

## ORIGINAL ARTICLE

# The costs of heparin-induced thrombocytopenia: a patient-based cost of illness analysis

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**Summary.** *Background and objectives:* Due to the complexity of heparin-induced thrombocytopenia (HIT), currently available cost analyses are rough estimates. The objectives of this study were quantification of costs involved in HIT and identification of main cost drivers based on a patient-oriented approach. *Methods:* Patients diagnosed with HIT (1995–2004, University-hospital Greifswald, Germany) based on a positive functional assay (HIPA test) were retrieved from the laboratory records and scored (4T-score) by two medical experts using the patient file. For cost of illness analysis, predefined HIT-relevant cost parameters (medication costs, prolonged in-hospital stay, diagnostic and therapeutic interventions, laboratory tests, blood transfusions) were retrieved from the patient files. The data were analysed by linear regression estimates with the log of costs and a gamma regression model. Mean length of stay data of non-HIT patients were obtained from the German Federal Statistical Office, adjusted for patient characteristics, comorbidities and year of treatment. Hospital costs were provided by the controlling department. *Results and conclusions:* One hundred and thirty HIT cases with a 4T-score  $\geq 4$  and a positive HIPA test were analyzed. Mean additional costs of a HIT case were 9008 €. The main cost drivers were prolonged in-hospital stay (70.3%) and costs of alternative anticoagulants (19.7%). HIT was more costly in surgical patients compared with medical patients and in patients with thrombosis. Early start of alternative anticoagulation did not increase HIT costs despite the high medication costs indicating prevention of costly complications. An HIT cost calculator is provided, allowing online calculation of HIT costs based on local cost structures and different currencies.

**Keywords:** cost of illness analysis, costs of HIT, heparin, heparin-induced thrombocytopenia.

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## Introduction

Heparins are the most frequently used anticoagulants for the prevention and treatment of thromboembolic complications. Due to their widespread use, the infrequent adverse effects of heparin also have clinical relevance. Besides bleeding complications due to heparin overdose, the adverse effect of immune-mediated heparin-induced thrombocytopenia (HIT) is of major importance. HIT is the most frequent immune-mediated adverse drug reaction and can cause devastating thromboembolic complications. In about 50–75% of affected patients, HIT leads to thromboembolic complications, most frequently thrombosis and pulmonary embolism. Despite major advances in treatment, the fatality rate for HIT is still about 10% [1–3].

Earlier studies have estimated the costs of a case of HIT based on methodology applying primarily theoretical considerations and rough indirect cost estimates [4–9]. Estimated costs in these studies ranged between 13 429 US\$ and 41 133 US\$ per case. Thus HIT has financial consequences that represent a significant factor in the central decision-making process concerning the anticoagulant treatment policy of a hospital. While unfractionated heparin is by far the least costly heparin, one factor making other anticoagulants potentially more cost effective, is the reduced risk of HIT, which has been shown for low molecular weight heparins and fondaparinux. The risk of HIT during low molecular weight heparin (LMWH) treatment is about 10% of the risk during unfractionated heparin (UFH) treatment, at least in patients undergoing major surgery [7,10,11], and it is minimal for fondaparinux (a synthetic pentasaccharide) [12]. The new anticoagulants such as oral thrombin inhibitors or oral factor (F) Xa inhibitors are not expected to induce HIT at all due to their different molecular structure. Economic decision processes for the choice of anticoagulant used in a health care system require total cost comparisons, including the frequency of HIT, costs of HIT and the cost effectiveness of managing HIT by different treatment strategies.

Furthermore, patients with acute HIT require alternative anticoagulants. Currently in Germany, there are three drugs approved for this: danaparoid, an indirect FXa inhibitor [13],

lepirudin, a bivalent thrombin inhibitor [14], and argatroban, a monovalent thrombin inhibitor [15].

Despite several studies on the cost issues of HIT, due to methodological flaws in diagnosing HIT and 'true' HIT-related complications and interventions or selection of non-representative patient populations, the costs of HIT are not reliably established. Moreover, most of these studies were performed in the USA, which makes comparison with costs in European health care systems rather difficult. A more reliable approach is

to base cost estimates on patient-specific factors. This requires calculation of costs based on the incidence of HIT-associated complications and HIT-associated subsequent diagnostic and therapeutic interventions. In addition, main cost drivers such as sociodemographic factors, illness-specific factors and medication-related costs need to be included.

