Reintroduction of anti-thrombotic therapy after a gastrointestinal haemorrhage: if and when?

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Summary

Gastrointestinal haemorrhage is a common clinical scenario and, in those using antithrombotic agents, the risk is significantly increased. Management of these patients, in terms of initial resuscitation is well established and numerous guidelines exist in this area. However, few studies have addressed the subsequent dilemma of if and when antithrombotic agents should be reintroduced. Consequently, practice is variable and not necessarily evidenced-based. Overall, for patients that are either anticoagulated or using antiplatelet drugs for secondary prophylaxis, there is a clear benefit to restarting these agents. However, there is limited data to guide when this should occur. For individuals at low risk of re-bleeding, current guidelines suggest single agent aspirin can be continued without interruption, assuming haemostatic control has been confirmed endoscopically. For those at higher bleeding risk, aspirin should be withheld, but reintroduced early (within 3 days of index endoscopy). However, randomised evidence is lacking, as are studies including more modern agents or combined anticoagulant/antiplatelet regimens. As such, guidance statements are limited and management suggestions must be extrapolated from clinical trials, retrospective studies and data relating specifically to warfarin and aspirin. The intention of this review is to summarise what evidence is available and, where this is lacking, suggest pragmatic management options based on a risk-benefit assessment of thromboembolism and recurrent bleeding.

Keywords: antiplatelet agents, anticoagulants, antithrombotics, gastrointestinal haemorrhage.

Gastrointestinal haemorrhage (GIH) is the consequence of bleeding from any point within the entire gastrointestinal (GI) tract. The most common cause of major GIH is peptic ulcer bleeding, which is often associated with *Helicobacter pylori* infection and the use of non-steroidal inflammatory drugs. In the UK, the incidence of GIH is somewhere between 50–190/10 000 patients/year (Palmer, 2007), with bleeds from the upper GI tract being 5 times more frequent than those occurring more distally. The mortality in patients admitted with upper GIH is around 10% and with lower GIH, 2–4%. However, when cases of in-patient bleeding are included, the overall mortality associated with GIH exceeds 30% (Palmer, 2007; Pipilis et al, 2014).

Although many risk factors predispose to GIH, the risk of bleeding is definitely enhanced by the concomitant use of antithrombotic drugs: anticoagulants and/or antiplatelets. The odds ratio for upper GIH whilst using either aspirin or clopidogrel is between 2.0 and 4.0 when compared to controls (Ibáñez et al, 2006); the risk associated with anticoagulants is approximately double this (Lanas et al, 2015).

In patients presenting with acute GIH, the management and requirement for reversal of anticoagulants [at least vitamin K antagonists (VKAs)] is well established, with close correlation across various guidelines. However, sparse literature exists to guide the decision of how to reintroduce these agents after a GIH, especially when the majority of the patients have a clear indication to continue these drugs. The guidance regarding the cessation and reintroduction of anti-platelet agents is also variable, acknowledging that the decision process is more complicated. Caution and multidisciplinary input is universally recommended, particularly regarding the withdrawal of clopidogrel and the more modern P2Y12 antagonists, but there appears to be no consensus regarding if these agents need to be stopped and, if so, when they should be reintroduced (Acosta et al, 2016; Gralnek et al, 2015; Holbrook et al, 2012; National Institute for Health and Care Excellence (NICE), 2012; Veitch et al, 2016).

Considering the frequency with which both anticoagulants and antiplatelets are prescribed, these are frequent dilemmas for the treating physician. Ideally, decisions should be evidence based and we have summarised any available evidence in the following review. Where evidence is lacking, pragmatic management choices may have to be made based on risk-benefit assessments and, where this is required, we have made some suggestions.
Anticoagulant therapy and GIH

Individuals using anticoagulants are, unsurprisingly, at greater risk of GIH than the general population. For instance, in patients treated with warfarin, the GI tract is the most frequent site of haemorrhage and around 8–15% of patients presenting with evidence of GIH will be using a VKA. The age-standardised incidence of GIH of any severity in patients’ anticoagulated with warfarin is 5–8 per 1000-person years, a three-fold increase compared with the general population. However, despite this, warfarin use by itself does not seem to increase the risk of mortality associated with GIH; this appears to be more closely related to other associated co-morbidities (Radaelli et al., 2015).

