS, post-thrombotic syndrome; Event counts (total VTE, total bleeding events, mortality, repeat VTE, PTS) are per 1000 patients. Data from Revankar 2013.

B. ORTHOPEDIC SURGERY PATIENTS

Table A2: Costs and cost-effectiveness of rivaroxaban vs enoxaparin following total hip or knee replacement surgery

Population	Outcome	# participants, # studies	Control event rate	Absolute difference (95% CI) (Risk with NOACs)	Relative effect	NNT	Quality (GRADE)
Apixaban vs enoxaparin							
Elderly patients	VTE events including VTE-related death	5862 (2 studies)	14 per 1000	1 fewer (1 fewer to 0 more) events per 100 patients	**RR** 0.53 [0.32, 0.89]	54 (49 to 265)	High
Elderly patients	Major bleeding	7110 (2 studies)	42 per 1000	0 fewer (1 fewer to 1 more) event per 100 patients	**RR** 0.95 [0.76, 1.19]	NA	High
Rivaroxaban vs enoxaparin							
Elderly patients	VTE events including VTE-related death	10555 (4 studies)	12 per 1000	1 fewer (1 fewer to 0 more) events per 100 patients	**RR** 0.35 [0.22, 0.56]	NA	High
Elderly patients	Major bleeding	10555 (4 studies)	23 per 1000	1 more (0 to 2 more) event per 100 patients	**RR** 1.40 [1.11, 1.76]	109 (58 to 396)	High
Dabigatran vs enoxaparin							
Elderly patients	VTE events including VTE-related death	5235 (3 studies)	30 per 1000	0 more (1 fewer to 1 more) event per 100 patients	**RR** 1.12 [0.81, 1.54]	NA	High
Elderly patients	Major bleeding	6797 (3 studies)	9 per 1000	0 more (0 fewer to 1 more) event per 100 patients	**RR** 1.08 [0.66, 1.79]	NA	High

Population	Outcome	# participants, # studies	Control event rate	Absolute difference (95% CI) (Risk with NOACs)	Relative effect	NNT	Quality (GRADE)
NOACs vs enoxaparin							
Elderly patients	VTE events including VTE-related death	21652 (9 studies)	16 per 1000	6 fewer (11 fewer to 4 more) event per 100 patients	**RR** 0.60 [0.29, 1.26]	NA	Moderate
Elderly patients	Major bleeding	24462 (9 studies)	26 per 1000	4 more (4 fewer to 13 more) event per 100 patients	**RR** 1.14 [0.86, 1.50]	64 (40 to 358)	Moderate

Data from Pathak <75 years old

Table B2: Summary of findings for NOACs vs LMWH in elderly patients (>75 years old)

Population	Outcome	# participants, # studies	Control event rate	Absolute difference (95% CI) (Risk with NOACs)	Relative effect	NNT	Quality (GRADE)
Apixaban vs enoxaparin							
Elderly patients	VTE events including VTE-related death	926 (2 studies)	21 per 1000	19 fewer (21 fewer to 4 fewer) events per 1000 patients	**RR** 0.11 [0.01, 0.82]	54 (49 to 265)	Moderate
Elderly patients	Major bleeding	1231 (2 studies)	92 per 1000	25 fewer (45 fewer to 6 more) event per 1000 patients	**RR** 0.73 [0.49, 1.07]	NA	High

