

# American College of Gastroenterology-Canadian Association of Gastroenterology Clinical Practice Guideline: Management of Anticoagulants and Antiplatelets During Acute Gastrointestinal Bleeding and the Periendoscopic Period

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## Abstract

We conducted systematic reviews of predefined clinical questions and used the Grading of Recommendations, Assessment, Development and Evaluations approach to develop recommendations for the periendoscopic management of anticoagulant and antiplatelet drugs during acute gastrointestinal (GI) bleeding and the elective endoscopic setting. The following recommendations target patients presenting with acute GI bleeding: For patients on warfarin, we suggest against giving fresh frozen plasma or vitamin K; if needed, we suggest prothrombin complex concentrate (PCC) compared with fresh frozen plasma administration; for patients on direct oral anticoagulants (DOACs), we suggest against PCC administration; if on dabigatran, we suggest against the administration of idarucizumab, and if on rivaroxaban or apixaban, we suggest against andexanet alfa administration; for patients on antiplatelet agents, we suggest against platelet transfusions; and for patients on cardiac acetylsalicylic acid (ASA) for secondary prevention, we suggest against holding it, but if the ASA has been interrupted, we suggest resumption on the day hemostasis is endoscopically confirmed. The following recommendations target patients in the elective (planned) endoscopy setting: For patients on warfarin, we suggest continuation as opposed to temporary interruption (1–7 days), but if it is held for procedures with high risk of GI bleeding, we suggest against bridging anticoagulation unless the patient has a mechanical heart valve; for patients on DOACs, we suggest temporarily interrupting rather than continuing these; for patients on dual antiplatelet therapy for secondary prevention, we suggest temporary interruption of the P2Y<sub>12</sub> receptor inhibitor while continuing ASA; and if on cardiac ASA monotherapy for secondary prevention, we suggest against its interruption. Evidence was insufficient in the following settings to permit recommendations. With acute GI bleeding in patients on warfarin, we could not recommend for or against PCC administration when compared with placebo. In the elective periprocedural endoscopy setting, we could not recommend for or against temporary interruption of the P2Y<sub>12</sub> receptor inhibitor for patients on a single P2Y<sub>12</sub> inhibiting agent. We were also unable to make a recommendation regarding same-day resumption of the drug vs 1–7 days after the procedure among patients prescribed anticoagulants (warfarin or DOACs) or P2Y<sub>12</sub> receptor inhibitor drugs because of insufficient evidence.

## INTRODUCTION

Antithrombotic drugs including vitamin K antagonists (VKAs; warfarin and acenocoumarol), direct oral anticoagulants (DOACs; apixaban, dabigatran, edoxaban, and rivaroxaban),

antiplatelet drugs such as the P2Y<sub>12</sub> receptor inhibitors (clopidogrel, prasugrel, and ticagrelor), and acetylsalicylic acid (ASA) are used in the management of patients with atrial fibrillation, ischemic heart disease, venous thromboembolism,

and valvular heart disease. These drugs also increase the risk of gastrointestinal (GI) bleeding from luminal sources such as ulcers or diverticula and after endoscopic procedures (1–3). Standardized, evidence-based protocols are lacking to inform best practices before and after endoscopic procedures in urgent and elective settings. Furthermore, uncertainty regarding best practice recommendations and associated levels of evidence has led to significant variation in adherence to guideline-directed practices (4).

The American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) convened an international, multisociety, and multidisciplinary working group to create a focused, pragmatic guideline after distillation of published literature to inform clinical practice in the periendoscopic period. In keeping with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach (5), the most pertinent clinical questions guided the systematic review of the literature, with the resulting rigorous methodological evaluation of the available published data informing recommendations. In this document, we propose an evidence-based approach to periprocedural antithrombotic drug management in common emergent and elective settings addressing clinical questions related to (i) temporary interruption of anticoagulant and antiplatelet drugs; (ii) reversal of anticoagulant and antiplatelet drugs; (iii) periprocedural heparin bridging; and (iv) postprocedural resumption of anticoagulant and antiplatelet drugs.

This document does not cover all possible clinical situations where multidisciplinary guidance may be necessary to manage periendoscopic antithrombotic therapy. Nor does it address the rapidly evolving menu of endoscopic approaches developed to minimize intraprocedural and postprocedural bleeding in situations such as removing large colonic polyps (6). Because of insufficient evidence, the panel could not recommend a best practice for all clinical questions. These clinical situations are identified as priorities for future research.

## METHODS

These guidelines are established to support clinical practice and suggest preferable approaches to a typical patient with a particular medical problem based on the currently available published literature. When exercising clinical judgment, particularly when treatments pose significant risks, healthcare providers should incorporate this guideline in addition to patient-specific medical comorbidities, health status, and preferences to arrive at a patient-centered care approach.

The methods for this guideline were agreed on *a priori* by the ACG and the CAG with the express intent to codevelop high-quality multisociety guidelines that reduce duplication of effort and improve impact. The methods have followed the GRADE approach (5). The target population of this guideline is patients receiving anticoagulants or antiplatelet drugs who are (i) hospitalized or under observation with acute GI bleeding or (ii) undergoing inpatient or outpatient elective GI endoscopic procedures. The target audience for this guideline includes healthcare providers, public health policymakers, patients, and caregivers.

The guideline panel was led by 2 gastroenterology cochairs (N.S.A. and A.N.B.). It included 6 voting content experts—4 gastroenterologists (N.S.A., A.N.B., L.L., and J.T.), 1 cardiologist (P.A.N.), 1 thrombosis expert (J.D.), and 2 nonvoting

gastroenterologists who served as the GRADE methodologists (G.I.L. and B.S.). No patients were included in the guideline process. The panel developed, prioritized, and finalized the clinical questions in Population, Intervention, Comparator, and Outcome (PICO) format through teleconferences before systematic literature reviews. The critical outcomes were 7-day further bleeding and 30-day thrombotic events for patients with acute GI bleeding and 30-day bleeding and 30-day thrombotic events after elective endoscopic procedures. The final PICO questions were shared with the leadership of the ACG Practice Parameters Committee and the CAG Clinical Affairs Committee.

The editorial office of the Cochrane Gut Group at McMaster University developed and ran searches in MEDLINE, EMBASE, and CENTRAL for randomized controlled trials (RCTs), controlled or uncontrolled observational studies, and systematic reviews of any study design published in the English language as full text (conference abstracts were not included) between January 1, 1995 (January 1, 1985, for some searches), and August 13, 2020. Full details of search strategies can be found in Supplementary Digital Content (see Appendix 1, <http://links.lww.com/AJG/C416>). Each identified abstract was screened for eligibility in duplicate by at least 2 of the 4 voting gastroenterologists. Potentially eligible studies were assessed as full-text articles by the GRADE methodologists or 1 of the 4 voting gastroenterologists. A GRADE methodologist verified data extraction. An evidence map was prepared for each PICO question. The panel reviewed the preliminary evidence map, proposed additional articles, and assisted in supplementary literature searches targeting broader populations when gaps in the evidence were identified. Where appropriate, more recent publications available after the formal literature search and evidentiary review are discussed for contextual information if deemed to provide critical additional contemporary insight.

The 2 GRADE methodologists prepared assessments of the risk of bias of each included study and developed complete evidence reports, including a summary of evidence tables (see Appendix 2, Supplementary Digital Content, <http://links.lww.com/AJG/C417>). The certainty of the evidence for each PICO question was categorized as very low, low, moderate, or high depending on the assessment of (i) limitations in the design and execution of the studies, (ii) indirectness, (iii) inconsistency, (iv) imprecision, and (v) other considerations including publication bias, according to the GRADE approach (7,8). Manuscripts initially deemed potentially eligible but eventually excluded are listed in Supplementary Digital Content (see Appendix 3, <http://links.lww.com/AJG/C418>) with reasons for exclusion. Each GRADE methodologist, in turn, prepared half of the evidence reports, whereas the other methodologist double-checked them, providing feedback until agreement was achieved. For each PICO, 3 versions of the wording of the potential recommendation were prepared *a priori* (in favor, against, or unable to recommend). The opinions of individual content experts were sought for specific issues. The evidence reports and risk of bias tables were shared with the whole panel on April 16, 2021, and discussed by email. The finalized document was shared before the voting videoconference meetings on May 8 and 15, 2021.

One cochair (A.N.B.) and 1 GRADE methodologist (G.I.L.) moderated the voting videoconference meetings. For each PICO, the GRADE methodologist presented a summary of the evidence, including the direction and magnitude of effect



**Table 1.** Guideline statements, the strength of recommendation, and certainty of the evidence for the management of antithrombotic agents in the setting of acute GI bleed**Management of antithrombotic agents in the setting of acute GI bleed****Vitamin K antagonist reversal**

1. For patients on warfarin who are hospitalized or under observation with acute GI bleeding, we suggest against FFP administration (conditional recommendation, very low certainty of evidence).
2. For patients on warfarin who are hospitalized or under observation with acute GIB, we could not reach a recommendation for or against PCC administration.
3. For patients on warfarin who are hospitalized or under observation with acute GIB, we suggest PCC administration compared with FFP administration (conditional recommendation, very low certainty of evidence).
4. For patients on warfarin who are hospitalized or under observation with acute GIB (upper and/or lower), we suggest against the use of vitamin K (conditional recommendation, very low certainty of evidence).

