Economic Evaluations of New Oral Anticoagulants for the Prevention of Venous Thromboembolism After Total Hip or Total Knee Replacement: A Systematic Review

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BACKGROUND

- Total hip replacement (THR) and total knee replacement (TKR) surgeries are being performed with increasing regularity, driven by ageing populations.
- Despite being well established and generally safe, THR and TKR are associated with an increased risk of venous thromboembolism (VTE), either deep-vein thrombosis (DVT) or pulmonary embolism (PE).
- Pharmacologic prophylaxis with anticoagulants following THR or TKR can reduce the rate of VTE events by half but is associated with increased rates of bleeding,[1] which can cause infections, delay wound healing, or require reoperation.[2]
- Traditional anticoagulants such as low molecular-weight heparin (LMWH), fondaparinux, and warfarin have been commonly used. Newer oral anticoagulants (NOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, have been developed.
- Meta-analyses of trials comparing NOACs with LMWH have concluded that NOACs are marginally more effective for the primary prevention of VTE following THR and TKR but are associated with increased risk of bleeding.[3,4]

OBJECTIVE

- To perform a systematic review of published economic analyses of NOACs for primary VTE prophylaxis following THR or TKR and summarise the modelling techniques used and the cost-effectiveness results.

METHODS

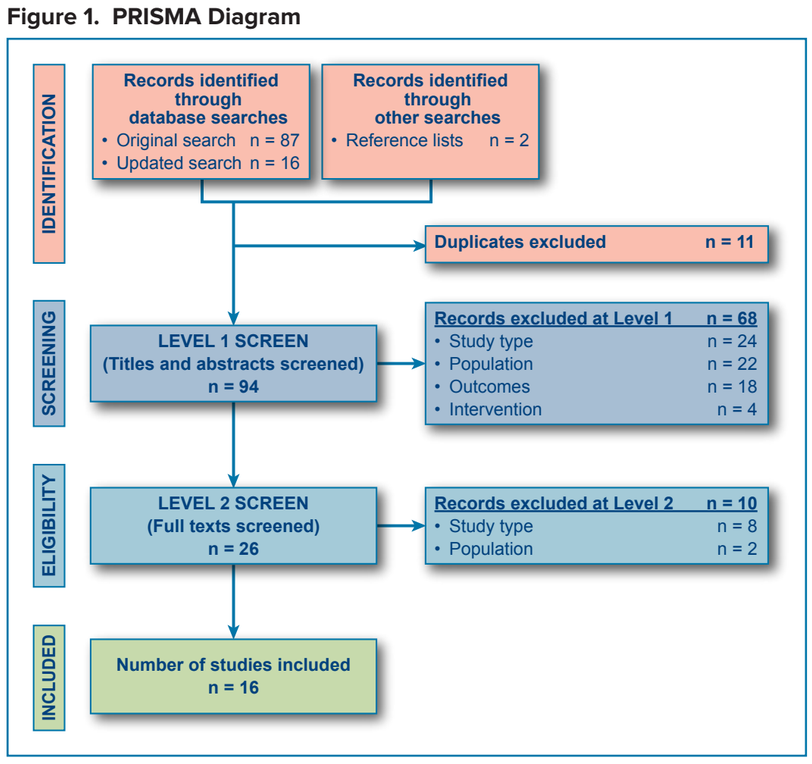
Search Strategy

- Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.
- Electronic searches of PubMed (via the MEDLINE platform), EconLit, and the Cochrane Library were performed from January 2008 to March 2014. The searches were updated from March 2014 to February 2015.
- Databases were searched using Medical Subject Headings and free-text terms grouped into categories: indication (terms for thromboembolism and orthopaedic surgery), intervention (terms for apixaban, dabigatran, edoxaban, and rivaroxaban), and study design (terms for economic analyses).
- The bibliographic reference lists of relevant economic analyses and systematic reviews were used to identify additional publications.

