

# HEALTH AND COST IMPLICATIONS OF DIFFERENT METHODS OF VENOUS THROMBOEMBOLISM PROPHYLAXIS IN GERMANY

Rhodri JK. Saunders<sup>1</sup>, Virginie Mittard<sup>1</sup>, and Michelle Sullivan<sup>2</sup>

1. Coreva Scientific, Freiburg, Germany; 2. Medtronic, Whitley, Hampshire, UK

## Introduction

Venous thromboembolism (VTE) is an important complication associated with total knee arthroplasty (TKA). While low-molecular weight heparin (LMWH) and pentasaccharide (PS) are commonly used in Germany to prevent VTE, multiple other methods of prophylaxis exist. Optimizing the selection of the VTE prophylaxis modality could improve patient outcomes and reduce healthcare expenditure.

## Objectives

Evaluation of how changes in the use of VTE prophylaxis impact on the incidence of deep-vein thrombosis (DVT), pulmonary embolism, major bleeding and the cost of healthcare provision in Germany.

## Materials & Methods

A health economic model of VTE prophylaxis was coded in Microsoft Excel<sup>®</sup> and included Markov models for both VTE onset/progression and incidence of adverse events associated with prophylaxis. The VTE model includes DVT, pulmonary embolism, recurrent VTE, and post-thrombotic syndrome. Adverse events included are minor bleeding, major bleeding, wound infection, and heparin-induced thrombocytopenia. A structured literature search of PubMed provided data to inform the model. Prophylaxis options modelled were: LMWH, unfractionated heparin, PS, rivaroxaban, warfarin and intermittent pneumatic compression (IPC). Efficacy and safety of prophylaxis were taken from meta-analyses, which were specific to orthopaedic surgery where possible. Relative efficacy of products is referenced to LMWH. Patient data are taken from a cohort of the ORTHO-TEP registry (mean age 66.9 years; 41.2% male; Dresden, Germany). [1] The incidences of VTE (6.44%) and bleeding events (6.93%) with LMWH are specific to TKA and taken from the same population, as is use of different prophylaxis methods. Prophylaxis costs are per German list pricing. Event costs from peer-reviewed literature were inflated to 2015 Euros and are all bar one (France) specific to Germany. Sensitivity analyses assessed the robustness of outcomes to model inputs, with 500 simulations performed to calculate 95% credible intervals (CrI).

## Results

For a cohort of 1,000 patients under current market conditions, the model estimates 50.3 DVT events, 8.5 pulmonary embolisms, and 85.8 major bleeds over the course of one year. The total cost to the healthcare provider is estimated at EUR 653,500. Accounting for mortality, the cost per patient year is EUR 659. In this scenario, LMWH and PS have market share of 29.5% and 39.4%, respectively. Patients receiving LMWH and PS account for 28.8% and 45.4% of total costs, respectively. Through transferring 1%-point of market share between products, the impact of changes in clinical practice were assessed. Considering costs associated with efficacy and safety outcomes, warfarin and IPC were likely to be the most cost-effective options (Figure 1). A 1%-point increase in IPC increased the cost per patient year by EUR 0.14 (not significant) compared with warfarin. Significant savings per patient year were apparent for 1%-point increase in IPC in comparison with LMWH (95% CrI -2.83 to -1.56) and PS (95% CrI -5.00 to -2.23). Similar results were found for warfarin. In both cases, savings were driven by reduction in bleeding events.

## Conclusion

Due to the incidence and cost of bleeding events, Warfarin and IPC are likely to be the two most cost-effective options for VTE prophylaxis. Mechanical prophylaxis targets another aspect of Virchow's triad and healthcare providers could consider extending its use.

## BACKGROUND

VTE is a major public health problem, with an estimated incidence of 80,000 cases per year in Germany [2]

- Methods of VTE prophylaxis include pharmaceutical (e.g. heparin) and mechanical (e.g. IPC) options
  - 84% of at-risk patients in Germany get prophylaxis [3]
  - Failure to prescribe appropriate VTE prophylaxis to at-risk patients may be considered a medical error [4]
- German guidelines recommend that all at-risk patients have pharmaceutical prophylaxis unless contraindicated [5]
  - Pharmaceutical prophylaxis can be supplemented with mechanical methods [5]
  - If patients are at increased risk of bleeding, mechanical methods should be used in these patients [5]
- In other countries, IPC is often used in combination with aspirin which would comply with German guidelines
  - Little is known about how increased use of IPC would impact on healthcare budgets and patient outcomes
  - In Germany, patients should be informed of all available prophylaxis options (*Patientenrechtsgesetz 630a-g*)

