**Appendix 3. Excluded papers with reasons**

This appendix explains the specific reason for excluding any studies/papers that a reader might plausibly expect to see among the included studies. This list includes studies that seem to be eligible for inclusion on the surface but are not on closer inspection. It also includes landmark studies that are well known to readers but did not meet the inclusion criteria.

1. Siau et al. Stopping antithrombotic therapy after acute upper gastrointestinal bleeding is associated with reduced survival. Postgraduate Medical Journal. 94 (1109) (pp 137-142), 2018.
   * Assessed whether restarting (**vs. permanently discontinuing**) antithrombotic therapy, **at hospital discharge** for AUGIB, affected clinical outcomes
   * Reported separate results for cardiac aspirin only
2. Qureshi et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. American Journal of Cardiology. 113 (4) (pp 662-668), 2014
   * Assessed whether restarting (vs. permanently discontinuing) antithrombotic therapy after acute GIB, affected clinical outcomes
   * Stratified analysis by duration of interruption of warfarin was also performed but the shortest duration window was “less than 7 days”.
   * Useful for the discussion (detailed results), but does not provide evidence for any of the PICOs chosen for this guideline
3. Khalid F et al. Impact of restarting warfarin therapy in renal disease anticoagulated patients with gastrointestinal hemorrhage. Renal Failure. 35 (9) (pp 1228-1235), 2013.
   * Assessed whether restarting (vs. permanently discontinuing) warfarin therapy after acute GIB in renal disease patients, affected clinical outcomes
4. Garcia D.A. et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Archives of Internal Medicine. 168 (1) (pp 63-69), 2008.
   * Prospective cohort: out of 1024 patients, 272 had colonoscopy, and a few (?) had EGD
   * Suspected selection bias (each of the 101 US centers recruited about 10 patients on average over 23 months - this must have been only a small fraction of the patients who interrupted warfarin for procedures)
   * Apparently small proportion of high risk for VTE patients; CHADS2 not reported
   * Not eligible for PICO 12 (heparin bridging vs not, when warfarin is held for GI procedures), but we were unable to extract separate data for GI procedures.
   * Not eligible for PICO 14 (timing of resumption after warfarin interruption for GI procedures). There are no data on the timing of warfarin resumption after the procedure.
5. Masic et al. Pharmacist Presence Decreases Time to Prothrombin Complex Concentrate in Emergency Department Patients with Life-Threatening Bleeding and Urgent Procedures. Journal of Emergency Medicine. 57 (5) (pp 620-628), 2019
   * The aim was to assess if pharmacist presence is predictive of faster time to 4F-PCC
   * 32 patients had bleeding other than intracranial, but there was no mention of GI bleeding in the results (although GI bleeding was listed as keyword)
6. Eikelboom et al. Dabigatran Reversal With Idarucizumab in Patients With Renal Impairment. Journal of the American College of Cardiology. 74 (14) (pp 1760-1768), 2019.
   * The aim was to assess outcomes according to baseline renal function in dabigatran-treated non-dialysis patients receiving idarucizumab
   * 137 (46%) of the Group A patients (“overt, uncontrolled, or life-threatening bleeding”) had GI bleeding, but there were no separate results for them
7. Hunt et al. Urgent Reversal of Vitamin K Antagonists. BMJ 2018 Jan 4;360:j5424. doi: 10.1136/bmj.j5424. 
   * Narrative review
8. Barton et al. Protocolized warfarin reversal with 4-factor prothrombin complex concentrate versus 3-factor prothrombin complex concentrate with recombinant factor VIIa. American Journal of Surgery. 215 (5) (pp 775-779), 2018.
   * 7 patients with GIB: no separate results
9. Sartori et al. Andexanet alfa to reverse the anticoagulant activity of factor XA inhibitors: A review of design, development and potential place in therapy. Journal of Thrombosis and Thrombolysis. 45 (3) (pp 345-352), 2018
   * Narrative review
10. Brekelmans et al. Clinical outcome of patients with a vitamin K antagonist-associated bleeding treated with prothrombin complex concentrate. Research and Practice in Thrombosis and Haemostasis. 2 (1) (pp 77-84), 2018.
