



Full Length Article

Assessing the clinical and cost impact of on-demand immunoassay testing for the diagnosis of heparin induced thrombocytopenia



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ABSTRACT

Background: The diagnostic work-up for heparin induced thrombocytopenia (HIT) can take several days. Consequently patients may be speculatively switched onto replacement anticoagulant therapy before a diagnosis is confirmed. On-demand immunoassay diagnostic testing enables timely treatment decisions, based on test results.

Objective: To estimate the clinical and cost impact of the use of on-demand versus batched diagnostic tests for HIT.

Methods: Literature was reviewed to identify test performance, clinical and cost data. Semi-structured interviews (n = 4) and a survey (n = 90) provided insights into current practice and challenges. Flow diagram models were developed to estimate the potential impact of on-demand testing.

Results: Modelling estimated more HIT-related outcomes for patients maintained on heparin whilst awaiting test results and patients switched onto replacement anticoagulant therapy awaiting test results, compared with on-demand testing and treatment based on the results. The budget impact model estimated that on-demand testing reduced replacement anticoagulant therapy costs from \$39,616 to \$12,799 per patient. There are limitations to the data available to inform modelling and the estimates should be treated with caution.

Conclusions: Using on-demand testing may drive positive effects on clinical and cost outcomes.

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1. Introduction

Heparin induced thrombocytopenia (HIT) is a prothrombotic, immune-mediated disorder caused by exposure to heparin [1]. Guidance on the diagnosis and management of HIT [2–4], recommends that patients whose platelet count drops by over 50% within 5–14 days of heparin administration undergo clinical assessment using the 4Ts score [5]. Those with a low score are unlikely to have HIT, while those with high or intermediate score should undergo HIT immunoassay testing. Those with positive immunoassay tests should undergo functional testing to confirm HIT diagnosis. Management of HIT involves cessation of heparin and initiation of alternative parenteral anticoagulants, such as a direct thrombin inhibitor or an indirect factor Xa inhibitor. The two major issues in HIT testing are test performance and test turnaround time [6, 7].

1.1. Test performance

The polyspecific enzyme-linked immunosorbent assay (ELISA IgGAM) is the most commonly used tests for diagnosing HIT. ELISAs have high sensitivity, but poor specificity and positive predictive value. An antibody-specific ELISA targeting IgG antibodies (most frequently implicated in HIT) partly addresses these performance issues [8], however, false positives remain a challenge [7]. Performance issues potentially lead to increased expense as patients are treated unnecessarily using replacement anticoagulant therapy and they may have poorer clinical outcomes if the true cause of their symptoms is not addressed. The gold standard diagnostic test for HIT is the functional serotonin release assay (SRA), which demonstrates higher specificity than ELISAs.

1.2. Test turnaround time

Immunoassay tests take 2–3 h to run, but batching of multiple patient samples into a single run is common, delaying the time-to-result to over 24 h. SRA testing is technically demanding, restricting its use to specialty laboratories [8]. Outsourcing to specialty laboratories is common, with turnaround times of over 24 h and a potential total turnaround time of several days for the diagnostic work-up. The total turnaround time may preclude following the pathway by increasing costs and worsen

Abbreviations: DDD, defined daily dose; DTI, direct thrombin inhibitor; ELISA, enzyme-linked immunosorbent assay; HIT, heparin induced thrombocytopenia; HITT, heparin induced thrombocytopenia with thrombosis; SRA, serotonin release assay; T&S, test and switch, continue; T&SR, test and switch, return; T&W, test and wait.

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clinical outcomes for people with HIT, as they may develop more serious complications if they are kept on heparin whilst awaiting laboratory confirmation of diagnosis. Therefore patients are often speculatively switched from heparin onto expensive replacement anticoagulant therapy based on the clinical assessment alone [2, 8], increasing drug costs.

The objective of this study was to review currently available assays for the diagnosis of HIT, and investigate the potential clinical and cost impact of on-demand testing. On-demand testing can be achieved using either automated tests such as HemosIL® HIT-Ab(PF4-H) (Instrumentation Laboratory, Bedford, MA), rapid tests such as particle gel immunoassay (PaGIA) and lateral flow immunoassay, as well as ELISA tests when performed on-demand. These options are not currently routinely used in most settings.

2. Materials and methods

2.1. Literature searches

Literature searches were conducted in Medline, Embase, the Cochrane Library and Scopus, to identify studies on the test performance of HIT diagnostics, clinical outcomes and cost data related to the diagnosis and management of HIT. Searches were carried out in the US National Guidelines Clearinghouse to identify relevant guidelines and in trial registries (ClinicalTrials.gov and the International Clinical Trials Registry Platform Search Portal) to identify on-going trials of relevance. A combination of relevant free text keywords and indexing terms (where available) were used to retrieve relevant guidelines, systematic reviews, randomised controlled trials, diagnostic studies and economic evaluations. The last searches were carried out on 25th February 2015 and limited to English language only.

2.2. Primary research

Primary research was conducted to understand real-world practice, as compared with the guideline pathways [2–4] and to identify challenges faced. The first phase was semi-structured interviews with US-based laboratory managers and haemostasis physicians ($n = 4$), questions were based on emergent themes from the literature review. Interview findings informed a second phase survey ($n = 90$) in Germany, the UK and US designed to validate the findings from phase one and fill in data gaps identified in the available literature. Primary research participants were recruited via a market research agency (Research Now) and were reimbursed. Informed consent was obtained prior to commencing the interview/survey. Interviews were carried out by telephone and recorded for transcription purposes. Surveys were completed online. Participants were informed about the overall aims of the project, but not that on-demand testing was the focus, to avoid biasing their responses.