In relation to the direct oral anticoagulants (DOACs), the risk of GIH in comparison to warfarin has not been conclusively established. The early licensing trials for both dabigatran and rivaroxaban suggested that, in comparison to warfarin, there was an overall increased risk of major GIH (Connolly et al., 2009; Patel et al., 2011). At the higher dose of 150 mg daily of dabigatran, the relative risk of major GIH, as compared to warfarin, was found to be increased by 50% (P < 0.001) (Connolly et al., 2009). Combined data for a 15 and 20-mg dose of rivaroxaban also demonstrated that major GIH was more common with the novel agent, occurring in 3–15% of patients compared to 2–16% using warfarin (P < 0.001) (Patel et al., 2011). More recent, “real-world” data seems to muddy this understanding, although this is complicated somewhat by both the variation in drug doses and indications between the populations examined and the definition of GIH used (Abraham et al., 2015; Chang et al., 2015). In one retrospective study involving a cohort of 92,816 propensity score-matched patients using oral anticoagulants, the overall risk of all GIH was actually reduced in patients younger than 65 years using a DOAC, in comparison to patients warfarinised for atrial fibrillation (AF) [dabigatran vs. warfarin, hazard ratio (HR) 0.79; rivaroxaban vs. warfarin, 0.93] and for indications other than AF [dabigatran vs. warfarin, HR 1.14; rivaroxaban vs. warfarin, 0.89]. With advancing age, the risk of GIH did gradually increase and, beyond 75 years of age, this risk exceeded that associated with warfarin in some groups (AF patients using dabigatran, HR 2.49; patients with and without AF using rivaroxaban, HR 2.91 and 4.58, respectively) (Abraham et al., 2015). However, these findings were not entirely corroborated in a similarly large, retrospective study including 46,163 patients. In this propensity-weighted analysis, a difference in risk between the DOACs and warfarin could not be conclusively demonstrated [dabigatran vs. warfarin HR 1.21; rivaroxaban vs. warfarin HR 0.98], although, with wide confidence intervals, an increased risk associated with either dabigatran or rivaroxaban could not be completely excluded (Chang et al., 2015). The two other DOACs that are currently available, apixaban and edoxaban, have been less extensively investigated in this context. However, from the trial data available, which has clear limitations in terms of real-world applicability, apixaban does not seem to increase the rate of GIH compared to warfarin (Granger et al., 2011). Edoxaban, at the higher dose (60 mg), causes more GIH than warfarin, but not at lower (30 mg) doses (Giugliano et al., 2013).

Studies on resumption of anticoagulation after a GIH

Studies are limited (summarised in Table I); the majority are retrospective and, in most instances, only include patients’ anticoagulated with warfarin. Two of these have recently been included in a meta-analysis of outcomes in patients restarting anticoagulation after a major haemorrhage (Chaisadaksophap et al., 2015). One prospective study exists, but the utility of its outcomes are limited; there is no current, randomised data available.

In a single centre, retrospective cohort study, administrative data was used to analyse outcomes for 442 patients presenting with GIH that had been anticoagulated with warfarin for diverse indications (Witt et al., 2012). Patients were grouped according to those that did and did not restart warfarin following a GIH; the median international normalised ratio (INR) at presentation across both groups was 3.0 and groups were generally well matched in terms of other risk factors for GIH and site of bleed. During a 90-day follow-up period, 260 patients restarted warfarin at a median of 4 days and, in 41 patients, anticoagulation was never interrupted. Those restarting early tended to have a more significant indication for anticoagulation, such as a prosthetic heart valve, or a lower bleeding risk. Only one patient restarting had a recurrent thrombosis (0.4%) compared to 11 (5.5%) of the patients who did not resume anticoagulation (HR 0.05). Of note, no thromboses developed if anticoagulation was restarted before 14 days. The thrombosis that did develop in the patient resuming warfarin was a non-fatal deep venous thrombosis, whereas, three of the thrombotic events in patients not-resuming warfarin were fatal (cerebrovascular events in patients anticoagulated for AF).

In terms of the risk of re-bleeding, when results were adjusted for a number of variables, this was increased, although insignificantly, in patients resuming warfarin (HR, 1.32). However, the rate of re-bleeding was significantly increased if warfarin was resumed between days 1 and 7 of the index bleed (6-23% vs. 12.4%, P = 0.03). During follow-up, 52 patients (11.8%) died in this study, although none were attributable to recurrent GIH. Resuming warfarin was associated with a lower, adjusted risk of death (HR, 0.31), which persisted even when patients with the most significant bleeds that died within the first 7 days of index GIH were excluded.

These results are supported somewhat by a larger study, including 1,329 patients (Qureshi et al., 2014). Although limited to individuals prescribed warfarin for AF, patients were followed-up for a longer, 2-year period. Again groups were
| Autor       | Type of study            | Anticoagulant | Indication | Severity of GI bleed | Patients (n) | Patients (n)/ When restarted | Mean age (years) | HR-TE (95% CI) | HR-GIH (95% CI) | HR-Mortality (95% CI) |
|-------------|--------------------------|---------------|------------|----------------------|--------------|------------------------------|------------------|----------------|-----------------|----------------------|
| Witt *et al* (2012) | Single centre, retrospective cohort study | Warfarin | AF (50.9%) | NS | 442 | 260/Median 4 days | 90 days | 0.05 | 1.32 | 0.31 |
| Qureshi *et al* (2014) | Single centre, retrospective cohort study | Warfarin | AF | Hb fall <20 g/l and/or transfusion >2 units RBC | 1329 | 653/Median 50 days | 90 days | GIH 1 year (TE) | 0.71 | 1.18 | 0.67 |
| Patsias *et al* (2013) | Single centre, retrospective cohort study | Warfarin | AF | Visible, occult or endoscopic evidence of bleeding | 1229 | 665/15–30 days | 3 months | CHADS2 High | 0.54–0.93 | 0.94–1.10 | 0.56–0.81 |