The primary objective of this study was to assess the costs of HIT by analysis of the procedures performed in patients with HIT. The secondary objective was the identification of major

**Table 1** Prices and cost parameters\* for the calculation of HIT costs

Cost groups	Cost parameters	Costs per unit (€)	Source
A. Daily ward costs at the university hospital of Greifswald (costs per day)	Internal medicine	440.12 (ic) 313.49 (rc)	University hospital Greifswald: costs per day include labor costs and material costs for each ward. Costs of medication and blood transfusions are not included because these costs are calculated as separate cost categories
	Neurology	238.06 (ic) 242.46 (rc)	
	Pediatrics	342.58 (rc)	
	Therapeutic radiology	518.83 (rc)	
	Surgery	298.05 (rc)	
	Orthopedics	211.07 (rc)	
	Gynecology	289.60 (rc)	
	Ear–nose–throat	242.00 (rc)	
	Urology	234.80 (rc)	
	Anaesthesia and intensive care	1257.94 (ic)	
B. Medication	Acetylsalicylic acid (100 mg tablet)	0.02	University hospital Greifswald
	Danaparoid sodium (750 IE/0.6 mL infusion)	25.35	
	Phenprocoumon (3 mg tablet)	0.02	
	Lepirudin (50 mg ampule)	59.28	
C. Diagnostic procedures	Angiography	188.97	DKG-NT <sup>†</sup> p.416, 418
	Computer tomography (CT)	184.68	DKG-NT <sup>†</sup> p.424
	Electroencephalography (EEG)	51.97	DKG-NT <sup>†</sup> p.150
	Ectrocardiogram (ECG)	13.06	DKG-NT <sup>†</sup> p.136
	PF 4/Heparin-ELISA	24.16	DKG-NT <sup>†</sup> p.327
	Endoscopy	62.28	DKG-NT <sup>†</sup> p. 138/139
	HIPA, heparin-induced platelet activation test	62.12	DKG-NT <sup>†</sup> p.324
	Lung scintigraphy	111.67	DKG-NT <sup>†</sup> p.431
	MR tomography thorax (MRT)	369.36	DKG-NT <sup>†</sup> p.445
	Phlebography	64.42	DKG-NT <sup>†</sup> p.419
	X-Ray thorax	24.05	DKG-NT <sup>†</sup> p.411
	Sonography	42.95	DKG-NT <sup>†</sup> p. 85/86
	Transesophageal echocardiography (TEE)	79.45	DKG-NT <sup>†</sup> p. 18/19
Transthoracic echocardiography(TTE)	38.66	DKG-NT <sup>†</sup> p. 19	
D. Blood transfusions	Red blood cell concentrate (RBC)	80.00	University hospital Greifswald
	Pre-transfusion testing (for each RBC given)	13.80	DKG-NT <sup>†</sup> p.328
E. Laboratory tests	Anti-FXa (per test)	31.75	DKG-NT <sup>†</sup> p.323
	Partial thromboplastin time (PTT, per test)	3.45	DKG-NT <sup>†</sup> p.298
	Platelet count (per test)	4.14	DKG-NT <sup>†</sup> p.287
	Prothrombin time value (per test)	3.45	DKG-NT <sup>†</sup> p.298
	Thrombolysis (per procedure)	333.98	DKG-N T <sup>†</sup> p.420/421/422
F. Vessel revascularization	Thrombectomy (per procedure)	559.42	DKG-NT <sup>†</sup> p.95/107/260/262
	PTCA (per procedure)	548.72	DKG-NT <sup>†</sup> p.420/422
	Costs per minute	0.35	University hospital Greifswald
G. Physiotherapy	Costs per minute	0.72	University hospital Greifswald
F. Consultations (25 minutes per consultation)	Costs per minute	0.72	University hospital Greifswald