**Direct thrombin inhibitor reversal (dabigatran)**

5. For patients on dabigatran who are hospitalized or under observation with acute GIB, we suggest against the administration of idarucizumab (conditional recommendation, very low certainty of evidence).

**Reversal of rivaroxaban/apixaban with andexanet alfa**

6. For patients on rivaroxaban or apixaban who are hospitalized or under observation with acute GIB, we suggest against andexanet alfa administration (conditional recommendation, very low certainty of evidence).

**Reversal of direct oral anticoagulant with PCC**

7. For patients on DOACs who are hospitalized or under observation with acute GIB, we suggest against PCC administration (conditional recommendation, very low certainty of evidence).

**Reversal of antiplatelet with platelet transfusion**

8. For patients on antiplatelet agents who are hospitalized or under observation with acute GIB, we suggest against platelet transfusions (conditional recommendation, very low certainty of evidence).

**Holding ASA vs continuing ASA**

9. For patients with GI bleeding on cardiac ASA for secondary prevention, we suggest against holding the ASA (conditional recommendation, very low certainty of evidence).

**Resumption of ASA after endoscopic hemostasis**

10. For patients with GI bleeding on ASA for secondary cardiovascular prevention whose ASA was held, we suggest the ASA be resumed on the day hemostasis is endoscopically confirmed (conditional recommendation, very low certainty of evidence).

ASA, acetylsalicylic acid; FFP, fresh frozen plasma; DOAC, direct oral anticoagulant; GI, gastrointestinal; GIB, GI bleeding; PCC, prothrombin complex concentrate.

**Conclusions.** Although there is biological plausibility of FFP administration to reverse VKA in patients with GI bleeding, there exists only very low certainty evidence, given serious concerns of risk of bias, imprecision, and indirectness. The panel also considered the low cost of FFP, relevant patient utilities, and the potential increased risk of transmission of infectious agents with FFP administration. The panel suggested that FFP should not be used routinely but could be considered for patients with a life-threatening GI bleed or a supratherapeutic INR substantially exceeding the therapeutic range. Its use could also be considered in those for whom massive blood transfusion is undesirable because of its effect on coagulopathy or dilution of blood components when PCC is unavailable (see below).

2. For patients on warfarin who are hospitalized or under observation with acute GI bleeding, we could not reach a recommendation for or against prothrombin complex concentrate administration.

**Summary of evidence.** The panel made an *a priori* decision to consider 3-factor PCC and 4-factor PCC equivalent for the intervention (PCC for reversal of warfarin and other VKAs). No eligible studies were identified exclusively in patients with GI bleeding. A backward (snowballing) citation search of previous guidelines was used to identify supporting evidence, including noncomparative cohort data derived from the PCC arms of 2 RCTs that compared PCC vs FFP (14,15). We also considered a cohort study of GI patients, which provided clinical outcomes

and results on the indirect outcome of INR reversal (17). This study was regarded as noncomparative data with the inclusion of the PCC group only.

From 7 studies, there were 223 patients on warfarin, all experiencing major bleeding and treated with PCC (14,15,17–21). Of these, 38.6% had GI bleeding. All patients received 4-factor PCC at various doses, with vitamin K administered to most patients. Further bleeding was observed in 25.5%, with a 7.2% incidence of thrombotic events and 30-day mortality of 7.0% (14,15,17–21). One study estimated transfusion-related events (fluid overload) of 4.9% within 7 days of PCC use (14). All studies demonstrated consistently rapid INR reduction of a large magnitude. Given the pharmacodynamics of warfarin treatment, it was implausible that this dramatic INR change could have occurred because of bias, confounding, or chance.

Studies were downrated for serious or very serious risk of bias (no comparator cohorts), indirectness of the outcome (“hemostatic efficacy” or active bleeding visualized at the time of endoscopy), and the concomitant use of vitamin K. The small number of events contributed to serious imprecision. Only a small proportion of the patients had GI bleeds, although the type of bleed would not have influenced the effect of PCC on the INR. Finally, the speed of INR correction is a surrogate outcome, not a clinical outcome.

**Conclusions.** There is insufficient evidence to judge the balance between desirable and undesirable effects with PCC administration; thus, the panel was unable to issue a



**Table 2.** Guideline statements, the strength of recommendation, and certainty of the evidence for the management of antithrombotic agents in the elective endoscopy setting**Management of antithrombotic agents in the elective endoscopy setting****Anticoagulant interruption vs continuation**

11. For patients on warfarin undergoing elective/planned endoscopic GI procedures, we suggest warfarin be continued, as opposed to temporarily interrupted (1–7 d) (conditional recommendation, very low certainty of evidence).
12. For patients on warfarin, who hold warfarin in the periprocedural period for elective/planned endoscopic GI procedures, we suggest against bridging anticoagulation (conditional recommendation, low certainty of evidence).
13. For patients on DOACs who are undergoing elective/planned endoscopic GI procedures, we suggest temporarily interrupting DOACs rather than continuing DOACs (conditional recommendation, very low certainty of evidence).

**Antiplatelet interruption vs continuation**

- 14a. For patients on dual antiplatelet therapy for secondary prevention who are undergoing elective endoscopic GI procedures, we suggest temporary interruption of the P2Y<sub>12</sub> receptor inhibitor while continuing ASA (conditional recommendation, very low certainty of evidence).
- 14b. For patients on single antiplatelet therapy with a P2Y<sub>12</sub> receptor inhibitor who are undergoing elective endoscopic GI procedures, we could not reach a recommendation for or against temporary interruption of the P2Y<sub>12</sub> receptor inhibitor.
15. For patients on ASA 81–325 mg/d (i.e., cardiac ASA monotherapy) for secondary prevention, we suggest against interruption of ASA (conditional recommendation, very low certainty of evidence).

**Timing of anticoagulant resumption after endoscopy**

16. In patients who are undergoing elective endoscopic GI procedures whose warfarin was interrupted, we could not reach a recommendation for or against resuming warfarin the same day vs 1–7 d after the procedure.
17. In patients who are undergoing elective endoscopic GI procedures whose DOAC was interrupted, we could not reach a recommendation for or against resuming the DOAC on the same day of the procedure vs 1–7 d after the procedure.

**Timing of P2Y<sub>12</sub> inhibitor resumption after endoscopy**

18. In patients who are undergoing elective endoscopic GI procedures whose P2Y<sub>12</sub> inhibitor was interrupted, we could not reach a recommendation for or against resuming P2Y<sub>12</sub> inhibitor on the same day of the procedure vs 1–7 d after the procedure.

ASA, acetylsalicylic acid; DOAC, direct oral anticoagulant; GI, gastrointestinal.

recommendation. The guideline panel implicitly considered evidence from the comparison of PCC with FFP for warfarin reversal that did reveal a favorable profile for PCC use and benefit in studies using the surrogate endpoint of INR correction. PCC is not necessary for most patients on warfarin with a GI bleed. PCC administration could be considered in patients with a life-threatening GI bleed, those with a supratherapeutic INR substantially exceeding the therapeutic range, or in patients in whom massive blood transfusion is undesirable because of its effect on coagulopathy or dilution of blood components.

3. For patients on warfarin who are hospitalized or under observation with acute GI bleeding, we suggest prothrombin complex concentrate administration compared with FFP administration (conditional recommendation, very low certainty of evidence).

**Summary of evidence.** We identified 2 randomized trials (14,15) and 1 cohort study (17) comparing PCC with FFP in patients on warfarin with bleeding. The 2 studies that included patients with GI bleeding reported inconsistent results (14,17). The RCT by Sarode et al. (14) did not find a difference in further bleeding among patients with acute GI bleeding with PCC (25.4%) compared with FFP (24.1%) (relative risk [RR] 1.05, 95% CI: 0.55–2.00). However, the study's definition of successful hemostasis allowed for up to 2 additional units of blood products after receiving FFP or PCC. It did not report whether this cointervention differed between the 2 groups. Furthermore, a higher proportion of patients in the FFP arm received vitamin K, including intravenously.

A prospective cohort study of patients with acute upper GI bleeding who received intravenous vitamin K and either

FFP or PCC found that the absolute risk of further bleeding was numerically lower in the PCC arm with zero of 20 patients diagnosed with bleeding compared with 7 of 20 patients (35%) in the FFP arm but without statistical significance (RR 0.07, 95% CI: 0–1.09) (17). An additional 3 patients in the FFP arm developed recurrent bleeding, but it was unclear whether these 3 patients were independent of the 7 patients already attributed. Regardless, their inclusion would not change the direction of the effect nor certainty of evidence.

The risk of thromboembolic events in patients on warfarin randomized to receive either FFP or PCC was evaluated in 2 studies. In 1 study, the bleeding site was intracranial, whereas in the second study, the bleeding site varied and included GI bleeding in some patients (14,15). Combining results from both studies, although not significant, the absolute risk of thromboembolic events was numerically higher in the PCC arm (RR = 1.60, 95% CI: 0.70–3.62), whereas the 30-day mortality (RR = 0.64, 95% CI: 0.17–2.49) and transfusion-related adverse events (1 transfusion-related anaphylaxis in the FFP group) (14) were numerically lower in the PCC arm. Both studies demonstrated a more rapid INR reduction in patients receiving PCC than FFP (RR = 6.99, 95% CI: 3.61–13.53). The heterogeneous study populations, variability in outcome definition and timing of assessment, and the wide confidence intervals for clinical outcomes led to a very low certainty of evidence.