2.3. Clinical and cost flow models

To estimate the potential clinical and cost impact of on-demand testing, the flow of a hypothetical cohort of patients through the care pathway was modelled using four scenarios. The first step for each cohort was a 4Ts clinical assessment, indicating high or intermediate score:

- “Test and wait” (T&W) – 4Ts score high or intermediate, antibody test is ordered (to be run in a batch), patient remains on heparin awaiting the results of the batched antibody test.
- “4Ts and switch, continue” (T&SC) – 4Ts score high or intermediate, antibody test is ordered, patient is placed onto replacement anticoagulant based on the 4Ts score. Patients continue replacement therapy regardless of antibody test result.
- “4Ts and switch, return” (T&SR) – 4Ts score high or intermediate, antibody test is ordered, patient is placed onto replacement anticoagulant based on the 4Ts score. Negative antibody test patients switched back to heparin.

- “On-demand and switch” – 4Ts score high or intermediate, on-demand antibody test is ordered, patient is placed onto replacement anticoagulant based on on-demand assay result.

These scenarios built upon previous research [6] and were designed to model the clinical and cost impact of different testing strategies, and test the importance of timely and accurate results in HIT diagnosis. T&W reflects following the guideline pathway and the impact of delayed test results [2–4]. The two 4Ts and switch using batched IgGAM scenarios represent speculatively switching based on clinical assessment alone, because half of survey respondents indicated that they do so. The on-demand scenario compared settings where test results are available on-demand. The on-demand scenario does not apply to the majority of settings, as the survey indicated that ELISA tests are often batched and results are not available on-demand. Fig. 1 provides an overview of the different scenarios.

Initially a different set of scenarios was used: T&W, a single “4Ts and switch” and separate “on-demand and switch” scenarios for HemosIL, IgG and IgGAM. However, the data from the survey indicated that a large proportion of patients are not switched back to heparin, even when test results indicate that they are HIT-negative. Therefore the decision was taken to change the scenarios to reflect these findings, in order to produce an analysis that was more representative of real practice. The most pronounced difference in the scenarios in terms of clinical outcomes was between the batched and on-demand scenarios, rather than between the different tests used on-demand. Given the limitations to the data available, the small difference seen between the on-demand tests (2 cases of new thrombosis) may not be reliable. Therefore results were grouped for the different on-demand tests.

Within each scenario, four diagnostic groups were established – true negatives, false positives, true positives, false negatives – based on the performance of the 4Ts clinical assessment reported in the literature. The prevalence of HIT varied across the included studies, making it difficult to compare their results, therefore a normalised frequency representation for prevalence was calculated. Prevalence for normalisation was based on median HIT prevalence (confirmed clinically or by SRA testing) in the included studies, and the median sensitivity and specificity of each class of diagnostic assay was used to calculate the false positive rate ($1 - \text{Specificity}$) and false negative rate ($1 - \text{Sensitivity}$). This approach enabled the calculation of the impact of each scenario on the hypothetical cohort by making the input data comparable. This approach is based on the methodology recommended by the Cochrane Collaboration for comparing diagnostic accuracy studies [9]. The normalised HIT prevalence was 20.4%.

Assay performance data for the flow models was derived from the identified literature comparing the index test (4Ts clinical assessment, HemosIL® HIT-Ab(PF4-H), ELISA IgG, ELISA IgGAM) to either clinical HIT or the gold standard SRA (see Table 1).

The treatment strategies included in each scenario assumed the following:

- True negatives continued to receive heparin.
- False positives were unnecessarily switched to a replacement anticoagulant therapy (argatroban, bivalirudin, danaparoid, fondaparinux, lepirudin) according to country-specific guidance.
- False negatives with isolated HIT continued to receive heparin, while those with HIT with thrombosis (HITT) were switched to replacement anticoagulant therapy.
- True positives in the T&S and on-demand scenarios were given replacement anticoagulant therapy. In T&W scenario, only HITT patients were treated early, and HIT patients were treated late, after the results of an ELISA IgGAM (the most common test) were obtained.

2.3.1. Clinical outcomes representing HIT complications

Clinical outcomes were defined as the aggregate of clinical outcomes representing HIT complications: new thrombosis, bleeding events and deaths. These were compared across the diagnostic groups for each