    * N=36 (36%) patients with GIB: no separate results
11. Subramaniam et al. Red Blood Cell Transfusion Is Associated With Further Bleeding and Fresh-Frozen Plasma With Mortality in Nonvariceal Upper Gastrointestinal Bleeding. Transfusion. 2016 Apr;56(4):816-26.
    * No results of relevance to the PICOs were reported separately for patients on warfarin
12. Dibu et al. The Role of FEIBA in Reversing Novel Oral Anticoagulants in Intracerebral Hemorrhage. Neurocritical Care. 24 (3) (pp 413-419), 2016
    * All patients had Intracerebral Hemorrhage
13. Jones et al. 3-Factor Versus 4-Factor Prothrombin Complex Concentrate for Warfarin Reversal in Severe Bleeding: A Multicenter, Retrospective, Propensity-Matched Pilot Study. Journal of Thrombosis and Thrombolysis. 42 (1) (pp 19-26), 2016
    * 3-Factor vs 4-Factor PCC. This comparison does not fit any of the PICOs of this guideline
    * 2 vs 2 patients with GIB, but no separate results
14. Barton et al. Risk of thromboembolic events after protocolized warfarin reversal with 3-factor PCC and factor VIIa. American Journal of Emergency Medicine. 33 (11) (pp 1562-1566), 2015.
    * Compared outcomes before and after implementation of a warfarin reversal protocol
    * Included 21 + 5 patients with GIB, but did not report separate outcomes

1. Tazarourte et al. Guideline-concordant administration of prothrombin complex concentrate and vitamin K is associated with decreased mortality in patients with severe bleeding under vitamin K antagonist treatment (EPAHK study). Critical Care. 18 (2) (no pagination), 2014 
   * Included 264 patients with GIB, but without separate outcomes
   * No comparator cohort
2. Hickey et al. Outcomes of urgent warfarin reversal with frozen plasma versus prothrombin complex concentrate in the emergency department. Circulation. 128 (4) (pp 360-364), 2013
   * Included 15 vs 12 patients with GIB, but without separate outcomes

1. Voils et al. Systematic review: 3-factor versus 4-factor prothrombin complex concentrate for warfarin reversal: Does it matter? Thrombosis Research. 130 (6) (pp 833-840), 2012 
   * 3-factor vs 4-factor PCC
   * Unclear if there were separate results for GIB
   * There were no direct comparisons of 3-factor and 4-factor PCCs in any study
2. Desmettre et al. Reversal of Vitamin K Antagonist (VKA) effect in patients with severe bleeding: a French multicenter observational study (Optiplex) assessing the use of Prothrombin Complex Concentrate (PCC) in current clinical practice. Critical Care. 16 (5) (no pagination), 2012.
   * Included 264 patients with GIB, but without clinical outcomes

1. Dara et al. Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. Critical Care Medicine. 33 (11) (pp 2667-2671), 2005
   * Included patients with coagulopathy (INR of >=1.5) but without active bleeding
2. Causada-Calo et al. Proton-pump inhibitors for the prevention of upper gastrointestinal bleeding in adults receiving antithrombotic therapy. Cochrane Database of Systematic Reviews. 8, 2019. Protocol.
   * Does not relate to our PICOs
3. Goldstein et al. “Four factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, noninferiority, randomised trial,” The Lancet, vol. 385, no. 9982, pp. 2077–2087, 2015.
   * Did not mention any patients with GI bleeding and/or undergoing GI endoscopy
   * Note: both groups received vit K too.
   * Given that it is an RCT it could be included as indirect evidence (indirectness with regards to the study population), but we have not done a systematic search for non-GI papers.
4. Shaw JR, Siegal DM. Pharmacological reversal of the direct oral anticoagulants-A comprehensive review of the literature. Res Pract Thromb Haemost. 2018;2(2):251–265.
   * Narrative review
5. Thiele T, Sümnig A, Hron G, Müller C, Althaus K, Schroeder HW, Greinacher A. Platelet transfusion for reversal of dual antiplatelet therapy in patients requiring urgent surgery: a pilot study. J Thromb Haemost. 2012 May;10(5):968-71.