**Conclusions.** The effect of PCC compared with FFP on further GI bleeding in patients on warfarin is unknown; however, the more rapid and reliable correction of the INR provides for a biological rationale supporting the efficacy of PCCs. Although there was a very low certainty of evidence, the panel determined

that the anticipated desirable effects of PCC compared with FFP were greater than the undesirable effects in patients with acute GI bleeding. The panel concluded that although most patients with acute GI bleeding on warfarin would not require PCC administration, PCC use could be considered in patients with a life-threatening GI bleed, in those with a supratherapeutic INR substantially exceeding the therapeutic range, or those in whom massive blood transfusion is undesirable because of its effect on coagulopathy or dilution of blood components.

4. For patients on warfarin who are hospitalized or under observation with acute GI bleeding, we suggest against the use of vitamin K (conditional recommendation, very low certainty of evidence).

**Summary of evidence.** In patients receiving a VKA such as warfarin, low-dose oral vitamin K 1–2 mg can be used when there is an elevated INR (typically an INR  $\geq 10$ ) to restore therapeutic-level anticoagulation (i.e., INR 2.0–3.0) (22). In the setting of clinically significant GI bleeding requiring therapeutic intervention, vitamin K 2–5 mg (oral or intravenous) reverses anticoagulant effect (to INR  $\leq 1.3$ ) in 24–48 hours. Vitamin K use does not achieve rapid hemostasis in patients with acute bleeding (22). Consequently, the clinical value of vitamin K is limited in most patients with acute GI bleeding, especially if the bleed is self-limiting, treatable through direct endoscopic hemostatic intervention, or if the INR is mildly elevated (e.g., INR 1.5–2.5). Vitamin K can be administered in patients with a supratherapeutic INR if the intent is to reverse the effect of a VKA over an extended period (i.e., 2–4 weeks) or if the objective is to stop the VKA altogether. This decision should be undertaken in consultation with hematologists, cardiologists, or other clinicians involved in patients' anticoagulant management.

No prospective studies have assessed whether giving vitamin K in VKA-treated patients with acute bleeding affects clinically meaningful outcomes. In a meta-analysis involving nonbleeding patients on a VKA with a supratherapeutic INR, administration of vitamin K was associated with small, nonsignificant increases in mortality (RR = 1.24; 95% CI: 0.62–2.47) and thrombotic events (RR = 1.29; 95% CI: 0.35–4.78) (23). One retrospective case-control study involving patients with VKA-associated bleeding (from both GI and non-GI sites) found vitamin K administration was associated with a significant decrease in mortality (adjusted OR = 0.47; 95% CI: 0.24–0.92). However, this study had significant methodological limitations, including cointerventions that confounded an association between vitamin K administration and clinical outcomes (13).

**Conclusions.** Overall, there is no clinical evidence that vitamin K administration in VKA-treated patients with acute GI bleeding prevents further bleeding or improves mortality or other clinically meaningful outcomes. Moreover, evidence is very weak that giving or not giving vitamin K will affect the risk of thromboembolism, such as stroke or venous thrombosis, presumed to be because of normalization of the INR.

#### Direct thrombin inhibitor reversal

5. For patients on dabigatran who are hospitalized or under observation with acute GI bleeding, we suggest against the administration of idarucizumab (conditional recommendation, very low certainty of evidence).

**Summary of evidence.** The available evidence addressing this recommendation included 1 cohort study that compared idarucizumab with no treatment and 2 additional cohort studies without a comparator. Singh et al. (24) performed a retrospective cohort study in the United States that included patients hospitalized for dabigatran-associated major nontraumatic GI bleeding or intracranial bleeding. Among those with GI bleeding (159 who received idarucizumab vs 1124 who did not), nonsignificant differences in mortality (OR: 1.39, 95% CI: 0.51–3.45) and venous thromboembolism (OR: 0.35, 95% CI: 0.08–1.58) were observed. In the Reversal Effects of Idarucizumab on Active Dabigatran study (25,26), Pollack et al. examined patients on dabigatran with multiple causes of acute bleeding, including GI (45.5%) and other patients on dabigatran about to undergo an urgent surgery or procedure. The reversal of dabigatran anticoagulant effect (before and up to 24 hours after the administration of idarucizumab) was assessed by dabigatran-specific coagulation function tests (dilute thrombin time or ecarin clotting time), and the reduction in the concentration of unbound dabigatran, both indirect measures of the outcome of interest. In a subgroup analysis of 137 patients with GI bleeding (27), Van der Wall et al. reported 30-day mortality and thrombotic event rates of 11.1% and 3.6%, respectively, among patients receiving idarucizumab.

**Conclusions.** Given the limited evidence of benefit and the high cost of idarucizumab, the panel felt it could not recommend routine use of idarucizumab for patients with GI bleeding who have taken dabigatran. However, selective use may be appropriate in patients with a life-threatening GI bleed who have taken dabigatran within the past 24 hours.

#### Reversal of rivaroxaban or apixaban with andexanet alfa

6. For patients on rivaroxaban or apixaban who are hospitalized or under observation with acute GI bleeding, we suggest against andexanet alfa administration (conditional recommendation, very low certainty of evidence).

**Summary of evidence.** Andexanet alfa, or “coagulation factor Xa (recombinant) inactivated-zhzo,” is a modified recombinant human factor Xa decoy protein that binds and sequesters apixaban and rivaroxaban. It also binds and inhibits tissue factor pathway inhibitor and has an elimination half-life of 5 hours (28). In clinical trials, andexanet alfa decreased apixaban activity by 94% and rivaroxaban activity by 92%. It restored thrombin generation in 100% of patients within 2–5 minutes.

A prospective, single-group cohort of 352 patients with major bleeding within 18 hours of factor Xa inhibitor administration (rivaroxaban n = 128, apixaban n = 194, enoxaparin n = 20, or edoxaban n = 10) examined outcomes after giving andexanet alfa. A subgroup (90 patients) suffered an episode of GI bleeding with all contributing to the “safety group,” whereas 62 contributed to the “efficacy group” (those with a baseline anti-Xa activity of at least 75 ng/mL and confirmed major bleeding) (29). Overall, the surrogate marker of median anti-F Xa activity decreased from 149.7 to 11.1 ng/mL (92% reduction; 95% CI: 91–93) in the apixaban group and from 211.8 to 14.2 ng/mL (92% reduction; 95% CI: 88–94) in the rivaroxaban group.

Among the 62 patients with GI bleeding, excellent or good hemostatic efficacy was noted 12 hours after the andexanet alfa infusion in 85% (95% CI: 76–94), although the clinical applicability of the chosen criteria may not reflect contemporary clinical standards in GI bleeding. In addition, methodological limitations included the absence of an intention-to-treat analysis, possible confounding covariates, and insufficient reporting of resuscitative, endoscopic, and pharmacological management. Surprisingly, there was no significant relationship between hemostatic efficacy and a reduction in anti-FXa activity during andexanet alfa treatment. Adverse events were reported only at the whole group level and included thrombotic events and mortality within 30 days in 9.7% of 352 patients and 13.9%, respectively. Infusion-related events at 7 days were noted in 2 patients but not in the 90 patients with GI bleeding.

**Conclusions.** The only published study presents a serious risk of bias because it lacks a control group. Indirectness of the outcomes is also a significant concern because data on patients with GI bleeding are limited, with missing information concerning specific management. Additional methodological limitations include very serious imprecision as event rates are low and the use of surrogate laboratory rather than clinical outcomes. Notably, the cost of using the drug is high (up to \$49,500 at high-dose regimen, with the low-dose regimen costing half as much) (30). Accordingly, the panel could not recommend the routine use of andexanet alfa in patients with GI bleeding. This intervention could be considered in the setting of life-threatening GI bleeding in hospitalized patients who have taken apixaban or rivaroxaban within the past 24 hours.

### Reversal of DOACs with PCC

7. For patients on direct oral anticoagulants who are hospitalized or under observation with acute GI bleeding, we suggest against prothrombin complex concentrate administration (conditional recommendation, very low certainty of evidence).

**Summary of evidence.** The literature search identified only 2 cohort studies with comparator arms (no PCC) (31,32), both of which have limitations. Schulman et al. (31) examined the reversal of dabigatran-associated major bleeding with activated prothrombin concentrate in a small prospective cohort study (N = 14). Among the 5 patients with GI bleeding compared with matched patients (N = 28) from 5 Phase III trials, the “effectiveness” rating was assessed at 24 hours by the treating physicians for GI bleeding. The effectiveness was considered good in 4 patients and moderate in 1, which was not statistically different from the comparator group. Smythe et al. (32) reported that among 28 patients with GI bleeding on dabigatran, 2 received 4-factor PCC, and both (100%) died within 30 days. However, the mortality results were not adjusted for confounding, and the comparator group’s death rate is unknown. Several systematic reviews (33–35) have reported mainly on low-quality, single-arm cohort studies.

**Conclusions.** Given the uncertainty of the available evidence, the panel felt they could not recommend routine use of PCC for patients with GI bleeding who have taken DOACs. However,

selective use may be clinically justifiable in some patients who have taken DOACs within the past 24 hours with a life-threatening GI bleed.

### Reversal of antiplatelet with platelet transfusion

8. For patients on antiplatelet agents who are hospitalized or under observation with acute GI bleeding, we suggest against platelet transfusions (conditional recommendation, very low certainty of evidence).