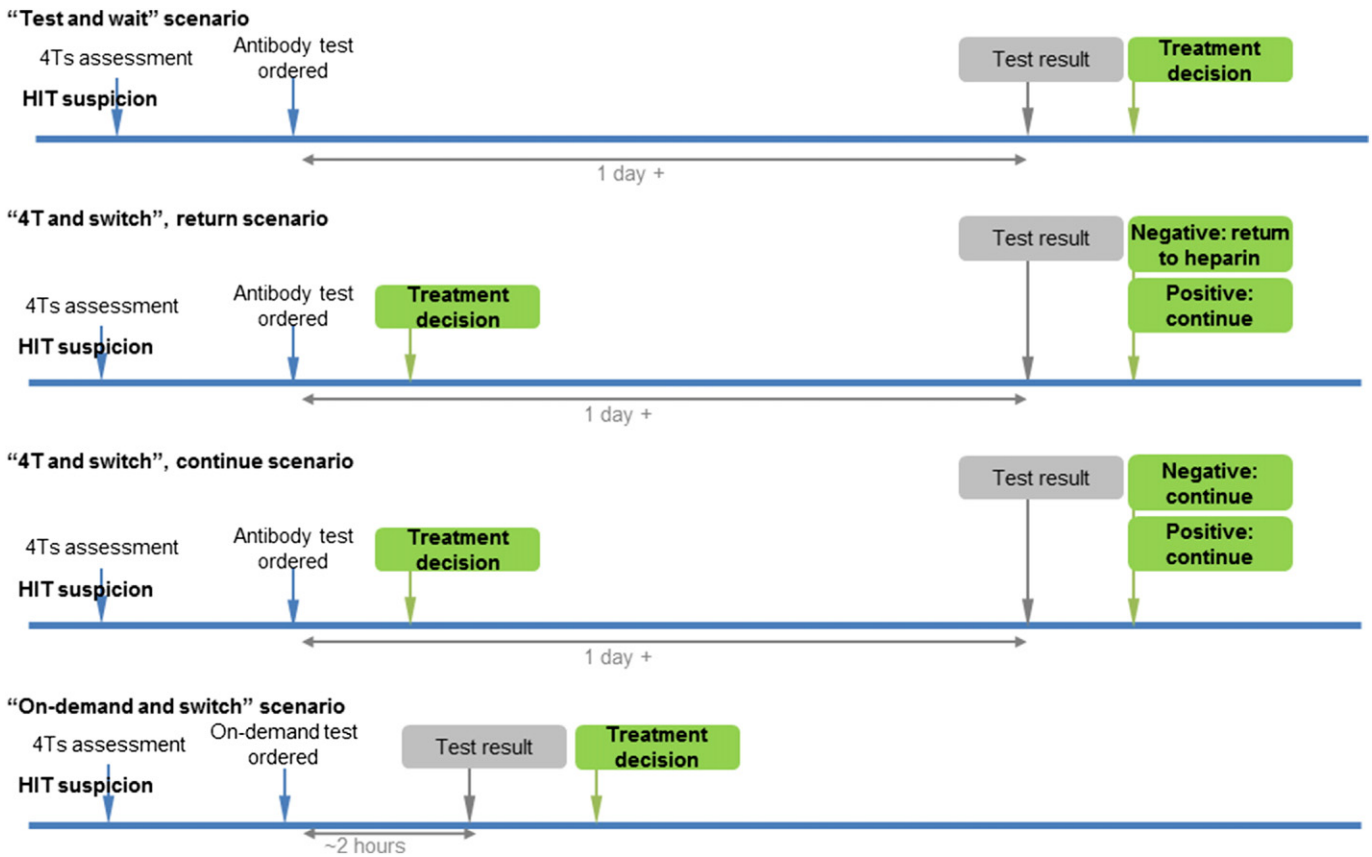


Fig. 1. Model scenarios overview.

scenario. The probability data for these clinical outcomes representing HIT complications was derived from the literature (see Table 2). Clinical outcomes representing HIT complications were calculated from the identified literature to represent the impact of the delay in getting test results. Based on the identified literature, different outcome probabilities were assigned based on HIT status (no HIT, isolated HIT, HITT) and treatment strategy (replacement anticoagulant therapy, continue heparin). Where data was limited or not available, assumptions were made based on the data available.

2.3.2. Cost outcomes

A retrospective cost-of-illness study identified two major costs of HIT: hospitalisation and replacement anticoagulant therapy costs [10].

The current study investigated three countries: the UK, US and Germany. There was a lack of reliable data on hospitalisation costs identified in the literature. Costs were also likely to be highly variable between and within countries. Therefore the primary cost outcome chosen for this study was the cost of replacement anticoagulant therapy.

The minimum and maximum recommended duration of replacement anticoagulant therapy was estimated based on the literature and treatment guidelines [6, 11, 12] (respectively for the US, UK and Germany 5, 7 and 7 minimum, and 9.2, 10 and 10 days maximum). Drug unit prices were identified using zenRx [13], which aggregates data from various sources, and the UK's Drugs and pharmaceutical electronic market information (eMit) [14]. The World Health Organization's Defined Daily Dose (DDD) was used to calculate daily drug doses [15].

Table 1
Parameter table for clinical impact flow model.

Category	HIT/HITT	Treatment	Outcomes (median)			Source
			Death	Bleeding	New thrombosis	
True negative	n/a	Replacement therapy	0.0%	6.1%	NA	[6, 23, 29] ^a
False positive	n/a	No replacement therapy	0.0%	6.1%	NA	[6, 23, 29] ^a
		Replacement therapy	0.0%	6.1%	NA	[6, 23, 29] ^a
True positive	HIT	No replacement therapy	0.0%	6.1%	NA	[6, 23, 29] ^a
		Early therapy	0.0%	13.2% ^b	6.0%	[6, 22, 23, 29, 30] ^a
		Late therapy	1.6%	13.2% ^b	14.2%	[6, 22, 23, 29, 30] ^a
		Late therapy	15.2%	20.3% ^b	34.8%	[6, 22, 23, 29] ^a
False negative	HIT	Replacement therapy	NA	NA	NA	NA
		No replacement therapy	18.5%	11.5%	25.2%	[23] ^a
	HITT	Replacement therapy	1.6%	20.3%	10.4%	[6, 22, 23, 30] ^a
		No replacement therapy	NA	NA	NA	NA

NR – not reported.

^a Data partly based on assumptions.

^b No data for late vs early treatment for bleeding – used the same data for both.

Table 2
Test performance compared to clinical diagnosis or the gold standard diagnostic (SRA).

Study	Index test	n =	4Ts score ≥ 4 (%)	HIT prevalence	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
<i>Compared to clinical diagnosis</i>								
Manufacturer data [23]	HemosIL HIT-Ab	77	73%	45.5%	94.3	92.9	91.7	95.1
Raschke [18]	ELISA IgG	1958	NR	11.8%	93.5–99.6 ^a	69.3–93.6 ^a	NR	NR
Bakchoul [19]	ELISA IgG	459	19%	7.6%	~95	~90	NR	NR
Leroux [17]	ELISA IgG	334	71%	12.0%	100.0	82.7	100.0	44.0
Raschke [18]	ELISA IgGAM	399	NR	NR	97.7–100.0 ^a	84.9–92.7 ^a	NR	NR
Leroux [5]	Lateral flow ^b	334	71%	12.0%	97.5	83.4	99.6	44.4
Leroux [5]	Lateral flow ^c	334	71%	12.0%	100	82.2	100.0	43.7
Leroux [5]	PaGIA	334	71%	12.0%	100	54.5	100.0	19.0
Lang [21]	PaGIA	39	NR	NR	75	100	97.0	100.0
Garritsen [20]	Flow cytometry	241	43%	7.1%	88.2	99.1	99.1	88.2
Mullier [22]	Flow cytometry	57	51%	17.0%	88.9–100.0 ^a	97.7–100.0 ^a	97.7–100.0 ^a	88.9–100.0 ^a
Mullier [22]	SRA	57	51%	17.0%	88.9	95.5	97.7	80.0
<i>Compared to SRA</i>								
Manufacturer data	HemosIL HIT-Ab	66	70%	47.0%	90.3	94.3	93.3	91.7
Galea [24]	ELISA IgG	200	58%	10.5%	86	93	98	60
Morel-Kopp [25]	ELISA IgG	97	23%	39.3%	NR	95.9	NR	NR
Morel-Kopp [25]	ELISA IgGAM	97	23%	39.3%	NR	86.5 to 87.5 ^a	NR	NR
Pouplard [26]	ELISA IgGAM	213	65%	10.3%	100	81.7	100.0	38.6
Ruf [27]	ELISA IgGAM	83	57%	12.0%	100	19.2	100.0	14.0
Galea [24]	ELISA IgGAM	200	58%	10.5%	90	90	99.0	53.0
Solano [28]	PaGIA	26	96%	53.8%	100	20	NR	NR
Pouplard [26]	PaGIA	213	65%	10.3%	95.5–100	20–91.6	99.4–100	37.5–56.8
Solano [28]	Flow cytometry	26	96%	53.8%	81	100.0	76.9	100.0

