Optimal timing of vitamin K antagonist resumption after upper gastrointestinal bleeding

A risk modelling analysis

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Summary
The optimal timing of vitamin K antagonists (VKAs) resumption after an upper gastrointestinal (GI) bleeding, in patients with continued indication for oral anticoagulation, is uncertain. We included consecutive cases of VKA-associated upper GI bleeding from three hospitals retrospectively. Data on the bleeding location, timing of VKA resumption, recurrent GI bleeding and thromboembolic events were collected. A model was constructed to evaluate the 'total risk', based on the sum of the cumulative rates of recurrent GI bleeding and thromboembolic events, depending on the timing of VKA resumption. A total of 121 (58 %) of 207 patients with VKA-associated upper GI bleeding were restarted on anticoagulation after a median (interquartile range) of one (0.2–3.4) week after the index bleeding. Restarting VKAs was associated with a reduced risk of thromboembolism (HR 0.19; 95 % CI, 0.07–0.34) and death (HR 0.61; 95 % CI, 0.39–0.94), but with an increased risk of recurrent GI bleeding (HR 2.5; 95 % CI, 1.4–4.5). The composite risk obtained from the combined statistical model of recurrent GI bleeding, and thromboembolism decreased if VKAs were resumed after three weeks and reached a nadir at six weeks after the index GI bleeding. On this background we will discuss how the disutility of the outcomes may influence the decision regarding timing of resumption. In conclusion, the optimal timing of VKA resumption after VKA-associated upper GI bleeding appears to be between 3–6 weeks after the index bleeding event but has to take into account the degree of thromboembolic risk, patient values and preferences.

Keywords
Gastrointestinal bleeding, warfarin, thromboembolism, stroke, mortality

Introduction
Gastrointestinal (GI) bleeding is a common bleeding complication associated with vitamin K antagonist (VKA) therapy (1, 2), occurring in up to 4–8 % per year, with a reported case fatality of 12–35 % (3, 4). Upper GI bleeding on VKA therapy is a common cause of hospital admission. A population-based study from Denmark reported a standardised incidence ratio of upper GI bleeding requiring hospitalisation of 2.8 for VKAs alone, 4.4 for VKAs in combination with acetaminophen, and 3.8 for VKAs combined with aspirin or corticosteroids (5).

Depending on its severity, the occurrence of an upper GI bleeding may necessitate a temporary or permanent discontinuation of VKAs. Withdrawal of anticoagulation may expose the patient to a substantial risk of thromboembolic complications, depending on the indication of anticoagulation. Annual rates of 12–22 % have been reported in patients with St. Judes Medical bileaflet heart valves (6), 4–18 % in patients with atrial fibrillation with additional risk factors for stroke (7), and 10 % for those with venous thromboembolism (8).

The optimal timing of VKA resumption after a GI bleeding requires the physician to balance the risk of a recurrent bleed if anticoagulation is re-started too soon after the bleeding event, with the risk of thromboembolism in the absence of anticoagulation. Only a few studies have tried to address this question, with diverging conclusions (3, 4). However, the causes of upper GI bleeding are clearly different from those of lower GI bleeding, and these two types of bleeding should therefore be studied separately. Furthermore, the role of a second endoscopic examination to confirm healing of the bleeding site before VKA resumption has not been addressed in the studies above.

This study was performed to assess the optimal timing of VKA resumption after a VKA-related major upper GI bleeding, by calculating the hazards of recurrent bleeding and of thromboembolic events with or without VKAs.
Methods

The institutional ethics committee in Sweden and in Canada approved the study as a retrospective cohort study, without the need for patient consent. The data used in the analysis did not contain any personal identifiers.

Study population

The study was conducted at Karolinska University Hospital in Stockholm, and Sundsvall Hospital, both in Sweden, and Hamilton Health Sciences-General Hospital, Hamilton, Ontario, Canada. Three investigators (AM, NW and JE) examined the medical records of all patients presenting to these centers with upper GI bleeding between 2004 and 2010.

Table 1: Characteristics of the patients at baseline.

