BMJ Open

Improving safety of unfractionated heparin: a retrospective, quasi-experimental, observational study of the impact of a pocket card and a computerised prescription aid tool in the University Hospitals of Geneva

Wedali E Jimaja ,[1] Jerome Stirnemann,[1,2] Pierre Fontana,[2,3] Katherine S Blondon [2,4]

To cite: Jimaja WE, Stirnemann J, Fontana P, *et al*. Improving safety of unfractionated heparin: a retrospective, quasi-experimental, observational study of the impact of a pocket card and a computerised prescription aid tool in the University Hospitals of Geneva. *BMJ Open* 2022;**12**:e056912. doi:10.1136/bmjopen-2021-056912

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-056912).

Received 30 August 2021
Accepted 26 January 2022

For numbered affiliations see end of article.

Correspondence to
Wedali E Jimaja;
wedali.jimaja@hcuge.ch

ABSTRACT

Background Despite the rapid rise of direct oral anticoagulants, unfractionated heparin (UFH) remains the mainstay anticoagulant in specific situations such as severe renal failure, perioperative setting or in critical care units. However, its titration is often challenging.

Objectives To investigate the effect of a pocket card and a computerised prescription aid tool (CPAT) on the quality of UFH anticoagulation.

Design Monocentric retrospective, quasi-experimental, observational study.

Setting Inpatient primary care centre between 1 January 2016 and 31 December 2019.

Participants >18 years-old treated with therapeutic UFH for more than 24 hours. There were 819 and 1169 anticoagulation episodes before and after intervention, respectively.

Intervention In October 2017, we implemented a pocket card with evidence-based recommendation for therapeutic UFH initiation, monitoring and dosing adaptation. In October 2019, we implemented a CPAT in a group subset.

Primary and secondary outcomes The primary outcome was the time needed to reach a therapeutic anti-Xa before and after the implementation of the pocket card. The secondary outcomes included a subgroup analysis assessing the effect of the CPAT. Other secondary outcomes were the anti-Xa status (infratherapeutic, therapeutic or supratherapeutic) at 7 and 24 hours of UFH treatment.

Results We found a significant increase in the time to reach therapeutic dosing with pocket card-guided recommendations implementation (10.1 vs 14 hours, HR of 0.8, 95% CI: 0.70 to 0.93). However, the CPAT was associated with a significant decrease in the time needed to reach the therapeutic range (13.9 vs 7.1 hours, HR of 1.74, 95% CI: 1.17 to 2.60).

Conclusion Although we observed an increase in time to reach therapeutic anti-Xa with the pocket card, possibly due to a selection bias (use of activated partial thromboplastin time for monitoring before the pocket card), the implementation of CPAT significantly decreased the delay for effective therapy. Further studies are needed to confirm these findings, and to determine the optimal initial dose of UFH anticoagulation.

Strengths and limitations of this study

- One strength is the large size of the sample.
- Another strength is its quasi-experiment design which is closer to real life.
- One limitation is its retrospective design.
- Other limitations include use of activated partial thromboplastin time for monitoring in the pregroup, and blood samples analysed outside of the hospital were not included in this study.
- Finally, the number of bleeding events could not be obtained reliably.

INTRODUCTION

The anticoagulant properties of unfractionated heparin (UFH) have been known for about a century,[1] and UFH has been prescribed for various indications (eg, prevention and treatment of thrombosis, acute coronary syndrome, coronary bypass graft or haemodialysis).[2] In the recent years, numerous other anticoagulant molecules have emerged, for instance low molecular weight heparin, fondaparinux and direct oral anticoagulants (DOACs), associated with several advantages including no systematic need for ongoing therapeutic drug monitoring. However, UFH remains the mainstay treatment in specific clinical situations such as in severe renal insufficiency, perioperative setting and critical care owing to its short half-life and the availability of a specific antidote.[2]

Due to the large interindividual pharmacokinetic variability, UFH requires close laboratory monitoring and titration to keep anticoagulation within the target range. The activated partial thromboplastin time (aPTT) remains the most commonly used method for this monitoring in spite of its standardisation issues and limitations such as variable levels of clotting factors masking the UFH anticoagulant effect.[3] The target aPTT (1.5–2.5 times basal aPTT) is based on a 1970s study.[4] The anti-Xa chromogenic assay is a valuable alternative that does not have the limitations of aPTT and is more standardised.[3] Its therapeutic range is set to 0.3–0.7 IU/mL.[5] Anti-Xa-based monitoring of UFH has been shown to shorten the time needed to reach the therapeutic range, to reduce the number of blood sampling and UFH dose adjustment compared with aPTT-based monitoring,[6 7] but is slightly more expensive than aPTT.[8] Moreover, the anti-Xa assay is less available worldwide and is sensitive to other anticoagulants such as DOACs.[9]

