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Management patterns of thrombosis prophylaxis and related costs in hip and knee replacement in Germany

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Abstract: The objective of the study was to depict treatment strategies, health care utilisation and cost evaluation of hip and knee replacement surgery in Germany, with a particular emphasis on thrombosis prophylaxis (TP) for the prevention of deep vein thrombosis (DVT). In this multi-centre prospective cohort study, medical record data (socio-demographics, risk factors for thrombosis, thrombosis prophylaxis, course of hospital stay) were collected for patients undergoing either total hip replacement (THR) or total knee replacement (TKR). One and three months post-operatively, post-operative outcomes and health care resource use were documented by patient and physician questionnaires. A total of 309 patients participated in the study (59% female, mean age 66 [SD 10] years). Parenteral anticoagulation was administered for a mean of 38 (SD 16) days. 27 (9%) patients received subsequent oral anticoagulation for a mean of 38 (SD 21) additional days. Symptomatic DVT was reported by four (1.3%) patients. Mean overall direct costs associated with surgery from baseline to 3 months were EUR 11 264 (median 11 564, SD 2 481). Hospital and rehabilitation accounted for 97% of direct costs; costs for medications, physical therapy, physician office visits, out-of-pocket expenses, as well as complication costs accounted for an additional 3% of direct costs. Within these direct costs, a mean of EUR 348 (SD 361) was related to thrombosis prophylaxis, accounting for 3% of direct costs. Mean overall cost was EUR 11 926 (SD 2 481), including 6% indirect costs of productivity loss. Extended thrombosis prophylaxis was observed in the usual care setting of the study and associated with low incidence of symptomatic DVT. Thrombosis prophylaxis is – within the considerable economic burden of joint replacement surgery – a relatively small cost component.

Keywords: Thrombosis prophylaxis, costs, treatment patterns, deep vein thrombosis, hip replacement surgery, knee replacement surgery

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1 Introduction

Venous thromboembolism (VTE) is a potentially serious vascular event, which most often occurs due to surgery or trauma. Contributing risk factors include previous VTE or a family history of VTE, immobility, venous stasis or obstruction, obesity (BMI >30), advancing age (> 50 years), cancer, sepsis, chronic heart failure (NYHA III°or IV°), nephrotic syndrome, as well as pregnancy and the first 3 months postpartum [1, 2].

VTE has two major clinical manifestations. Most common is deep vein thrombosis (DVT), which normally arises in the deep veins of the calf and spreads proximally. The other, pulmonary embolism (PE), is much more serious and can be life-threatening. Long-term consequences of VTE can be an increased risk of a recurrence, including PE, as well as chronic venous insufficiency (CVI) caused by damage to the valves of the veins by the thrombotic process, resulting in chronic pain, oedema and ulceration of the leg [3, 4].

Recommended measures in the prophylaxis of VTE include anticoagulation with low molecular weight heparin (LMWH), regional anaesthesia, combined with the use of graduated compression stockings and/or intermittent pneumatic compression devices [5, 6].

Patients undergoing hip replacement or with hip fractures are among the groups at highest risk of VTE [7, 8]. Without prophylaxis, venogram-diagnosed DVT following total hip replacement (THR) occurs in 45-57% of patients and in 40-84% following total knee replacement (TKR). The incidence of fatal PE following hip or knee replacement surgery is between 0.2 and 0.7% [9–11].

Even with conventional (7-10 day) LMWH anticoagulation, the prevalence of DVT remains at 27% (95% CI 23-31) following THR and 31% (95% CI 29-33) in TKR [12, 13]. A subsequent CVI, which can dramatically impair quality of life and have a significant financial impact on both the patient and the health system, has a prevalence of 2 - 33% following DVT [14–16].

The primary objectives of the TOCA (Thrombosis Prophylaxis: Outcomes and Care Assessment) study were to depict treatment strategies, health care utilisation and cost evaluation of hip and knee replacement surgery in Germany, with a particular emphasis on thrombosis prophylaxis (TP) for the prevention of DVT. Additional objectives included the assessment of the typical prophylaxis treatment patterns in comparison to the current published guidelines, as well as the occurrence of VTEs and complications in anticoagulation.

2 Statistical methods and Experimental Procedures

2.1 Study Design and Subjects

This multi-centre, prospective observational cohort study was conducted in 17 hospital centres in Germany from September 2002 through May 2003. Centres chosen for the study were required to conduct a minimum of 25 total joint replacement surgeries per month.

Eligibility for participation in the study included elective total hip or total knee replacement surgery and the ability to understand and complete the written questionnaires. Patients were recruited consecutively by their attending surgeon into the study after providing written informed consent. Participation in the study was voluntary and patients were assured in writing that refusal to participate would not affect their care in any way. Ethical approval of the protocol was obtained by the ethics committee of the investigating centre; the study was conducted in accordance with the Declaration of Helsinki and under International Conference on Harmonisation, Good Clinical Practice and Good Epidemiological Practice guidelines.

2.2 Study Organisation

Data were collected postoperatively from the patient hospital chart by trained personnel using a standardised, printed data collection form and included risk factors for thrombosis, co-morbidities, physical measures initiated as part of a thrombosis prophylaxis regime, type of anaesthesia, complications of either the surgery and/or the thrombosis prophylaxis, as well as the type, duration and complications of anticoagulation. In addition, information regarding the size of the hospital centre, academic status, the level of quality management in the hospital and/or department and patient education programmes, both general and specific to thrombosis prophylaxis, was documented using a standardised survey form.

The patient was sent by post a written, standardised questionnaire one and three months postoperatively, each of which took approximately 30 minutes to complete. The respective post-operative periods were documented, including socio-demographic information as well as clinical and cost data, including length of stay in the acute care hospital and the customary rehabilitation following surgery, number and purpose of physician office visits, any additional costs not covered by their health insurance, all medications, number and type of physical therapy visits, as well as medical devices and aids.