Inclusion and Exclusion Criteria

- All cost-effectiveness, cost-utility, and cost-consequence analyses of NOACs for primary VTE prevention following THR or TKR were included.
- Studies of treatment of VTE, secondary prevention of recurrent VTE, or VTE prophylaxis for surgeries other than THR or TKR were excluded.
- Budget-impact, cost-benefit, cost-minimisation, and cost-only analyses were excluded.

Figure 1. PRISMA Diagram



Adapted from Moher et al., 2009.[5]

RESULTS

Study Selection

- A total of 103 study titles were retrieved from the database searches, of which 11 were duplicates.
- After review of titles and abstracts, 26 articles were selected for full-text review. Of these, 16 economic analyses were included.
- Two relevant systematic literature reviews were identified[6,7] and were excluded after reviewing their reference lists.

Model Structures and Events

- Table 1 presents an overview of the key features and events included in the identified models.

Table 1. Model Features and Events

Feature	Studies
Acute phase structure[a]	**16**
Model structure = decision tree	16
Time horizon = 10 weeks/90 days/180 days/1 year	3/10/2/1
Symptomatic and asymptomatic VTE events[b]	16
Distal and proximal DVT events[c]	9
Major/minor/NMCR bleeding events	16/6/3
Heparin-induced thrombocytopenia	3
Chronic phase structure[d]	**13**
Model structure = Markov	13
Time horizon = 5 years/lifetime	8/5
Recurrent VTE events	13
Postthrombotic syndrome	13
Chronic thromboembolic pulmonary hypertension[e]	1

NMCR = nonmajor clinically relevant bleeding.

[a] Captures prophylaxis following surgery and the prevention phase thereafter.

[b] Asymptomatic events should be captured because patients may later develop postthrombotic syndrome.[8]

[c] The distinction is important because proximal DVT events are much more likely to be symptomatic.

[d] Captures long-term complications of VTE and recurrent VTE events.

[e] Chronic thromboembolic pulmonary hypertension is relatively rare after a first VTE; however, patients who have experienced a recurrent PE are at a greater risk for developing pulmonary hypertension.[9]

Cost-effectiveness of NOACs Versus LMWHs

- Table 2 presents the cost-effectiveness results for analyses that compared an NOAC with an LMWH.
- The results suggested that rivaroxaban, dabigatran, and apixaban are cost-effective alternatives to LMWHs for primary VTE prophylaxis following THR or TKR.
- For THR, rivaroxaban was dominant in 8 of 11 studies, dabigatran was dominant in 4 of 7 studies, and apixaban was dominant in 2 of 2 studies.
- For TKR, rivaroxaban was dominant in 8 of 10 studies, dabigatran was dominant in 5 of 6 studies, and apixaban was dominant in 2 of 2 studies. Enoxaparin was the most cost-effective strategy for TKR in Norway when compared with rivaroxaban and dabigatran.

Cost-effectiveness of NOACs Versus NOACs

- Table 3 presents the cost-effectiveness results for analyses that compared a NOAC with an alternative NOAC.
- The results suggested that dabigatran is the least cost-effective option for primary VTE prophylaxis following THR or TKR.
- For THR, rivaroxaban was dominant in 4 of 5 studies, and apixaban was dominant versus dabigatran in 2 of 2 studies.
- For TKR, rivaroxaban was dominant versus dabigatran in 5 of 5 studies, and apixaban was dominant versus dabigatran in 2 of 2 studies.
- Rivaroxaban was compared with apixaban in 1 study and was associated with more QALYs for THR and TKR; it also was less expensive for TKR.[10]