NR – Not reported.

^a Depending on cut-off selected.

^b Serum.

^c Plasma.

Data from the survey about the proportion of patients prescribed each replacement anticoagulant therapy was used to weight the costs of different drugs, giving an average daily cost for replacement anticoagulant therapy. This daily cost was multiplied by the average treatment duration. Minimum and maximum drug costs for the diagnostic groups were calculated for each scenario. Drug costs were calculated using minimum and maximum ranges for drug unit price and days recommended treatment.

There were no figures in the literature for other costs such as reagent or labour costs (lab technician time required to run tests multiplied by hourly wage). To address this data gap the survey asked respondents who were aware of costs to provide an estimate of the total cost per test. However, only a small proportion (26%, n = 23) stated that they were aware of costs and there was a large variation in cost estimates given (between \$84 and \$235 in the US). Therefore the data was judged to not be sufficiently robust to incorporate into the model.

Data was extracted by one researcher and checked by other researchers.

3. Results

3.1. Current HIT diagnosis landscape in selected countries

The survey found that immunoassay tests were ordered as part of the pathway by over half of respondents. Functional tests were ordered at the same time as immunoassay tests by about a third of respondents, ordered after immunoassay test results by 38% and 30% did not order functional tests. Over half of respondents stopped heparin based on the 4Ts score without waiting for immunoassay test results. When a negative diagnosis is confirmed there were geographical variations in treatment, with 43% of US-based respondents switching patients back to heparin, compared to over 70% in Germany and the UK.

3.2. Test performance

Six studies assessing the performance of available diagnostic tests against clinical outcomes representing HIT complications were

identified [16–21]. These studies evaluated four classes of immunoassays (ELISA IgG/IgGAM, HemosIL® HIT-Ab(PF4-H), DiaMed ID-PaGIA spin column and STiC Expert HIT lateral flow) and two functional assays (HiT Alert and Platelet Microparticle Generation Assay – PMGA). Unpublished performance data for HemosIL® HIT-Ab(PF4-H) was supplied by the manufacturer, who funded the analysis. Unpublished data was not obtained from other manufacturers.

3.2.1. Immunoassay test performance

Using clinical HIT diagnosis as the reference standard, IgG ELISAs ranged in sensitivity between 93.5% [16] and 100% [17], and in specificity between 69.3% and 93.6% [16] (depending on the cut-off selected). The IgGAM ELISA ranged in sensitivity from 97.7% [16] to 100% [16] and in specificity between 84.9% [16] and approximately 90% [16, 18] (sensitivity and specificity varied depending upon the cut-off selected). In the manufacturer's data, HemosIL® HIT-Ab(PF4-H) demonstrated a sensitivity of 94.3%, similar to that of the ELISA IgG when it was performed using a higher cut-off than recommended by the manufacturer, and a specificity of 92.9%, higher than the reported range for the ELISA IgGAM and IgG tests. The DiaMed ID-PaGIA spin column assay reported wide-ranging sensitivity between 75% [19] and 100% [17] and specificity of 54.4% [17] to 100% [19]. The STiC Expert HIT lateral flow assay (testing both plasma and serum) had a high sensitivity 97.5% [17] to 100% [17], but lower specificity 82.2% [17] to 83.4% [17].

Using SRA as the reference standard, HemosIL® HIT-Ab(PF4-H) demonstrated lower sensitivity than IgGAM ELISAs and PaGIA spin column assay, and higher or comparable sensitivity to ELISA IgG and the STiC Expert HIT lateral flow cytometry assay. HemosIL® HIT-Ab(PF4-H) had higher specificity than the alternative immunoassays.

Overall, HemosIL® HIT-Ab(PF4-H) had comparable to lower sensitivity compared to other available immunoassays, but higher specificity (see Table 1).

3.2.2. Functional assay performance

When compared with HIT clinical diagnosis, two flow cytometry assays (HiT Alert and PMPGA) exhibited sensitivity between 88.2% [20] and 100% [21], and specificity between 97.7% [21] and 100% [21],

sensitivity and specificity both depended on the cut-off value used. One study evaluated SRA against clinical HIT as the reference standard, with a resultant sensitivity of 88.9% [21] and specificity of 95.5% [21].

Across the identified studies, HemosIL® HIT-Ab(PF4-H) had lower specificity, but higher sensitivity than the functional flow cytometry (with clinical HIT diagnosis or SRA as reference standard) and SRA tests (see Table 1).

3.3. Clinical impact

The clinical impact flow model measured the performance of batched and on-demand immunoassay testing. The flow diagram modelled the movement of 1000 hypothetical patients through the care pathways using the four scenarios and by diagnostic group, evaluating the impact on major clinical outcomes (see Fig. 2).

There was limited clinical outcome data available in published studies for individual groups, therefore a number of assumptions had to be made to obtain figures for use in the model. For example, data on HIT outcome rates for true negatives and false positives was inconsistent, and an assumption was made that these figures ought to be the same.