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| Autor          | Type of study                                      | Anticoagulant | Indication | Severity of GI bleed | Patients (n) | Patients restarting (n)/ When restarted | Mean age (years) | HR-TE (95% CI) | HR-GIH (95% CI) | HR-Mortality (95% CI) |
|----------------|---------------------------------------------------|---------------|------------|----------------------|--------------|------------------------------------------|------------------|---------------|----------------|---------------------|
| Sengupta et al (2015) | Single centre, prospective observational cohort study | Warfarin (145) | AF (58%)   | Visible bleeding or guaiac-positive stools and significant Hb drop (NS) | 197 (M = 58%) | 122/Median 5 days | 90 days | 0.12 (0.006–0.81) | 2.17 (0.86–6.67) | 0.63 (0.22–1.89) |
| Staerk et al (2015) | National retrospective registry study              | Single OAC (21.3%) | AF | NS | 3409 (M = 55%) | 2485/NS | 5 years | 78 | 0.41 (0.3–0.54) | 1.22 (0.84–1.77) | 0.39 (0.34–0.46) |
|                |                                                  | Single AP (38.5%) | NS          |                       |              |                                          |                  |               |                |                     |
|                |                                                  | DAPT (1.5%)     | NS          |                       |              |                                          |                  |               |                |                     |
|                |                                                  | OAC + AP (11.3%) | NS          |                       |              |                                          |                  |               |                |                     |
|                |                                                  | OAC + DAPT (0.3%) | NS          |                       |              |                                          |                  |               |                |                     |
| Lee et al (2012) | Single centre, retrospective cohort study         | Warfarin       | VHD         | NS                   | 58 (M = 57%) | 22/NS | Mean 255 days (182–330) | 63 | NS | NS | Thromboembolism: Resuming: 0 Non-resuming: 6 Earliest event 21st day after index GIH Recurrent GIH: Resuming: 3 Non-resuming: 0 Earliest event 5 days after index GIH |

95% CI, 95% confidence interval; AF, atrial fibrillation; AP, antiplatelet; CHADS2, congestive heart failure; hypertension; age ≥75 years; diabetes mellitus; and stroke or transient ischaemic attack; DAPT, dual antiplatelet treatment; GI, gastrointestinal; GIH, gastrointestinal haemorrhage; HAS-BLED, hypertension; abnormal renal and liver function; stroke; bleeding; labile international normalised ratios; elderly; drugs or alcohol; HR, hazard ratio; M, male; NS, not specified; OAC, oral anticoagulant; PS, post-surgery; RBC, red blood cells; TE, thromboembolism; VHD, valvular heart disease; VTE, venous thromboembolism.
generally well matched in terms of risk factors for GIH and mean presenting INR in both groups was within therapeutic range. Warfarin was restarted in 653 (49.1%) patients at a median of 50 days. Again, a significant reduction in the risk of thromboembolism (TE) (HR 0.71) and mortality (HR 0.67), at the expense of a non-significant increase in risk of re-bleeding (HR 1.18), was demonstrated. In terms of mortality, four of the total number of deaths were thromboembolic in nature and these were all in patients that did not restart warfarin; there was one death due to recurrent GIH in the warfarin group.

Results were subsequently stratified according to the time-point when warfarin was re-instated. Overall, in those restarting warfarin between 7 and 30 days, there was no increase in the risk of re-bleeding, but the benefit in terms of a reduced risk of TE and death persisted. In the stratified groups, mortality was lowest if warfarin was restarted before 7 days, although there was also a 2-fold increase in re-bleeding and a non-significant decrease in the risk of TE associated with this group, compared with those restarting warfarin after 30 days. In all the groups restarting after 7 days, the incidence of re-bleeding was similar. Overall, the period of restarting associated with the best risk to benefit profile, appeared to be between 7 and 15 days; in this group there was a significantly reduced risk of recurrent TE (HR 0.48) and mortality (HR 0.56) associated with a non-significant difference in the risk of recurrent GIH (HR 1.03).

In an analysis of similar data, the risk of re-bleeding, death and recurrent thrombosis was calculated for 665 patients who restarted warfarin within 15–30 days of an index GIH in comparison to patients restarting after 30 days. All patients were stratified into 4 groups according to their bleeding and thrombotic risk, calculated using the HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol) and CHADS2 (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke/transient Ischaemic attack/thromboembolism) scoring systems. In all patients, the risk of stroke within 12 months was significantly reduced and, in those with a low HAS-BLED score (<3), the risk of re-current GI haemorrhage within 3 months was no different. However, in patients with an elevated HAS-BLED score (>3), the rate of re-bleeding within 3 months was twice as high and the death rate within 12 months was also significantly higher (Patsias et al, 2013).