<table>
<thead>
<tr>
<th></th>
<th>VKA resumption</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>N (%)</td>
<td>86 (42)</td>
<td>121 (58)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>79 (72–84)</td>
<td>76 (69–82)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>56 (65)</td>
<td>75 (62)</td>
</tr>
<tr>
<td>VKA indication, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>54 (63)</td>
<td>76 (63)</td>
</tr>
<tr>
<td>Aortic MHV</td>
<td>2 (2)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Mitral MHV</td>
<td>0</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Aortic + Mitral MHV</td>
<td>0</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>14 (16)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (19)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>CHADS2, median (IQR)*</td>
<td>2.0 (2.0–3.0)</td>
<td>2.5 (2.0–3.0)</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>16 (19)</td>
<td>19 (16)</td>
</tr>
<tr>
<td>Anticoagulants at time of bleeding, n (%)</td>
<td>26 (30)</td>
<td>39 (32)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>19 (22.1)</td>
<td>37 (30.6)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>3 (3.5)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Aspirin + Clopidogrel</td>
<td>4 (4.7)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>INR, median (IQR)</td>
<td>3.5 (2.7–5.5)</td>
<td>3.2 (2.5–4.3)</td>
</tr>
<tr>
<td>Bleeding site, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenum</td>
<td>37 (43)</td>
<td>49 (41)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>2 (2)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Stomach</td>
<td>45 (52)</td>
<td>63 (52)</td>
</tr>
<tr>
<td>More than one location</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Re-endoscopy, n (%)</td>
<td>38 (44)</td>
<td>60 (50)</td>
</tr>
<tr>
<td>Follow-up duration, weeks, median (IQR)</td>
<td>92 (18–193)</td>
<td>145 (77–239)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>52 (61)</td>
<td>51 (42)</td>
</tr>
</tbody>
</table>

IQR; interquartile range, VKA; vitamin K antagonist, MHV; mechanical heart valve, INR; international normalised ratio. *For patients with atrial fibrillation.

Data extraction

Data were collected from medical records on the demographics of patients, comorbidities including any additional risk factors for stroke and arterial thromboembolism in patients with atrial fibrillation, concomitant treatment with platelet inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs), the indication for VKA treatment, international normalised ratio (INR) at the time of the bleeding, and the cause and site of the bleeding as described in the gastroscopy report. Follow-up information extracted from the records included repeat endoscopy to document healing of the bleeding site before resumption of VKA, duration of follow-up after the upper GI bleeding, whether VKAs were resumed or not, the timing of VKA resumption, the occurrence of recurrent GI bleeding as well as arterial or venous thromboembolic events before and after resumption of VKA, death and the timing of such clinical events in relation to the index GI bleeding.

Statistical analysis

Continuous variables are presented as medians and inter-quartile ranges (IQR), and analysed with Mann-Whitney test for skewed distributions. Binomial data were presented as proportions or percent, and compared using Chi-square or Fisher’s exact test. A p-value less than 0.05 was considered statistically significant in a two-sided test. Kaplan-Meier curves were constructed separately for bleeding and for thromboembolism, and used to calculate the cumulative risks. Hazard ratios (HR) of recurrent bleeding and thromboembolic events with and without VKAs, with confidence intervals and p-values, were calculated using Cox model. The model was adjusted for age, sex, indication for VKAs, INR at the time of bleeding, concomitant treatment with non-steroidal anti-inflammatory drugs or platelet inhibitors, and bleeding location.

A model was constructed to estimate the “total risk” depending on the timing of resumption of VKA. The total risk was calculated as the sum of the risks of recurrent bleeding and of thromboembolism before and after the time point of resumption. For constructing this total risk model, a Cox model was fitted for recurrent GI bleeding and separately for thromboembolic events, with a time-dependent variable indicating the time at which VKAs were resumed, assuming that VKAs exert a constant proportional effect on the risk of recurrent GI bleeding, and of ischaemic events from the time of resumption. When a patient resumed VKA at a certain time point, the period before VKA resumption contributed to the time at risk of the group who did not resume VKA after the index
GI bleeding. The time period after VKA resumption, however, contributed to the total time at risk of the group who resumed VKA. In other words, the period of time for all patients not on anticoagulation (regardless of whether they resumed VKAs later) was analysed together as the "unexposed period", and the period of time for all patients on anticoagulation (after resumption of VKAs) was analysed together as the "exposed period". Using this approach, the whole observation period after the index GI bleeding, both for those who resumed VKA and those who did not, is incorporated into the risk modelling depending on their VKA exposure status at any point of time. Statistical analyses were performed with the Stata13 and SAS 9.4.