**Summary of evidence.** ASA and the thienopyridine P2Y<sub>12</sub> receptor inhibitors clopidogrel and prasugrel irreversibly block platelet function for the 7–10-day life span of platelets, whereas ticagrelor is a reversible nonthienopyridine P2Y<sub>12</sub> receptor inhibitor (a cyclopentyltriazolopyrimidine) that impairs platelet function for 3–5 days. For this guideline, we refer most frequently to thienopyridine antiplatelet agents in discussing P2Y<sub>12</sub> receptor inhibitors because the evidence reviewed examined clopidogrel or prasugrel. However, the mechanism of action of the nonthienopyridine P2Y<sub>12</sub> receptor inhibitor, ticagrelor, is similar, permitting reasonable extrapolation of results. Previous guidelines have suggested platelet administration as a therapeutic option in patients on antiplatelet agents with severe GI bleeding (36,37). However, the possibility of thrombotic events with an infusion of functional platelets in patients taking antiplatelet drugs, who are at higher cardiovascular risk, along with potential risks related to the transfusion of blood products, also needs to be considered.

A single fully published study directly relevant to this PICO was identified: a cohort study in patients without thrombocytopenia taking antiplatelet agents and admitted with GI bleeding. This study compared 204 patients who received platelet transfusion with a matched control group of 204 patients who did not. Adjusted analyses revealed a significant increase in mortality (OR = 5.57, 95% CI: 1.52–27.1) and small, nonsignificant increases with platelet transfusion vs no transfusion in further bleeding (OR = 1.47, 95% CI: 0.73–3.05) and thrombotic events (OR = 1.35, 95% CI: 0.74–2.49) (36).

Studies of platelet transfusion in patients for indications other than GI bleeding provide additional indirect evidence. An RCT of 190 patients with intracerebral hemorrhage reported an increase in the primary endpoint of death or dependence (because of significant neurological deficit) with platelet transfusion vs standard care (adjusted OR = 2.05, 95% CI: 1.18–3.56), as well as a small, nonsignificant increase in mortality (RR = 1.38, 95% CI: 0.78–2.44) and a large, nonsignificant increase in thrombotic events (RR = 3.84, 0.44–33.68) with platelet transfusion (38). A retrospective analysis of data from double-blind placebo-controlled RCTs of patients undergoing coronary artery bypass graft surgery reported higher mortality with platelet transfusion on multivariable analysis with propensity scoring (OR = 4.76, 95% CI: 1.65–13.73) (39).

**Conclusions.** Given a possible mortality increase in patients with GI bleed and other medical conditions, and the lack of benefit in decreasing further bleeding in patients with GI bleeding, the panel suggests against platelet transfusion in patients with antiplatelet-related GI bleeding who are not thrombocytopenic.



## Holding ASA vs continuing ASA

9. For patients with GI bleeding on cardiac ASA for secondary cardiovascular prevention, we suggest against holding the ASA (conditional recommendation, very low certainty of evidence).
10. For patients with GI bleeding on ASA for secondary cardiovascular prevention whose ASA was interrupted, we suggest the ASA be resumed on the day hemostasis is endoscopically confirmed (conditional recommendation, very low certainty of evidence).

**Summary of evidence.** Current recommendations suggest that patients with upper GI bleed undergo endoscopy within 24 hours, and in those with a lower GI bleed, diagnostic testing be performed within ~24–36 hours (40–42). In addition, hemostasis generally occurs before endoscopy or, in the minority with active bleeding identified endoscopically, at the time of endoscopy after hemostatic therapy is applied. ASA's pharmacodynamic effect occurs through irreversible inhibition of platelet cyclooxygenase-1, which mediates thromboxane synthesis. After ASA ingestion, thromboxane synthesis normalizes by 7–10 days, although *in vitro* studies suggest 70% of arachidonic acid-mediated platelet function may normalize by 3 days after ASA ingestion (43,44). Therefore, interruption of ASA in patients presenting with GI bleeding will have little impact on the initial clinical course because of the persistent antiplatelet effect of ASA in the first day or 2 after the patient's presentation. Furthermore, the suggestion to resume ASA immediately after hemostasis means that ASA resumption will occur in most cases well before the antiplatelet effect has substantially waned. Thus, the initial interruption of ASA after presentation would not be expected to have much impact on either bleeding or cardiovascular clinical outcomes if ASA is restarted once endoscopic hemostasis is established.

Only 1 study was identified relevant to the PICO regarding interruption vs continuation of ASA when patients present with GI bleeding (GIB); this was a retrospective study in patients hospitalized with acute myocardial infarction who subsequently developed ulcer bleeding during hospitalization (45). This comparison of 64 patients interrupting ASA vs 38 continuing ASA reported similar 30-day rates for both further bleeding and for mortality of 16% (10/64) vs 11% (4/38) (RR = 1.48, 0.50–4.41), respectively. The results for further bleeding are opposite than expected for interruption of ASA (i.e., slightly more bleeding reported with interrupted ASA), although confidence intervals are wide and consistent with benefit or harm. No statistical adjustments were made for potential confounders, limiting the utility of the results. Furthermore, since outcomes were at 30 days, the results may be viewed as primarily relevant to the timing of ASA resumption after bleeding stops.

The most pertinent study relevant to the PICO regarding resumption of ASA after hemostasis is an RCT in patients taking ASA for secondary cardiovascular protection with high-risk ulcer bleeding requiring endoscopic therapy. In this RCT, 156 patients with peptic ulcer bleeding and high-risk endoscopic stigmata treated with successful endoscopic therapy and proton pump inhibitor were randomized to continued low-dose ASA for secondary prevention vs placebo for the 8 weeks of the study (a much longer interruption than

typical in current clinical practice) (46). Recurrent bleeding rates at 30 days were not significantly greater in the ASA group (10.3% vs 5.4%); difference 4.9% (95% CI: –3.6 to 13.4), whereas 8-week mortality attributable to cardiovascular, cerebrovascular, or GI complications was significantly greater in the placebo group (1.3% vs 10.3%; difference 9% [95% CI: 1.7–16.3]). Thrombotic events at 30 days did not differ between groups (3/78 vs 9/78 favoring early ASA resumption, RR = 0.33 [95% CI: 0.09–1.19]) with 6 nonfatal, recurrent acute ischemic events reported (2 in the ASA and 4 in the placebo group). However, the 2-month interruption of ASA in the placebo group imparts serious indirectness of observed outcomes. There also exists very serious imprecision because of very low event rates.

Two additional cohort studies that compared patients who continued ASA after GIB to others who discontinued ASA and did not resume ASA could not be included. In 1, the life-table analysis curves did not permit accurate extraction of results for the first 1–7 days (the relevant timeframe for this recommendation) (47). The second study was unclear when patients along the x axis were on or off ASA (48).

We wish to stress that our recommendations do not apply to patients taking ASA for primary cardiovascular prevention. Recent RCTs suggest little if any benefit of primary prevention for reduction of cardiovascular outcomes despite significant increases in serious GI bleeding (49–51), and current guidelines suggest ASA for primary prevention be considered only in a very limited population and should not be used in those with increased risk of bleeding (52,53).

**Conclusions.** The panel weighed the important and well-documented cardiovascular benefit of secondary preventive ASA therapy and the potential risk of further GI bleeding with continued ASA therapy. The trend to reduced mortality in an observational study of patients with myocardial infarction with continued aspirin (45) coupled to the significant reduction in mortality among patients with high-risk ulcer bleeding who had aspirin resumed immediately after endoscopic hemostasis (46) were important considerations in the panel's decision to recommend continuation rather than an interruption of aspirin therapy. If ASA is discontinued at clinical presentation, we recommend rapid resumption within 24 hours of successful endoscopic hemostasis.

Increased further bleeding with continued ASA at presentation was not shown in the observational study, but results of the RCT did raise the possibility of increased rebleeding with early resumption of ASA in patients with high-risk ulcer bleeding. The panel also weighed the preferences of providers and patients for a cardiovascular event vs a GIB event, as discussed in Supplementary Digital Content (see Appendix 2, <http://links.lww.com/AJG/C417>) in formulating their recommendation.

## Management of antithrombotic agents in the elective endoscopy setting

The 9 remaining statements inform antithrombotic therapy management in patients undergoing scheduled, elective endoscopic procedures. These recommendations exclude patients at high risk of thromboembolic events in whom elective procedures should be deferred. Such high-risk patients include those within 3 months of acute venous thromboembolism (comprising lower-limb deep vein



thrombosis or pulmonary embolism), stroke, or transient ischemic attack (Table 4); and patients within 3 months of acute coronary syndrome (ACS) event, within 6 months of a drug-eluting stent or 1 month of a bare-metal coronary stent placement without ACS history (54); or after ACS event within 12 months of a drug-eluting stent placement or 2 months of bare-metal stent placement (54). Recent data suggest that dual antiplatelet therapy (DAPT) with ASA and P2Y<sub>12</sub> receptor inhibitor can be converted to platelet P2Y<sub>12</sub> receptor inhibitor monotherapy among patients at 3 months or less in patients with a drug-eluting stent placed after ACS event (55,56).

A review of published guidelines highlights the lack of consensus regarding high vs low baseline risk of endoscopic procedures (Table 3) (37,57–59). Procedural bleeding risk and patient-specific thromboembolic risk were empirically framed using the risk stratification endorsed by the International Society on Thrombosis and Haemostasis Guidance Statement (60), the BRIDGE Trial (61), previously published guidelines, and expert opinion (Table 4) (37,57–59,61). A structured and exhaustive GRADE assessment of procedural bleeding risk is beyond the scope of this clinical practice guideline.