Information concerning anticoagulation was requested, including duration of anticoagulation and its monitoring, complications arising from anticoagulation, inpatient and outpatient treatment, changes made to the anticoagulation regime, ability of self-administration and any instruction given. Returned questionnaires were individually reviewed by the study office for completeness, clarity and logic. In case of missing data, patients were contacted by telephone to supply missing items or to provide clarification, according to standard operating procedures. Patients who did not return a questionnaire were sent two reminders by post, followed by a telephone reminder, before they were designated as being lost to follow-up.

Following the one-month questionnaire, the information provided by the patient was confirmed and supplemented by a telephone interview with the attending physician. The physician time required for this interview was reimbursed by a flat fee.

2.3 Resource Use and Costs

In order to determine direct and indirect costs, each unit of resource use was valued by cost factors specific to Germany, based on the 2003 costs to the public sickness funds. The individual cost valuation is described below.

2.3.1 Hospital and rehabilitation costs

Hospital costs for each patient were based on the specific case rate of hip and knee replacement surgery for their hospital and state [17]. At the time of the study, reimbursement to hospitals for procedures were case-based and included surgery and anaesthesia costs, medications, physical therapy and aids, hotel, nursing and physician costs for the procedure, as well as any ensuing complications during that admission.

In Germany, a three-week rehabilitation, usually on an in-patient basis, is routinely prescribed following hip or knee replacement surgery, with the goal of restoring the patient to reasonable post-operative functionality. Rehabilitation was calculated at an average daily rate multiplied by the number of days in the rehabilitation centre [18].

2.3.2 Physician visit costs

Physician office visits and phlebotomy as stated by patients and/or physician were calculated on an average visit cost to a general practitioner or orthopaedic surgeon, based on a point worth of EUR 0.04. Payment to physicians in Germany is a fee-for-service system using a uniform scale of services, each of which is allocated a corresponding number of points. Payment is calculated by multiplying the points by a quarterly ex-post fixed-point value. Costs are reimbursed to the physician's association from the sickness funds on the basis of a fixed annual budget.

2.3.3 Medication costs

Patients were asked to list their daily doses of all medications. The direct cost of medications, other than those for TP, was then calculated from the daily dose multiplied by the number of days the medication was taken within the evaluation period. Medication costs were calculated based on the list price in the *Gelbe Liste* [19].

2.3.4 Physical therapy and patient aid costs

Physical therapy costs were calculated per session attended, according to the treatment received and patient aids utilised, such as canes and crutches and other assists for activities of daily living (ADLs), were calculated as an average local cost.

2.3.5 Other direct out-of-pocket costs

Other direct costs to the patient were calculated from patient information of additional expenses they or their family had incurred.

2.3.6 Costs specific to thrombosis prophylaxis

Within the above cost calculations, costs related specifically to TP are an intrinsic component. The following concepts were used to differentiate and determine the costs specific to TP:

2.3.7 In-patient care (acute-care hospital and rehabilitation)

The cost for parenteral anticoagulation was calculated from the total duration of LMWH, as reported by the patient, multiplied by an average medication cost from the study centres. From the literature [20], personnel costs were based on the delivery of one injection per day, an average personnel time of 0.66 minute per injection at a wage rate of EUR 0.50 per minute. Thrombocyte counts used for monitoring the onset of heparin-induced thrombocytopenia (HIT) are part of the normal pre- and post-operative blood count. Costs related to TP monitoring were calculated based on an average charge in the study centres and six blood draws post-operatively from day one to day 20 or the discontinuance of LMWH, whichever came first.

To calculate the cost of re-hospitalisation due to complications, the daily bed rate for a general medical ward for each hospital was used. At the time of the study, hospital costs for medical admissions were calculated on a daily rate, specific for each hospital and state. With the introduction of DRG payments in 2004, this payment structure has now changed to a prospective rate.

2.3.8 Out-patient care

The cost for LMWH was based on the continuance of one dose per day after discharge from the acute care or rehabilitation hospital, as reported by the patient, multiplied by the number of days received after discharge, including pharmacy rebate, co-pay and the need for home care to provide the injection [21]. Oral anticoagulation with Marcumar was determined with a two-day titration at onset and average subsequent daily dose for the number of days prescribed or until the end of the study period [21]. Monitoring costs of INR were based on physician costs [22].

Physician visits related to thrombosis prophylaxis were identified by the patient and confirmed during the physician interview. Anti-embolic stockings and their aids for applying were calculated based on an average local price.

Out-of-pocket expenses related to TP were determined as specifically reported by the patient.

2.3.9 Indirect costs

Indirect costs, denoted by absence from work, were also considered. The cost of workdays lost was included only for patients who were absent from work or forced to take early retirement during the study period because of their joint replacement surgery. The rate was calculated on the average German annual wage of EUR 28 518 or EUR 78.13 per day [23].

Costs of the specific resource components evaluated are detailed in Table 1.

Table 1 Resource Cost Components (based on 2003 German costs).

Resource	Cost
Direct Costs	
Initial hospitalisation (state- and hospital-specific)	
THR	
All hospitals (range)	€ 5 620 – 8 908
University medical centre (n=2, range)	€ 5 721 – 5 721
Teaching hospital (n=8, range)	€ 5 620 – 8 908
Orthopaedic hospital (n=5, range)	€ 8 108 – 8 743
Private hospital (n=2, range)	€ 8 823 – 8 823
TKR	
All hospitals (range)	€ 8 932 – 10 380
University medical centre (n=2, range)	€ 10 380 – 10 380
Teaching hospital (n=8, range)	€ 8 932 – 10 380
Orthopaedic hospital (n=5, range)	€ 8 932 – 9 533
Private hospital (n=2, range)	€ 9 606 – 9 606
Rehabilitation (average day rate)	€ 138.38
Physician visit (average cost/visit)	
General practitioner	€ 12.26
Orthopaedist	€ 13.76
Outpatient medications (other than for TP)	Daily dose times days taken
Costs specific to thrombosis prophylaxis	
Parenteral LMWH Heparin (average cost/injection)	
In patient (including € 0.33 personnel costs)	€ 6.13
Out-patient (with pharmacy rebate and co-pay)	
Requiring home care	€ 7.66
Self-injected	€ 6.22
Monitoring costs (thrombocyte count, average cost/test)	€ 1.20
Compression stockings (average local cost)	€ 89.48
Stocking placement aids (average local cost)	€ 22.00
Oral anticoagulation (unit cost Marcumar)	
2-day titration	€ 0.73
average subsequent daily dose	€ 0.16
monitoring (per test)	€ 4.60
Re-hospitalisation for TP complications (range of specific hospital day rates for a general medical ward bed)	€ 161 - 298
Physical Therapy (cost range per session for specific treatment)	€ 9.37 – 21.09
Patient aids (range) e.g. cane, walker, bathing aids	€ 11.48 – 360.00
Transport	
Taxi fare per ride (mean)	€ 13.83 or as stated by patient
Out-of-pocket expenses	As given by patient
Indirect costs	
Productivity loss per day (German mean)	€ 78.13