   * No patients with GIB or GI endoscopy
6. Thiele T, Greinacher A. Platelet Transfusion in Perioperative Medicine. Semin Thromb Hemost. 2020 Feb;46(1):50-61.
   * Narrative review
7. Biondi-Zoccai et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50 279 patients at risk for coronary artery disease. Eur Heart J. 2006 Nov;27(22):2667-74.
   * A SRMA on the hazards of discontinuing or not adhering to aspirin among patients at risk for CAD.
   * One study focused on adherence to aspirin therapy in the secondary prevention of CAD, two studies on aspirin discontinuation in acute CAD, two studies on adherence to aspirin therapy before or shortly after coronary artery bypass grafting, and another on aspirin discontinuation among patients undergoing drug-eluting stenting
   * Did not include patients with GIB or undergoing GI endoscopy
   * Could be used in the discussion, as indirect evidence
8. Kar et al. Hepatic coagulopathy-intricacies and challenges; A cross-sectional descriptive study of 110 patients from a superspecialty institute in North India with review of literature. Blood Coagulation and Fibrinolysis. 24 (2) (pp 175-180), 2013.
   * All patients had hepatic coagulopathy
   * This is not a study on patients on antithrombotic medications
9. Healey et al. Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin. Results From the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial. Circulation 2012.
   * This is an RCT. It could theoretically provide cohort type data for our PICOs. However, it did not report separate results for patients who underwent GI procedures (= colonoscopy 8.6%) or for the outcome of GI bleeding.
   * Not clear what interventions (e.g. polypectomy) were performed during colonoscopy.
   * About 20% of patients were bridged, 2.2% had vit K and 1.5% had FFP- no separate results
   * So, in the end, for our PICOs, these are observational type data without separate GI results
10. Sherwood et al. Gastrointestinal Bleeding in Patients With Atrial Fibrillation Treated With Rivaroxaban or Warfarin: ROCKET AF trial. JACC 2015
    * Compared ribaroxaban vs warfarin
    * Does not relate to any of our PICOs, not even as cohort-type data
    * I could be mentioned in the intro, or discussion if we want to refer to comparisons between the two drugs
11. Blacker et al. Stroke risk in anticoagulated patients with atrial fibrillation undergoing endoscopy. Neurology 2003
    * Retrospective cohort study
    * Compared stoke risk among various groups of patients with AF on anticoagulation undergoing endoscopy (most of them had GI endoscopies). Some patients had periprocedural “adjustment” of the anticoagulation (but without explanation of what this meant)
    * Does not report separate data for patients who had GI procedures
    * Does not report bleeding outcomes
12. Steinberg et al. Use and Outcomes Associated With Bridging During Anticoagulation Interruptions in Patients With Atrial Fibrillation. Findings From the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). Circulation. 2015 Feb 3;131(5):488-94.
    * Cohort study: Compared bridging vs no bridging.
    * Endoscopy was 18% of the procedures, but did not report separate data.
13. Douketis et al. Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure. Substudy of the RE-LY trial. Thromb Haemost 2015
    * Cohort type data from an RCT
    * According to previous publications, a small proportion of patients had colonoscopies, but the proportion is not mentioned in this paper
    * No separate results for GI procedures
14. Pohl et al. Clip Closure Prevents Bleeding After Endoscopic Resection of Large Colon Polyps in a Randomized Trial. Gastroenterology 2019 Oct;157(4):977-984.e3
    * The randomization refers to the use or no use of clips, therefore the question is if it reports cohort-type data for any of our PICO questions
    * No separate data are reported that relate to any of our PICOs.
    * Reported that “the effect of clip closure was independent of antithrombotic medications”, but this does not relate to any PICO of ours
    * The stratified analysis according to antithrombotic use or not, does not inform any of our PICOs either
15. Albeniz et al. Clip Closure After Resection of Large Colorectal Lesions With Substantial Risk of Bleeding. Gastroenterology. 2019 Nov;157(5):1213-1221.e4.
    * The randomization refers to the use or no use of clips, therefore the question is if it reports cohort-type data for any of our PICO questions
    * No separate data are reported that relate to any of our PICOs.