Results

Patient characteristics

Altogether, a total of 3535 consecutive patients in Sweden and 1614 in Canada with upper GI bleeding were identified during the study period, of which 207 patients were on VKAs at the time of the bleeding (▶Table 1). The Swedish sites identified 111 (54%) and 18 (9%) patients in Stockholm and Sundsvall, respectively, while 78 (38%) patients were identified at the Canadian site. The median age was 77 years, and 37% were females. The most common VKA indication was atrial fibrillation (63%), and 17% had suffered from a previous stroke. Concomitant therapy with platelet inhibitors was recorded for 32% of the patients as specified in ▶Table 1. The INR was therapeutic in 33% of the patients at the time of the bleeding, while 57% had supra-therapeutic INR, and 11% had an INR below 2.0 (▶Figure 1). The most common bleeding site was the stomach (52%), followed by the duodenum (42%) and esophagus (5%). The patients were followed after the index bleeding event for a median of 124 weeks (IQR 46–223).

VKA resumption

In total, 121 (58%) patients resumed VKA treatment after a median (IQR) of one (0.2–3.4) week. Patients with mechanical heart valves were resumed on VKAs after a median (IQR) of 0.25 (0–1) week. Patients that resumed VKAs were significantly younger (median 76 vs 79 years, p=0.03), and had longer follow-up (median 145 vs 92 weeks, p<0.001) as compared to patients who did not resume VKAs (▶Table 1). A significantly higher proportion of patients with mechanical heart valves (26 of 28; 93%) resumed VKAs.

![INR distribution at the time of the upper gastrointestinal bleeding](figure1.png)

Figure 1: INR distribution at the time of the upper gastrointestinal bleeding.
as compared to patients with atrial fibrillation (76 of 130; 58%, p=0.0004), or venous thromboembolism (9 of 23; 39%, p<0.0001). However, there was no difference in the rate of resumption of VKAs in patients with or without previous stroke (p=0.6). The median CHADS2 score was also comparable in patients with atrial fibrillation who resumed VKAs and those that did not (median; 2.5 vs 2.0, p=0.8).

When analysed according to the bleeding site, VKAs were resumed in a higher proportion in patients with esophageal bleeding site (n=9, 82%) as compared to those with gastric (n=63, 58%) or duodenal (n=49, 57%) site of bleeding. Of the 121 patients who resumed VKAs, 60 (50%) underwent a repeat endoscopic examination before VKA resumption. However, the proportion of patients who resumed VKAs and the median time to resumption of VKAs were comparable in those who underwent this repeat endoscopy and those who did not (61% vs 56%, and 1.7 vs 0.7 weeks, respectively).

Recurrent upper GI bleeding

A total of 56 events of recurrent GI bleeding occurred during follow-up. Of these events, 17 occurred in patients who had not resumed VKA treatment by the time of the recurrent bleeding, and 39 events in patients who were restarted VKAs after the index GI bleeding. Seven recurrent GI bleeding events were observed within the first week after VKAs resumption. Recurrent bleeding oc-
curred in 12 (46 %) of mechanical heart valves patients, and in 29 (31 %) of patients with other indications who resumed anticoagu-
lation. There was no association between the presence of suprathera@
thapeutic INR in the initial presentation, and the risk of recur-
gent GI bleeding (p=0.34).

Recurrence bleeding occurred after a median (IQR) of 24 (5–95) weeks from the index bleeding event in those who restarted VKAs, and 23 (1.7–92) weeks in those who did not (p=0.72). The log-
rank test did not show a difference in the rates of recurrence in pa-
tients with bleeding from esophagus, stomach or duodenum
(p=0.6). There were no differences in the rates of recurrent bleed-
ing, and time to such event in patients who underwent a repeat en-
doscopy before VKA resumption, and those who did not (p=0.57
and p=0.80, respectively). At a median follow-up of six months, counted from the index GI bleeding in those who did not resume
VKAs, or from the time point of resumption of anticoagulation in
those who resumed VKAs, the cumulative risk of recurrent GI
haemorrhage was 7.9 % and 19.6 %, respectively. The correspond-
ing rates at 12 months were 7.9 % and 26.1 %, respectively ( ▶ Fig-
ure 2 A and B ). The location of recurrent GI bleeding was classified
as upper GI bleeding in 31 (55 %) patients, lower GI in four (7 %),
and unspecified in 21 (38 %) patients. For the recurrent upper GI
bleeds there was rarely sufficient information to know if it was
from the original lesion.