2.4 Statistical Analysis

Data analysis included demographic and cost data specific to joint replacement surgery and thrombosis prophylaxis and are descriptively presented. Demographic data were compiled for the entire study period, cost data were analysed as an aggregate, as well as by individual components. Depending on the particular variable, mean, standard deviation,

minimum, maximum and interquartile range were analysed for each continuous variable; for categorical data, frequencies and percentages were calculated. Results are reported as mean ± standard deviation except where otherwise noted. All analyses were performed by SPSS® Version 11.0.

2.4.1 Care Assessment

The clinical guidelines of the German Society for Surgery [24] were used to evaluate the typical course of treatment for patients with joint replacement. These guidelines specifically address the measures for optimum thrombosis prophylaxis in hip and knee replacement surgery, emphasising the use of a combination of both physical measures and anticoagulation medications in thrombosis prophylaxis. Recommended physical measures include early mobilisation, carefully fitted anti-embolic stockings, peri-operative active and passive exercises, such as 'bed-bicycling', rhythmic pneumatic calf compression, as well as circulatory and breathing exercises. Pharmacological therapy recommended includes LMWH, recombinated hirudin, Factor Xa inhibitors and Vitamin-K antagonists; however, the prescribed duration of anticoagulation is left to the discretion of the physician.

3 Results

From October through December 2002, 309 patients were consecutively recruited preoperatively into the study by their surgeon, after providing written informed consent. 286 patients (93%) completed the one-month follow-up questionnaire; 277 (90%) completed the entire study. Of the 32 patients who did not complete all questionnaires, five (15%) cited poor health unrelated to their surgery, eight (25%) too much paperwork, four (13%) no further interest as reasons to drop out of the evaluation. 15 (47%) were designated lost to follow-up after questionnaires were not returned despite three reminders. Unless otherwise noted, the analyses were conducted on an intention-to-treat basis, with all 309 patients included, and based on data from the entire 3-month follow-up period.

181 (59%) patients received a total hip replacement and 128 (41%) a total knee replacement. Table 2 summarises the demographic characteristics and risk factors of the study participants. 92% were aged 50 or older. One patient had documented nephrotic syndrome. Patients receiving a total knee replacement were significantly older, more obese and less likely to be employed outside the home.

3.1 Hospital and Rehabilitation Stays

The study hospitals were classified in four groups: university medical centres (n=2, 12%), teaching hospitals associated with a university (n=8, 47%), specialised orthopaedic hospitals (n=5, 29%) and private hospitals (n=2, 12%). The level of quality management was assessed by the use of specific guidelines for anticoagulation and continuing education for

the physicians and nurses. The characteristics of the 17 study hospitals can be found in Table 3.

Table 2 Socio-demographics of patients and risk factors for thrombosis development.

	THR	TKR	All Patients
No. of patients (n, %)	181 (59%)	128 (41%)	309
Mean Age (years ± SD, range)	63.8 ± 11 31 - 84	69.6 ± 8 33 - 90	66.2 ± 10 31 - 90
Gender (female) (n, %)	100 (55%)	84 (66%)	184 (59%)
Living situation (n, %)			
With partner/other	138 (76%)	86 (67%)	224 (73%)
Alone	43 (24%)	42 (33%)	85 (27%)
Employment status (n, %)			
Retired	123 (68%)	108 (84%)	231 (75%)
Unemployed	12 (7%)	2 (2%)	14 (4%)
Housewife/Houseman	8 (4%)	11 (9%)	19 (6%)
Employed outside the home	38 (21%)	7 (5%)	45 (15%)
Risk Factor for VTE (n,%)			
Age $\geq$ 50 years	159 (89%)	126 (98%)	131 (42%)
Obese (BMI > 30)	33 (18%)	42 (33%)	75 (26%)
Previous thrombosis (also in medical history of 1°relative)	10 (6%)	12 (9%)	22 (7%)
Malignancy	7 (4%)	1 (1%)	8 (3%)
Concurrent infection	2 (1%)	0	2 (1%)

Table 3 Characteristics of Recruiting Hospitals.

	University medical centre (n=2)	Teaching hospital (n=8)	Orthopaedic hospital (n=5)	Private hospital (n=2)
Patients recruited (n, %)	22 (7%)	112 (36%)	123 (40%)	52 (17%)
Size of facility (beds)				
mean ± SD	550 ± 579	248 ± 251	154 ± 89	365 ± 212
range	141 - 960	45 - 600	83 - 297	215 - 515
Annual THR performed				
mean ± SD	310 ± 269	364 ± 238	1036 ± 1102	750 ± 71
range	120 - 500	102 - 750	440 - 3000	700 - 800
Annual TKR performed				
mean ± SD	298 ± 286	177 ± 125	718 ± 718	475 ± 177
range	95 - 500	48 - 400	340 - 2000	350 - 600
Quality management				
Use guidelines (n, %)	2 (100%)	8 (100%)	5 (100%)	2 (100%)
Attend continuing education in anticoagulation (n, %)	2 (100%)	7 (88%)	4 (80%)	2 (100%)
Offer patient education in anticoagulation (n, %)	1 (50%)	7 (88%)	3 (60%)	1 (50%)

The overall mean length of hospital stay was 17.4 days (SD 6.2, range 7 - 47) and mean length of inpatient rehabilitation stay was 21.6 days (SD 4.6, range 3 - 42). The total inpatient hospital and rehabilitation stay was not significantly different between patients who received a THR and those who received a TKR.