Table 2. Cost-effectiveness of NOACs Versus LMWHs

Setting and Study	THR			TKR		
	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Rivaroxaban vs. enoxaparin						
Canada[11]	–$300	0.0006	Dom	–$129	0.0018	Dom
Canada[12]	–$297	0.0033	Dom	–$150	0.0019	Dom
US[13]	–$695	NA	Dom[a]	–$411	NA	Dom[a]
US[14]	–$512	0.0019	Dom	–$466	0.0024	Dom
ROI[15]	–€17	0.010	Dom	–€158	0.013	Dom
ROI[16]	NR	NR	Dom	NR	NR	NR
UK[10]	NR	NR	Dom	NR	NR	Dom
France[17]	–€160	0.0005	Dom	–€65	0.0005	Dom
Italy[17]	–€31	0.0011	Dom	–€69	0.0011	Dom
Spain[17]	–€108	0.0011	Dom	–€137	0.0011	Dom
Germany[18]	€32	NA	€1,564[a]	€21	NA	€1,014[a]
Norway[19]	NOK8,000	0.1750	NOK45,000	–NOK313	–0.018	NOK17,000
Sweden[20]	SEK119	0.0040	SEK29,378	–SEK873	0.0029	Dom
Rivaroxaban vs. dalteparin						
Sweden[20]	SEK143	0.0040	SEK35,436	–SEK880	0.0029	Dom
Dabigatran vs. enoxaparin						
UK[10]	NR	NR	Dom	NR	NR	Dom
UK[21]	–£101	0.0060	Dom	–£17	0.007	Dom
UK[22]	–£155	0.0120	Dom	–£97	0.024	Dom
ROI[15]	NR	NR	€17,835	NR	NR	Dom
ROI[16]	NR	NR	€1,868	NR	NR	NR
Norway[19]	–NOK610	–0.3040	NOK2,006	–NOK175	–0.020	NOK9,000
Russia[23]	–RUB2,326	NA	Dom[b]	–RUB2,381	NA	Dom[b]
Apixaban vs. enoxaparin						
UK[10]	NR	NR	Dom	NR	NR	Dom
Canada[24]	NR	NR	Dom	NR	NR	Dom

Dom = dominant; NA = not applicable. NR = not reported; ROI = Republic of Ireland; UK = United Kingdom; US = United States.

[a] Cost-effectiveness was analysed using VTE events avoided as the measure of effect.

[b] Cost-effectiveness was analysed using life-years gained as the measure of effect.

Table 3. Cost-effectiveness of NOACs versus NOACs

Setting and Study	THR			TKR		
	Δ Cost	Δ QALYs	ICER	Δ Cost	Δ QALYs	ICER
Rivaroxaban vs. dabigatran						
ROI[15]	NR	NR	Dom	NR	NR	Dom
ROI[16]	NR	NR	Dom	NR	NR	NR
UK[10]	NR	NR	Dom	NR	NR	Dom
France[17]	–€57	0.0011	Dom	–€8	0.0011	Dom
Italy[17]	–€58	0.0012	Dom	–€17	0.0012	Dom
Spain[17]	–€116	0.0011	Dom	–€28	0.0011	Dom
Norway[19]	NR	NR	NR	NR	NR	Dom
Apixaban vs. dabigatran						
Spain[25]	–€5	0.005	Dom	–€108	0.0169	Dom
UK[10]	NR	NR	Dom	NR	NR	Dom
Rivaroxaban vs. apixaban						
UK[10]	NR	NR	NR	NR	NR	Dom

ICER = incremental cost-effectiveness ratio.

LIMITATIONS

- Unpublished articles and health technology assessment agency websites were not searched and were excluded from the review.
- The inclusion and exclusion of articles was performed by one researcher.
- A formal quality assessment of models was not performed.
- The results of the analyses are not directly comparable between different jurisdictions and different cost-years.

CONCLUSIONS

- Economic analyses of NOACs for primary VTE prophylaxis following THR and TKR showed reasonable consistency in the model structures used and events captured.
- NOACs appear to be cost-effective alternatives to traditional anticoagulants; improved VTE prevention outweighs the increased risk of bleeding.
- Cost-effectiveness analyses published since 2008 suggest that rivaroxaban is the most cost-effective NOAC. However, more research is needed to assess the cost-effectiveness of apixaban and edoxaban.

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REFERENCES

Please see handout for complete reference list.

Presented at: ISPOR 18th Annual European Congress, November 7-11, 2015, Milan, Italy