## AIMS

To use current literature to estimate how changes in the use of VTE prophylaxis impact on healthcare costs and the incidence of deep-vein thrombosis (DVT), pulmonary embolism (PE), and major bleeding

## METHODS

### Data identification

Structured literature searches of PubMed were performed to identify recent publications relating to the incidence and costs of VTE and adverse events (AEs) in the German setting

- Title and abstract searches and MeSH terms restricted returned hits to those specific to VTE, anticoagulation, prophylaxis, or bleeding published from 2010 onwards
  - Searches were performed on February 19, 2015
  - Title and abstract screening against pre-defined exclusion criteria selected hits that provided cost and/or incidence data

### Budget-impact model

Markov models were developed in Microsoft Excel<sup>®</sup> to simulate the onset and progression of VTE and AEs

- The semi-Markov model for VTE included: 'no VTE', 'DVT', 'PE', 'DVT and PE', 'previous VTE', 'post-thrombotic syndrome (PTS)', 'Fatal VTE', and 'death'
- The AE Markov model included: 'no AE', 'minor bleed', 'major bleed', 'fatal bleed', 'wound infection' and 'heparin-induced thrombocytopenia (HIT)'
  - Flexible Markov model order can assess structural uncertainty
  - Death was consolidated between the two Markov models
  - The AE model only ran during the duration of prophylaxis

- Prophylaxis options included: LMWH, unfractionated heparin, rivaroxaban, pentasaccharide (PS), warfarin, IPC, and no prophylaxis

## Base case

A hospital performing 1,000 TKA procedures per year in patients with mean characteristics of age 66.9 years, body mass index (BMI) 28.8 kg/m<sup>2</sup>, 41.2% male, and 3.5% with previous VTE [1]

- Prophylaxis duration (35 days) and market share came from published data specific to TKA [1]
- Event rates with LMWH (Table 1) were taken from the ORTHO-TEP registry, with DVT and PE occurring at a rate of 5.90% and 0.54%, respectively, per 35 days [1]
- Costs (Table 1) were derived from the literature review and adjusted to 2014 EUR using a healthcare-specific CPI [6]
  - Intervention costs were taken from the Rote Liste [7]
- The model time horizon was 1 year with no cost discounting, and one percentage point of market share was moved from LMWH to IPC plus aspirin

Table 1. Event rates and costs

Event	Incidence rate	Value in 2014 EUR
DVT	5.90% per 35 days [1]	1,153 [13]
PE	0.54% per 35 days [1]	2,443 [13]
DVT and PE	1.4% of DVT cases [8]	3,596 [13]
PTS	24.50% per 3 years [9]	2,012 [14]
HIT	0.04% per 15 days [10]	9,807 [10]
Major bleed	6.93% per 35 days [1]	1,775 (Other) to 9,477 (ICH) [15]
Minor bleed	9.90% per 42 days [11]	37 [15]
Deep infection	1.54% of patients [12]	3,213 [16]

DVT, Deep-vein thrombosis; HIT, Heparin-induced thrombocytopenia; ICH, Intracranial hemorrhage; PE, Pulmonary embolism; PTS, Post-thrombotic syndrome.

## Sensitivity analyses

Probabilistic analyses evaluated the robustness of results to changes in all input parameters via sampling

- Results from 500 simulations are presented with the median and 95% credible intervals (CrI)

## RESULTS

Literature review identified 386 articles. After title and abstract screening, 108 hits remained for analysis and 11 were specific to the German setting

### Budget impact analysis

In the base case, a 1%-point market share change from LMWH to IPC resulted in a significant cost reduction of €2,245 (95% CrI €1,500 to €2,804; Table 2)