The number of clinical outcomes representing HIT complications was higher for the T&W scenario, compared with all other scenarios (batched and on-demand). There was no difference in clinical outcomes representing HIT complications between the two “4Ts and switch” scenarios, regardless of whether patients returned to heparin. Clinical

outcomes representing HIT complications were lower in the on-demand scenarios than all others. See Fig. 3 for detailed numbers.

3.4. Cost impact

The cost impact flow model was designed to assess the potential cost impact of on-demand testing facilitating treatment decisions based on test results.

The estimated average total cost of HIT varies across countries ranging from €2090 to €3200 [10] in Germany, and €3330 to €3700 [12] in other European countries to approximately \$35,400 [22] to \$64,800 [23] in the US. A retrospective cost of illness study identified two key drivers of the additional average cost of HIT in a German hospital: lengthened hospital stay, which accounted for 70.3% (€6330) of the additional costs, and medication costs, which accounted for 19.7% (€1777) of total additional costs [10].

The speculative treatment approach of both “4Ts and switch” scenarios resulted in high replacement anticoagulant therapy costs of a maximum of \$39,616, \$11,839, \$6833 respectively per patient in the US, UK and Germany for the scenario where patients remain on replacement anticoagulation therapy. Costs are lower when some of the 4Ts false positive patients are switched back to heparin when their test “4Ts and Switch, Return”. “On-demand and Switch” resulted in reduced replacement anticoagulant therapy costs from a maximum of \$14,017 with “T&S” to \$12,799 in the US, from \$4007 to \$3811 in the UK, from \$2333 to \$2201 in Germany per patient. The data in the “Test and

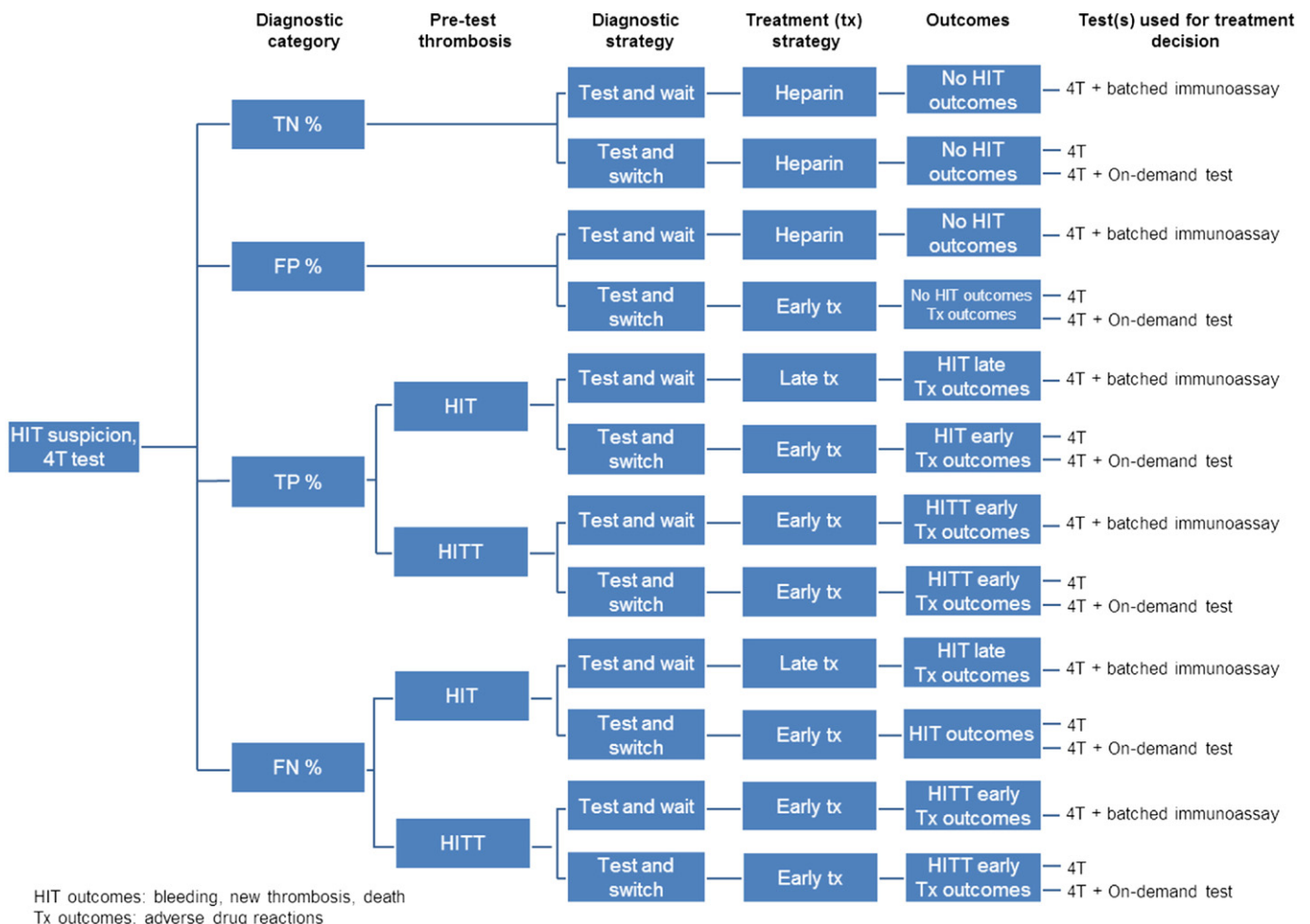


Fig. 2. Clinical impact flow model for a hypothetical cohort of 1000 HIT suspected patients

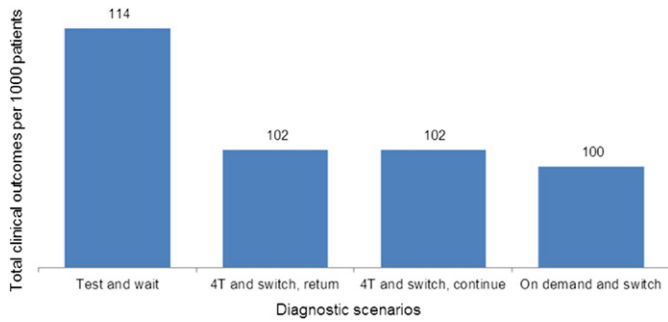


Fig. 3. Comparison of clinical outcomes across diagnostic categories for four scenarios among a hypothetical cohort of 1000 HIT suspected patients.