Population	Outcome	# participants, # studies	Control event rate	Absolute difference (95% CI) (Risk with NOACs)	Relative effect	NNT	Quality (GRADE)
Rivaroxaban vs enoxaparin							
Elderly patients	VTE events including VTE-related death	1828 (4 studies)	17 per 1000	4 fewer (11 fewer to 10 more) events per 1000 patients	**RR** 0.75 [0.36, 1.58]	NA	Moderate
Elderly patients	Major bleeding	1828 (4 studies)	41 per 1000	9 fewer (21 fewer to 11 more) event per 1000 patients	**RR** 0.79 [0.49, 1.26]	109 (58 to 396)	High
Dabigatran vs enoxaparin							
Elderly patients	VTE events including VTE-related death	965 (3 studies)	48 per 1000	11 fewer (28 fewer to 21 more) event per 1000 patients	**RR** 0.78 [0.42, 1.44]	NA	Moderate
Elderly patients	Major bleeding	1338 (3 studies)	37 per 1000	15 fewer (26 fewer to 4 more) event per 1000 patients	**RR** 0.59 [0.31, 1.22]	NA	High
NOACs vs enoxaparin							
Elderly patients	VTE events including VTE-related death	3719 (9 studies)	27 per 1000	10 fewer (19 fewer to 7 more) event per 1000 patients	**RR** 0.63 [0.31, 1.26]	NA	Moderate
Elderly patients	Major bleeding	4397 (9 studies)	56 per 1000	16 fewer (25 fewer to 3 fewer) events per 1000 patients	**RR** 0.72 [0.55, 0.95]	64 (40 to 358)	High

Data from Pathak >75 years old

C. MIXED POPULATIONS (MEDICALLY ILL)

Table C: Summary of findings for NOACs vs LMWH in a mixed population of patients

Population	Outcome	# participants, # studies	Risk with LMWH	Absolute difference (95% CI) (Risk with NOACs)	Relative effect	NNT	Quality (GRADE)
Apixaban vs enoxaparin							
Medically ill	Major bleeding	6401 (1 study)	1 per 1000	2 more (0 fewer to 6 more) events per 1000 patients	**RR 2.53** [0.98, 6.50]	NA	High
Rivaroxaban vs enoxaprin							
Medically ill	Major bleeding	7998 (1 study)	3 per 1000	6 more (2 to 12 more) events per 1000 patients	**RR 2.87** [1.60, 5.16]	179 (81 to 556)	High
NOACs vs enoxaparin							
Medically ill	Major bleeding	14,399 (2 studies)	2 per 1000	4 more (1 more to 7 more) events per 1000 patients	**RR 2.77** [1.68, 4.56]	283 (141 to 736)	High

D. SYNTHEISIS OF GUIDELINE FINDINGS

Table C: Recommendations for venous thromboprophylaxis with NOACs

NOAC	Population or clinical category	ACCP guide-lines	Aussie guidelines	NICE guide-lines	SIGN guide lines	AAOS guide-lines	APTP guide lines	ASCO guide lines	com-ments
Dabigatran	THA/TKA	✓	✓	✓	✓	?	NA	NA	Com-pared to enoxap-arin
	Hip surgery	?	?	NA	NA	NA	NA	NA	
	Patients with in-creased bleeding risk	X	?	X	NA			NA	
	Patients undergo-ing major surgery who de-cline injec-tions	✓	NA	NA	NA	NA	NA	NA	Based on pa-tient prefer-ences
	Patients with lower leg injuries requiring leg immo-bilization	X	?	NA	NA	NA	NA	NA	
	Knee ar-throscopy without a history of VTE	X	X	NA	NA	NA	NA	NA	
	Atrial fibril-lation with risk factors for stroke	✓	NA	NA	?	NA	NA	NA	Com-pared to warfarin
	Acutely ill medical patients at increased risk of thrombosis	NA	NA	NA	NA	NA	NA	NA	

NOAC	Population or clinical category	ACCP guidelines	Aussie guidelines	NICE guidelines	SIGN guidelines	AAOS guidelines	APTP guidelines	ASCO guidelines	comments
Dabigatran	Acutely ill medical patients at low risk of thrombosis	X	NA	NA	NA	NA	NA	NA	
	Acutely ill medical patients who are bleeding or at high risk of bleeding	X	NA	NA	NA	NA	NA	NA	
	Critically ill patients	NA	NA	NA	NA	NA	NA	NA	
	Critically ill patients who are bleeding or at high risk of bleeding	NA	NA	NA	NA	NA	NA	NA	
	General surgery	NA	NA	NA	?	NA	NA	NA	
	Urological surgery	NA	NA	NA	?	NA	NA	NA	
	Gynecological surgery	NA	NA	NA	?	NA	NA	NA	
	Abdominal surgery	NA	NA	NA	?	NA			
	Cardiac, thoracic, and vascular surgery	NA	NA	NA	?	NA	NA	NA	
	Neurosurgery	NA	NA	NA	?	NA	NA	NA	
	Trauma surgery and spinal surgery	NA	NA	NA	?	NA	NA	NA	
	Ischemic stroke and atrial fibrillation	✓	?	NA	NA	NA	NA	NA	Compared to no antiplatelets