**Thromboembolic events**

There were 21 arterial and venous thromboembolic events in the
cohort during the follow-up period ( ▶ Table 2 ). Twelve events oc-
curred in patients who did not resume VKAs, with an additional
four events in patients who were subsequently restarted on VKAs.
Only five thromboembolic events occurred in patients while taking
VKAs.

Sixteen of the 21 events occurred in patients on VKAs for
stroke prevention in atrial fibrillation. A new arterial thromboem-
bolic event occurred in only 11 (6 %) patients without previous
stroke, as compared to eight (23 %) events in those with previous
stroke (p=0.006). At a median follow-up of six months, calculated
from the index GI bleeding in those who did not resume VKAs, or
from the time point of resumption of anticoagulation for those
who resumed VKAs, the cumulative risks of thromboembolic
events were 9.8 % and 1.2 %, respectively. The corresponding rates
at 12 months were 11.5 % and 2.3 %, respectively ( ▶ Figure 2 A and
B ).

**Mortality**

The overall crude mortality rates at 7 and 28 days after the index
upper GI bleeding were 4.8 % and 7.3 %, respectively. Considering
the entire follow-up period, death was observed in 52 (60 %) pa-
tients who did not resume VKAs as compared to 51 (42 %) patients
who resumed VKAs (log rank p-value=0.002), occurring at a
median (IQR) of 70 (16–131) weeks, and 118 (50–164) weeks, re-
spectively (p-value=0.02). Not resuming VKAs after GI bleeding
was significantly associated with long-term mortality in the multi-

variate analysis (HR, 1.64; 95 % CI, 1.06–2.56; p-value=0.03). Age
≥ 75 years (HR 2.02; 95 % CI, 1.30–3.15; p-value=0.002), recurrent
GI bleeding (HR 3.34; 95 % CI, 2.13–5.24; p-value<0.001), and the
INR at the index event (HR 1.10; 95 % CI, 1.03–1.16;
p-value=0.002) were also associated with long-term mortality. We
did not have sufficient information to evaluate if the decision not
to resume anticoagulation was associated with comorbidities with
limited life expectancy. The cause of death was registered as ‘bleed-
ing’ in eight cases (4 who resumed VKA and 4 who did not), and
“thromboembolic event” in five patients (2 ischaemic strokes and 2
myocardial infarctions occurring in patients who did not resume
VKA, and myocardial infarction in a patient who resumed VKA).
The cause of death in the remaining cases was infection (n=17),
malignancy (n=6), multiple organ failure (n=21), and unspecified
in 46 patients. Thus, the number of fatal recurrent GI bleeds in pa-
tients who resumed VKA therapy (n=4, 3.3 %) was comparable to
fatal thromboembolic events in patients who did not resume
VKAs (n=4, 4.7 %).

### Risk modelling

A Cox model with a time dependent variable indicating the time
point of VKAs resumption was fitted to assess the effect of antico-
agulation resumption at different time points on the risk of recur-
gent GI bleeding and thromboembolic events. On average, restar-
ting VKAs reduced the risk of thromboembolic events by more
than 80 % (HR 0.19; 95 % CI, 0.07–0.55; p=0.002), at the cost of
more than double the risk of recurrent GI bleeding (HR 2.5; 95 %
CI, 1.4–4.5, p=0.003).

Observed rates of recurrent GI bleeding and of thromboem-
bolic events over time in patients who resumed VKAs and those
who did not are presented in ▶ Table 3 . The follow-up period is
divided into intervals of relatively constant risks. These time pe-
riods for recurrent GI bleeding differed from those for thromboem-
bolic events as these two events have different and independent
natural courses over time. In each time period, information is
presented in the table on the number of events, days at risk and
calculated event rates, separately for patients on or not on VKAs.
The ratios of rates between the groups receiving and not receiving
VKAs give the HRs for the respective time period. The HR ob-

<table>
<thead>
<tr>
<th>VKA status</th>
<th>No*, n(%)</th>
<th>Yes, n(%)</th>
<th>Hazard ratio (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>8 (9.3)</td>
<td>1 (0.8)</td>
<td>0.08 (0.01–0.65)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>7 (8.1)</td>
<td>3 (2.5)</td>
<td>0.13 (0.01–1.17)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>1 (1.2)</td>
<td>1 (0.8)</td>
<td>0.41 (0.02–9.68)</td>
</tr>
<tr>
<td>Death</td>
<td>52 (60)</td>
<td>51 (42)</td>
<td>0.61 (0.39–0.94)</td>
</tr>
</tbody>
</table>

CI, confidence interval; VKA, vitamin K antagonists. * Including 4 patients that were subsequently restarted on VKAs.
tained from the Cox model is essentially a weighted average of the separate HRs from the individual time periods.