Although an anti-Xa-based monitoring trial showed improvement in a surrogate outcome (decrease of red blood cell transfusions),[10] trials comparing aPTT and anti-Xa-based monitoring for clinical outcomes have not found clear benefits.[11]

Beyond the issue of the most appropriate monitoring assay, dose adaptation is often poorly standardised in hospitals, although some authors such as Schurr *et al* proposed algorithms that try to organise such a standardisation.[12] In this retrospective study, they examined the effect of nurse-driven UFH non-customisable weight-based normograms on the time elapsed to reach therapeutic anticoagulation. In the group using normograms, they observed a decrease in the time needed to reach therapeutic anticoagulation.

The aim of the present study was to investigate the impact of a pocket card exhibiting recommendations on UFH dosing according to anti-Xa result as well as a computerised prescription aid tool (CPAT) on the quality of UFH anticoagulation for therapeutic (as opposed to prophylactic) treatment in an inpatient setting.

MATERIALS AND METHODS

Setting

This was a single-centred retrospective, quasi-experimental, observational study that took place in the University Hospitals of Geneva. The data were obtained for the period of 1 January 2016 to 31 December 2019 and were extracted from the hospital's electronic medical records (EMR).

Population

This study included hospitalised patients that were 18 years of age or older, who received a continuous intravenous infusion of UFH aiming for a therapeutic anticoagulation for at least 24 hours. This 24-hour threshold was chosen to exclude patients with acute coronary syndrome, who usually receive therapeutic dose of UFH for a short period before catheterisation. We included patients with UFH doses of ≥10 000 IU/day, which we considered as most likely prescribed for a therapeutic anticoagulation. Patients receiving doses below this threshold but with explicit mention of a therapeutic anticoagulation indication in the medical record were also included. Patients with anticoagulation episodes that were not associated with at least one monitoring test over the therapeutic threshold (anti-Xa value >0.3 IU/mL) were excluded from the analyses, as they were assumed to be prescribed as prophylactic purpose. Those with less than one value of anti-Xa per day were also discarded as this suggests that aPTT was used for the monitoring of the UFH therapy. Finally, patients staying in neurology, neurosurgery and haematology units were not included in the analysis as they were assumed to often not follow the usual protocol due to the very high bleeding risk associated their corresponding pathologies.

Two groups were defined: a baseline pregroup with patients included and followed up to the 1st of October 2017, when the pocket card was implemented, and another group referred to as the postgroup with patients included thereafter.

Intervention

In our institution, both aPTT and/or anti-Xa assays were used for UFH monitoring at the beginning of the period studied. In October 2017, a pocket card guideline was distributed to all the physicians to standardise the preparation, prescription and administration of therapeutic UFH (available at https://www.hug.ch/sites/interhug/files/a6_heparine_web2.pdf, or online supplemental file 1) for an English version). The card indicated the initial dose according to weight, as well as instructions to adjust the dosage according to anti-Xa values based on a protocol published in 2010 by Smith *et al*.[13] The guideline recommended using anti-Xa assay 4–6 hours after introducing or modifying UFH dosing. It also proposed a platelet count 2–3 times a week during the first 2 weeks of UFH treatment.[14] The content of the guideline was also available in the computerised UFH prescription aid tool implemented in October 2019 in the internal medicine wards. This CPAT proposes initial and titration doses of UFH according to the patient's weight and anti-Xa results, and adds an anti-Xa assay 6 hours after each change of dose: prescribers can choose to bypass the recommended UFH doses at any time.

Hospital stays and UFH anticoagulation episodes

We considered each hospital stay as the main unit for our analysis, therefore patients hospitalised more than once during the study period have multiple hospital stays. An UFH anticoagulation episode was defined as an UFH treatment of more than 24 hours during one hospital stay, with possible interruptions of less than 48 hours. During one hospital stay, a patient could therefore have more than one UFH anticoagulation episode. Because we supposed that the therapeutic range would be reached

faster on a second episode based on the data of the first episode, only the first anticoagulation episode was used for each hospital stay. An anti-Xa value was associated with a UFH treatment modification if the blood sample was collected more than 4 hours after initiation of treatment. The therapeutic range was defined as an anti-Xa value between 0.3 and 0.7 IU/mL.