\*Cost categories B–F are direct, non-fully allocated costs (medication costs, charges in categories C, D, F, personnel costs per minute in categories G and F). Daily ward costs include personnel costs and material costs for medical needs; cost categories such as heat, electrical power supply, etc., are not included, also cost categories B–F are excluded from ward costs. <sup>†</sup>Deutsche Krankenhausgesellschaft (German hospital society): DKG-NT Band I – Tarif der deutschen Krankenhausgesellschaft zugleich BG-T— vereinbarter Tarif für die Abrechnung mit den gesetzlichen Unfallversicherungsträgern (charges for standard hospital procedures), Kohlhammer (2005), Stuttgart/Germany. rc, regular care; ic, intensive care.

cost drivers. Therefore we identified all HIT patients in our center based on stringent clinical and laboratory characteristics and analysed costs based on the individual data retrieved from the patient files. We also adjusted for potential confounders by multivariate regression analysis and provide a 'HIT-calculator', which is available online and allows recalculation of costs by using the local costs for the key factors identified.

## Methods

### Study design

The primary objective of this retrospective study was to assess the costs of HIT by the analysis of the procedures performed in patients with a very high likelihood of having HIT. The secondary objectives were the identification of major cost drivers, including patient characteristics, medication costs, and the dependence of costs on start of alternative anticoagulation.

### Patients

Between 1995 and 2004, a positive HIT antibody test was obtained from 243 patients with clinical suspicion of HIT, out of 335 981 in-hospital patients (University Hospital Greifswald, Germany). Between 1995 and 1999 only the heparin-induced platelet activation (HIPA) test had been performed [16], and from then on both an in-house PF4/heparin ELISA detecting IgG, A and M [17], and the HIPA test. Only patients who tested positive in the HIPA test (1995–1999) or positive in the HIPA test and the PF4/heparin ELISA were regarded as testing positive for clinically relevant antibodies. In addition, the files of 232 patients were evaluated by two medical experts applying the 4T-score [18]. Only patients with a 4T-score  $\geq 4$  and a positive HIPA test were included in the analysis.

For the patients identified as HIT patients, the following data were retrieved from the patient file: gender, age, underlying disease(s), thromboembolic complications, type of heparin (UFH, LMWH) given before HIT was diagnosed, patient type (surgical or medical), diagnostic procedures and interventions such as thrombolysis and thrombectomy related to HIT-associated complications, HIT-related laboratory tests, type and dose of alternative anticoagulation, in-hospital rehabilitation measures, duration of in-hospital stay, amount of blood transfusions, and consultations. Costs were estimated conservatively (i.e. if an intervention could have also been caused by the underlying condition, it was not calculated as HIT related).

### Cost analysis

Cost-related data were calculated from the day HIT started clinically. This we defined retrospectively as either start of decrease of platelet counts or a new thrombotic complication. Events occurring before day 5 of heparin were not considered as HIT related. Costs for interventions and diagnostic measures were calculated based on the German healthcare reimbursement system (DKG-NT) for the year 2005 [19]. Ward costs,

medication costs, blood transfusion costs and costs for consultations were calculated by the controlling department of the hospital (Table 1).

An important cost-driving parameter in HIT is prolonged in-hospital stay. The actual in-hospital stay for each patient was retrieved from the patient file and compared with the 'normal' mean diagnosis-related in-hospital stay in Germany of patients with the same comorbidity, age, gender, and the same year of treatment. These data are publicly available from the Federal Statistical Office of Germany [20]. For patients with more than one underlying disease we also aimed to generate an individual comparison. For this we could not use the data from the Federal Statistical Office as only patients with one underlying disease are listed there. We therefore calculated three scenarios. First, only the mean in-hospital stay of patients with one of the comorbidities was used (obtained from the Federal Statistical Office). For this we selected the comorbidity with the longest mean stay under the assumption that the other comorbidities were treated within the same time period. This was defined as minimum in-hospital stay. Secondly, the mean duration of the in-hospital stay for each of the comorbidities of the patient were added under the assumption that comorbidities were treated sequentially. This was defined as maximum in-hospital stay. Thirdly, the mean between minimum and maximum in-hospital stay was taken (intermediate duration of stay scenario) to provide a more realistic scenario. The additional HIT-related in-hospital days were then calculated by subtracting minimum, maximum and intermediate stay from the actual stay of the individual patient. This method provides a range. Our assumption was that the intermediate stay scenario most probably reflects the clinical situation best.