In total, 275 (96%) patients received in-patient rehabilitation. Of the 286 patients who completed the 1-month follow-up, 249 (87%) were admitted directly to an inpatient rehabilitation program. 25 (9%) patients were discharged home for a mean of 11.4 days (SD 20.0, range 1 - 91) before being admitted to an in-patient rehabilitation centre and 20 (80%) of these patients continued parenteral anticoagulation at home before receiving rehabilitation. Three (1%) patients received only outpatient rehabilitation. Additionally, nine patients (3%) were discharged home from the acute-care hospital and reported no rehabilitation or outpatient physical therapy.

3.2 Post discharge care

3.2.1 Anticoagulation

Table 4 describes the anticoagulation therapy in the 3-month follow-up study period. All patients (309, 100%) received one dose of LWMH per day in the acute care hospital. 125 (41%) patients who received parenteral anticoagulation following discharge from hospital or rehabilitation were able to self-inject their medication. The remaining 123 patients required assistance from nursing personnel, their physician, partner or other family member.

Table 4 Duration of Anticoagulation.

Parenteral anticoagulation (LMWH)	THR n=181	TKR n=128	Total n=309
Initial hospital dose (I.U.)			
Mean ± SD	4 241 ± 554	4 435 ± 643	4 324 ± 600
range	2 000 – 6 000	3 000 – 6 000	2 000 – 6 000
Length of parenteral anticoagulation (days)			
Mean ± SD	35.2 ± 14.4	41.7 ± 17.6	37.8 ± 16.1
Interquartile range	28 - 42	30 - 50	5 - 91
In hospital (mean ± SD)	16.0 ± 5.0	18.1 ± 6.5	16.9 ± 5.8
In rehabilitation (mean ± SD)	13.4 ± 9.3	12.4 ± 9.1	13.0 ± 9.2
Out-patient (mean ± SD)	5.2 ± 11.3	10.1 ± 16.1	7.2 ± 13.7

Oral anticoagulation following parenteral anticoagulation	THR n=20 (11%)	TKR n=7 (6%)	Total n=27 (9%)
Length of oral coagulation (days)			
Mean ± SD	37.3 ± 22.4	38.5 ± 19.4	37.6 ± 21.3
Interquartile range	2 - 60	10 - 60	2 - 60

Following the course of parenteral anticoagulation, 27 (9%) patients received a further course of an oral thrombosis prophylaxis (37% Vitamin-K antagonist, 63% aspirin)

following parenteral anticoagulation. 19 of these 27 patients (70%) were considered high-risk for a deep vein thrombosis, due to age, previous individual or family history of a thrombosis, BMI > 30, or a diagnosis of cancer.

3.2.2 Physician visits

234 (76%) patients reported a mean of 2.3 physician office visits (SD 2.5, median 2.0, range 0-21) after discharge from hospital or rehabilitation in the 3-month follow-up period. 27 (12%) of these patients had office visits directly related to their thrombosis prophylaxis (mean 2.7, SD 2.3, median 2.0, range 1-21). Additional physician visits made by the 234 patients (mean 1.7, SD 1.5, median 1.0, range 0-11) were stated to be surgery-related.

3.2.3 Physical therapy

Following discharge, 36 of the 275 (13%) patients who had received inpatient rehabilitation received further outpatient physical therapy, including exercise and massage treatments.

3.3 Costs associated with THR, TKR and related TP

The results of the evaluation of costs in joint replacement surgery and the 3-month post-operative period can be found in Table 5. Mean direct costs incurred were EUR 11 264 (SD 1 747), 97% of which were hospital and rehabilitation costs. Other costs for medication, physical therapy, physician office visits, out-of-pocket expenses, such as co-payments for physician visits, medical aids not covered by insurance and home help, as well as complication costs accounted for an additional 3% of direct costs. Within these, costs related to thrombosis prophylaxis accounted for 3% of direct costs. Indirect costs of productivity loss were responsible for 6% of the mean overall cost of EUR 11 926 (SD 2 481).

3.3.1 Complications

Four patients (1.3%), all of whom were at an increased risk for VTE due to age and/or a previous DVT, reported developing a thromboembolism during the 3-month follow-up period. These patients received parenteral anticoagulation for a mean of 55.8 days (SD 32.1, range 27-90) and a further course of oral anticoagulation for a mean of 16.3 days (SD 9.7, range 9-30). Two patients required re-hospitalisation for a mean of 12.1 days (SD 2.8, range 10-14) for treatment of this complication.

The most common complication reported was bruising at the injection site (n=103, 33%) followed by lesser incidences of itching, pain, increased tendency to bleeding or bruising, induration at the injection site and pain and discolouration of the big toes (Table 6).

No cases of HIT were reported and 147 patients (48%) reported no problems or complications with their parenteral anticoagulation.

Table 5 Costs in hip (THR) and knee (TKR) replacement surgery, including costs relating to thrombosis prophylaxis (TP).