Data collection

Data were extracted from the EMR system to obtain patient demographics (age, gender, comorbidities and indication of anticoagulation), type of ward and length of stay, anti-Xa results (sampling time and result value), renal function, UFH initiation time, and dose modification.

Comorbidities were used to calculate the Multipurpose Australian Comorbidity Scoring System (MACSS) index. It is a comorbidity score integrating 102 conditions, with higher scores representing the presence of more comorbidities.[15]

Statistical analysis

Primary outcome

The primary outcome was the time needed to reach anti-Xa within the therapeutic anticoagulation range after UHF initiation. The Kaplan-Meier method was used to compute the cumulative incidence of anti-Xa reaching the therapeutic range for each group and the log-rank test was used to compare the two. Cox proportional hazards regression analysis was used to obtain non-adjusted and adjusted HRs.

Secondary outcomes

Subgroup analysis on events occurring after the 1st of October 2019 was also performed to explore the effect of a newly implemented CPAT recapitulating the pocket guide. This analysis was also performed using the Kaplan-Meier method and the log-rank test.

We investigated the difference between the two groups in terms of anti-Xa status after 7 hours and 24 hours of anticoagulation, respectively. We chose a first timepoint at 7 hours after the start of UFH infusion to decrease the risk of missing the first anti-Xa dosing. Indeed, even though the recommended time is between 4 and 6 hours, some samples may be collected beyond this interval. The anti-Xa status was defined as therapeutic, if at least one anti-Xa reached the therapeutic range during the time interval. It was deemed infratherapeutic or supratherapeutic if the last measured anti-Xa value was below or above the therapeutic range, respectively. In the case where no anti-Xa was measured during the considered period, the status was defined as missing. For the anti-Xa status after 7 hours of anticoagulation, missing values were not included in the analysis as they represented a significant amount of the overall values and because our aim was to assess adherence to pocket guide recommendations, which use anti-Xa monitoring. Within the supratherapeutic status, the anti-Xa with values higher than 1 IU/mL were analysed separately, as they represent a significant increase in the risk of major bleeding events.[16] To further explore the effect of the CPAT, we conducted the same anti-Xa status analyses comparing the CPAT subgroup with the episodes in the postgroup in internal medicine units occurring before the introduction of the CPAT. This latter group was named post-Internal Medicine (post-IM) group. Fisher's exact test was used in this subgroup analysis.

In tables 1–3, t-test and χ^2 test were used for continuous and categorical, respectively. Continuous variables were expressed as mean and SD and categorical variables as percentages. The RStudio software (V.1.2.5033, 2009–2019 RStudio) was used to perform the statistical analyses.

Table 1 *Patients characteristics*

Variable	PRE	POST	P value
Number of hospitalisation events	819	1169	
Number of patients	777	1054	
Age (years)	71.3 (14.8)	73.5 (14.8)	<0.01
Weight (kg)	73.8 (18.5)	74.0 (19.6)	0.81
Length of stay (days)	18.1 (19.4)	18.7 (17)	0.5
Female (%)	329 (40.2%)	478 (40.9%)	0.78
eGFR <30 mL/min/1.73 m^2 (%)	152 (18.6%)	273 (23.4%)	<0.01
Anticoagulation indications*			
AF	269 (32.8%)	393 (33.6%)	0.76
VTE	197 (24.1%)	243 (20.8%)	0.09
Mechanical valvular replacement	38 (4.6%)	65 (5.6%)	0.42
	315 (38.5%)	468 (40.0%)	0.51
Wards:			
General internal medicine	375 (45.8%)	452 (38.7%)	<0.01
Surgery	333 (40.7%)	507 (43.4%)	0.25
Geriatrics	55 (6.7%)	145 (12.4%)	<0.01
Others	56 (6.8%)	65 (5.6%)	0.28
MACSS index			
0	60 (7.3%)	61 (5.2%)	0.07
1–2	159 (19.4%)	187 (16.0%)	0.06
3+	600 (73.3%)	921 (78.8%)	<0.01

*Other indications included: intracerebral venous thrombosis, inferior limb arterial thrombosis, intracardiac thrombus, splenic vein thrombosis, renal vein thrombosis and portal thrombosis.
AF, atrial fibrillation or flutter; eGFR, estimated glomerular filtration rate; MACSS, Multipurpose Australian *Comorbidity* Scoring System (with higher score representing a more comorbid state); VTE, venous thromboembolism.