In a much smaller, retrospective study, 58 patients anticoagulated with warfarin for valvular heart disease were followed up for a mean duration of 255 days after an index upper GIH (Lee et al, 2012). There was a total 3 recurrent bleeds, all in patients resuming anticoagulation: two with warfarin and one with bridging heparin. Although no detail is given as to when anticoagulation was reinstated, all the recurrent bleeds were relatively early, occurring on the 5th, 11th and 14th day after the index bleed; none were fatal. There were no thromboembolic events in patients re-starting warfarin; however, in the 36 patients that stopped warfarin, there were 6 thromboembolic events. All of these occurred beyond the 20th day following the index GIH.

More recently, a large retrospective, registry study included all 4602 patients with AF on anticoagulation and/or an antiplatelet agent discharged from Danish hospitals following GIH over a 6-year period (Staerk et al, 2015). Patients were followed up for a maximum of 5-years. A number of high-risk groups were excluded, including patients with valvular heart disease, those that had undergone hip or knee surgery in the previous 8-weeks and patients with a recent (6 months) history of venous thromboembolism (VTE) diagnosis. After exclusions, 3409 patients were included in this study, 2485 of whom restarted treatment with single (n = 2039), dual (n = 435) or triple (n = 11) anticoagulant/antiplatelet treatment.

Restarting single agent anticoagulation, antiplatelet or combined treatment, when compared with non-resumption of treatment, was associated with an overall reduction in risk of both all-cause mortality (HR 0.39; 0.76 and 0.41 respectively) and recurrent TE (HR 0.41; 0.76 and 0.54, respectively). Surprisingly, although restarting single-agent anticoagulation was associated with the lowest risk of mortality and recurrent TE, it was also the only regimen associated with an increased risk of recurrent major GIH (HR 1.37), although this was not statistically significant. It should be noted that follow-up did not commence until after a 90-day blanking period, during which 1193 events (TE, recurrent GIH and death) occurred that were excluded from the final analysis. In fact, the highest risk of recurrent GIH in this study was within the first month of discharge from hospital, but data is only presented for patients surviving beyond 90-days. However, a subsequent sensitivity analysis did show that results were broadly similar if follow-up commenced on the day of discharge.

Currently, only one prospective study exists that specifically addresses the issue of anticoagulation resumption after GIH (Sengupta et al, 2015). This was a single-centre study, including 197 patients on systemic anticoagulation (warfarin n = 145, enoxaparin n = 15, dabigatran n = 12, rivaroxaban n = 11, apixaban n = 2, unfractionated heparin n = 12) for a range of indications, admitted with, or developing a clinically significant GIH. Patients were classified according to whether they restarted anticoagulation at discharge, or if their anticoagulation was interrupted for more than 72 h after discharge. They were followed-up by telephone at 90 days, and measured outcomes were TE events; readmission related to recurrent GIH and mortality. The median hospital stay was 5 days (range, 1–44 days) and all patients resuming anticoagulation had reinitiated this by the time of hospital discharge. Patients requiring anticoagulation for prosthetic heart valves, previous cerebrovascular events or with a previous history of GIH were more likely to restart prior to discharge. However, no information is presented to detail how and when this was reinstated; in particular, it is not clear if high-risk patients received any form of bridging therapy. Controlling results according to a propensity score, resuming anticoagulation was
associated with a lower risk of TE (HR 0.121), with the majority of TE events occurring between 2 and 8 weeks. Overall, 14% of patients were readmitted with recurrent GIH at a median of 13 days. There was no significant difference in the time to readmission between groups and, although patients resuming anticoagulation were at a higher risk of recurrent GIH, this did not reach statistical significance (HR 2.17). There were no deaths in this group and the majority of events were not associated with a significant drop in haemoglobin or requirement for interventional treatment. On multivariate analysis, resumption of anticoagulation was not associated with an increased risk of mortality (HR 0.632).

Although these results are consistent with the retrospective studies in terms of overall outcomes, there is no data presented to describe at what time-point antithrombotic agents were reintroduced or to indicate the duration of hospital admission. So, although there seems to be a clear benefit in restarting these medications, no further clarity is provided as to when this should be done and in which patient groups.

**Antiplatelet therapy and GIH**

In terms of antiplatelet agents, although frequently implicated in GIH, the absolute increased risk associated with their use is modest. In a meta-analysis including 14 clinical trials, low dose aspirin (75–300 mg per day) was associated with a 107% relative increase in the risk of major GIH compared to placebo. Although this only equates to a small absolute increase in risk of 0.12% per year (McQuaid & Laine, 2006), considering that aspirin users number in the tens of millions, 35% of whom will be elderly, this small absolute risk translates to a significant overall effect on the incidence of GIH (Valkhoff et al, 2012). The absolute risk associated with single-agent clopidogrel is slightly less than aspirin; however, the more modern P2Y12 antagonists, ticagrelor and prasugrel, exhibit a more potent anti-platelet effect and are associated with higher rates of GIH compared to clopidogrel (Wiviott et al, 2007; Wallentin et al, 2009). Data regarding the use of dual antiplatelet agents is less readily available, but the rate of major GIH has been reported to be around 1.3–2.7% (Yusuf et al, 2001; Alli et al, 2011).