### Multivariate regression analysis

To identify main cost-drivers, the level and significance of the factors influencing the patient-based HIT costs were calculated in a multivariate regression analysis using spss version 17.0.1 software (SPSS Inc., Chicago, IL, USA). Calculations were made for HIT costs, including costs for additional days of in-hospital stay (for this we used the intermediate stay scenario as defined above). The regression analysis was carried out by estimating the influence of nine potentially clinically and economically relevant independent variables, including patient-related characteristics and the underlying disease (surgical or medical), the occurrence of any thromboembolic complication, the medication used for anticoagulation after diagnosis of HIT, and the start of alternative medication in relation to onset of HIT. A preliminary multivariate linear regression analysis showed that the residuals in this model were not normally distributed. Therefore we used two alternative more appropriate regression models: first, a linear regression model with the Log of HIT costs as dependent variable (intermediate scenario); and, second, a gamma regression model with HIT costs (intermediate scenario) as dependent variable.

**Table 2** Patient characteristics of the HIT patients included in the cost analysis study

Criteria		Patients	
		<i>n</i>	%
Gender	Male	57	43.85
	Female	73	56.15
Age in years (mean)		62.26	
HIT developed during therapy with UFH only		101	77.69
HIT developed during therapy with UFH and LMWH		18	13.85
HIT developed during therapy with LMWH only		11	8.46
TEC		67	51.54
TEC: Venous thrombosis		35	26.92
TEC: PE		23	17.69
TEC: Arterial thrombosis		9	6.92
Death		7	10.45
Patient group	Surgical	41	31.54
	Medical	81	62.31
	Intensive care	6	4.61
	Pediatrics	2	1.54

Patients may have had more than one event.  
TEC, thromboembolic complication.

## Results

### Costs of HIT

One hundred and thirty patients, representing 0.037% of the patient population treated during the study period, were

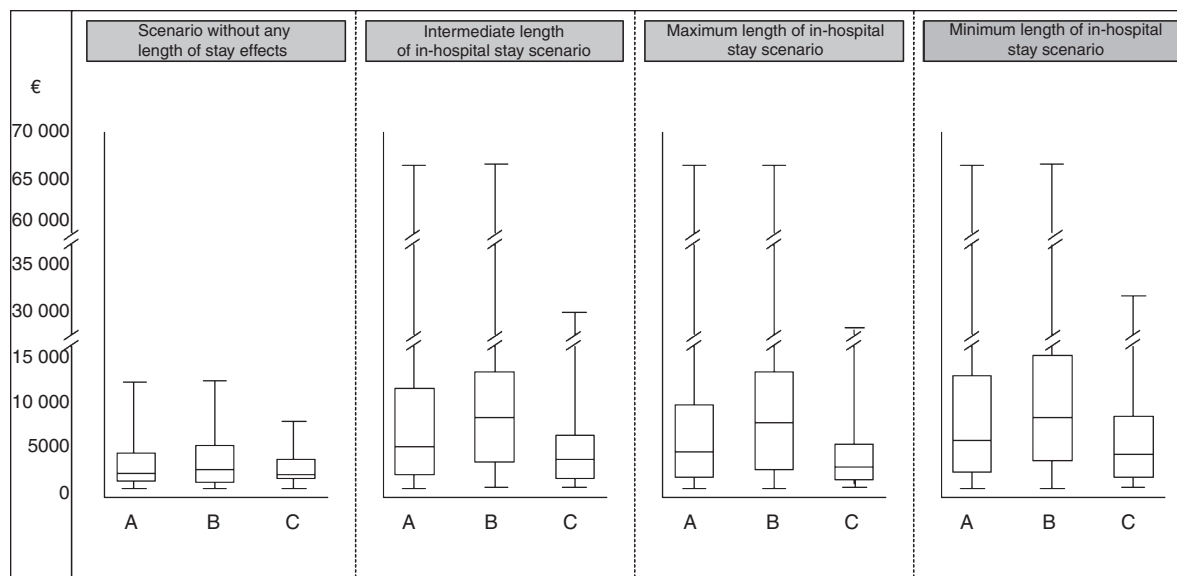
retrospectively confirmed as definite HIT cases. Many of the patients excluded from further analysis were ICU patients in whom it was very difficult to differentiate whether thrombocytopenia was induced by HIT or by the underlying disease. Thus our scenario followed the most conservative approach. This potentially underestimated HIT frequency and, as ICU patients are very cost intensive, also HIT costs. Table 2 shows the main descriptive characteristics of HIT patients included in the data base.