Table 2 Anti-Xa within the seven first hours of anticoagulation

Variable	PRE	POST	P value
Number of anticoagulation episodes	819	1169	<0.01
Baseline UFH dosing, IU/kg (median, IQR)	276 (111)	336 (139)	<0.01
UFH dosing at 7 hours, IU/kg (median, IQR)	278 (111)	339 (140)	
Episodes reaching therapeutic anti-Xa within 7 hours after initiation of unfractionated heparin treatment (n, %)	151 (49)	214 (40)	0.02
Episodes without therapeutic anti-Xa within 7 hours after initiation of unfractionated heparin treatment (n, %)			
Infratherapeutic (anti-Xa <0.3 IU/mL)	118 (38)	205 (38)	1
Supratherapeutic (anti-Xa >0.7 IU/mL)	41 (13)	116 (22)	<0.01
Of which anti-Xa >1 IU/mL	15 (5)	48 (9)	<0.04
No anti-Xa available*	509 (62)	634 (54)	<0.01

*For these percentages and this p-value missing values were integrated, but not for the rest of the table.
UFH, unfractionated heparin.

Patient and public involvement

Due to the retrospective design of the study, patients were not involved its design and the results have not been disseminated to the participants.

RESULTS

From the 7757 hospital stays of patients treated with UFH during the study period, 1988 met the inclusion criteria, the main reason for exclusion being an anticoagulation duration inferior to 24 hours. Out of these, 819 stays from 777 patients were part of to the pregroup, while 1169 stays of 1054 patients were part of the postgroup.

The mean ages were 71.3 (±14.8) and 73.5 (±14.8) years old for the pre and postgroups, respectively. There was a predominance of male gender, with female gender representing 40.2% and 40.9% in pre and postgroups, respectively (p=0.78). The most prevalent identified indications for anticoagulation were atrial fibrillation/flutter and VTE in both groups, and most patients were in either surgery or general internal medicine wards (table 1)

Primary outcome

Heparin anticoagulation quality and efficiency

A total of 819 and 1169 anticoagulation episodes were extracted in the pre and postgroups, respectively. After removing the episodes without anti-Xa values within the 7 hours after the beginning of anticoagulation, 310 episodes remained in the pre group and 535 in the postgroup. For the pregroup, the median time to reach an anti-Xa within therapeutic range was 10.1 hours (95% CI: 7 to 13 hours) and for the postgroup, it was 14 hours (95% CI: 13 to 15 hours), with a statistically significant difference (p<0.01). The HR of reaching a therapeutic anti-Xa is 0.8 for the postgroup (95% CI: 0.70 to 0.93, p<0.01) when comparing both groups. When adjusted for age, wards, gender and weight, the statistical significance remains, with a HR of 0.8 of the postgroup to reach therapeutic anticoagulation (95% CI: 0.69 to 0.92, p<0.01) (figure 1).

Table 3 Anti-Xa within the 24 first hours of anticoagulation

Variable	PRE	POST	P value
Number of anticoagulation episodes	819	1169	<0.01
Baseline UFH dosing, IU/kg (median, IQR)	276 (111)	336(139)	<0.01
UFH dosing at 24 hours, IU/kg (median, IQR)	273 (88.9)	349 (143)	
Episodes reaching therapeutic anti-Xa within 24 hours after initiation of unfractionated heparin treatment (n, %)	550 (67)	778 (67)	0.82
Episodes without therapeutic anti-Xa within 24 hours after initiation of unfractionated heparin treatment (n, %)			
Infratherapeutic (anti-Xa <0.3 IU/mL)	181 (22)	241 (21)	0.46
Supratherapeutic (anti-Xa >0.7 IU/mL)	59 (7)	136 (12)	<0.01
Of which anti-Xa >1 IU/mL	22 (3)	64 (5)	<0.01
No anti-Xa available	29 (4)	14 (1)	<0.01

UFH, unfractionated heparin.