Wait” scenario is based on IgGAM test performance results. See Fig. 4 and Table 3 for the total cost of replacement anticoagulant therapy for each of the four scenarios (in thousands of dollars) per 1000 patients.

4. Discussion

The two main issues in HIT diagnostic testing are test performance and test turnaround time, with the survey indicating that only 6% of respondents were satisfied with current test performance, with ELISA test specificity in particular viewed as suboptimal. There was also dissatisfaction with turnaround times of over 24 h. Delays in diagnosis caused by test turnaround time can lead to speculative treatment, increasing drug costs as people without HIT are speculatively switched to replacement anticoagulant therapy. Such delays may increase costs if replacement anticoagulant therapy is used unnecessarily, conversely if people with HIT are kept on heparin whilst awaiting laboratory confirmation of diagnosis they may develop more serious complications. In addition to the increased expense of unnecessary replacement anticoagulant therapy for false positive patients, delays in test results could potentially lead to poorer clinical outcomes as the true cause of the symptoms causing HIT suspicion is not addressed.

The literature review showed that HemosIL® HIT-Ab(PF4-H) has a higher specificity, and comparable or lower sensitivity than currently available tests (ELISAs, spin column assays and lateral flow assays). Its higher specificity means that HemosIL® HIT-Ab(PF4-H) has a lower false positive rate than other immunoassay tests.

The clinical impact flow diagram using a hypothetical cohort of 1000 patients found that different tests performed on-demand performed comparably (figures not shown, available on request). The only difference was two fewer cases of new thrombosis with on-demand IgG than with other on-demand tests (17 versus 19) and therefore two fewer overall cases of clinical outcomes representing HIT complications. The difference in clinical and cost impact was most pronounced between batched and on-demand testing scenarios. There was a lack of

good quality data on clinical outcomes representing HIT complications for false positives and no distinction between treated groups and non-treated false positives. Therefore it was not possible to calculate the clinical value for false positives of avoiding either overtreatment or lack of treatment for any underlying cause of HIT suspicion. The T&W scenario entailed delayed test results and subsequently a delayed treatment approach, which resulted in higher HIT outcome events than all of the other scenarios. This finding points the importance of timely test results in HIT diagnosis and treatment.

Estimates of the costs of HIT varied, with notably higher costs in the US. Costs were mainly driven by hospitalisation and drug costs [10]. A retrospective cost of illness study found no significant difference in overall costs between early vs. delayed replacement anticoagulant therapy; despite high medication costs in the former group, suggesting that early initiation of replacement anticoagulant therapy may avoid costly complications [10]. Tests with a quicker turnaround would enable earlier treatment of patients who are positive for HIT and therefore potentially reduce costs to healthcare systems. Additional benefit of using on-demand testing can be expected from reduced length of stay, further to a lower rate of adverse events in HIT patients. Given the highly variable hospitalisation costs and lack of reliable data, this cost has not been measured in this work, rather, could be assessed on an ad-hoc basis depending on the local costs. Similarly the cost of the test reagents and labour to perform them has not been assessed in this work, due to a lack of robust data.

4.1. Limitations

The assessment of the number of clinical outcomes representing HIT complications relied on the availability of data from the studies included in the literature review. For example it was not possible to quantify the difference in bleeding because there is no data reporting the impact of early vs. late treatment on bleeding. For clinical outcomes representing HIT complications, we therefore used the incidence rates of thrombosis and death, which have been reported. The data on adverse outcomes for false positives and true negative (i.e. those without HIT) is based on small samples, and there is no data from robust samples for each group and subgroup (e.g. stratified by 4Ts score). We therefore used the most robust data available and made the assumption that the incidence was similar across “non-HIT” groups. As some of this data is based on small sample sizes and assumptions, the data should be viewed with caution.

Test performance data for HemosIL® HIT-Ab(PF4-H) was provided by the manufacturer. Unpublished data for other tests was not sought from other manufacturers, and this may affect results.

The overall validity of these results is limited by differences in the selected study populations and in the gold standard definitions of HIT used, which may affect the comparability of the study populations. The lack of reported data on the characteristics of those suspected of

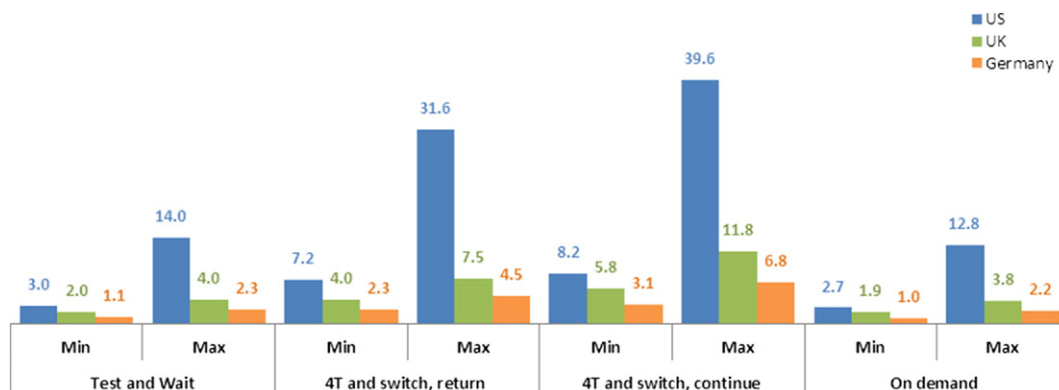


Fig. 4. Replacement anticoagulant therapy costs (US\$ million per thousand patients) per country for the hypothetical cohort of 1000 HIT suspected patients for the four scenarios.