Also pertinent to this section are considerations of patient preference. The targeted review performed for this guideline initiative (see Appendix 2, Supplementary Digital Content, <http://links.lww.com/AJG/C417>) demonstrated substantial variability in the threshold number of bleeds observed for oral anticoagulation therapy to be considered acceptable both within individuals and between different studies (62). Furthermore, country-specific differences exist in patients' perceptions of atrial fibrillation, concerns about stroke, and preference for involvement in oral anticoagulation therapy treatment decisions, with recent experience of stroke and GI bleeding both significantly influencing patient values and

preferences (63,64). Indeed, patients placed more weight (more disutility) on stroke prevention than GI bleeding unless they had previously experienced a GI bleed (64). Among the latter, 87% placed the highest utility on rebleeding risk followed by thrombosis risk (64). The panel members concluded that for most PICO, there is possibly significant uncertainty about or variability in how much people value the critical outcomes.

### Anticoagulant interruption vs continuation

11. For patients on warfarin undergoing elective/planned endoscopic GI procedures, we suggest warfarin be continued, as opposed to temporarily interrupted (1–7 days) (conditional recommendation, very low certainty of evidence).

*Summary of evidence.* The published data examining uninterrupted warfarin before endoscopic procedures and associated GI bleeding risk is heterogeneous and methodologically flawed. When formulating our recommendation, we considered 3 cohort studies with a control group (temporary interruption of warfarin) (65–67) and 2 cohort studies without a control group (68,69). These 5 studies provided very low certainty of evidence because of imprecision of the results, lack of adjustment for confounders, lack of standardized procedure technique (e.g., biopsy, cold snare polypectomy, hot snare polypectomy, and routine hemostatic clipping), comparator groups that differ in prognostic factors for bleeding, differences in population, lack of blinding of the endoscopist, and incomplete follow-up.

The desirable anticipated effect with continued warfarin (compared with interrupted warfarin) is reduced thromboembolic events. A single small cohort study without adjustment for confounding factors reported a nonsignificant

**Table 3.** Empiric endoscopic procedural bleeding risk stratification

High bleeding risk procedures (30-d risk of major bleed >2%)	Low/moderate bleeding risk procedures (30-d risk of major bleed ≤2%)
Polypectomy (≥1 cm)	EGD with/without biopsy
PEG/PEJ placement	Colonoscopy with/without biopsy
ERCP with biliary or pancreatic sphincterotomy	Flexible sigmoidoscopy with/without biopsy
EMR/ESD	ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy
EUS-FNA	EUS without FNA
Endoscopic hemostasis (excluding APC)	Push enteroscopy and diagnostic balloon-assisted enteroscopy
Radiofrequency ablation	Enteral stent deployment
POEM	Argon plasma coagulation
Treatment of varices (including variceal band ligation)	Balloon dilation of luminal stenoses
Therapeutic balloon-assisted enteroscopy	Polypectomy (<1 cm)
Tumor ablation	ERCP without biliary or pancreatic sphincterotomy
Cystogastrostomy	Marking (including clipping, electrocoagulation, and tattooing)
Ampullary resection	Video capsule endoscopy
Pneumatic or bougie dilation	
Laser ablation and coagulation	

The sources used for the empiric classification of procedures included the International Society on Thrombosis and Haemostasis Guidance Statement, the BRIDGE trial, previously published guidelines, and expert opinion by the authors.

APC, argon plasma coagulation; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; ERCP, endoscopic retrograde cholangiopancreatography; ESD, endoscopic submucosal dissection; EUS, endoscopic ultrasound; FNA, fine-needle aspirate; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; POEM, peroral endoscopic myotomy.

**Table 4.** Empiric periprocedural thromboembolic risk stratification for patients receiving anticoagulant therapy

Risk stratum	Indication for anticoagulation		
	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High <sup>a</sup>	<ul style="list-style-type: none"> <li>Any mitral valve prosthesis</li> <li>Any caged-ball or tilting disc aortic valve prosthesis</li> <li>Recent (within 3 mo) stroke or transient ischemic attack</li> </ul>	<ul style="list-style-type: none"> <li>CHADS<sub>2</sub> score: 5 or 6</li> <li>CHA<sub>2</sub>DS<sub>2</sub>-VaSc score: ≥7</li> <li>Recent (within 3 mo) stroke or transient ischemic attack</li> <li>Rheumatic valvular heart disease</li> </ul>	<ul style="list-style-type: none"> <li>Recent (within 3 mo) VTE</li> <li>Severe thrombophilia (e.g., deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies, and multiple abnormalities)</li> </ul>
Moderate	<ul style="list-style-type: none"> <li>Bileaflet aortic valve prosthesis and ≥1 of the following: atrial fibrillation, previous stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, and age ≥75 yr</li> </ul>	<ul style="list-style-type: none"> <li>CHADS<sub>2</sub> score: 2–4 (no previous stroke or transient ischemic attack)</li> <li>CHA<sub>2</sub>DS<sub>2</sub>-VaSc score: 5 or 6</li> </ul>	<ul style="list-style-type: none"> <li>VTE within the past 3–12 mo</li> <li>Nonsevere thrombophilia (e.g., heterozygous factor V Leiden or prothrombin gene mutation)</li> <li>Recurrent VTE</li> <li>Active cancer (treated within 6 mo or palliative)</li> </ul>
Low	<ul style="list-style-type: none"> <li>Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke</li> </ul>	<ul style="list-style-type: none"> <li>CHADS<sub>2</sub> score: 0 or 1</li> <li>CHA<sub>2</sub>DS<sub>2</sub>-VaSc score: 1–4</li> </ul>	<ul style="list-style-type: none"> <li>VTE more than 12 mo ago and no other risk factors</li> </ul>

The sources used for the empiric classification of procedures included the International Society on Thrombosis and Haemostasis Guidance Statement, the BRIDGE trial, previously published guidelines, and expert opinion by the authors. VTE, venous thromboembolism.

<sup>a</sup>High-risk patients may also include patients with a previous stroke or transient ischemic attack occurring >3 mo ago and a CHADS<sub>2</sub> score <5, patients with previous thromboembolism during temporary interruption of VKAs, or those patients undergoing certain types of surgery (e.g., cardiac valve replacement, carotid endarterectomy, and major vascular surgery).

reduction with uninterrupted vs interrupted warfarin with 0/43 vs 1/19 thromboembolic events, respectively (RR 0.15; 95% CI: 0.006–3.56) (67).

Our ability to estimate the direction and magnitude of the effect of uninterrupted warfarin (compared with interrupted warfarin) on GI bleeding and mortality using data from the 3 cohort studies with controls (65–67) is limited by small sample size and few events, resulting in extremely wide confidence intervals compatible with considerable benefit and considerable harm. When the continuous warfarin arms from all 5 studies are pooled (65–69), we observe 0/239 bleeding events (95% CI: 0%–12.5%), suggesting a risk of postprocedural bleeding with continuous warfarin as low as 0% and as high as 12.5%.

**Conclusions.** It is impossible to confidently estimate the GI procedural bleeding risk associated with uninterrupted warfarin therapy (vs warfarin interruption), given the limitations of the published literature, heterogeneity of patient populations and procedure type, and imprecision of the results. The absence of studies in advanced endoscopic procedures (with higher baseline bleeding risk), and differences in clinical consequences of luminal and extraluminal bleeding associated with such endoscopic GI procedures, limits our ability to comment on the safety of proceeding without interrupting warfarin. The evolving role of mechanical hemostasis may render some advanced procedures safer with continued warfarin in the future; however, current evidence supporting this strategy is scant.

The planned procedure type (Table 3) and its associated risk of postprocedural bleeding, and the baseline risk of thromboembolism will influence the recommendation, as will resource requirements associated with discontinuation and reinitiation of anticoagulation (e.g., laboratory tests and clinic visits). For patients on warfarin who are undergoing elective and planned outpatient endoscopic GI procedures, we suggest warfarin be continued unless they are undergoing an

advanced endoscopic procedure (Table 3), which may incur a higher risk of procedural bleeding, in which case 5 days of temporary interruption without bridging heparin would be appropriate, as discussed in PICO 12.

- For patients on warfarin, who hold warfarin in the periprocedural period for elective/planned endoscopic GI procedures, we suggest against bridging anticoagulation (conditional recommendation, low certainty of evidence).

**Summary of evidence.** In patients receiving warfarin who require its temporary interruption, heparin bridging, typically with subcutaneous, full-dose low-molecular-weight heparin (LMWH), is sometimes used for 3 days before and 3–5 days after the surgery or procedure. The premise for heparin bridging is that by minimizing the time patients are not therapeutically anticoagulated periprocedurally during warfarin interruption and resumption, the risk of stroke and other thromboembolic events will be reduced. However, heparin bridging may not affect the pathophysiologic pathway that mediates periprocedural stroke and thromboembolism and may place patients at increased risk of procedure-site bleeding, especially if heparin bridging is administered in too close proximity to the time of the procedure (70,71).