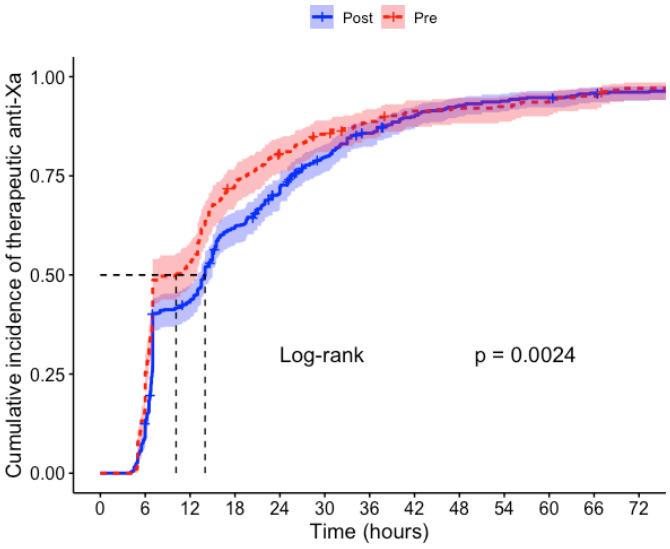

Figure 1 Evolution of therapeutic anti-Xa cumulative incidence expressed as a ratio on the Y-axis over time expressed as hours on the X-axis. The pregroup is represented by a red line and the postgroup as a blue dashed line.

Secondary outcomes

Time to reach therapeutic anticoagulation in subgroup analysis

In the subgroup analysis, the postgroup was divided into two groups: one with hospital stays occurring after the 1st of October 2019 in the internal medicine ward that used the CPAT, and those occurring before, that did not. The analysis compared only hospital stays in the internal medicine wards; 424 episodes were found in the post-IM group, and 28 in the CPAT group.

The median time to reach the therapeutic range was 13.9 hours (95% CI: 11.9 to 15 hours) in the post-IM group, whereas it was 7.1 hours (95% CI: 6.8 to 15.8 hours) in the CPAT group, with a p<0.01 (figure 2).

When compared with the post-IM group, the CPAT group exhibited a HR of 1.74 (95% CI: 1.17 to 2.60, p<0.01).

After performing an adjusted analysis, the CPAT group had a HR of 1.77 (95% CI: 1.18 to 2.65, p<0.01) of having a therapeutic anti-Xa value compared with the post-IM group.

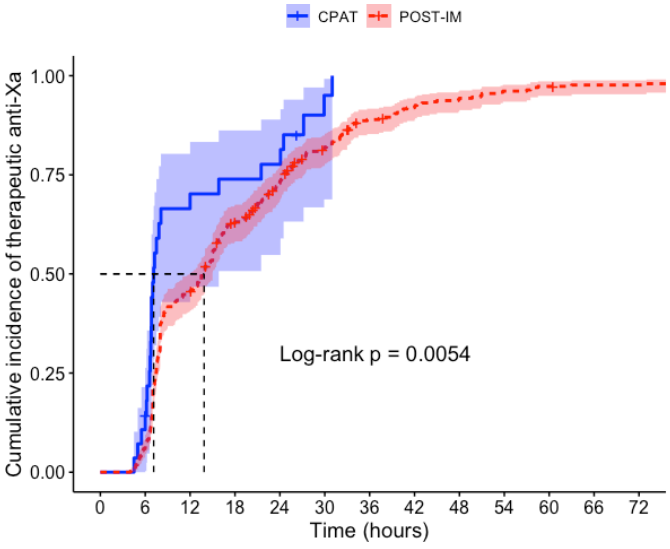

Figure 2 Evolution of therapeutic anti-Xa cumulative incidence expressed as a ratio on the Y-axis over time expressed as hours on the X-axis. The computer-aid group is represented as a blue line and the post-IM group as a red dashed-line.

Anti-Xa status in the 7 first hours of anticoagulation

The anti-Xa status were first checked after 7 hours of UFH infusion. In the pregroup, 509 (62%) episodes had no anti-Xa measured, compared with 634 (54%) in the postgroup, with a statistically significant difference (p<0.01).

Initial UFH dosing was 276 IU/kg (IQR=111 IU/kg) in the pregroup and 336 IU/kg (IQR=139 IU/kg) in the postgroup, with a p<0.01. After 7 hours of UFH infusion, the doses were 278 IU/kg (IQR=111 IU/kg) and 339 IU/kg (IQR 140 IU/kg) in the pre and postgroups, respectively, p<0.01.

The percentage of episodes reaching the therapeutic range was higher in the pregroup than in the postgroup with a statistically significant difference (151 (49%) vs 214 (40 %) episodes, p=0.02).