Identifying which individuals prescribed anti-platelet agents are at highest risk of GIH is not necessarily straightforward. It could be assumed that traditional risk factors for GIH also apply to this patient group, but this has not been comprehensively examined. For instance, a number of studies have shown that in aspirin users, increasing age has no significant effect upon the risk of GIH beyond that associated with non-aspirin users (Valkhoff et al, 2012).

**Studies on resumption of antiplatelets after a GIH**

In a small, but randomised, blinded and placebo controlled study (Sung et al, 2010), 156 patients that required secondary prophylaxis with aspirin, were assigned to either continue the drug (80 mg per day), or commence a placebo, following an endoscopically controlled GIH. All patients received a concomitant proton-pump inhibitor (PPI) and were followed up for 8 weeks. The primary endpoint was recurrent GIH within 30 days of endoscopy. Secondary endpoints included all-cause mortality and death attributable to cardiovascular, cerebrovascular and GI complications.

The risk of recurrent GIH was increased in the aspirin group, but not significantly (HR 1.9) and, of these bleeds, none were fatal or, using surrogate markers, more severe than the placebo group. Most episodes of recurrent GIH in the aspirin group were within the first 5 days of the index event. There was a significant risk reduction in all-cause mortality associated with continuation of aspirin (HR 0.2). In contrast, 5 patients in the placebo arm died of TE events, 3 of which occurred between day 1 and 12.

Using a similar, but smaller patient group, a retrospective study examined cardiovascular mortality as a primary objective (Derogar et al, 2013). Although all patients underwent endoscopy, results were not stratified according to those that achieved endoscopic control of the GIH and those where bleeding could not be controlled or no bleeding point was identified. Of 118 patients on low dose aspirin (75–160 mg) presenting with GIH, 60% continued treatment after the index event; 23 (20%) of these patients restarted aspirin within a median of 1 week (2 days–2 months) and 48 (41%) continued without any interruption. In those with baseline cardiovascular co-morbidity, stopping aspirin treatment was associated with an increased risk of death or acute cardiovascular event (HR 6.8) in the first 6-months of follow-up. Beyond this period, there was no difference in survival. 7 patients were readmitted with recurrent GIH (3 in the aspirin group), none of which were fatal; however, these numbers were too small to infer any statistical significance.

We were unable to identify any studies that investigated the withdrawal and/or resumption of antiplatelet agents other than aspirin.

**Suggested approach based on the literature**

**Anticoagulants**

Overall, restarting warfarin after GIH appears to be associated with a favourable risk-benefit profile compared to not reinitiating treatment, certainly in terms of recurrent TE and overall mortality. Although the majority of studies did find increased rates of recurrent GIH, in general, these were not statistically significant.

TE events that do occur in individuals that resume anticoagulation tend to be both less frequent and less frequently fatal. However, early resumption of anticoagulation (before day 7 of the index bleed) may be associated with an unacceptably high risk of recurrent GIH and, as most TE events tend to occur after this 7-day period, should be avoided in
most instances. Only one study closely examined at what time-point anticoagulation could be optimally restarted (Qureshi et al., 2014) and this appears to be somewhere between 7 and 15 days. In this group there was a significantly reduced risk of recurrent TE and mortality associated with a non-significant increase in the risk of recurrent GIH.

There is too little data available to determine if these findings are universal to anticoagulants other than warfarin. Given what is known from the licencing trials and recent work (Abraham et al., 2015; Chang et al., 2015), it may be reasonable to make this assumption. However, the timing of reintroduction of these agents may need further consideration in terms of both the pharmacokinetic properties of these drugs and individual patient characteristics. Future prospective studies are required to fully address this issue. The RATHER (Early Versus Late Resumption of Anticoagulation in Patients With Both High Thrombosis Risk and Major HemoRrhage) trial (NCT02091479), was due to report on this issue in 2017 but was terminated because of insufficient recruitment.

An approach to the management of anticoagulants in patients presenting with GIH is suggested in Table II and Figs 1–3. When making decisions, of paramount importance is an assessment of the balance of risks between re-bleeding and recurrent TE (Tables III and IV). In addition to the issue regarding when to resume anticoagulation, this process should include additional steps to further minimise the risk of recurrent bleeding. This includes the use of PPI agents and the eradication of H. pylori, if appropriate. In patients receiving warfarin with previously labile control, it could include tighter INR monitoring or, in those cases using a DOAC, a long-term switch to apixaban, which is associated with a lower risk of GIH. In those individuals already anticoagulated with apixaban, a dose reduction to 2.5 mg twice daily, which provides similar efficacy but slightly lower bleeding risk, could be considered (Granger et al., 2011; Desai et al., 2013; Halvorsen et al., 2014).