Two randomized trials assessed heparin bridging among warfarin-treated patients who required anticoagulant interruption for elective surgery/procedure, including GI procedures. One randomized, double-blind, placebo-controlled trial (BRIDGE) assessed the need for heparin bridging in patients with atrial fibrillation who required temporary warfarin interruption for an elective surgical procedure, including 758 GI procedures (98.7% were minor or low bleeding risk procedures) (72). Excluded from the BRIDGE trial were patients with a very high thrombotic risk (i.e., a mechanical heart valve; stroke, systemic embolism, or transient ischemic attack within the past 12 weeks) or significant risk factors

for major bleeding (i.e., history of a bleeding event within the past 6 weeks; creatinine clearance <30 mL/min; and thrombocytopenia < 100,000 per microliter). Patients with planned cardiac, intracranial, or intraspinal surgeries were also excluded (72).

There were 1,813 patients enrolled in the BRIDGE trial, of whom 918 were allocated to receive bridging with therapeutic-dose LMWH before and after the surgical procedure, and 895 to matching placebo, with a 30-day follow-up period after procedure. Forgoing bridging anticoagulation was noninferior to perioperative bridging with LMWH for the prevention of arterial thromboembolism (0.4% vs 0.3%, respectively, with a risk difference, of 0.1%; 95% CI: -0.6 to 0.8;  $P = 0.01$  for noninferiority) and decreased the risk of major bleeding (1.3% vs 3.2%, respectively,  $P = 0.005$ ) (72).

Another randomized trial of bridging (Postoperative low molecular weight heparin bridging treatment for patients at high risk of arterial thromboembolism [PERIOP-2]) was performed in 1,471 warfarin-treated patients who required an elective surgery or procedure in which all patients received preprocedure LMWH bridging and were randomly allocated to receive bridging, with either a therapeutic-dose or low-dose LMWH regimen (determined by the procedure bleed risk) or no bridging after procedure (73). This study was unique in that it included patients with mechanical heart valve ( $n = 304$ ) in addition to patients with atrial fibrillation ( $n = 1,167$ ). PERIOP-2 was not included in the evidence profile because it had only been published in abstract form. A few weeks after the final panel voting meeting, the PERIOP-2 trial was published as full text showing similar results to the BRIDGE trial (72). Two additional observational studies of lower methodological quality involving only warfarin-treated patients who required an elective GI procedure further suggest that the use of periprocedural heparin bridging increases the risk of postprocedure bleeding (74,75).

**Conclusions.** Overall, evidence is lacking that routine periprocedural heparin bridging during VKA interruption provides a therapeutic benefit to reduce thromboembolism and seems to increase patients' risk of postprocedural bleeding. Periprocedural bridging may be appropriate in the subset of patients with mechanical valves, atrial fibrillation with CHADS<sub>2</sub> score >5, patients with previous thromboembolism during temporary interruption of VKAs, or those patients undergoing certain types of surgery (e.g., cardiac valve replacement, carotid endarterectomy, and major vascular surgery). Consultation with a cardiologist and hematologist is recommended in these high-risk thromboembolic patients.

13. For patients on direct oral anticoagulants (DOACs) who are undergoing elective/planned endoscopic GI procedures, we suggest temporarily interrupting DOACs rather than continuing DOACs (conditional recommendation, very low certainty of evidence).

**Summary of evidence.** No RCTs addressed this clinical question. However, 3 cohort studies with control arms (65,67,76) and 2 cohort studies without control arms (69,77) were used to indirectly estimate the risk of GIB with continuous DOAC anticoagulation (3.6%; 8/224) vs that with temporary interruption (3.1%; 18/578). In the PAUSE

study (77), the incidence of 30-day thrombotic events and mortality was 0.7% and 0.5%, respectively, after DOAC temporary interruption (77).

The absolute risk of increased delayed bleeding with continuous DOAC anticoagulation could not be reliably calculated nor the results reliably pooled, given the zero event rates in one or both arms of comparative studies (65,67,69,76), the unclear denominator for patient numbers (76), and the absence of control arms (69,77). Furthermore, we noted a lack of adjustment for known confounders (65,67,76), limited sample sizes, and low event rates. In addition, there was a diversity of GI procedure types, endoscopic techniques, and protocols for DOAC interruption. These factors contribute to the serious risk of bias, inconsistency, indirectness, and imprecision in estimates, leading to the very low certainty of evidence.

The most informative study was the prospective PAUSE cohort study (77), which provided a standardized protocol for DOAC interruption, complete follow-up, and valid outcome assessment. However, there was no comparator of interest (i.e., uninterrupted anticoagulation). The panel was provided with the raw data for the subgroup of patients undergoing GI procedures enrolled in this cohort study. The calculated GI bleeding incidence rate was 2.5% (95% CI: 1.4%–4.2%), with 35.7% of GI bleeding events considered major bleeding episodes (Jim Douketis, Alan Barkun, written communication, May 15, 2021). The 30-day thromboembolic (0.7%; 95% CI: 0.3%–1.8%) and mortality (0.5%; 95% CI: 0.2%–1.6%) incidence rates were also very low and nonsignificant with temporary DOAC interruption. Of the 556 endoscopic procedures performed, most were colonoscopies, gastroscopies, and flexible sigmoidoscopies with and without biopsy or polypectomy. Before endoscopic procedures, the duration of DOAC interruption was  $2.0 \pm 0.5$  days (including the day before the procedure and the day of the procedure in 91.7%). Only 8.1% of patients undergoing scheduled endoscopic procedures held their DOACs for >2 days before the procedure. DOAC resumption after procedure was  $1.9 \pm 1.5$  days providing endoscopic hemostasis had been achieved, for a total time off DOACs of  $3.9 \pm 1.6$  days in the periendoscopic period (Jim Douketis, Alan Barkun; personal communication).

**Conclusions.** From the limited available data, for patients on DOACs undergoing elective, planned endoscopic GI procedures, we suggest temporary interruption of the DOACs is preferred over continued DOAC administration. The duration of temporary DOAC interruption before endoscopic procedures associated with favorable outcomes is between 1 and 2 days, excluding the day of the procedure, which permits the shortest preprocedural duration of DOAC interruption while balancing bleeding and thromboembolism risk.

As the window of temporary interruption evaluated in this clinical question was 1–5 days before endoscopy, the panel discussed if withholding DOACs for 1–5 days could trigger a prothrombotic state that might result in thrombosis with any subsequent postendoscopic delays in DOAC resumption. It was argued that the prothrombotic risks seem to be more related to the periprocedural milieu (e.g., nature of the intervention such as vascular surgery vs nonvascular surgery and patient characteristics) than the brief interruption of DOACs (78). Furthermore, given the rapid action of onset and half-life



of DOACs, the thrombotic risk of interruption is anticipated to be lower than with interruption of warfarin (61,79).

### Antiplatelet interruption vs continuation

- 14A. For patients on dual antiplatelet therapy for secondary cardiovascular prevention who are undergoing elective endoscopic GI procedures, we suggest temporary interruption of the P2Y<sub>12</sub> inhibitor while continuing ASA (conditional recommendation, very low certainty of evidence).

**Summary of evidence.** The panel considered 2 RCTs and numerous observational studies that examined the temporary interruption of DAPT (stopping the P2Y<sub>12</sub> inhibitor while continuing ASA) in patients undergoing elective endoscopic GI procedures. Chan et al. (80) conducted a double-blinded RCT to examine the bleeding and thrombosis rates among patients treated with either clopidogrel 75 mg or placebo for 7 days before the colonoscopy (N = 387; of which N = 216 had cold snare polypectomy). Of the 387 patients enrolled, 78.5% were on continuous ASA. There were similar rates of immediate and delayed postpolypectomy bleeding and a modest trend toward fewer cardiothromboembolic events with thienopyridine interruption: 1.3% (95% CI: 0.3%–5.0%) of patients receiving placebo vs 2.7% (95% CI: 1.0%–7.0%) in those with continued clopidogrel; RR = 0.47 (95% CI: 0.09–2.55). By contrast, Won et al. (81) reported no thrombotic events with similar bleeding rates among 87 patients randomized to continue DAPT through a scheduled cold snare polypectomy (0/45 with placebo and 1/42 [2.4%] with DAPT).

The numerous observational studies examining periprocedural antiplatelet regimens have been summarized in a systematic review by Eisenberg et al. (82). They assessed the time to late stent thrombosis (occurring between 30 days and 1 year after stent implantation) in patients with drug-eluting stents on DAPT after discontinuing thienopyridine alone or discontinuing both thienopyridine and ASA. However, the absolute risk of stent thrombosis within 10 days when a P2Y<sub>12</sub> inhibitor is discontinued while continuing ASA cannot be calculated because the denominator (patients at risk) is unknown. Nonetheless, among the 94 patients with stent thrombosis after discontinuing a P2Y<sub>12</sub> inhibitor but continuing ASA, only 6 cases (6%) occurred within 10 days, suggesting that late stent thrombosis is a greater problem than immediate stent thrombosis. There were no events reported in the 3–4 days after coronary intervention in this study. We note that this PICO considered only data regarding events occurring in the first 30 days after the intervention.

**Conclusions.** Among patients on DAPT (P2Y<sub>12</sub> inhibitor [clopidogrel, prasugrel, or ticagrelor and ASA 81–325 mg/d]) for secondary cardiovascular prevention, we suggest temporary interruption of the P2Y<sub>12</sub> inhibitor. This recommendation applies only to elective and not emergency procedures.

- 14B. For patients on single antiplatelet therapy with P2Y<sub>12</sub> inhibitor agents who are undergoing elective endoscopic GI procedures, we could not reach a recommendation for or against temporary interruption of the P2Y<sub>12</sub> inhibitor.