Concerning the episodes with an infratherapeutic status, 118 (38%) were found in the pregroup and 205 (38%) in the postgroup with no statistical significance for these results (p=1). For the supratherapeutic episodes, however, there were more episodes in the postgroup than in the pregroup (116 (22%) vs 41 (13%), with a p value<0.01). Among these supratherapeutic episodes, 15 (5%) had anti-Xa above 1 IU/mL in the pregroup and 48 (9%) in the postgroup, with a statistically significant difference (p=0.04) (table 2).

In the subgroup analysis, we compared the CPAT group with the post-IM group. No significant difference was observed between the two groups for therapeutic anti-Xa (59% vs 43%, OR 1.94, 95% CI: 0.73 to 5.39, p=0.18). While there were no infratherapeutic episodes (0%) in the CPAT group, there were 71 infratherapeutic episodes (34%) in the post-IM group. There were 9 (41%) supratherapeutic episodes in the CPAT group and 49 (23%) in the post-IM group. Episodes with an anti-Xa >1 IU/mL were 1 (5%) in the CPAT group and 23 (11%) in the post-IM group. Six episodes had no anti-Xa values within the first 7 hours in the CPAT group, and there were 215 episodes without anti-Xa values in the post-IM group. These episodes were not included in the analysis.

Anti-Xa status in the 24 first hours of anticoagulation

Within the first 24 hours of anticoagulation, 550 (67%) episodes reached the therapeutic range in the pregroup compared with 778 (67%) in the postgroup, with no statistically significant difference (p=0.82). There were 181 (22%) episodes with the infratherapeutic status in the pregroup and 241 (21%) in the postgroup (p=0.46). The 59 (7%) supratherapeutic episodes in the pregroup was significantly lower

than the 136 (12%) in the postgroup (p<0.01). In particular, the 64 (5%) episodes with anti-Xa over 1 IU/mL in the postgroup was significantly higher than the 22 (3%) episodes in the pregroup (p<0.01). Finally, there were more episodes missing anti-Xa in the 24 first hours of anticoagulation in the pregroup than in the postgroup (4% vs 1%) (table 3).

In the subgroup analysis, episodes reaching therapeutic range were 21 (75%) in the CPAT group compared with 308 (73%) in the post-IM group, with no statistical difference (OR 1.13, 95% CI: 0.45 to 3.23, p=1). For infratherapeutic episodes, 1 (4%) were found in the CPAT group and 52 (12%) in the post-IM group. Episodes with supratherapeutic status were 6 (21%) in the CPAT group and 60 (14%) in the post-IM group. Episodes with anti-Xa over 1 IU/mL were 2 (7%) in the CPAT group compared with 31 (7%) in the post-IM group. Finally, the episodes without any anti-Xa in the first 24 hours were 0 (0%) in the CPAT group and 4 (1%) in the post-IM group.

DISCUSSION

This study showed that after the dissemination of a pocket card of recommendations for heparin treatment initiation, monitoring, and dosage adaptation, a significant increase in the time to reach the first anti-Xa was found. Several factors may contribute to these results. First, our definition of therapeutic versus prophylactic anticoagulation was based on heparin dose, since it is not specified in the medical chart. Second, we only considered anticoagulation episodes with anti-Xa monitoring for this analysis, with a large proportion of missing data for anti-Xa values: at the time of the study, access to anti-Xa tests, especially during weekends and nights was limited, and heparin was still often monitored with aPTT rather than the anti-Xa assay. It is therefore possible that anti-Xa monitoring was preferentially used in the pregroup by doctors that were also already using the new recommendation and nomogram for heparin doses. The postgroup included these 'good prescribers' as well as other prescribers who may have continued prescribing without the recommended doses and titration. To test this hypothesis, we conducted the same analysis within the first 7 hours with aPTT instead of anti-Xa tests and found a decrease of the missing values (18% in the pregroup and 15% in the postgroup); the number of episodes with aPTT in the therapeutic range was not significantly different between the two groups (12% in the pregroup vs 15% in the POST, p=0.13). A selection bias due to missing data is therefore highly possible. Future studies with defined therapeutic goals for anticoagulation and more reliable anti-Xa values are needed to verify our findings.