### HIT cost calculator

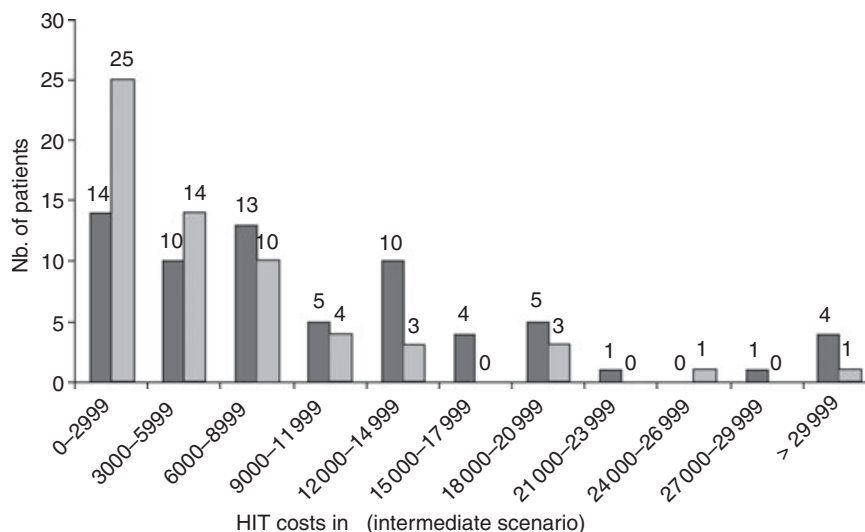
In-hospital costs depend very much on the local cost scenarios. Indications for interventions, however, are much more likely to be similar in different health care systems. We therefore developed a HIT cost calculator, available under supplementary material [[http://www.wi.hs-wismar.de/~ipam/html\\_neu/hittool.html](http://www.wi.hs-wismar.de/~ipam/html_neu/hittool.html)]. This calculator requires filling in 44 cost positions with the local costs. Using the frequencies of certain interventions and diagnostic and therapeutic measures as determined in our study, the calculator will then provide an approximation of the mean costs of a HIT patient under the local cost conditions.

### Costs of HIT based on the costs in Germany in €

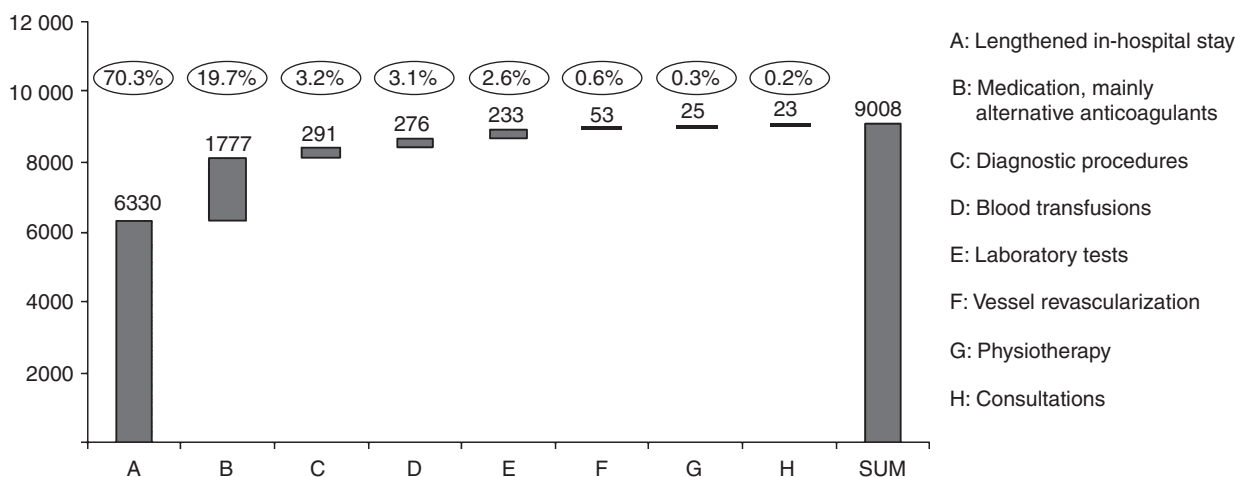
Figure 1 shows the costs of an average case of HIT based on 128 evaluable patients. For these calculations, two extreme cases with costs of 107 356.37 € and 163 356.37 € were excluded. The costs of HIT without taking the prolonged hospital stay into account amounted to mean costs per patient of 2677.71 € ( $n = 128$ ), with median costs of 1944.89 €. For