Patients with a particularly high thrombotic risk are not well represented in current studies, but are not an infrequent clinical dilemma and require close attention. Our management suggestions are based on a risk-stratified approach to bleeding patients with high thrombotic risk, in whom we aim to reintroduce anticoagulation early, but in a graduated manner according to the clinical context. One strategy would be to adapt guidance suggested for the peri-operative management of anticoagulated patients, using short-acting and reversible parenteral anticoagulants to bridge those at high risk of TE (Douketis et al., 2012; Keeling et al., 2016). For instance, in those at highest risk of recurrent TE, but with the highest bleeding risk, prophylactic low molecular weight heparin (LMWH) could be introduced at 48 h following endoscopic control of a GIH, escalating to treatment dose at

Table II. Summary recommendations for the management of patients presenting with acute GIH that are therapeutically anticoagulated.

| Recommendation |
|----------------|
| 1. The majority of patients will benefit from restarting. It will be useful at this time to revisit the need for anticoagulation. For example, if in the case of atrial fibrillation (AF), would it be worthwhile discussing the non-pharmacological option of ablation therapy. |
| 2. Patients should have a risk assessment made in terms of the risk of recurrent TE and recurrent GIH. Patients receiving anticoagulants for AF can have CHADS2-VASC and HAS-BLED scores calculated and used for this risk stratification. It seems pragmatic to delay re-initiation of anti-thrombotic treatment as long as possible in those at highest risk of bleeding and reintroduce early in those at high risk of TE. |
| 3. If restarting, restart after day 7 – there is no established benefit to restarting before 7 days and the risk of recurrent GIH is increased. However, in those at highest risk of TE, an early, graduated reintroduction of anticoagulation using short-acting agents such as LMWH, may need to be considered. |
| 4. In patients who developed GIH while receiving dabigatran, rivaroxaban, or higher dose edoxaban, particularly those aged over 75 years, consider switching to apixaban 5 mg twice daily (2.5 mg twice daily if two or more of the following: Age >80 years, weight <60 kg or serum creatinine >133 μmol/l). |
| 5. If patient is on concomitant antiplatelet therapy, discuss the need for dual antithrombotics with a cardiologist. |
| 6. Consider *Helicobacter pylori* eradication therapy and the addition of a proton pump inhibitor, if appropriate. |

AF, atrial fibrillation; CHADS2-VASC, congestive heart failure; hypertension; age ≥75 years (2 points); diabetes mellitus; prior stroke or transient ischemic attack or thromboembolism (2 points); vascular disease (peripheral artery disease; myocardial infarction; or aortic plaque); age 65–74 years; sex category female; GIH, gastrointestinal haemorrhage; HAS-BLED, hypertension; abnormal renal and liver function; stroke; bleeding; labile international normalised ratios; elderly; drugs or alcohol; LMWH, low molecular weight heparin; TE, thromboembolism.
72 h, if no further bleeding occurs. It is stressed that this approach is not evidence-based, which is still lacking.

**Antiplatelets**

The body of evidence to guide practice is very limited and relates only to aspirin monotherapy. However, of the studies that are available, both demonstrate that there is a benefit in continuing aspirin therapy in terms of both mortality and recurrent TE events (Sung et al., 2010; Derogar et al., 2013). The best available evidence suggests that there is no need to stop aspirin therapy, even transiently, in patients where endoscopic control of the GIH can be achieved (Sung et al., 2010). As the evidence is limited, particularly in respect to antiplatelet agents other than aspirin, any further treatment recommendations for patients receiving these agents need to be made using a pragmatic, risk-benefit approach. These are not necessarily evidence-based, but, where available, do reflect current guideline suggestions (Fig 3).

Treatment guidelines do vary in their recommendations, but the use of antiplatelets for the primary prevention of cardiovascular disease is, generally, no longer advocated as any benefit is recognised to be small. In contrast, in those patients that have experienced a myocardial event, treatment with long-term aspirin, combined with an additional antiplatelet agent, for a period of up to 12 months has been shown to be of overall benefit in the prevention of further episodes and is advocated (Yusuf et al., 2001; Vandvik et al., 2012). Recent evidence suggests that selected patients may benefit from treatment with dual antiplatelet agents (DAPT) for a period of up to 30 months, although at the expense of increased rates of non-fatal bleeding (Mauri et al., 2014). For those patients that have undergone percutaneous coronary intervention and stent placement, DAPT is mandatory, but the minimum duration of this is determined by the type of stent employed. Where a bare metal stent (BMS) has been used, early re-endothelialisation of the stent allows potential for step-down to single agent antiplatelets at 4–6 weeks. With drug eluting stents, this process is prolonged due to the inflammatory characteristics of the stent coating and DAPT must be continued for a minimum of 3 (sirolimus-coated stents) or 6 months (paclitaxel-coated stents) (Vandvik et al., 2012). It should be stressed that these are the minimum duration of DAPT suggested and, in the absence of contraindications, at least 12 months of dual treatment is still advocated. However, in patients assessed to be at high bleeding risk that require stent placement, it would seem prudent to consider use of a BMS in order to curtail...