**Summary of evidence.** We identified 1 randomized trial and 1 cohort study evaluating patients on P2Y<sub>12</sub> inhibitors undergoing elective endoscopic procedures that compared interruption with the continuation of antithrombotic therapy (80,83). In their study, Chan et al. randomized 216 patients on clopidogrel, with or without concomitant ASA, to continued medication or placebo. The method of polypectomy included cold snare, hot snare, cold biopsy, and hot biopsy without a prophylactic clip or endoscopic loop placement. None of the 46 patients on clopidogrel alone were diagnosed with GIB; however, the study was underpowered to detect a difference in this subgroup (80).

A retrospective cohort study of 1,050 patients on antiplatelet therapy undergoing colonoscopy with hot snare polypectomy and, in most cases, prophylactic clip placement included 37 patients receiving P2Y<sub>12</sub> inhibitors (83). The authors reported that 3 of 18 patients (16.7%, 95% CI: 4.4–42.3) who interrupted P2Y<sub>12</sub> inhibitor therapy developed bleeding compared with none of the 19 patients who continued therapy (RR 7.37, 95% CI: 0.41–133.37). This study was limited by potential confounding because patient factors may have determined whether P2Y<sub>12</sub> inhibitor was interrupted and the behavior of the endoscopist during the colonoscopy. Both studies reported thromboembolic events. There was a single event in the interrupted P2Y<sub>12</sub> inhibitor arm of 38 patients (2.6%, 95% CI: 0.4–17.3) compared with none of the 58 patients continuing therapy (RR 4.54, 95% CI: 0.19–108) (80,83). One study reported 30-day mortality, and there were no deaths in either group (83).

**Conclusions.** Although interruption of a P2Y<sub>12</sub> inhibitor should decrease a patient's risk of bleeding, the available evidence reported a nonsignificant increased bleeding risk in patients who stop a P2Y<sub>12</sub> inhibitor for an elective endoscopic procedure compared with those who continue the medication. This result is biologically implausible and, coupled to the very large confidence intervals, speaks to the very low certainty of evidence. Ultimately, the panel was unable to make a recommendation.

15. For patients on ASA 81–325 mg/d (monotherapy) for secondary cardiovascular prevention, we suggest against interruption of ASA (conditional recommendation, very low certainty of evidence).

**Summary of evidence.** The risk of clinically significant bleeding with diagnostic endoscopic procedures and standard biopsies is so low that the panel agreed that ASA does not need to be held for these procedures (Table 3). A prospective observational study of the risk of clinical bleeding (>2-g/dL hemoglobin drop necessitating endoscopic hemostasis) after endoscopic biopsies revealed bleeding events in 0 of 142 patients continuing ASA and 1 of 61 (1.6%) interrupting ASA (65). Using the ASA arm of an RCT comparing clopidogrel with ASA in healthy volunteers undergoing duodenal and antral biopsies, none of the 280 biopsies on ASA led to bleeding events (84).

The risk of bleeding with polypectomy is higher than biopsies, especially for larger polyps and with the use of cautery rather than a cold snare. A case-control study examined 81 patients with postpolypectomy bleeding matched to 81 patients who had polypectomies without complication. In this

study, 87% of polypectomies were performed with cautery, and 3% of polyps were >10 mm in size (85). ASA use within 3 days before polypectomy exhibited a small, nonsignificant trend to being more common in the bleeding group (40% vs 33%; OR = 1.41, 95% CI: 0.68–3.04). Several factors limit the utility of this study, including the indirectness of the population studied and lack of adjustment for confounding factors. For example, the number of polyps removed was ~2-fold higher in the postpolypectomy bleeding group, which might suggest ASA use was less commonly associated with postpolypectomy bleeding when assessed on a per-polyp rather than per-patient basis. The cases and controls were derived from different databases, and the data are not generalizable to current practice in which most polyps <10 mm are removed with a cold snare. Furthermore, it is not clear that DAPT was excluded. An observational study with information on a control group of 297 patients undergoing 867 polypectomies (mean size of largest polyp 6.5 mm; 29% hot snare, 4% cold snare, and 71% cold forceps) revealed delayed rebleeding in 0 (95% CI: 0%–3%) of the 119 patients on ASA monotherapy (86).

Procedures with the highest bleeding risk include wide-field endoscopic mucosal resection, endoscopic submucosal dissection (ESD), biliary or pancreatic sphincterotomy, and ampullectomy (Table 3). A retrospective study in patients undergoing gastric ESD revealed bleeding in 1 (1.9%) of 53 patients interrupting ASA 7 days before ESD vs 2 (16.7%) of 12 patients continuing ASA (RR 0.11; 95% CI: 0.01–1.15) (87). No RCTs directly relevant to this PICO were identified on our search. Recently, an RCT of 552 patients undergoing gastric ESD was published in abstract form after the final panel voting meeting showing similar results (88). As the study was available only in abstract form, it was not included in the formal evidence report.

Given the extremely limited evidence from studies in GI bleeding, especially on our critical outcome of thrombotic events, we also assessed studies in non-GI procedures to assess the impact of ASA interruption vs continuation on thrombotic events. A meta-analysis of 4 RCTs in patients undergoing noncardiac surgery revealed a nonsignificant increase in thrombotic events (RR = 1.49; 95% CI: 0.56–3.96) with ASA interruption (89–92). Meta-analysis with these 4 RCTs and a 5th RCT (99) revealed a nonsignificant decrease in postprocedural bleeding when ASA is interrupted (RR = 0.81; 95% CI: 0.66–1.01); the panel did not believe that bleeding rates with surgery could be generalized to GI endoscopic procedures.

**Conclusions.** The panel weighed the potential desirable effects (reduction in thrombotic events) and undesirable effects (increased bleeding) of continuing ASA, limited by the availability of only scant, very low certainty evidence. The known important benefit of ASA for secondary cardiovascular prevention and the possible reduction in thrombotic events seen in RCTs of nonendoscopic surgical procedures led the panel to conditionally suggest the continuation of ASA for endoscopic procedures, in general. However, a blanket recommendation cannot be made for all procedures and patients, given that bleeding risk varies markedly among endoscopic procedures, and cardiovascular risk also varies among patients.

The panel felt comfortable that the bleeding risk was very low in diagnostic endoscopic procedures, biopsies, and

most polypectomies. Nevertheless, when removing larger and more complex polyps and other procedures with the highest bleeding risk (e.g., ESD, biliary or pancreatic sphincterotomy, ampullectomy, peroral endoscopic myotomy, and radiofrequency ablation), the panel felt that interruption of ASA could be considered. Such decisions require consideration of other factors such as cardiovascular risk and patient preference regarding cardiovascular vs bleeding events. Patients taking ASA as primary prevention should have ASA stopped before higher-risk endoscopic procedures because the bleeding risk outweighs the minimal cardiovascular benefit.

### *Timing of anticoagulant resumption after endoscopy*

16. In patients who are undergoing elective endoscopic GI procedures whose warfarin was interrupted, we could not reach a recommendation for or against resuming warfarin the same day vs 1–7 days after the procedure.

**Summary of evidence.** The appropriate timing of warfarin resumption after an elective endoscopic procedure is not known. No prospective trials exist comparing different strategies. Three single-arm prospective cohort studies were identified that reported outcomes of interest, grouped by the timing of warfarin resumption. Douketis et al. (93) evaluated 650 consecutive patients who required interruption of warfarin for an invasive procedure, including 5 patients undergoing colonoscopic polypectomy and 65 patients undergoing endoscopy with or without biopsy. All patients resumed warfarin on the procedure day and received standardized LMWH bridging therapy. The endoscopic procedures were analyzed as part of a subgroup of 542 patients undergoing non-high bleeding risk procedures (e.g., cholecystectomy, bowel resection, angiography, and joint replacement). There were 4 (0.74%; 95% CI: 0.20–1.47) cases of major bleeding, none of which were GI bleeding.

Dunn et al. (94) studied 260 patients, including 46 GI invasive procedures, who resumed warfarin the day of their procedure. All patients received a standardized LMWH bridging therapy. One of the 46 patients (2%; 95% CI: 0–13) undergoing colonoscopy was diagnosed with GI bleeding during the follow-up period of 28 days. Paik et al. (95) reported on 96 patients undergoing endoscopic sphincterotomy who interrupted their warfarin therapy before the procedure and, we assume, resumed warfarin on the day of the procedure. Patients received different regimens of bridging therapy with heparin. The study may be further limited in generalizability because of the high rate of biliary stent placement (75% of cases) and precut sphincterotomy (23% of cases). Including the 6 patients excluded for postprocedural bleeding before the resumption of heparin, 11 of 102 patients (11%; 95% CI 6%–19%) had postprocedure bleeding within the 14 days after endoscopic retrograde cholangiopancreatography.

Thromboembolic events were reported in all 3 studies but assessed at different times. There were 2 thromboembolic events in the 542 patients (0.37%; 95% CI: 0.04%–1.32%) undergoing non-high bleeding risk procedures at a median of 13.8 days, including 1 event in a patient undergoing endoscopy (93). Dunn et al. (94) reported 5 thromboembolic events in 260 patients (1.9%; 95% CI: 0.6%–4.4%) within 28 days of their procedure, none occurring in the 46 who underwent GI procedures. Finally, among the 96 patients

undergoing endoscopic sphincterotomy, 3 thromboembolic events (3.4%; 95% CI: 0.7%–8.9%) were diagnosed within the 30 days after procedure (95). Two studies reported mortality, and there were no deaths in either study at 13.8 or 28 days, respectively (93,94).