NOAC	Population or clinical category	ACCP guidelines	Aussie guidelines	NICE guidelines	SIGN guidelines	AAOS guidelines	APTP guidelines	ASCO guidelines	comments
Dabigatran	Myocardial infarction/ Acute coronary syndromes	?	?	NA	?	NA	NA	NA	
	General medical patients	NA	?	NA	NA	NA	NA	NA	
	Cancer patients undergoing general surgery	?	?	NA	NA	NA	NA	X	
	Non-surgical cancer patients	?	?	NA	NA	NA	NA	X	
	Patients in palliative care who have potentially reversible acute pathology	NA	NA	NA	NA	NA	NA	NA	
Rivaroxaban	THA/TKA	✓	✓	✓	✓	?	NA	NA	Compared to enoxaparin
	Hip surgery	?	?	NA	NA	NA	NA	NA	
	Patients with increased bleeding risk	X	?	X	NA	NA	NA	NA	
	Patients undergoing major surgery who decline injections	✓ if dabigatran or apixaban are unavailable	NA	NA	NA	NA	NA	NA	Based on patient preferences
	Patients with lower leg injuries requiring leg immobilization	X	?	NA	NA	NA	NA	NA	

NOAC	Population or clinical category	ACCP guide-lines	Aussie guidelines	NICE guide-lines	SIGN guide lines	AAOS guide-lines	APTP guide lines	ASCO guide lines	com-ments
Rivaroxaban	Knee arthroscopy without a history of VTE	X	X	NA	NA	NA	NA	NA	
	Atrial fibrillation with risk factors for stroke	?	NA	NA	NA	NA	NA	NA	Compared to warfarin
	Acutely ill medical patients at increased risk of thrombosis	NA	NA	NA	NA	NA	NA	NA	
	Acutely ill medical patients at low risk of thrombosis	X	NA	NA	NA	NA	NA	NA	
	Acutely ill medical patients who are bleeding or at high risk of bleeding	X	NA	NA	NA	NA	NA	NA	
	Critically ill patients	NA	NA	NA	NA	NA	NA	NA	
	Critically ill patients who are bleeding or at high risk of bleeding	NA	NA	NA	NA	NA	NA	NA	
	General surgery	NA	NA	NA	?	NA	NA	NA	

NOAC	Population or clinical category	ACCP guidelines	Aussie guidelines	NICE guidelines	SIGN guidelines	AAOS guidelines	APTP guidelines	ASCO guidelines	comments
Rivaroxaban	Urological surgery	NA	NA	NA	?	NA	NA	NA	
	Gynecological surgery	NA	NA	NA	?	NA	NA	NA	
	Abdominal surgery	NA	NA	NA	?	NA	NA	NA	
	Cardiac, thoracic, and vascular surgery	NA	NA	NA	?	NA	NA	NA	
	Neurosurgery	NA	NA	NA	?	NA	NA	NA	
	Trauma surgery and spinal surgery	NA	NA	NA	?	NA	NA	NA	
	Ischemic stroke	?	?	NA	NA	NA	NA	NA	
	Myocardial infarction/ Acute coronary syndromes	NA	?	NA	?	NA	NA	NA	
	General medical patients	NA	?	NA	NA	NA	NA	NA	
	Cancer patients undergoing general surgery	NA	?	NA	NA	NA	NA	X	
	Non-surgical cancer patients	NA	?	NA	NA	NA	NA	X	
	Patients in palliative care who have potentially reversible acute pathology	NA	NA	NA	NA	NA	NA	NA	