Table 3

Comparison of replacement anticoagulant therapy costs (US\$) among a hypothetical cohort of 1000 HIT suspected patients for the four scenarios.

Scenario	Test and wait		4Ts and switch, return		4Ts and switch, continue		On demand	
	Min	Max	Min	Max	Min	Max	Min	Max
US	2961	14,017	7215	31,628	8196	39,616	2652	12,799
UK	1985	4007	4017	7452	5759	11,839	1857	3811
Germany	1084	2333	2261	4521	3124	6833	1008	2201

having HIT, such as the 4Ts score cut-off used, means that it is not clear whether these cohorts can be directly compared because they may represent different pre-test probabilities. The definition of 'clinical HIT' was also either not reported or poorly described in studies, therefore there may be variations in the definitions of the gold standard 'clinical HIT' diagnosis.

The sample sizes for our primary research were not large enough to make definitive statements based on the findings. Hence data was not incorporated where it was judged to not be sufficiently robust (such as the cost estimates for reagents and labour costs). There is a potential for bias where respondents try to give the answer that they think the surveyor wants. To minimise this bias we included cross-checking questions, designed to test respondents' previous answers and rotated options in multi-choice questions. The primary research was not designed to be comprehensive, but to give additional insight into real-world practice and to help to fill gaps identified in the literature if possible.

Analyses were adapted during the study to explore areas of difference between scenarios and make them more representative of real practice. Similar sensitivity and specificity of the tests meant that analyses which did not incorporate length of treatment with replacement anticoagulant therapy did not capture potential differences between the scenarios. Therefore duration of use of the different replacement anticoagulant therapy was incorporated in the model. The three on-demand scenarios were combined after analyses showed that the most pronounced difference in clinical outcomes was between the batched and on-demand scenarios. The limitations to the data available and the small difference seen between the on-demand tests (2 cases of new thrombosis) meant that these differences may not have been reliable. Similarly the "4Ts and switch" scenarios were split into those returning to heparin and those continuing on replacement anticoagulant therapy after data from the survey indicated that in reality a large proportion of patients are not switched back to heparin, even when test results indicate that they are HIT-negative.

5. Conclusion

On-demand HIT testing has the potential to have a positive clinical and economic impact. Rapid testing enables earlier informed treatment based on high performance tests, rather than speculative treatment or delayed decision making. This could potentially improve clinical outcomes in HIT patients by enabling earlier appropriate treatment and reduce costs by preventing expensive complications. In patients speculatively treated who turn out to be HIT negative, on-demand testing could reduce replacement anticoagulant therapy drug costs.

Further research is needed to enable more definitive conclusions to be reached about the overall clinical and economic value of on-demand testing. In particular there is a need for comparable data about clinical outcomes representing HIT complications for individual groups and subgroups (e.g. stratified by 4Ts score). There is also a need for improved reporting of patient characteristics and definitions of 'clinical HIT'. Furthermore, economic evaluations that take into account costs of testing itself, and any system-wide cost savings, such as reduced length of stay due to earlier treatment, would be useful in understanding the overall cost impact of on-demand testing.

Conflicts of interest

This work was funded by Instrumentation Laboratory, Bedford (MA), the manufacturers of HemosIL® HIT-Ab(PF4-H). The funders did not influence study design or analysis, and editorial independence was maintained.

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AP and EO: designed and conducted interviews; survey design, primary data analysis. EO: literature searches. SC: study selection. AP, EO and SC: generated study design; data extractions; writing. AP and SC: data analysis and modelling. RC: expert input into study design and methodology; editorial contribution. All authors have reviewed and approved the final article.

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References

- [1] T.E. Warkentin, Heparin-induced thrombocytopenia: pathogenesis and management, *Br. J. Haematol.* 121 (4) (2003) 535–555.
- [2] H. Watson, S. Davidson, D. Keeling, Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition, *Br. J. Haematol.* 159 (5) (2012) 528–540.
- [3] A. Cuker, T.L. Ortel, ASH evidence-based guidelines: is the IgG-specific anti-PF4/heparin ELISA superior to the polyspecific ELISA in the laboratory diagnosis of HIT? *Hematology Am. Soc. Hematol. Educ. Program.* 250-2 (2009).
- [4] Linkins LA, Dans AL, Moores LK, Bona R, Davidson BL, Schulman S, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012 Feb;141(2 Suppl):e495S-530S. PubMed PMID: 22315270. PMCID: PMC3278058. English.
- [5] G.K. Lo, D. Juhl, T.E. Warkentin, C.S. Sigouin, P. Eichler, A. Greinacher, Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings, *J. Thromb. Haemost.* 4 (4) (2006 Apr) 759–765 (16634744; English).
- [6] A.R. Patrick, W.C. Winkelmayr, J. Avorn, M.A. Fischer, Strategies for the management of suspected heparin-induced thrombocytopenia: a cost-effectiveness analysis, *Pharmacoeconomics* (2007) 949–961.
- [7] T.E. Warkentin, A. Greinacher, Heparin-induced thrombocytopenia: recognition, treatment, and prevention – the seventh ACCP conference on antithrombotic and thrombolytic therapy, *Chest* 126 (3 SUPPL.) (2004) 311S–337S.
- [8] A. Cuker, Clinical and laboratory diagnosis of heparin-induced thrombocytopenia: an integrated approach, *Semin. Thromb. Hemost.* 40 (1) (2014 Feb) 106–114 (24363239; English).
- [9] P. Bossuyt, C. Davenport, J. Deeks, C. Hyde, M. Leflang, R. Scholten, Chapter 11: interpreting results and drawing conclusions, in: J.J. Deeks, P.M. Bossuyt, C. Gatsonis (Eds.), *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 0.9 Cochrane Collaboration*, 2013.
- [10] T. Wilke, S. Tesch, A. Scholz, T. Kohlmann, A. Greinacher, The costs of heparin-induced thrombocytopenia: a patient-based cost of illness analysis, *J. Thromb. Haemost.* 7 (5) (2009) 766–773.
- [11] A. Bryant, J. Low, S. Austin, J.E. Joseph, Timely diagnosis and management of heparin-induced thrombocytopenia in a frequent request, low incidence single centre using clinical 4 T's score and particle gel immunoassay, *Br. J. Haematol.* 143 (5) (2008) 721–726.
- [12] I. Elalamy, G. Le Gal, F. Nachit-Ouinekh, A. Lafuma, C. Emery, C. Le-Fur, et al., Heparin-induced thrombocytopenia: an estimate of the average cost in the hospital setting in France, *Clin. Appl. Thromb. Hemost.* 15 (4) (2009 Jul-Aug) 428–434 (18544593; English).