	THR n=181 Mean cost € ± SD Median (range)	TKR n=128 Mean cost € ± SD Median (range)	Total n=309 Mean cost € ± SD Median (range)
Hospitalisation	7 947 ± 1 178 8 125 (5 620 – 8 908)	9 478 ± 443 9 606 (8 932 – 10 380)	8 581 ± 1 209 8 846 (5 620 – 10 380)
Costs related to TP	104 ± 32 98 (43 – 234)	117 ± 41 110 (38 – 277)	109 ± 36 110 (38 – 277)
LMWH	93 ± 29 87 (35 – 215)	105 ± 38 99 (29 – 255)	98 ± 34 99 (29 – 255)
Personnel	6 ± 2 6 (2 – 12)	6 ± 2 6 (2 – 15)	6 ± 2 6 (2 – 15)
Monitoring	6 ± 1 6 (4 – 7)	6 ± 1 6 (4 – 7)	6 ± 1 6 (4 – 7)
Rehabilitation	2 460 ± 1 329 2 906 (0 – 5 812)	2 101 ± 1 410 2 905 (0 – 5 812)	2 311 ± 1 373 2 906 (0 – 5 812)
Costs related to TP	71 ± 61 75 (0 – 221)	61 ± 59 53 (0 – 174)	67 ± 60 74 (0 – 221)
LMWH	66 ± 57 70 (0 – 209)	57 ± 55 49 (0 – 162)	62 ± 56 70 (0 – 209)
Personnel	4 ± 3 4 (0 – 12)	3 ± 3 2 (0 – 9)	4 ± 3 4 (0 – 12)
Monitoring	1 ± 1 0 (0 – 4)	1 ± 1 0 (0 – 4)	1 ± 1 0 (0 – 4)
Outpatient medications	149 ± 178 81(0 – 737)	195 ± 189 142(0 – 1 089)	168 ± 183 105(0 – 1 089)
Costs related to TP	57 ± 78 31 (0 – 406)	94 ± 106 51 (0 – 476)	72 ± 92 33 (0 – 476)
LMWH	36 ± 75 0 (0 – 406)	71 ± 104 12 (0 – 460)	50 ± 89 0 (0 – 460)
Oral anticoagulant	1 ± 2 0 (0 – 10)	1 ± 2 0 (0 – 10)	1 ± 2 0 (0 – 10)
Monitoring	21 ± 16 28 (0 – 54)	23 ± 19 28 (0 – 85)	21 ± 17 28 (0 – 85)
Physical therapy and aids	107 ± 90 101 (0 – 554)	110 ± 131 101 (0 – 862)	108 ± 109 101 (0 – 862)
Costs related to TP (Anti-embolic stockings and aids)	64 ± 43 90 (0 – 112)	60 ± 43 90 (0 – 112)	63 ± 43 90 (0 – 112)
Physician office visits	49 ± 35 14 (12 – 291)	56 ± 43 28 (12 – 310)	52 ± 38 26 (12 – 310)
Cost of TP-related visits	2 ± 8 0 (0 – 61)	5 ± 21 0 (0 – 172)	4 ± 15 0 (0 – 172)
Cost of TP complications	13 ± 174 0 (0 – 2 263)	60 ± 467 0 (0 – 4 763)	32 ± 328 0 (0 – 4 763)
Out-of-pocket expenses	6 ± 37 0 (0 – 365)	23 ± 220 0 (0 – 2 492)	13 ± 144 0 (0 – 2 492)
Costs related to TP	2 ± 12 0 (0 – 110)	3 ± 12 0 (0 – 110)	2 ± 12 0 (0 – 110)

Table 5 (continued) Costs in hip (THR) and knee (TKR) replacement surgery, including costs relating to thrombosis prophylaxis (TP).

	THR n=181 Mean cost € ± SD Median (range)	TKR n=128 Mean cost € ± SD Median (range)	Total n=309 Mean cost € ± SD Median (range)
Direct costs	€ 10 731 ± 1 660 11 325 (5 633 – 13 909)	€ 12 018 ± 1 587 12 287 (8 962 – 17 663)	€ 11 264 ± 1 747 11 564 (5 633 – 17 663)
Direct costs related to TP	€ 313 ± 213 297 (75 – 2 640)	€ 398 ± 499 325 (93 – 5 126)	€ 348 ± 361 310 (75 – 5 126)
Indirect costs (Productivity loss)	954 ± 2 164 0 (0 – 7 110)	252 ± 1 216 0 (0 – 7 110)	663 ± 1 862 0 (0 – 7 110)
Total costs	€ 11 686 ± 2 756 11 480 (5 633 – 20 966)	€ 12 270 ± 1 989 12 368 (8 962 – 20 385)	€ 11 926 ± 2 481 11 888 (5 633 – 20 966)

Table 6 Complications of thrombosis prophylaxis after 3 months, total and by total hip (THR) and knee (TKR) replacement.

Complication reported	THR n=181 n (%)	TKR n=128 n (%)	Total n=309 n (%)
symptomatic deep vein thrombosis	3 (1.7%)	1 (0.8%)	4 (1.3%)
bruising at the injection site	61 (33.7%)	42 (32.8%)	103 (33.3%)
itching	7 (3.9%)	1 (0.8%)	8 (2.6%)
pain	6 (3.3%)	2 (1.6%)	8 (2.6%)
increased bleeding immediately post-operative	4 (2.2%)	6 (4.7%)	10 (3.2%)
general increase in tendency to bruise	3 (1.7%)	2 (1.6%)	5 (1.6%)
induration at the injection site	1 (0.6%)	2 (1.6%)	3 (1.0%)
pain and discolouration of the big toes	1 (0.6%)	2 (1.6%)	3 (1.0%)

3.3.2 Adherence to Clinical Guidelines

The compliance to clinical guidelines is shown in Table 7. 246 (79%) patients were mobilised by the first post-operative day; compliance to the use of anti-embolic stockings as well as active, passive and deep-breathing exercises was over 90%. 309 (100%) of the study participants received LMWH post-operatively.

The use of regional anaesthesia, initiated no sooner than 10-12 hours before surgery to reduce the possibility of perispinal haematoma, has been shown to reduce the risk of postoperative DVT and is recommended in hip and knee replacement [25, 26]. Regional anaesthesia increases blood flow to the lower extremity during and immediately after surgery, thereby minimizing venous stasis and reducing the risk of deep venous thrombosis, as well as facilitating early mobilisation. 196 (63%) patients underwent regional anaesthesia, with anticoagulation initiated on the previous day in 188 (96%). Anticoag-

ulation was initiated on the day of surgery in the other eight (4%) patients.

Table 7 Compliance to Clinical Guidelines [24] for prevention of deep vein thrombosis (DVT) for total hip (THR) and knee (TKR) replacement surgery.