**Fig. 1.** Costs of HIT in € for different scenarios. The figure shows cost ranges and box plots for the 2nd and 3rd quartile with minimum and maximum values for four different cost scenarios. Median costs are identified by a line inside the box. The first part of the figure shows costs without including in-hospital stay costs; the other three figures provide costs including prolonged in-hospital stay costs calculated as defined under methods; (A) costs for all HIT patients ( $n = 128$ ); (B) costs for HIT patients with thromboembolic complications ( $n = 67$ ); (C) costs for HIT patients with isolated thrombocytopenia without thromboembolic complications ( $n = 61$ ). Patients with HIT and thrombosis caused higher costs than patients with HIT without thrombosis. Despite different methods used to calculate the additional days of in-hospital stay, the median costs remained very similar in the three cost scenarios.



**Fig. 2.** Distribution of costs for HIT patients with and without thromboembolic complications. HIT costs refer to the intermediate length of in-hospital stay scenario as described under Methods. Patients were arranged according to their individual HIT costs. Left red column shows number of patients with thromboembolic complications in each cost category ( $n = 67$ ), right grey column shows number of patients without thromboembolic complications in each cost category ( $n = 61$ ). Costs are given in Euro (€).



**Fig. 3.** Main cost drivers for HIT determined from the analysis of 128 patients. For calculation of additional days of in-hospital stay the intermediate length of stay scenario was applied as defined under Methods. Costs are given in Euro (€). Above the columns the relative costs are given in %.

patients with HIT-related thromboembolic complications, the mean costs were 3209.40 € ( $n = 67$ ), with median costs of 2117.84 €. For patients with isolated thrombocytopenia (without thromboembolic complications), the mean costs were 2093.72 € ( $n = 61$ ), with median costs of 1824.00 €. When cost calculations were performed including prolonged duration of in-hospital stay, the costs increased. In the following, the mean costs per patient are given with minimal and maximal costs given in parenthesis. The intermediate-length duration of stay scenario costs were 9007.90 € [62.12 € (min) – 67 557.64 € (max)] ( $n = 128$ ), with median costs of 6155.32 €. For patients with HIT-related thromboembolic complications, the mean costs were 11 804.84 € [62.12 € (min) – 67 557.64 € (max)] ( $n = 67$ ), with median costs of 7840.72 €. For patients with isolated thrombocytopenia (without thromboembolic compli-

cations), the average costs were 5935.86 € [62.12 € (min) – 32 017.77 € (max)] ( $n = 61$ ), with median costs of 4202.65 €.

The maximum-length duration of stay scenario costs were 7648.96 € [62.12 € (min) – 66 588.30 € (max)] ( $n = 128$ ), with median costs of 4180.46 €. For patients with HIT-related thromboembolic complications, the mean costs were 10 830.46 € [62.12 € (min) – 66 588.30 € (max)] ( $n = 67$ ), with median costs of 7304.99 €. For patients with isolated thrombocytopenia (without thromboembolic complications), the average costs were 4154.33 € [62.12 € (min) – 28 715.66 € (max)] ( $n = 61$ ), with median costs of 2267.34 €.

The minimum-length duration of stay scenario costs were 10366.84 € [62.12 € (min) – 68 526.97 € (max)] ( $n = 128$ ), with median costs of 7834.69 €. For patients with HIT-related thromboembolic complications, the mean costs were 12 799.12

€ [62.12 € (min) – 68 526.97 € (max)] ( $n = 67$ ), with median costs of 9387.49 €. For patients with isolated thrombocytopenia (without thromboembolic complications), the average costs were 7717.30 € [62.12 € (min) – 35 639.59 € (max)] ( $n = 61$ ), with median costs of 5069.92 €.