The CPAT in the subgroup analysis significantly decreased the interval between the initiation of UHF and the first anti-Xa in therapeutic range (7.1 hours (95% CI: 6.8 to 15.8 hours) in the CPAT subgroup vs 14 hours (95% CI: 13 to 15 hours) for the postgroup) and is also lower than in the pregroup (10.1 hours, 95% CI: 7 to 13 hours). This result could be a consequence of the regulating aspects of the integration of the recommendation in the prescription tool. Since prescriptions are computerised, the CPAT provides the right assistance at the right time for each prescription of heparin. This significant finding although based on a small sample size in the CPAT, is consistent with a previous study by Kershaw *et al*.[17]

Furthermore, use of a computerised prescription tool was more effective, with a decrease of the number of infratherapeutic episodes of anticoagulation, both within the first seven or 24 hours of therapy. The initial heparin dose is 400 IU/kg in the CPAT and pocket guide, and is only dependent on the patient's weight. A possible collateral effect of this initial dose and higher efficacy may be seen in the increased number of supratherapeutic episodes with CPAT, with the subsequent risk of bleeding with higher anti-Xa values.[16] A further study with a larger data set of CPAT use is being conducted to verify these findings, and to determine if adjustments are needed for the initial heparin dose.

Regarding the anti-Xa status, the analysis in the first 7 hours was used as a surrogate to assess the efficiency of the anticoagulation initiation: again, the missing data need to be considered to interpret the lower proportion of results in the therapeutic range in the postgroup compared with the pregroup. The infratherapeutic status were not different between the two groups, but the postgroup had a higher number of supratherapeutic anti-Xa and especially anti-Xa above 1 IU/mL. This may be due to several reasons. The missing values of anti-Xa (where perhaps aPTT testing was used instead) could also be a source of bias. We did not explore aPTT values in this analysis because of its lower reliability of heparin effect.[18] The identification of anticoagulation episodes with a therapeutic aim may have been suboptimal: a bias may have been induced when we removed certain specialties (neurology, haematology, etc.), where dosing does not follow recommendations because of a higher risk of bleeding complications. The higher supratherapeutic values in the postgroup suggest may also be due to the initial recommended dose, which may be higher than the doses used by clinicians for certain populations (eg, elderly patients).

When looking at the anti-Xa status in the 24 first hours of anticoagulation, there is no difference between groups for anti-Xa in the therapeutic range and an increased proportion of supratherapeutic anti-Xa in the postgroup.

The main limitations of this study are its retrospective and quasi-experimental design, and the possible inherent bias. Other limitations arise from the clinical documentation: the time of UFH administration and of blood samples were approximated from times registered in the EMR, thus less accurate. When blood samples were analysed outside of the hospital (*eg*, for baseline data), they could not be integrated to the analysis. Information concerning the occurrence of bleeding could not be obtained and were thus lacking in the analysis. Indications were inferred from ICD codes entered in the system after the hospital stay and thus could not be assessed with certainty. Moreover, their acute or chronic nature were not known. There was also a bias induced by the exclusion of the neurology, neurosurgery and haematology wards, because they represent a significant portion of the therapeutically anticoagulated patients.

Finally, the therapeutic intent of UFH treatment is not clearly identified in the EMR, and our identification method may have not excluded all the prophylactic events in the analysis.

One of the strengths of this study is the size of the sample. Moreover, the quasi-experiment nature of this study also has the upside of offering real-life results of the intervention. Indeed, there is no one controlling that physician strictly observe the pocket card recommendation usually, and a more controlled design would have more accurately extracted the efficiency of this pocket card use but might have overestimated its impact.

CONCLUSION

In conclusion, the results of our study showed that disseminating a pocket card of recommendations did not reduce the time to reach therapeutic anti-Xa range, nor did it decrease the number of infratherapeutic events. This result should be verified in a separate, more specific study with less missing anti-Xa data, as it might change the initial dosage of UFH used in our protocol. The implementation of a computerised UFH prescription tool showed potential in bolstering the efficiency of the pocket card recommendation, with a significant decrease in the time to therapeutic range. This study reinforces the concept of providing the right tool (computerised tool) at the right time (prescription entry) to optimise the impact of the intervention. A further study with a larger sample of CPAT is needed to confirm the findings of this study.

Author affiliations
[1]Medecine, Division of general internal medicine, University Hospitals of Geneva, Geneva, Switzerland
[2]Faculty of medecine, University of Geneva, Geneva, Switzerland
[3]Medicine, Division of angiology and hemostasis, University Hospitals of Geneva, Geneva, Switzerland
[4]Medical directorate, University Hospitals of Geneva, Geneva, Switzerland

Acknowledgements We thank Alexandre Andrey and Roxane Dumont for useful discussions about statistical analysis. We acknowledge Sètuhn Jimaja for his help on manuscript reviewing.