NOAC	Population or clinical category	ACCP guide-lines	Aussie guidelines	NICE guide-lines	SIGN guide lines	AAOS guide-lines	APTP guide lines	ASCO guide lines	com-ments
Apixaban	THA/TKA	ü	NA	NA	NA	?	NA	NA	Com-pared to enoxap-arin
	Hip surgery	?	NA	NA	NA	NA	NA	NA	
	Patients with increased bleed-ing risk	X	NA	X	NA	NA	NA	NA	
	Patients under-going major sur-gery who decline injections	ü if dabigatran is unavail-able	NA	NA	NA	NA	NA	NA	Based on pa-tient prefer-ences
	Patients with lower leg injuries requiring leg immobilization	X	NA	NA	NA	NA	NA	NA	
	Knee arthrosco-py without a his-tory of VTE	X	NA	NA	NA	NA	NA	NA	
	Atrial fibrillation with risk factors for stroke	NA	NA	NA	NA	NA	NA	NA	Com-pared to warfarin, aspirin
	Acutely ill medi-cal patients at increased risk of thrombosis	X	NA	NA	NA	NA	NA	NA	
	Acutely ill medi-cal patients at low risk of thrombosis	X	NA	NA	NA	NA	NA	NA	

NOAC	Population or clinical category	ACCP guidelines	Aussie guidelines	NICE guidelines	SIGN guidelines	AAOS guidelines	APTP guidelines	ASCO guidelines	comments
Apixaban	Acutely ill medical patients who are bleeding or at high risk of bleeding	X	NA	NA	NA	NA	NA	NA	
	Critically ill patients	X	NA	NA	NA	NA	NA	NA	
	Critically ill patients who are bleeding or at high risk of bleeding	?	NA		NA	NA	NA	NA	
	General surgery	?	NA	NA	NA	NA	NA	NA	
	Urological surgery	?	NA	NA	NA	NA	NA	NA	
	Gynecological surgery	?	NA	NA	NA	NA	NA	NA	
	Abdominal surgery	?	NA	NA	NA	NA	NA	NA	
	Cardiac, thoracic, and vascular surgery	?	NA	NA	NA	NA	NA	NA	
	Neurosurgery	?	NA	NA	NA	NA	NA	NA	
	Trauma surgery and spinal surgery	?	NA	NA	NA	NA	NA	NA	
	Ischemic stroke	?	NA	NA	NA	NA	NA	NA	

NOAC	Population or clinical category	ACCP guide-lines	Aussie guidelines	NICE guide-lines	SIGN guide lines	AAOS guide-lines	APTP guide lines	ASCO guide lines	com-ments
Apixaban	Myocardial infarction/Acute coronary syndromes	NA	NA	NA	NA		NA	NA	
	General medical patients	NA	NA	NA	NA	NA	NA	NA	
	Cancer patients undergoing general surgery	NA	NA	NA	NA	NA	NA	X	
	Non-surgical cancer patients	NA	NA	NA	NA	NA	NA	X	
	Patients in palliative care who have potentially reversible acute pathology	NA	NA	NA	NA	NA	NA	NA	

NOAC	Population or clinical category	ACCP guidelines	Aussie guidelines	NICE guidelines	SIGN guidelines	AAOS guidelines	APTP guidelines	ASCO guidelines	comments
LMWH		✓ (preferred AC)	✓	✓	✓	?	NA	NA	Compared to UFH/ no treatment
	Hip surgery	✓ (preferred AC)THA/ TKA	✓	✓	NA	NA	NA	NA	Compared to UFH/ no treatment
	Patients with increased bleeding risk	X	NA	X	NA	NA	NA	NA	
	Patients undergoing major surgery who decline injections NA	X	NA	NA	NA	NA	NA	NA	
	Patients with NA lower leg injuries requiring leg immobilization	X	✓	✓	NA	NA	NA	NA	Compared to no treatment
	Knee arthroscopy without a history of VTE	X	X	NA	NA	NA	NA	NA	Compared to no treatment/ GCS
	Atrial fibrillation with risk factors for stroke	✓(if undergoing elective electrical or pharmacologic cardioversion)	NA	NA	ü	NA	NA	NA	Compared to warfarin/ aspirin/ no treatment