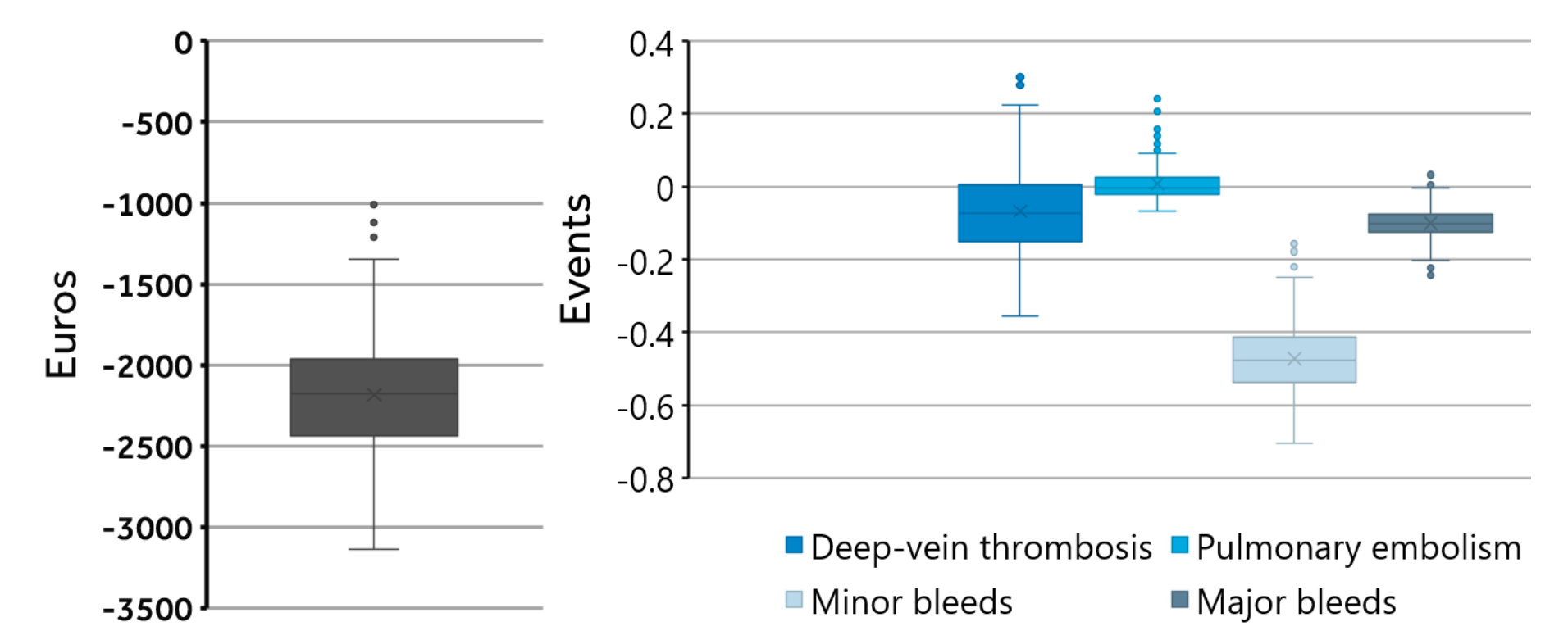
- Accounting for mortality, the saving per patient-year was significant at €2.27 (95% CrI: €1.56 to €2.83)
  - Cost savings were significant although the changes in DVT (95% CrI: -0.28 to +0.15 events) and PE (95% CrI: -0.05 to +0.12 events) were not (Figure 1)
  - Significant reductions in minor (95% CrI: -0.66 to -0.27) and major (-0.18 to -0.01) bleeds were estimated (Figure 1)
- Cost of prophylaxis was the largest cost driver, but if LMWH was at no cost the total cost saving with IPC was €425
  - IPC was estimated to be cost saving in 86.4% of all simulations
  - In the worst-case scenario, IPC would likely be considered cost-effective at €978 and €26,3396 per minor and major bleed avoided, respectively

Table 2. Base case results

Outcomes at 1 year	Current care	LMWH -1%, IPC +1%
Total cost, EUR	653,183	650,938
Cost per patient year, EUR	659	657
DVT, N patients	50.3	50.2
PE, N patients	8.5	8.5
Major bleed, N patients	85.8	85.7
Minor bleed, N patients	71.4	70.9

Current care, Market share as per [1]; DVT, Deep-vein thrombosis; IPC, Intermittent pneumatic compression; LMWH, Low-molecular weight heparin; PE, Pulmonary embolism; Column 2 (LMWH -1%, IPC+1%), as per Current Care, but with 1%-point of market share moved from LMWH to IPC

Figure 1. Model estimated incremental outcomes per 1,000 patients for IPC compared with LMWH



- In the base case, 39.4% of patients received PS, which accounted for 45.4% of total costs
  - For LMWH, these values were 29.5% and 28.8%, respectively
- Comparing all VTE prophylaxis options, warfarin and IPC were estimated to be the most cost saving (Table 3)
  - Warfarin reduce cost most substantially but was associated with significantly increased DVT compared with LMWH

Table 3. Estimated cost saving in EUR per patient-year for every 1 %-point change in market share

1%-point of market share gained by	1%-point of market share taken from					
	LMWH	UFH	Riv	PS	War	IPC
LMWH	-0.33	0.57	-1.17	2.40	2.27	
UFH	0.33	0.91	-0.83	2.74	2.60	
Riv	-0.57	-0.91	-1.71	1.83	1.69	
PS	1.17	0.83	1.71	3.57	3.43	
War	-2.40	-2.74	-1.83	-3.57	-0.14	
IPC	-2.27	-2.60	-1.69	-3.43	0.14	