- [13] zenRx. zenRx Research: Global Pharmaceutical Pricing and Reimbursement Database Massachusetts: zenRx; 2015. Available from: <http://www.zenrx.org/>.
- [14] DH. eMit national database London: Department of Health; [2011]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/421098/eMIT_NATIONAL.xls.
- [15] WHO. WHOCC - ATC/DDD Index: WHO Collaborating Centre for Drug Statistics Methodology; 2013. Available from: http://www.whocc.no/atc_ddd_index/?code=B01AE&showdescription=no.
- [16] R.A. Raschke, S.C. Curry, T.E. Warkentin, R.D. Gerkin, Improving clinical interpretation of the anti-platelet factor 4/heparin enzyme-linked immunosorbent assay for the diagnosis of heparin-induced thrombocytopenia through the use of receiver operating characteristic analysis, stratum-specific likelihood ratios, and Bayes theorem, *Chest* 144 (4) (2013) 1269–1275.
- [17] D. Leroux, N. Hezard, A. Lebreton, A. Bauters, P. Suchon, E. de Maistre, et al., Prospective evaluation of a rapid nanoparticle-based lateral flow immunoassay (STic Expert® HIT) for the diagnosis of heparin-induced thrombocytopenia, *Br. J. Haematol.* 166 (5) (2014) 774–782.
- [18] T. Bakchoul, A. Giptner, G. Bein, S. Santoso, U.J. Sachs, Performance characteristics of two commercially available IgG-specific immunoassays in the assessment of heparin-induced thrombocytopenia (HIT), *Thromb. Res.* 127 (4) (2011 Apr) 345–348 (21232785; English).
- [19] S. Lang, H. Moriarty, D. Rosenfeld, A comparison of the Diamed PaGIA with an ELISA method for detection of HIT antibodies, *Australian Journal of Medical Science.* 27 (3) (2006) 107–112.
- [20] H.S. Garritsen, M. Probst-Keppler, N. Legath, W. Eberl, S. Samaniego, J. Woudenberg, et al., High sensitivity and specificity of a new functional flow cytometry assay for clinically significant heparin-induced thrombocytopenia antibodies, *Int. J. Lab. Hematol.* 36 (2) (2014 Apr) 135–143 (23981347; English).
- [21] F. Mullier, V. Minet, N. Bailly, B. Devalet, J. Douxfils, C. Chatelain, et al., Platelet microparticle generation assay: a valuable test for immune heparin-induced thrombocytopenia diagnosis, *Thromb. Res.* 133 (6) (2014 Jun) 1068–1073 (24360929; English).
- [22] R.J.G. Arnold, R. Kim, B. Tang, The cost-effectiveness of argatroban treatment in heparin-induced thrombocytopenia: the effect of early versus delayed treatment, *Cardiol. Rev.* 14 (1) (2006) 7–13.
- [23] N.L. Whitlatch, S.L. Perry, T.L. Ortel, Anti-heparin/platelet factor 4 antibody optical density values and the confirmatory procedure in the diagnosis of heparin-induced thrombocytopenia, *Thromb. Haemost.* 100 (4) (2008 Oct) 678–684 (18841292; PMID: NIHMS59926; PMC2575642; English).
- [24] V. Galea, A. Khaterchi, F. Robert, G. Gerotziafas, M. Hatmi, I. Elalamy, Heparin-induced multiple electrode aggregometry is a promising and useful functional tool for heparin-induced thrombocytopenia diagnosis: confirmation in a prospective study, *Platelets* 24 (6) (2013) 441–447.
- [25] M.C. Morel-Kopp, M. Aboud, C.W. Tan, C. Kulathilake, C. Ward, Heparin-induced thrombocytopenia: evaluation of IgG and IgGAM ELISA assays, *Int. J. Lab. Hematol.* 33 (3) (2011 Jun) 245–250 (21118381; English).
- [26] C. Pouplard, P. Gueret, M. Fouassier, C. Ternisien, M. Trossaert, S. Régina, et al., Prospective evaluation of the '4Ts' score and particle gel immunoassay specific to heparin/PF4 for the diagnosis of heparin-induced thrombocytopenia, *J. Thromb. Haemost.* 5 (7) (2007) 1373–1379.
- [27] K.M. Ruf, E.S. Bensadoun, G.A. Davis, J.D. Flynn, D.A. Lewis, A clinical-laboratory algorithm incorporating optical density value to predict heparin-induced thrombocytopenia, *Thromb. Haemost.* 105 (3) (2011 Mar) 553–559 (21264443; English).
- [28] C. Solano, H. Mutsando, M. Self, M.C. Morel-Kopp, P. Mollee, Using HitAlert flow cytometry to detect heparin-induced thrombocytopenia antibodies in a tertiary care hospital, *Coagul. Fibrinolysis.* 24 (4) (2013 Jun) 365–370 (23429257; English).
- [29] S. Baroletti, C. Piovela, J. Fanikos, M. Labreche, J. Lin, S.Z. Goldhaber, Heparin-induced thrombocytopenia (HIT): clinical and economic outcomes, *Thromb. Haemost.* 100 (6) (2008) 1130–1135.
- [30] J.L. Reagan, R.R. Ingham, S. Dalia, J.N. Butera, J.D. Sweeney, Differences in the clinical course of heparin induced thrombocytopenia before and after the availability of HIT IgG class testing, *Thromb. Res.* 134 (1) (2014) 90–92.