The data presented in Table 3 suggests a pattern of decreasing risk of recurrent GI bleeding over time, both for patients who restarted VKA therapy, and those who did not, with a steeper reduction in the rates in the initial period after the index GI bleeding. The risk of thromboembolic events is initially also high and declines over time. Although no thromboembolic events were observed during the initial time periods in patients who resumed VKAs, it is implausible that the actual risk of such events is 0. Given a sufficiently large sample size, a number of thromboembolic events would have been observed in the group of patients on VKAs, and it can be assumed that the ratios in the different time intervals would be comparable to the HR obtained from the Cox model for thromboembolic events (0.19). This assumption would allow us to calculate presumed rates of events for the time intervals where we, in the actual data set and due to sample size limitation, did not observe any events.

Resumption of VKAs at any time will reduce the subsequent risk of thromboembolism at the cost of increased risk of GI bleeding. The optimal timing of resumption of VKA must balance these two competing risks over the entire treatment period. Assuming that a recurrent bleeding event would have a comparable prognostic effect as that of a thromboembolic event, these two competing events were each given similar weights in the risk analysis model. To calculate the optimal resumption point of VKAs, we calculated a “total risk” of events, taking into account the risk of recurrent GI bleeding and of thromboembolic events, both before and after the time point of VKAs resumption, allowing that point to vary from t=0 (representing patients who did not discontinue VKAs after index GI bleeding) up to t=52 weeks after the index event. The rates used in the model were a combination of observed rates, and rates calculated from the HR of the Cox model when no events were observed in the original data set.

The results of the final model are presented in Figure 3A, showing the cumulative risk of recurrent GI bleeding and of thromboembolic events, and the combined total risk over a three-year period, depending on the time of VKA resumption. As evident from the figure, the risk of recurrent GI bleeding remains higher than that of thromboembolic events. The total risk decreases initially rapidly over a period of three weeks, and reaches a nadir at six weeks after the index bleeding. To account for any selection by indication, the analysis was repeated for each of the three VKA indications. When the model was restricted to mechanical heart valves or VTE patients, the number of events was too small to allow for accurate model construction. Analysis of patients on VKA for atrial fibrillation showed results comparable to the overall model, with the total risk reaching a nadir after three weeks of the index GI bleeding (Figure 3B).

Discussion

Recently, a meta-analysis (10), a national registry-based study (11), and a prospective cohort study (12) have all demonstrated the benefit of resumption of anticoagulation after GI-bleeding, with reduction of thromboembolic events (10–12) and probably also of mortality (10, 11). We identified the same benefit in patients with VKA-related upper GI-bleeding. The main purpose of our study was, however, to assess the optimal timing for resumption of anticoagulation. Our main finding was the higher initial rates of recurrent GI-bleeding in the first 3–6 weeks after the index GI bleeding, based on the results obtained from our statistical modelling. The majority of patients in our cohort were males, probably reflecting

<table>
<thead>
<tr>
<th>Warfarin status</th>
<th>Risk of recurrent GI bleeding per day</th>
<th>Risk of thromboembolic events per day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/Days of observation (rate)</td>
<td>Events/Days of observation (rate)</td>
</tr>
<tr>
<td></td>
<td>1–21 days</td>
<td>22–42 days</td>
</tr>
<tr>
<td></td>
<td>(0.209 %)</td>
<td>(0.096 %)</td>
</tr>
<tr>
<td>Yes</td>
<td>7/1335</td>
<td>4/1690</td>
</tr>
<tr>
<td></td>
<td>(0.52 %)</td>
<td>(0.24 %)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>2.55</td>
<td>2.45</td>
</tr>
<tr>
<td>95 % CI</td>
<td>0.86–7.57</td>
<td>0.45–13.36</td>
</tr>
</tbody>
</table>

Rates used in prediction model

- No: 0.21 %, 0.096 %, 0.021 %, 0.012 %, 0.073 %, 0.019 %, 0.017 %
- Yes: 0.52 %, 0.237 %, 0.061 %, 0.024 %, 0.014 %§, 0.0036 %§, 0.005 %

Calculated rates from Cox model for thromboembolic events. * Adjusted odds-ratios. CI, confidence intervals. § Including 4 events in the first 3 weeks, and 1 event between 3–6 weeks.
the higher prevalence of males in the background population anticoagulated for atrial fibrillation.