Guideline	THR n=181 n (%)	TKR n=128 n (%)	Total n=309 n (%)
Mobilisation by second postoperative day	166 (93%)	123 (96%)	289 (94%)
Anti-embolic surgical stockings	167 (92%)	115 (90%)	282 (91%)
Active and passive exercises	171 (95%)	126 (98%)	297 (96%)
Deep breathing exercises	174 (96%)	126 (98%)	300 (97%)
LMWH			
Minimum 7-10 days	176 (97%)	126 (98%)	302 (98%)
Minimum 30 days	123 (68%)	95 (74%)	218 (71%)

4 Discussion

This study presents an overview of typical treatment patterns and outcomes of thrombosis prophylaxis, including related costs, in patients undergoing total hip and knee replacement surgery in Germany. The study, with prospective observational patient data, provides a unique assessment of actual practice of and related costs to thrombosis prophylaxis.

The 17.4-day mean hospital length of stay is close to that in other European countries but considerably longer than the 6.5-day average length of stay in the United States [27–29]. Even with the introduction of a DRG prospective payment system, the listed average length of stay expected for joint replacement remains between 17 and 24 days [30], depending on the surgery performed. In Germany, a three-week in-patient rehabilitation is routinely prescribed following major orthopaedic surgery [31], which correlates to the results from this study. Given that the total hospital and rehabilitation stay of 39 days was on average similar to the average length of thrombosis prophylaxis, parenteral anticoagulation could be relatively easily integrated into usual in-patient care and should not impact too heavily on the need for home care or self-administration of an anticoagulant by the patient after discharge.

The clinical guidelines [24] describe basic physical and pharmacological measures for thrombosis prophylaxis, such as early mobilisation, anti-embolic surgical stockings and active and passive exercises in addition to anticoagulation. The majority of the study centre physicians adhered to recommended guidelines of physical measures for thrombosis prophylaxis. A limitation of the study, however, is that surgeons in the centres were aware that the care and outcomes were being evaluated, a fact that could have contributed to greater attention to guideline compliance. In addition, the centres recruited to participate in the evaluation conducted on average a relatively large number (1000/year) of joint replacement surgeries, which could introduce a performance bias. In comparison to

hospitals in which the procedures are performed less frequently, the quality of care in the study hospitals could be expected to be superior [32]. Centres were requested to enrol patients consecutively over the recruitment period but a patient selection bias cannot be ruled out completely.

For this group of patients, all of whom would be considered at high risk for a thrombosis due to joint arthroplasty, the pharmacological measures of thrombosis prophylaxis recommended in the guidelines were followed in 100% of the cases, which exceeded our expectations. However, contraindications to heparin, such as a diagnosis of nephrotic syndrome, were not always observed.

The duration of LWMH after joint replacement is not specifically defined in the clinical guidelines from 2000 which were in use at the time of this study, although 7-10 days are recommended by the American College of Chest Physicians (ACCP) [33]. The utilisation of extended prophylaxis with LMWH has been shown to reduce the incidence of DVT following arthroplasty but the implementation of its use remains controversial. Cohen et al. [34] examined the relevance of the length of prophylaxis to the occurrence of VTE in a meta-analysis of six randomised controlled studies. The results showed an incidence of symptomatic DVT of 1.6% with a four to five week prophylaxis of parenteral anticoagulation. Other research [35–37] verify these results, although these findings could not be confirmed in a study by Heit, et al. [38].

The 1.3% incidence of symptomatic DVT in this study with a mean duration of parenteral anticoagulation of nearly 38 days is in line with these findings. However, complete follow-up data for 10% of the patients were not available, which could impact the incidence of DVT and related treatment costs found in this evaluation. As well, as this study addressed thrombosis prophylaxis only during the initial post-operative and rehabilitation time frame, this limitation does not take into consideration any late complications, such as chronic venous insufficiency, a late-onset or recurrent DVT. The recommendation for a 4-5 week duration of LWMH has now been included in the 2003 revised clinical guidelines of the German Society for Surgery for patients undergoing hip replacement surgery and hip fracture, as well as after extensive cancer surgeries [39]. Patients in this study who underwent a hip replacement received LWMH for an average of 35 days, demonstrating that this standard was indeed already in practice.

The escalating costs of health care in the industrialised countries is of increasing concern to decision makers who are responsible for allocating scarce medical resources. Formal assessments, such as cost-of-illness analyses or modelling of costs and outcomes, provide the necessary information to optimise decision-making. Data regarding the effectiveness of prevention and therapy strategies of DVT can be obtained from both controlled international studies and uncontrolled observational studies. However, the cost-effectiveness of new treatment strategies should be evaluated whenever possible from the societal perspective in light of normal practice. The TOCA study specifically examined the costs of hip and knee replacement and associated thrombosis prophylaxis generated in usual practice in Germany and the results, showing a total mean cost of EUR 11 686 for THR and EUR 12 270 for knee replacement, are comparable to that reported in the lit-

erature [40]. The 5% higher cost of knee replacement surgery can be explained primarily through the higher cost for hospitalisation.

The significance to health care payers of the fact that over 90% of the costs of joint replacement are due to hospital and rehabilitation admissions could influence strategies aimed at reducing these costs while still achieving similar clinical outcomes, including retaining adequate control of the incidence of complications. The efficiency improvement potential in the overall management of joint replacement in Germany through a reduced in-hospital length of stay and ambulatory rehabilitation could be considerable and deserves further investigation, especially in light of the DRG prospective payment system for hospitals now in effect.

However, given the demonstrated practice of extended TP, this would most likely necessitate outpatient management of thrombosis prophylaxis, including self-injection of parenteral heparin. This practice has been shown to be effective and safe, as long as the patients are carefully selected and supported by health professionals [41]. This was corroborated in this study by the fact that a large proportion of the patients reported being able to inject their anticoagulation. The introduction of oral anticoagulants could further simplify outpatient management.