    * The stratified analysis according to antiplatelet use or not (suppl table 2), does not inform any of our PICOs either
16. Ikarashi S, Katanuma A, Kin T, Takahashi K, Yane K, Sano I, Yamazaki H, Maguchi H (2017) Factors associated with delayed hemorrhage after endoscopic sphincterotomy: Japanese large single-center experience. J Gastroenterol 52(12):1258–1265
    * Assessed whether heparin bridging vs no use of heparin bridging was associated with higher risk of post- sphincterotomy bleeding, but most, if not all of the patients that did not receive heparin bridging were not taking anticoagulants
17. Chai-Adisaksopha et al. Mortality outcomes in patients receiving direct oral anticoagulants: A systematic review and meta-analysis of randomized controlled trials. Journal of Thrombosis and Haemostasis. 13 (11) (pp 2012-2020), 2015.
    * Not eligible for any PICO (the comparison of warfarin vs DOACs was not included in any of the PICOs in this guideline)
18. Chai-Adisaksopha et al. Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding. Thromb Haemost 2015; 114: 819–825
    * Considered for PICO#16 (Resumption of warfarin after endoscopic procedures: on the same day of the procedure vs 1-7 days after the procedure)
    * SRMA of 3 observational studies at high risk of bias
    * Very serious indirectness because:
      + the intervention/comparator (permanent discontinuation of warfarin vs delayed resumption) are not the ones needed for this PICO
        - * In the group where warfarin was resumed, the resumption was delayed - it was not immediate resumption: the median (IQR) of the duration of withholding warfarin was 50.0 (21.0–78.0) days and 4.0 (2.0 -9.0) days respectively in two studies, unclear in the 3rd study. The results were driven by the former 2 studies (with the documented delayed resumption) that had 65% to 95% of the weight in the meta-analyses. Also, a fixed effect model was incorrectly used in the meta-analyses for re-bleeding and mortality (despite substantial heterogeneity) – if we use the appropriate random effects model, the statistical significance is lost for all outcomes: the statistically significant effect on thromboembolism becomes non-significant (HR 0.41, 95% CI 0.10 to 1.67), and the statistically significant effect on mortality also becomes non-significant (HR 0.68, 95% CI 0.41 to 1.12). The effect on re-bleeding remains non-significant.

* + - * + Therefore, none of these studies compared immediate (on the same day) resumption vs. resumption within 1-7 days
    - The population (patients who had GI bleeding) is different from the population of interest for this PICO (patients undergoing endoscopy).
      * + Results on bleeding are not relevant to this PICO, due to the different baseline risks and mechanisms of bleeding compared to this PICO
        + Results on thromboembolism and mortality are not relevant to this PICO, because of different baseline risks compared to this PICO
  + For all the above reasons:
    - it is impossible to extract estimates on the relative effect (relative risk) of the intervention vs comparator for this PICO
    - also, it is impossible to extract non-comparative data regarding the event rates for either the intervention or the comparator for this PICO (i.e., we cannot estimate “baseline risk” for our PICO from this study)

1. Timothy SK, Hicks TC, Opelka FG, et al. Colonoscopy in the patient requiring anticoagulation. Dis Colon Rectum 2001;44:1845-8
   * See Evidence Profile #16 for reasons for exclusion
2. Sawhney MS, Salfiti N, Nelson DB, et al. Risk factors for severe delayed postpolypectomy bleeding. Endoscopy 2008;40:115-9
   * See Evidence Profile #16 for reasons for exclusion
3. Tinker JH, Tarhan S. Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses. Observations in 180 operations. JAMA. 1978;239:738–9.
   * See Evidence Profile #16 for reasons for exclusion
4. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med. 1997;336:1506–11.
   * See Evidence Profile #16 for reasons for exclusion
5. Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin: assessment of a standardized periprocedural anticoagulation regimen. Arch Intern Med. 2004; 164 (12):1319-1326
   * Included only for feasibility outcomes
   * See Evidence Profile #16 for reasons for exclusion regarding efficacy/safety outcomes
6. Kovacs MJ, Kearon C, Rodger M, et al. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. Circulation. 2004; 110 ( 12 ): 1658 - 1663.