#### Main cost drivers

Figure 2 shows the distribution of costs (intermediate length of stay scenario) for patients with and without thromboembolic complications. It becomes obvious that HIT costs are not normally distributed. The detailed cost structure is given in Fig. 3. Two major factors influenced the costs of a case of HIT. The main cost driver is lengthened in-hospital stay, which explains 70.3% (6330.22 €) of the total additional costs of an average HIT case. The second most important factor is the medication costs, primarily the costs of the alternative anticoagulants. They account for 19.7% (1777.33 €) of the total average additional costs.

#### Multivariate regression analysis

Table 3 shows the results of the multivariate regression analysis of HIT-related costs, which can be summarized as follows. Of the patient characteristics, age and gender of the patient had only a minor influence on HIT costs. In contrast, HIT in surgical patients leads to higher HIT costs as compared with medical patients. As expected, if HIT is associated with thromboembolic complications, costs of HIT increase. The use of the alternative anticoagulation increases the costs of HIT as compared to just stopping heparin. This is true for danaparoid and lepirudin. However, when comparing patients with early vs. delayed start of alternative anticoagulation, despite the high medication costs, the overall costs did not increase significantly. This indicates that early start of treatment may avoid cost-intensive complications. Finally, death of a patient has hardly any influence on HIT costs.

**Table 3** Multivariate linear regression analysis of HIT costs ( $n = 128$ )

Independent variables	Dependent variable: log of HIT costs (intermediate length of hospital stay scenario); linear regression model*	Significance	Dependent variable: HIT costs (intermediate length of in-hospital stay scenario); gamma regression model*	Significance
Age (increase of costs per year of patient age)	-0.006	0.466	-0.011	0.100
Gender (increase of costs for male patients)	0.213	0.352	0.262	0.160
Surgical patients	0.440	0.067	0.601	0.002
Thromboembolic complications	0.759	0.001	0.638	<0.001
Use of danaparoid only	2.080	<0.001	1.028	<0.001
Use of lepirudin only	2.578	<0.001	1.437	<0.001
Use of danaparoid and lepirudin	2.857	0.307	1.421	<0.001
Day of start of alternative medication (change of costs due to delayed start of alternative medication)	0.077	0.034	0.082	0.212
Death of patient	-0.132	0.633	0.422	0.081
$R^2$	0.441		n.a.	

\*Intermediate length of stay calculation as defined under methods.

## Discussion

This study provides an approach to define the additional costs induced by HIT based on real world cost analysis. We used a unique data base of 128 patients with HIT identified in a single center. All patients tested positive in a functional assay for HIT antibodies and all had at least an intermediate likelihood for HIT based on the 4T scoring system [18]. In this regard, our study gives an important estimate of the incidence of HIT, which seems to be about 0.04% in a mixed patient population of a large teaching hospital.

Our study shows that HIT is a relevant cost factor. However, the costs we determined (mean costs for the intermediate length of stay scenario of 9007.90 € with a median of 6155.32 €) were lower than those determined in studies performed in the USA in which HIT-related costs ranged between 13 429 US\$ and 41 133 US\$ [8,9]. One reason might be that we calculated the additional costs very conservatively and excluded all costs of interventions and medications, which would not have been necessary due to the underlying disease. Two additional likely reasons for the differences in cost estimates are that neither of the other studies based the cost analysis on detailed HIT-related individual case data and secondly health care costs in the USA are much higher than those in Germany.

This prompted us to develop a HIT cost calculator, which is available as supplementary material under [[http://www.wi.hs-wismar.de/~ipam/html\\_neu/hittool.html](http://www.wi.hs-wismar.de/~ipam/html_neu/hittool.html)]. This calculator allows insertion of the local costs of all cost variables we identified as contributing to the costs of an HIT case and will then calculate the approximate case costs of HIT for the respective hospital. This is a feasible approach, as treatment guidelines and recommendations for HIT do not differ substantially in Europe and North America [2]. These data might be helpful for including HIT-related costs in the decision making process for selection of the anticoagulant to be used in a hospital.