The proportion of direct costs related to TP comprises a very small portion of direct costs. On the other hand, the costs saved by the provision of adequate TP can be large through the prevention of DVT. The costs to the German health care system incurred by this complication have been previously estimated only by modelling. Hansen et al. [42] calculated the cost of sequelae following a DVT to be between EUR 10-20 000. Optimising prophylaxis could result in a significant decrease in the costs of continuing complications, which for a recurrent DVT are estimated at EUR 2 300 and for CVI, around EUR 1 800 [14]. Risk assessment and subsequent stratification of patients to more specific management in order to achieve better outcomes in thrombosis prophylaxis will continue to be a challenge in this area and warrant further investigation.

This study is an important step in providing patient-based data on the actual practices, costs and outcomes in thrombosis prophylaxis in hip and knee replacement surgery in Germany. The data and results present guidance and insight for organisations taking decisions in the provision of care for these patients. Whether the conclusions hold true for other countries is dependent on particular aspects of the health care system, however in most social insurance-based healthcare systems, the challenges appear similar.

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References

[1] G. Agnelli and C. Becattini: "Clinical and economic aspects of managing venous thromboembolism in the outpatient setting", *Semin. Hematol.*, Vol. 38(2), Suppl 5, (2001), pp. 58–66.

[2] T.M. Hyers, G. Agnelli, R.D. Hull, J.G. Weg, T.A. Morris, M. Samama and V. Tapson: "Antithrombotic therapy for venous thromboembolic disease 1998", *Chest*, Vol. 114(5), (1998), pp. 561S–578.

[3] T.M. Hyers, G. Agnelli, R.D.H ull, J.G. Weg, T.A. Morris, M. Samama and V. Tapson: "Antithrombotic therapy for venous thromboembolic disease 1998", *Chest*, Vol. 114(5), (1998), pp. 561S–5578S.

[4] P.K. Schädlich, J.G. Brecht and E. Huppertz: "Treatment costs of venous thromboembolic complications in acutely ill medical patients in Germany", *Perfusion*, Vol. 16(4), (2003), pp. 141–152.

[5] W.H. Geerts, J.A. Heit, G.P. Clagett, G.F. Pineo, C.W. Colwell, F.A. Anderson, Jr. and H.B. Wheeler: "Prevention of venous thromboembolism 2001", *Chest*, Vol. 119(1), Suppl, (2001), pp. 132S–175S.

[6] E.A. Salvati, V.D. Pellegrini, Jr., N.E. Sharrock, P.A. Lotke, D.W. Murray, H. Potter and G.H. Westrich: "Recent advances in venous thromboembolic prophylaxis during and after total hip replacement", *J. Bone Joint Surg. Am.*, Vol. 82(2), (2000), pp. 252–270.

[7] T.M. Hyers, G. Agnelli, R.D. Hull, J.G. Weg, T.A. Morris, M. Samama and V. Tapson: "Antithrombotic therapy for venous thromboembolic disease 1998", *Chest*, Vol. 114(5), (1998), pp. 561S–578S.

[8] W.H. Geerts, J.A. Heit, G.P. Clagett, G.F. Pineo, C.W. Colwell, F.A. Anderson, Jr. and H.B. Wheeler: "Prevention of venous thromboembolism 2001", *Chest*, Vol. 119(1), Suppl, (2001), pp. 132S–175S.

[9] D.N. Mohr, M.D. Silverstein, D.M. Ilstrup, J.A. Heit and B.F. Morrey: "Venous thromboembolism associated with hip and knee arthroplasty: current prophylactic practices and outcomes", *Mayo Clin. Proc.*, Vol. 67(9) (1992), pp. 861–870.

[10] D.W. Murray, A.R. Britton and C.J. Bulstrode: "Thromboprophylaxis and death after total hip replacement", *J. Bone Joint Surg. Br.*, Vol. 78(6), (1996), pp. 863–870.

[11] S. Ansari, D. Warwick, C.E. Ackroyd and J.H. Newman: "Incidence of fatal pulmonary embolism after 1,390 knee arthroplasties without routine prophylactic anticoagulation, except in high-risk cases", *J. Arthroplasty*, Vol. 12(6), (1997), pp. 599–602.

[12] W.H. Geerts, J.A. Heit, G.P. Clagett, G.F. Pineo, C.W. Colwell, F.A. Anderson, Jr. and H.B. Wheeler: "Prevention of venous thromboembolism 2001", *Chest*, Vol. 119(1), Suppl, (2001), pp. 132S–175S.

[13] J. Edelsberg, D. Ollendorf and G. Oster: "Venous thromboembolism following major orthopedic surgery: review of epidemiology and economics", *Am. J. Health Syst. Pharm.*, Vol. 58, Suppl. 2, (2001), pp. S4–13.

[14] B. Kirchhof, A.J. Palmer, V.V. Kakkar and R. Bergemann: "Langzeitfolgen der tiefen Beinvenenthrombose: ihre wirtschaftliche Bedeutung", *Gesundh.ökon. Qual. Manag.*, Vol. 2, (1997), pp. 40-44.

[15] J.S. Ginsberg, F. Turkstra, H.R. Buller, B. MacKinnon, D. Magier and J. Hirsh: "Postthrombotic syndrome after hip or knee arthroplasty: a cross-sectional study", *Arch. Intern. Med.*, Vol. 160(5), (2000), pp. 669–672.

[16] E. Bernardi and P. Prandoni: "The post-thrombotic syndrome", *Curr. Opin. Pulm. Med.*, Vol. 6(4), (2000), pp. 335–342.

[17] AOK-Verband: *Zugelassene Krankenhäuser: Betriebsstrukturen und Vergütungsregelungen 2003,* AOK-Verlag, 2003.

[18] Verband der Angestellten-Krankenkassen: "Vergütungsliste", (2002), http://www.vdak.de/.

[19] Multimedia GmbH: "Gelbe Liste Pharmindex 2003." http://www.gelbe-liste.de/ (2003, http://www.gelbe-liste.de/.

[20] C. Juhra, N. Roeder and N. Loskamp: "Thromboseprophylaxe im Zeitalter der DRGs", *Vascular Care*, Vol. 5, (2003), pp. 56–61.