The lack of a comparator group limited these studies, as did the diversity of the populations studied, the small proportion of patients undergoing endoscopic procedures, the use of bridging therapy, and the outcomes assessment occurring at variable follow-up times. The 2016 American Society for Gastrointestinal Endoscopy clinical practice guidelines (37) recommend resuming warfarin the day of an elective endoscopic procedure while referencing 2 studies lacking valid comparator arms and unclear resumption timing; these studies were excluded from the current evidence profile.

**Conclusions.** We could not find studies comparing same-day resumption of warfarin with resumption in 1–7 days after the temporary interruption of warfarin before an elective endoscopic procedure. Therefore, the panel was unable to make a recommendation. In PICO 11, the panel suggested continuing warfarin in patients undergoing elective endoscopic procedures considered to be at low risk of postprocedural bleeding (Table 3). However, we recognize that there may be a clinical concern of delayed procedural bleeding in a subgroup of patients undergoing advanced endoscopic procedures. In those patients, decisions regarding warfarin resumption should be informed by achieving adequate hemostasis at the time of the procedure, the risk of delayed bleeding associated with the endoscopic procedure performed, the patient's risk of thrombosis, and patient preferences in consultation with a cardiologist and hematologist.

17. In patients who are undergoing elective endoscopic GI procedures whose DOAC was interrupted, we could not reach a recommendation for or against resuming the DOAC on the same day of the procedure vs 1–7 days after the procedure.

**Summary of evidence.** One prospective cohort study was identified that compared the risk of bleeding based on the timing of DOAC resumption but did not compare same day with 1–7 days. Radaelli et al. (96) evaluated 529 patients who interrupted DOAC therapy for an elective endoscopic procedure, including 327 with a low bleeding risk procedure and 202 with a high bleeding risk procedure, with 18 in the latter group receiving LMWH bridging therapy, and were then followed for 30 days. Comparing patients who resumed the DOAC on day 0–3 vs those who resumed the DOAC after day 3, the risk of bleeding was 2.3% and 11.5%, respectively (RR 0.20; 95% CI: 0.08–0.52). The patients receiving LMWH were not reported separately, and this use of bridging anticoagulation may have increased the bleeding risk in patients in whom DOAC was resumed after day 3.

The PAUSE study was a single-arm, prospective cohort study that included 3,007 patients with atrial fibrillation undergoing elective surgery or procedures requiring DOAC interruption (77). The panel was provided the raw data for the subgroup of patients undergoing a GI procedure, as described in PICO 13. All GI procedures were classified as a low bleeding risk in the PAUSE study. The DOAC was resumed at  $1.9 \pm 1.5$  days after

the procedure. Fourteen patients developed GI bleeding after endoscopy (2.5%, 95% CI: 1.4–4.2;  $n = 554$ ) during the 30 days of follow-up after the resumption of DOACs, of which 5 were considered major bleeding episodes (77).

Radaelli et al. (96) reported thromboembolic events in 1 of 477 patients resuming DOACs on day 0–3 and 1 of 52 patients resuming DOACs after day 3 (RR 0.11; 95% CI: 0.01–1.57). Douketis et al. (77) reported an overall rate of thromboembolic events of 21 in the entire cohort of 3,007 (0.7%; 95% CI: 0.45%–1.09%) and 5 in the subgroup of patients undergoing GI endoscopic procedures (0.7%; 95% CI: 0.3%–1.8%). Mortality ranged from 0 in both arms of the Radaelli study to 0.3% (95% CI: 0.15%–0.59%) among all patients in the PAUSE cohort, to 0.5% (95% CI: 0.2%–1.6%) in the *post hoc* analysis of the GI PAUSE data (77,96). Previously published clinical practice guidelines have made informal and formal recommendations regarding DOAC resumption after elective endoscopic procedures; however, none were informed by studies that evaluated the timing of DOAC resumption (37,59,97).

**Conclusions.** We did not identify a study comparing the timing of DOAC resumption proposed in this recommendation. Hence, the panel was unable to make a recommendation. Decisions regarding resumption of DOAC therapy should consider the rapid onset of action, achievement of adequate hemostasis at the time of the procedure, the risk of delayed bleeding for the endoscopic procedure performed, the patient's risk of thrombosis, and patient preferences in consultation with a cardiologist and hematologist.

#### **Timing of P2Y<sub>12</sub> inhibitor resumption after endoscopy**

18. In patients who are undergoing elective endoscopic GI procedures whose P2Y<sub>12</sub> inhibitor was interrupted, we could not reach a recommendation for or against resuming P2Y<sub>12</sub> inhibitor on the same day of the procedure vs 1–7 days after the procedure.

**Summary of evidence.** Theoretically, earlier resumption of P2Y<sub>12</sub> inhibitor monotherapy would tend to reduce thrombotic events and increase postprocedure bleeding. However, we did not identify any studies providing evidence relevant to this PICO. Thus, we cannot estimate the potential thrombotic or bleeding risk and cannot assess the balance between the desirable and undesirable effects of earlier resumption.

Patients on P2Y<sub>12</sub> inhibitor monotherapy are at lower cardiovascular risk than those on DAPT because cardiovascular events are generally more remote in those on monotherapy. For example, US guidelines recommend patients remain on DAPT for at least 12 months after ACS before the transition to antiplatelet monotherapy, with a reduction to monotherapy considered after 6 months in those with high bleeding risk (54). P2Y<sub>12</sub> inhibitor monotherapy can also substitute for ASA monotherapy in those with ASA hypersensitivity or GI intolerance (98,99).

Recent RCTs in patients with percutaneous coronary intervention for ACS have shown that DAPT for 1–3 months followed by P2Y<sub>12</sub> inhibitor monotherapy reduces major bleeding with no increase in cardiovascular events compared with continuation of DAPT for 12–24 months (55,56). Thus, patients now placed on P2Y<sub>12</sub> inhibitor monotherapy may



have higher CV risk (because of more recent ACS), preventing extrapolation of baseline thrombotic risk in patients on ASA monotherapy to those on P2Y<sub>12</sub> inhibitor monotherapy. Similarly, we may not be able to extrapolate bleeding risk with ASA to P2Y<sub>12</sub> inhibitor monotherapy. Although studies have not assessed postendoscopic procedural bleeding risk, a meta-analysis of 5 RCTs revealed a lower risk of GIB in patients taking P2Y<sub>12</sub> inhibitor monotherapy vs ASA monotherapy (OR = 0.59, 0.39–0.89) (100).

## FUTURE DIRECTIONS

The greatest limitation to the panel's ability to provide unequivocal clinical recommendations was the certainty of evidence in the published literature. As highlighted throughout this clinical practice guideline, insufficient high-quality evidence exists in antithrombotic and antiplatelet drug users to evaluate strategies for the temporary interruption, drug reversal, and resumption against a comparator group with great certainty. In addition, we found too few studies focusing on advanced endoscopic procedures to inform our recommendations.

The GRADE approach has clearly defined criteria for grading the certainty of evidence and the strength of recommendations. Accordingly, the certainty of much of the relevant evidence was downgraded mainly because of indirectness, risk of bias, and imprecision. For some clinical questions, we could not make a recommendation for or against the treatment strategy examined, given the very low certainty or absence of evidence comparing a treatment strategy that is now a common clinical practice (e.g., reversal of warfarin with vitamin K) with alternative treatment strategies. For all remaining clinical questions, the recommendations were conditional (rather than strong) because the certainty of the evidence was low or very low, and the criteria for paradigmatic situations as described in the "METHODS" section were not met.

We suggest future studies focus on areas where insufficient evidence currently exists to inform clinical decisions. In particular, the potential benefit of PCC use for reversal of warfarin in the setting of acute GIB, the appropriate timing of resumption of P2Y<sub>12</sub> receptor inhibitors and anticoagulants (VKA and DOACs) after elective endoscopy, and whether it is necessary to interrupt P2Y<sub>12</sub> inhibitor antiplatelet monotherapy before elective endoscopy. There is also a lack of high certainty evidence informing optimal antithrombotic drug management before and after advanced endoscopic procedures.

Future observational studies hoping to influence the management of antithrombotic agents in the periendoscopic period must standardize endoscopic techniques to eliminate confounders for GI bleeding and ensure adequate adjustment for confounders of both GI bleeding and thromboembolism. These studies should ensure the existence of an appropriate comparator group and report results in sufficient detail to allow for inclusion in future meta-analyses. Ideally, double-blinded RCTs with adequate allocation concealment should be undertaken to rigorously examine the questions of temporary interruption, reversal, and postprocedural resumption of antiplatelets and anticoagulants. Standardization of endoscopic techniques will increase the generalizability of RCT

results. Multicenter studies are likely required, given the low event rate of postprocedural bleeding and thrombosis.

Finally, there is a fundamental knowledge gap in the evaluation and characterization of GI endoscopic procedural bleeding risk groups. The current estimation of procedural bleeding risk is highly inconsistent, derived from studies with a serious risk of bias. A rigorous evaluation of procedural bleeding risk with the GRADE approach will clarify and improve the classification of endoscopic procedures and highlight knowledge gaps.

## CONFLICTS OF INTEREST

Guarantors of the article: Neena S. Abraham and Alan N. Barkun.

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