   * See Evidence Profile #16 for reasons for exclusion
7. Spyropoulos AC, Turpie AG, Dunn AS, et al; REGIMEN Investigators. Clinical outcomes with unfractionated heparin or low-molecular-weight heparin as bridging therapy in patients on long-term oral anticoagulants: the REGIMEN registry. J Thromb Haemost. 2006; 4 ( 6 ): 1246 - 1252 .
   * See Evidence Profile #16 for reasons for exclusion
8. Little et al. Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: A systematic review and meta-analysis. Thromb Res 2019;175:102-109.
   * Included 12 observational studies.
   * 11/12 studies were at high risk of bias due to confounding. The resumption or not of anticoagulation was not done by chance: the characteristics of the patients and their comorbidities as well as the severity of the GI bleed, risk of rebleeding and risk of death in case of rebleed, would be confounders because they would affect both the decision to resume anticoagulation and the outcomes in these patients.
   * Critically serious indirectness for PICO#16 or PICO#17 (timing of resumption of OAC after a GI procedure: on the same day vs at 1-7 days)
     1. These studies included patients who discontinued anticoagulation because of a GI bleed
     2. They reported results according to resumption (of note the delay was long: median delay ranged in studies from 1 day to 50 days) vs non-resumption. No data on day 0 vs day 1-7 resumption.
     3. Mixed population of warfarin (majority) and DOACs (minority) users
9. Schulman S, Carrier M, Lee AY, et al; Periop Dabigatran Study Group. Perioperative management of dabigatran: a prospective cohort study. Circulation. 2015;132(3):167-173.
   * Considered for PICO#17 (timing of resumption of NOAC after a GI procedure: on the same day vs at 1-7 days).
   * No comparator arm.
   * Included 118 patients who had “endoscopy or bronchoscopy” out of 541 patients.
   * No separate results for endoscopy
   * No further description of endoscopy, although it was noted that “high-risk endoscopy was typically combined with polyp removal or multiple biopsies”
10. Hussain N, Alsulaiman R, Burtin P, Toubouti Y, Rahme E, Boivin JF, Barkun AN (2007) The safety of endoscopic sphincterotomy in patients receiving antiplatelet agents: a case-control study. Aliment Pharmacol Ther 25:579–58
    * Considered for PICO#18 (timing of resumption of thienopyridine after a GI procedure: on the same day vs at 1-7 days) and PICOs 14 and 14.B (temporary interruption of thienopyridine agents)
    * Case-control study
    * No data on timing of resumption (not eligible for PICO#18)
    * No data on whether any patient was on thienopyridine agents and interrupted the agents for the procedure – no comparison of patients who interrupted vs those who did not interrupt (not eligible for PICOs #14 and #14.5).
11. Komatsu T, et al. Study for determination of the optimal cessation period of therapy with anti-platelet agents prior to invasive endoscopic procedures. J Gastroenterol 2005; 40: 698-707.
    * Considered for PICO#18 (timing of resumption of thienopyridine after a GI procedure: on the same day vs at 1-7 days)
    * No data on timing of resumption
12. Ket S, Metz A, Moss A, Ogra R, Tam W, Secomb R, Reynolds J, Gibson PR, Brown G. Study design of endoscopic polypectomy on clopidogrel (EPOC): a randomised controlled trial. Contemporary clinical trials communications. Vol.16, 2019.
    * Protocol of ongoing trial
    * The EPOC trial will examine whether continuation of antiplatelet therapy (clopidogrel, prasugrel or ticagrelor) as single or dual therapy with aspirin, is inferior or superior to temporary interruption of antiplatelet therapy, current standard of care, with regard to the use of endoscopic rescue clips or clinically significant post-polypectomy bleeding after cold snare polypectomy of polyps ≤10 mm
13. Gandhi et al. Meta-analysis: colonoscopic post-polypectomy bleeding in patients on continued clopidogrel therapy. Aliment Pharmacol Ther 2013; 37: 947–952
    * Included 5 cohort studies
    * Search done in 2013
    * Only bleeding outcomes
    * Considered for PICOs 14 and 14b
    * Excluded because the comparator was patients who were never on clopidogrel (we need patients who discontinue clopidogrel). Patients never on clopidogrel are a different population and, furthermore, there would be differences in performance of polypectomy and in detection of complications
14. Tounou S., Morita Y., Hosono T. Continuous aspirin use does not increase post-endoscopic dissection bleeding risk for gastric neoplasms in patients on antiplatelet therapy. Endoscopy International Open. 3 (1) (pp E31-E38), 2015.