NOAC	Population or clinical category	ACCP guidelines	Aussie guidelines	NICE guidelines	SIGN guidelines	AAOS guidelines	APTP guidelines	ASCO guidelines	comments
LMWH	Acutely ill medical patients at increased risk of thrombosis	X	NA	NA	NA	NA	X	X	Compared to no treatment
	Acutely ill medical patients at low risk of thrombosis	X	NA	NA	NA	NA	✓*	✓	Compared to no treatment
	Acutely ill medical patients who are bleeding or at high risk of bleeding	X	NA	NA	NA	NA	X	X	Compared to no treatment
	Critically ill patients	✓	NA	Consider VTE prophylaxis depending on the reason for admission – any planned interventions and use of other therapies that may increase risk of complications	?	NA	NA	NA	Compared to no treatment
	Critically ill patients who are bleeding or at high risk of bleeding	X	NA	NA	NA	NA	NA	NA	Compared to no treatment
	General surgery	✓ (at moderate risk for VTE)	✓	✓	✓	NA	NA	NA	Compared to UFH

NOAC	Population or clinical category	ACCP guidelines	Aussie guidelines	NICE guidelines	SIGN guidelines	AAOS guidelines	APTP guidelines	ASCO guidelines	comments
LMWH	Urological surgery		?	✓	✓	NA	NA	NA	Compared to no treatment
	Gynecological surgery	✓	✓	✓	✓	NA	NA	NA	Compared to UFH
	Abdominal surgery	✓ (at moderate risk for VTE)	✓	✓	✓	NA	NA	NA	Compared to no treatment/ UFH
	Cardiac, thoracic, and vascular surgery	✓	✓	✓	✓	NA	NA	NA	Compared to UFH
	Neurosurgery	✓	✓	✓	✓	NA	NA	NA	Compared to no treatment
	Trauma surgery and spinal surgery	✓	✓ (in addition with another thromboprophylactic agent)	✓	✓	NA	NA	NA	Compared to LMWH + foot pump
	Ischemic stroke	✓	✓	✓	✓	NA	NA	NA	Compared to no treatment
	Myocardial infarction/ Acute coronary syndromes	?	?	NA	✓	NA	NA	NA	Compared to UFH

NOAC	Population or clinical category	ACCP guidelines	Aussie guidelines	NICE guidelines	SIGN guidelines	AAOS guidelines	APTP guidelines	ASCO guidelines	comments
LMWH	General medical patients	NA	ü	ü		NA	NA	NA	Compared to UFH
	Cancer patients undergoing general surgery	ü	ü	ü	ü	NA	ü	ü	Compared to UFH
	Non-surgical cancer patients	NA	ü	ü	ü	NA	ü	ü	Compared to no treatment
	Patients in palliative care who have potentially reversible acute pathology	NA	NA	ü	NA	NA	P	NA	
	Elderly	NA	NA	NA	NA	NA	P	P	

ACCP=American College of Chest Physicians; NICE=National Institute for Health and Care Excellence; SIGN= Scottish Intercollegiate Guidelines Network; AAOS= American Academy of Orthopaedic Surgeons clinical; APTP= Alberta Provincial Tumour Program; ASCO= American Society of Clinical Oncology

✓ = recommended;

X = not recommended;

? = no conclusive evidence to recommend or not;

NA = not assessed

* Prophylactic doses of tinzaparin have been shown to be a safer alternative to other LMWH options in patients with renal insufficiency (i.e., serum creatinine ≥300 µmol/L and creatinine clearance >20 or creatinine clearance between 20-30 mL/min). LMWH can be used in patients with liver disease, at the discretion of the treating physician.

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