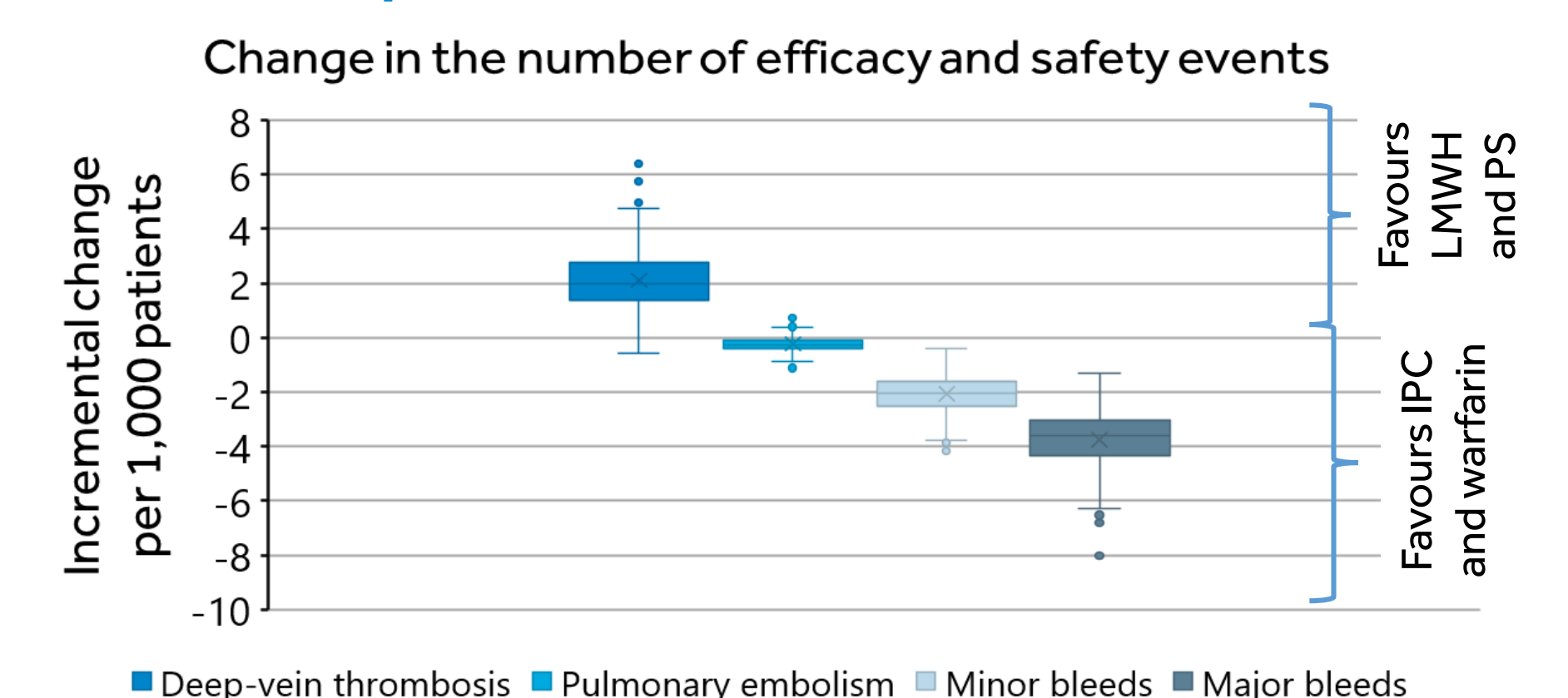
IPC, Intermittent pneumatic compression; LMWH, Low-molecular weight heparin; PS, Pentasaccharide; Riv, Rivaroxaban; UFH, Unfractionated heparin; War, Warfarin

## Scenario analysis

Given that warfarin and IPC are the least cost-intensive options, a scenario was run for a 5 %-point increase in these two products and a 5 %-point decrease in LMWH and PS

- Significant savings of €29 per patient-year are estimated, driven by reduction in major bleeds (-3.7 events) and lower product costs
- DVT would likely be increased but would be outweighed by reduced major bleeding (Figure 2)

Figure 2. Most safety events are less frequent with IPC and Warfarin compared with LMWH and PS



## CONCLUSIONS

- Cost savings with IPC plus aspirin compared with LMWH are significant
- Per patient cost saving are small and minor market share changes will not substantially reduce expenditure
- The model demonstrates that there are significantly fewer bleeding events with IPC plus aspirin
- Model estimates support offering patients the option of IPC prophylaxis

## ACKNOWLEDGMENTS

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