[21] B. Raming: *Kosteneffektivität der Thromboseprophylaxe mit niedermolekularem Heparin bei Hüft- und Kniegelenksersatzoperationen*, Institut für Sozialmedizin, Epidemiologie und Gesundheitsökonomie der Medizischen Fakultät der Charité - Universitätsmedizin Berlin, 2004.

[22] "Einheitlicher Bewertungsmaßstab", (2003), http://www.e-bis.de/ebm/Default.htm.

[23] Verband Deutscher Rentenversicherungsträger, (2002), http://www.vdr.de/internet/vdr/statzr.nsf/($URLRef)/57D0E2AA78C75849C1256A390043F7AD.

[24] Deutsche Gesellschaft für Chirurgie: "Leitlinien zur stationären und ambulanten Thromboembolie-Prophylaxe in der Chirurgie 2000", *AWMF-Leitlinien-Register Nr.003/001 Grundlagen der Chirurgie, Beilage zu den Mitteilungen der Dt.Ges.f.Chirurgie*, (2000), http://www.awmf-leitlinien.de/.

[25] E.A. Salvati, V.D. Pellegrini, Jr., N.E. Sharrock, P.A. Lotke, D.W. Murray, H. Potter and G.H. Westrich: "Recent advances in venous thromboembolic prophylaxis during and after total hip replacement", *J. Bone Joint Surg. Am.*, Vol. 82(2), (2000), pp. 252–270.

[26] M.H. Prins and J. Hirsh: "A comparison of general anesthesia and regional anesthesia as a risk factor for deep vein thrombosis following hip surgery: a critical review", *Thromb. Haemost.*, Vol. 64(4), (1990), pp. 497–500.

[27] G.P. Westert, R.J. Lagoe, I. Keskimaki, A. Leyland and M. Murphy: "An international study of hospital readmissions and related utilization in Europe and the USA", *Health Policy*, Vol. 61(3), (2002), pp. 269–278.

[28] E. Sheehan, M. Neligan and P. Murray: "Hip arthroplasty, changing trends in a national tertiary referral centre", *Ir. J. Med. Sci.*, Vol. 171(1), (2002), pp. 13–15.

[29] D.A. Ollendorf, M. Vera-Llonch and G. Oster: "Cost of venous thromboembolism following major orthopedic surgery in hospitalized patients", *Am. J. Health Syst. Pharm.*, Vol. 59(18), (2002), pp. 1750–1754.

[30] "Spitzenverbände der Krankenkassen, Verband der privaten Krankenversicherung, Deutsche Krankenhausgesellschaft", *Internet*, (2005), http://www.g-drg.de/.

[31] B. Kladny, C. Albrecht, I. Haase and B. Swoboda: "[Inpatient rehabilitation of patients following total hip replacement–a study using the Harris hip score]", *Z. Orthop. Ihre Grenzgeb.*, Vol. 139(6), (2001), pp. 536–540.

[32] E.L. Hannan, J.F. O'Donnell, H. Kilburn, Jr., H.R. Bernard and A. Yazici: "Investigation of the relationship between volume and mortality for surgical procedures performed in New York State hospitals", *JAMA*, Vol. 262(4) (1989), pp. 503–510.

[33] W.H. Geerts, J.A. Heit, G.P. Clagett, G.F. Pineo, C.W. Colwell, F.A. Anderson, Jr. and H.B. Wheeler: "Prevention of venous thromboembolism 2001", *Chest*, Vol. 119(1), Suppl, (2001), pp. 132S–175S.

[34] A.T. Cohen, C.S. Bailey, R. Alikhan and D.J. Cooper: "Extended thromboprophylaxis with low molecular weight heparin reduces symptomatic venous thromboembolism following lower limb arthroplasty–a meta-analysis", *Thromb. Haemost.*, Vol. 85(5), (2001), pp. 940–941.

[35] G. Agnelli and C. Becattini: "Clinical and economic aspects of managing venous thromboembolism in the outpatient setting", *Semin. Hematol.*, Vol. 38(2), Suppl 5, (2001), pp. 58–66.

[36] M. Marchetti, N.L. Liberato, N. Ruperto and G. Barosi: "Long-term cost-effectiveness of low molecular weight heparin versus unfractionated heparin for the prophylaxis of venous thromboembolism in elective hip replacement", *Haematologica*, Vol. 84(8), (1999), pp. 730–737.

[37] R.H. White and M.C. Henderson: "Risk factors for venous thromboembolism after total hip and knee replacement surgery", *Curr. Opin. Pulm. Med.*, Vol. 8(5), (2002), pp. 365–371.

[38] J.A. Heit, M.D. Silverstein, D.N. Mohr, T.M. Petterson, W.M. O'Fallon and L.J. Melton, III: "Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study", *Arch. Intern. Med.*, Vol. 160(6), (2000), pp. 809–815.

[39] Deutsche Gesellschaft für Chirurgie: "Leitlinien zur stationären und ambulanten Thromboembolie-Prophylaxe in der Chirurgie 2003", *AWMF-Leitlinien-Register Nr.003/001 Grundlagen der Chirurgie, Beilage zu den Mitteilungen der Dt.Ges.f.Chirurgie*, (2003), http://www.awmf-leitlinien.de/.

[40] J. Edelsberg, D. Ollendorf and G. Oster: "Venous thromboembolism following major orthopedic surgery: review of epidemiology and economics", *Am. J. Health Syst. Pharm.*, Vol. 58, Suppl 2, (2001), pp. S4–13.

[41] G. Agnelli and C. Becattini: "Clinical and economic aspects of managing venous thromboembolism in the outpatient setting", *Semin. Hematol.*, Vol. 38(2), Suppl 5, (2001), pp. 58–66.

[42] R. Hansen, V. Bruchhausen and R. Rychlik: "Thromboembolie - Risiken, Ereignisse und Kosten der modernen Prophylaxe mit niedermolekularen Heparinen", *Fortschritte der Medizin*, Vol. 117, (1999), pp. 155–58.