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**Fig 1.** A suggested approach to the timing and management of anticoagulant reintroduction following an acute gastrointestinal haemorrhage. LMWH, low molecular weight heparin.
exposure to DAPT. Single-agent secondary prophylaxis with an antiplatelet is also recommended following cerebrovascular events and in patients with peripheral and multi-vascular disease (National Institute for Health and Care Excellence (NICE), 2010; Perk et al, 2012). Caution is suggested when considering the use of the newer P2Y12 antagonists in patients at higher bleeding risk, but overall their use is still considered beneficial (Hamm et al, 2011).

In view of these guideline recommendations, in patients receiving antiplatelets for primary prophylaxis that present with GIH, it would seem reasonable to stop these agents long-term. However, this decision becomes much less simple when these agents are used as secondary prophylaxis. Certainly in the elective setting, the omission of antiplatelet agents is associated with significant risk of recurrent thromboembolic events. In a meta-analysis of studies in which aspirin had been stopped perioperatively, withdrawal was associated with 10-2% increased risk of subsequent cardiovascular events (Burger et al, 2005). In a second meta-analysis focusing on patient adherence to and withdrawal of aspirin used for secondary prophylaxis for cardiovascular disease, discontinuation of aspirin was associated with a 3-fold increased risk of major adverse cardiac events. This risk was staggeringly higher in patients with coronary stents, where the odds ratio of a major event was almost 90-00 (Biondi-Zoccai et al, 2006). The risk in the acute, unstable and hypercoagulable patient is potentially even higher, but this has not been so extensively examined.

Where antiplatelet agents are to be reinstated following a GIH, most recent guidance is to do this as soon as haemostasis is achieved, advising particular caution in the withdrawal of agents for patients with recent coronary stenting and/ or acute cardiac syndromes. In those at particularly high risk of thrombosis (eg those with recent coronary stent insertion), it is suggested dual antiplatelet treatment (DAPT) can be continued, providing early endoscopy and haemostasis can be achieved (Acosta et al, 2016; Veitch et al, 2016). However, as summarised, the trial evidence to guide these recommendations is somewhat sparse. In fact, only one prospective study exists and this only examines aspirin mono-therapy. In addition, this trial did not include patients in whom the bleeding site could either not be identified or controlled, so the findings cannot be universally applied (Sung et al, 2010).

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**Fig 2.** A suggested approach to the long-term management of anticoagulants in patients presenting with acute gastrointestinal haemorrhage. Any change to treatment suggested is intended to be long-term. INR, international normalised ratio.
In cases of life-threatening or significant GIH, current recommendations are, after discussion with a cardiologist, to withhold antiplatelet agents (Acosta et al., 2016). It would seem reasonable to adhere to the same advice in patients where the source of the bleed can either not be identified or controlled. However, the question remains, how long can these agents be safely withheld for? In answering this, the indication for secondary prevention has to be carefully considered. In Burger’s meta-analysis, the time interval from discontinuation of aspirin to an adverse event was around 8 days for acute coronary syndromes, 14 days for cerebrovascular syndromes and 25 days for acute peripheral arterial syndromes (Burger et al., 2005). On the other hand, and in the acute setting, in patients without coronary stents remaining on aspirin, most of the death attributable to recurrent GIH occurred in the first 3–5 days (Sung et al., 2010). Therefore, in patients where a bleeding site cannot be identified, and who are at low risk of a cardiovascular event, it may be reasonable to omit single agent antiplatelets for up to 7 days. In the case of aspirin, this would also be physiologically logical as, although its antiplatelet action is irreversible and persists for 5–7 days, the inhibition of endothelial prostaglandin synthesis is much shorter lived. The maintenance of vascular perfusion promoted by this prostaglandin secretion is a critical factor in the maintenance of mucosal defence of the gut epithelium after an acute insult (Wallace, 2008).

In patients with coronary stents requiring DAPT, withdrawal decisions are more complex and must be made in consultation with a cardiologist.

In those patients on antiplatelet agents other than aspirin, in addition to minimising other risk factors (such as eradicating H. pylori and adding a PPI), it would seem reasonable to switch to a lower risk agent, if antiplatelet therapy is to be resumed. In a prospective, randomised study of patients on low dose aspirin presenting with GIH, subjects were randomised to resume treatment with either clopidogrel (75 mg daily) and a placebo or low dose aspirin (80 mg daily) plus esomeprazole (20 mg daily), once ulcer healing had been confirmed by endoscopy. The cumulative incidence of recurrent ulcer bleeding during a 12-month period was 8.6% in the clopidogrel group versus 0.7% in the aspirin group (P = 0.001) (Chan et al., 2005). There are no studies...
Table III. Thrombotic risk of therapeutically anticoagulated patients, according to indication.