Contributors KSB (lead investigator and guarantor) conceived the study, obtained funding, developed the analysis plan and supervised the study analysis. PF and JS contributed to the study design and analysis plan. WEJ contributed to the study design, did the statistical analysis and wrote the first draft of the manuscript. All authors critically revised and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding This quality improvement project was funded by the Private Foundation of the University Hospitals of Geneva (Grant number: N/A).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This quality improvement study was granted an exemption status by the local ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Not applicable.

ORCID iDs
Wedali E Jimaja http://orcid.org/0000-0002-9688-3164
Katherine S Blondon http://orcid.org/0000-0002-9407-8516

REFERENCES

1 Hemker HC. A century of heparin: past, present and future. *J Thromb Haemost* 2016;14:2329–38.
2 Despas N, Larock A-S, Jacqmin H, *et al*. Heparin monitoring: clinical outcome and practical approach. *Ann Biol Clin* 2016;74:637–52.
3 Kitchen S, Olson JD, Preston FE. *Quality in laboratory hemostasis and thrombosis*. 2 edn. Wiley-Blackwell, 2013.
4 Basu D, Gallus A, Hirsh J, *et al*. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. *N Engl J Med* 1972;287:324–7.
5 Hirsh J, Guyatt G, Albers GW, *et al*. Antithrombotic and thrombolytic therapy. *Chest* 2008;133:110S–2.
6 Vandiver JW, Vondracek TG. A comparative trial of anti-factor Xa levels versus the activated partial thromboplastin time for heparin monitoring. *Hosp Pract* 2013;41:16–24.
7 Rosborough TK. Monitoring unfractionated heparin therapy with antifactor Xa activity results in fewer monitoring tests and dosage changes than monitoring with the activated partial thromboplastin time. *Pharmacotherapy* 1999;19:760–6.
8 Bürki S, Brand B, Escher R, *et al*. Accuracy, reproducibility and costs of different laboratory assays for the monitoring of unfractionated heparin in clinical practice: a prospective evaluation study and survey among Swiss institutions. *BMJ Open* 2018;8:e022943.
9 Macedo KA, Tatarian P, Eugenio KR. Influence of direct oral anticoagulants on anti-factor Xa measurements utilized for monitoring heparin. *Ann Pharmacother* 2018;52:154–9.
10 Belk KW, Laposata M, Craver C. A comparison of red blood cell transfusion utilization between anti-activated factor X and activated partial thromboplastin monitoring in patients receiving unfractionated heparin. *J Thromb Haemost* 2016;14:2148–57.
11 Coons JC, Iasella CJ, Thornberg M, *et al*. Clinical outcomes with unfractionated heparin monitored by anti-factor Xa vs. activated partial thromboplastin time. *Am J Hematol* 2019;94:1015–9.
12 Schurr JW, Stevens CA, Bane A, *et al*. Description and evaluation of the implementation of a weight-based, nurse-driven heparin nomogram in a tertiary academic medical center. *Clin Appl Thromb Hemost* 2018;24:248–53.
13 Smith ML, Wheeler KE. Weight-based heparin protocol using antifactor Xa monitoring. *Am J Health Syst Pharm* 2010;67:371–4.
14 Gruel Y, De Maistre E, Pouplard C, *et al*. Diagnosis and management of heparin-induced thrombocytopenia. *Anaesth Crit Care Pain Med* 2020;39:291–310.
15 Holman C D'Arcy J, Preen DB, Baynham NJ, *et al*. A multipurpose comorbidity scoring system performed better than the Charlson index. *J Clin Epidemiol* 2005;58:1006–14.
16 Nieuwenhuis HK, Albada J, Banga JD, *et al*. Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular weight heparin. *Blood* 1991;78:2337–43.
17 Kershaw B, White RH, Mungall D, *et al*. Computer-assisted dosing of heparin. management with a pharmacy-based anticoagulation service. *Arch Intern Med* 1994;154:1005–11.
18 Whitman-Purves E, Coons JC, Miller T, *et al*. Performance of anti-factor Xa versus activated partial thromboplastin time for heparin monitoring using multiple nomograms. *Clin Appl Thromb Hemost* 2018;24:310–6.