Our study has two additional findings that are of relevance for defining cost-effective treatment of HIT. Early alternative anticoagulation does not increase HIT costs despite its clear cost-enhancing effect on medication costs. Thus it must prevent costly complications of HIT. This confirms and extends earlier findings [6,21]. Early introduction of alternative anticoagulants is mostly seen as cost effective as it reduces the total length of in-hospital stay. This is consistent with the findings of three prospective studies [22], which showed that the risk for a new thromboembolic complication is about 5% per patient day between cessation of heparin and start of alternative anticoagulation. New thromboembolic complications are very likely to increase the length of in-hospital stay and also require expensive diagnostic procedures (e.g. perfusion CT scan for pulmonary embolism).

It is important to bear in mind that we only analyzed cases with a very high likelihood of HIT. Our study did not assess the costs induced by liberal ordering of HIT antibody tests and by an early change to alternative anticoagulants. This will result in the change of anticoagulation in a considerable number of patients who ultimately do not have HIT. This is a potentially very relevant cost factor in HIT, as we recently showed that only 1 out of 10 patients referred to a reference laboratory for diagnosis of HIT finally has laboratory evidence for HIT [23]. Our center is always applying a combination of the clinical 4T score [18], a PF4/heparin IgG antibody test and a functional assay using washed platelets in patients suspected for HIT, with results provided the same day, and anticoagulation is only changed in case of the functional assay being positive. This laboratory back-up is not available in many hospitals and it would be interesting to also assess the cost effectiveness of providing this infrastructure with relatively rapid turn around time of HIT antibody testing.

When we compared the costs associated with the alternative anticoagulants danaparoid (an indirect FXa inhibitor) and lepirudin (a direct thrombin inhibitor), in a descriptive analysis, danaparoid seemed to be more cost effective than lepirudin. However, costs were not linearly distributed. In most patients costs of HIT were moderate but in a few patients very high additional costs were caused by HIT. When applying the more appropriate gamma regression model, no significant differences remained.

A strength of our study is the inclusion of HIT-related additional therapeutic/diagnostic measures only, which allows calculation of the real HIT-related costs. To our knowledge, the applied methodology to determine length of stay is the most sophisticated way to identify patient-specific additional length of stay in a cost analysis study. We identified for each individual patient, adjusted for gender, age, comorbidity and year of treatment, the average length of in-hospital stay in Germany, taking advantage of the data base of the Federal Statistical Office of Germany. However, a limitation is that the method bears some uncertainties in patients with more than one underlying disease as there are no data available on mean in-hospital duration of stay in patients with several comorbidities. In these cases we used an intermediate

duration of stay scenario (mean between minimum and maximum length of stay scenarios). Although it sounds plausible, this method has not been evaluated systematically. However, as shown in Fig. 1, our calculations seem to be rather robust as the median costs did not differ substantially between these scenarios.

As with any single-center, retrospective study, there is a certain probability that some patient characteristics are not equally distributed between age-, gender-, illness-specific or between the danaparoid- and the lepirudin-treated patient groups. We approached this by adjusting the cost parameters by a multivariate regression analysis. However, not all patient characteristics can be included in such an analysis. While it is a definite strength that the data presented here have been gathered at a hospital, which, on the basis of its emphasis on research, has paid special attention to the diagnosis and treatment of HIT, the awareness of HIT and therefore the selection of patients might be different in other medical settings. Also, all cost data are based on the analysis of individual cases that reflect the medical treatment standard maintained by this hospital. This standard may not be applicable to every hospital.

In conclusion, HIT is a relevant cost factor in hospitals. The 10-year analysis of individual HIT patients in a large teaching hospital provides a reasonable estimate of interventions, laboratory tests and required alternative anticoagulants in patients with a very high likelihood for HIT. Together with the HIT calculator (online available) this study enables calculation of the costs of HIT according to the local community health care cost structure. This may help to make a decision on the cost effectiveness of treatment of HIT and on a more general basis on substituting heparin by other anticoagulants with a reduced (e.g. low molecular weight heparin) or nearly absent (fondaparinux, new oral agents) risk of HIT.

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### Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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