| Thrombotic risk | Indication for anticoagulation                                                                                     | Atrial fibrillation (AF)                                                                 | Venous thrombosis                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Very high*      | Any mitral valve prosthesis                                                                                         | CHA2DS2-VASc score of ≥6 (or CHADS2 score of 5–6)                                        | Recent (within 3 months) VTE                                                    |
|                 | Any caged-ball or tilting disc aortic valve prosthesis                                                             | CHA2DS2-VASc score of 4–5 or CHADS2 score of 3–4                                        | Severe thrombophilia (e.g., deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities) |
|                 | Recent (within 6 months) stroke or transient ischaemic attack                                                      | Rheumatic valvular heart disease                                                         | VTE within the past 3 to 12 months                                               |
|                 | Bileaflet aortic valve prosthesis and one or more of the following risk factors:                                  | CHA2DS2-VASc score of 2–3 or CHADS2 score of 0–2 (assuming no prior stroke or transient ischaemic attack) | Nonsevere thrombophilia [e.g., heterozygous F5 R506Q (factor V Leiden) or F2 (prothrombin gene) mutation] |
|                 | AF, prior stroke or transient ischaemic attack, hypertension, diabetes, congestive heart failure, age >75 years    |                                           | Recurrent VTE Active cancer (treated within 6 months or palliative)               |
| High            | Bileaflet aortic valve prosthesis                                                                                  |                                           |                                                                                  |
|                 |                                                                                                                    |                                           |                                                                                  |
| Moderate        | Bileaflet aortic valve prosthesis without AF and no other risk factors for stroke                                 |                                           |                                                                                  |
|                 |                                                                                                                    |                                           |                                                                                  |

Modified from: Chest, 141, Douketis, J.D., Spyropoulos, A.C., Spencer, F.A., Mayr, M., Jaffer, A.K., Eckman, M.H., Dunn, A.S. & Kunz, R. (2012) Perioperative management of antithrombotic therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest, 141, e326S–e350S, Copyright (2012), with permission from Elsevier.

VTE, venous thromboembolism; CHADS2, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or transient ischaemic attack; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years (2 points), diabetes mellitus, prior stroke or transient ischaemic attack or thromboembolism (2 points), vascular disease (peripheral artery disease, myocardial infarction, or arterial plaque), age 65–74 years, sex category female.

*Very high risk patients may also include those with a prior stroke or transient ischemic attack occurring ≥3 months before the planned surgery and a CHA2DS2-VASc score <6 (or CHADS2 score <5), those with prior thromboembolism during temporary interruption of anticoagulation, or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (e.g., cardiac valve replacement, carotid endarterectomy, major vascular surgery).

Table IV. Risk stratification for discontinuation of antiplatelets based on the risk of thrombosis.

| High risk                                | Low risk                                |
|------------------------------------------|------------------------------------------|
| Drug eluting coronary artery stents within 12 months of placement | Ischaemic heart disease without coronary stents |
| Bare metal coronary artery stents within 1 month of placement | Cerebrovascular disease |
|                                          | Peripheral vascular disease               |

Adapted from: Veitch, A., Vanhiervliet, G., Gershlick, T., Boustiere, C., Baglin, T., Smith, L., Radadeli, F., Knight, E. & Gralnek, L.M. (2016) Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy (ESGE guidelines. Gut, 65(3), 374–389. (Open Access Article covered by https://creativecommons.org/licenses/by-nc/4.0/legalcode.

including the newer P2Y12 inhibitors or patients on DAPT, but after discussion with a cardiologist, it may be prudent to switch to less potent agents if it is felt the risk-benefit profile is acceptable. Unlike aspirin mono-therapy, there is no data to guide the timing of reintroduction of these agents. This clearly needs addressing, but as these agents are considered to have a more powerful antiplatelet effect, in patients that have not recently undergone coronary stenting, it may be reasonable to delay their reintroduction until active bleeding has settled. It would be imperative that these decisions are made in consultation with a cardiologist and in the context of the type of coronary stent the patient may have in situ. Initial advice for patients at high risk of GIH requiring DAPT was to prescribe a concomitant PPI; however, more recent evidence of a metabolic interaction between the thienopyridines and PPIs, particularly clopidogrel and omeprazole, complicates this decision. In terms of cardiovascular outcome, it is not clear if these pharmacokinetic and pharmacodynamic interactions are necessarily of clinical significance and the results of various, non-randomised studies are conflicting. Clinical decisions should be made on an individual basis, with respect to both GI and cardiovascular risk factors. A suitable option, where concomitant treatment is required, would be to consider use of PPI, such as pantoprazole or rabeprazole, with weaker evidence for thienopyridine interaction (Abraham et al, 2010; Scott et al, 2014).
Conclusions

Although patients treated with antithrombotic agents are at increased risk of GIH, there is surprisingly little evidence to guide the management of these agents beyond initial resuscitation. In general, for patients on anticoaguants and antiplatelets used as secondary prophylaxis, there is an overall benefit to reinstate these agents relatively early. However, these decisions need to be balanced and risk-assessed according to the degree of control of GIH that is achieved; the indication for the antithrombotic agent; patient comorbidities; bleeding and thrombotic risks. The evidence base to guide these decisions is very limited and although we make some practice suggestions in this review, it should be emphasised that these are opinion-based and therefore potentially contentious. There is a clear need for further prospective and randomised trials addressing these issues, particularly with regard to the newer oral anticoagulant and antiplatelet agents.

Authorship

MS and JT conceived the review topic, wrote and edited the manuscript. AV provided additional content expertise and critically revised the manuscript.

Conflicts of Interest

None.
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