The clinical burden or disutility of a recurrent GI bleed is obviously less than that of a stroke but there is substantial variability among physicians in the assignment of trade-offs between bleeding and stroke, with many indicating a neutral trade-off (13). In view of this heterogeneity we performed our primary analysis with equal weights. Patients seem, however, to be more stroke averse than bleeding averse (13). A systematic review of patient values and preferences also demonstrated high variability regarding decisions on antithrombotic therapy (14). The authors concluded that the ratio of disutility of non-fatal stroke to GI bleed is in the range of 2:1 to 3:1. This is thus balancing against the HR for recurrent GI bleeding identified by us and would mean that there might be equipoise for resumption of VKA at any time between the index bleeding and several weeks or even months ahead. Notably, a recurrent GI bleed, which according to our estimates occurs in \((21 \times 0.52\% =) 11\%\) of patients with resumed anticoagulation during the first three weeks (or \([21 \times 0.52\%] + [21 \times 0.24\%] = 16\%\) during the first 6 weeks), will lead to another interruption of all antithrombotics, entering the patient into a new period of high risk for serious events.

One of our important observations is the significantly shorter follow-up for patients who were not restarted on VKAs (92 weeks) as compared to those who were restarted (145 weeks, \(p<0.001\)).
This might reflect the assumption that patients who were not started on VKAs are at lower risk of developing serious events, such as bleeding. Our data suggest, however, that this group of patients remains at a risk of developing bleeding and thrombotic events. Therefore, even patients who permanently discontinue VKAs after an upper GI bleeding ought to be followed closely.

Few studies have addressed the risk of recurrent bleeding and thromboembolic events after VKA-associated GI bleeding, however, none of them presented separate analysis for upper versus lower GI bleeding. Two studies concluded that the optimal timing of VKAs resumption after GI bleeding is within the first week (3, 4). Several factors might explain the differences between these two studies and ours. First, those studies did not try to determine the optimal time point of VKA resumption using a specific model that takes into account the balance of the risks of recurrent GI bleeding or thromboembolism. Second, these studies included both upper and lower GI bleeding.

The proportion of patients with GI bleeding on VKAs in this cohort (4%) was lower than that reported in two other publications (15, 16). This can be attributed to differences in the demographics, as 16–17% of the patients in the previously published studies were inpatients who developed GI bleeding during hospitalisation. Such patients may have more comorbidities and higher proportion of anticoagulation as a consequence of these comorbidities. Also, the re-bleeding rates reported here were higher than those presented in a recent meta-analysis (10). The meta-analysis included both patients with upper and lower GI bleeding events, which might have influenced the reported rates of recurrent bleeding.

Interestingly, recurrent bleeding in our cohort occurred after a median of 24 weeks from the index bleed in patients who restarted VKAs, and 23 weeks in those who did not resume VKAs. This might suggest that the cause of recurrent GI bleeding is different from the initial one. However, the site of recurrent bleeding was reported to be in the same part of the GI tract (esophagus, stomach or duodenum) as the index GI bleeding in 67% of the cases. One explanation is the presence of a persistent ulcerogenic or local factor that increases the risk of bleeding from the respective site. It is therefore important to assess the patient both for the short-term and long-term risks of recurrent GI bleeding. The longer follow-up in this study is therefore an advantage as compared to other published studies (4).

Some of the patients received low-molecular-weight heparins (LMWH), usually at a prophylactic dose, briefly after the index upper GI bleeding. However, it was not possible to take this factor into account in our model because information on the dose of LMWH and the time point of introducing such treatment was not always available from the records. Another important factor that we could not take into account is whether platelet inhibitors or NSAIDs were discontinued/resumed after the GI bleeding due to the sporadic availability of this information, since many patients buy it over the counter. Information on whether VKAs were only discontinued or also reversed at the time of the GI bleeding, and the mode of reversal was not captured in our study, and we were therefore, unable to assess whether the reversal is associated with the risk of recurrent GI bleeding-though such an association seem unlikely.

Several aspects in this study design add to its strength. First, we focused on cases with upper GI bleeding and without malignancy. The resulting cohort is more homogenous in bleeding etiology, with similar natural course. Second, we included consecutive cases of upper GI bleeding from three different centers, reducing the risk for selection bias. Third, we had a relatively long follow-up that allowed us to observe long-term thromboembolic and bleeding event rates. Fourth, and most importantly, we used a model that takes into account the total risk of thromboembolic and bleeding events before and after VKA resumption to determine the optimal timing of resumption.

The results presented here need some careful consideration. First, the cases and data were collected retrospectively, with resumption of VKAs occurring at different intervals after the upper GI bleeding. The exact timing of resumption in the individual patients could have been influenced by several factors, including the fear for thromboembolic events while off VKAs, introducing a degree of bias. This is evident from the earlier and higher rate of resumption of VKAs for patients with mechanical heart valves. Interestingly, we did not find a difference in the CHADS2 score or in the proportion with previous stroke between patients that resumed VKAs and those who did not. Patients with high CHADS2 score have comparable rates of systemic thromboembolism to that of mechanical heart valves when not on anticoagulation (6, 7). Furthermore, our data show that previous stroke is an important predictor of recurrent thromboembolic events off anticoagulation. When analysis was restricted to patients with atrial fibrillation, results of the model for the optimal timing of VKA resumption was similar to that for the whole population. Taken together, these factors minimise the effect of any bias that would have been introduced by selecting a specific time point of VKA resumption according to indication. Second, due to the small number of patients with mechanical heart valves, the results of the study should be applied with caution to those patients. Third, we assigned similar weights for recurrent GI bleeding and for thromboembolic events in the formal risk modelling. However, some thromboembolic events might have had a worse outcome than some bleeding events, and vice versa and we have discussed the variability in physician and patient preferences above with introduction of disutility according to published ratios. Fourth, we had a limited number of events in some of the time bands during follow-up. However, we used adequate statistical methods to deal with this problem, including the utilisation of HRs from the Cox model to predict rates in some of the time bands from observed data in the study. Fifth, our model assumes that VKAs have a constant and proportional effect when it comes to thromboembolic risk reduction and increased risk of bleeding. Even though it is difficult from the current data set to verify these assumptions, other trials have shown a consistent proportional effect of VKA on both outcomes (17).

We conclude that rates of recurrent GI bleeding after VKA-associated upper GI bleeding remained relatively high both in patients who resumed VKA therapy and in those who did not. The
What is known about this topic?
- Discontinuing vitamin K antagonists (VKAs) due to a GI bleeding, exposes the patient to an increased risk of thromboembolism.
- Restarting VKAs after a GI bleeding is associated with an increased risk of recurrent GI bleeding.
- The optimal timing of VKAs resumption must balance the risk of recurrent GI bleeding if VKAs are restarted too early after GI bleeding, and that of thromboembolism if restarting VKAs is delayed.

What does this paper add?
- The optimal timing of VKAs resumption seems to be 3–6 weeks after the index GI bleeding.
- Restarting VKAs is associated with lower mortality rates during follow-up.

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total risk, taking into account the risk of recurrent bleeding or thromboembolic events seems to decrease after three weeks and reaches a nadir at six weeks after the index GI bleeding. A repeat endoscopy to confirm healing of the culprit lesion did not seem to reduce the risk of recurrent bleeding. Restarting VKAs before three weeks leads to a higher total risk, driven by the high risk for recurrent GI bleeding, which will lead to new interruption of antithrombotic therapy. Depending on the associated risk of thromboembolism as well as patient values and preferences, the timing for resumption of VKAs after an upper GI bleeding event might still require modification from our suggested interval.

Author contributions
Sam Schulman designed the study, assisted in data collection, interpreted data, wrote the manuscript and gave final approval to the version to be published. Ammar Majeed designed the study, collected data, interpreted and analysed data, wrote manuscript and gave final approval to the version to be published. Niklas Wallvik collected data, gave critical review of the contents, and gave final approval to the version to be published. Jonas Höijer collected data, gave critical review of the contents, and gave final approval to the version to be published. Joakim Eriksson collected data, gave critical review of the contents, and gave final approval to the version to be published. Matteo Bottai assisted in data collection, gave critical review of the contents and gave final approval to the version to be published. Margareta Holmström assisted in data collection, gave critical review of contents and gave final approval to the version to be published.

Conflicts of interest
None declared.

References