    * Population: N = 350 patients undergoing gastric ESD
    * Intervention: n = 58 patients on antiplatelet treatment (APT; 53 patients on LDA and 5 patients on a thienopyridine)
    * n = 31 patients on DAPT
    * Comparator: n = 261 patients not on any APT
    * Outcome: Post-ESD bleeding occurred in 16 of 261 patients in the no APT group (6.1 %), 9 of 58 patients in the single APT group (15.5 %), and 11 of 31 patients in the DAPT group (35.5 %).
    * Considered for PICO 14 and 14b
    * Excluded because there is no comparator group relevant to these PICOs (we would need a group that did not discontinue thienopyridine)
15. Matsumoto et al. Safety of Cold Polypectomy for Colorectal Polyps in Patients on Antithrombotic Medication. Digestion. 97 (1) (pp 76-81), 2018
    * PICOs 14, 15
    * Population: N = 1003 patients (N = 2466 polyps) undergoing cold polypectomy (CP)
    * Intervention: n = 186 patients (n = 549 polyps) on antithrombotic medications
    * Comparator: n = 817 patients (n = 1917 polyps) not on any antithormbotic medications
    * Outcome:
    * PPB occurred in 3/549 polyps (0.55%) in patients who were on antithrombotics (1 ASA user with 1 polyp and 1 ASA + clopidogrel user with 2 polyps) and in 2/1917 polyps (0.10%) in patients not on antithrombotics
    * Excluded: Table 3b describes the 4 bleeders, but it is impossible to calculate the denominators for the comparators: we don’t know how any users of specific antithrombotic agents had interrupted treatment
16. Kono et al. Postoperative bleeding risk after gastric endoscopic submucosal dissection during antithrombotic drug therapy. Journal of Gastroenterology and Hepatology. 33 (2) (pp 453-460), 2018.
    * Assessed for PICO 11, 12, 13, 14, 14B, 15
    * Case-control study
    * Population: N = 872 patients treated by ESD
    * Zero thromboembolic events in all groups.
    * Unable to extract data for the “clean” comparator groups that are required for our PICOs (mainly because it is a case control study and denominators cannot be calculated)
    * Even for the zero-event comparisons for thromboembolic events, no data can be extracted for any of the PICOs required for this guideline
17. Li et al. Colonoscopic post-polypectomy bleeding in patients on uninterrupted clopidogrel therapy: A systematic review and meta-analysis. Exp Ther Med. 2020 May;19(5):3211-3218.
    * SR with critically severe methodological limitations (one of the two “RCTs” (Feagins CGH 2013) is a cohort study not an RCT but study, RCTs and observational studies were pooled together, the x-axis in the forest plot is inverted, RR was extracted from case-control studies, adjusted data were ignored, risk of bias assessments are seriously wrong). We assessed the individual included studies ourselves, but none was eligible (with the exception of Chan 2019, which we had already included)
      1. Feagins CGH 2013 is not an RCT as the authors of the systematic review stated. It is a prospective cohort study, that compared patients who did not discontinue thienopyridine for more than 2 days, vs. those who were not taking thienopyridines at all. Some patients were on ASA. Not eligible for PICO 14 or 14b.
      2. Feagins DDS 2011: retrospective cohort study (not a case-control study as its own authors and the SR authors stated). Compared patients who did not discontinue thienopyridine vs. those who were not taking thienopyridines at all.
      3. Grossman GEI 2010: abstract publication. Case-control study. Compared clopidogrel use vs non-use.
      4. Singh GIE: retrospective cohort study (not a case-control study as the SR authors stated). Compared patients who did not discontinue thienopyridine vs. those who were not taking thienopyridines at all.
      5. Chan Gastro 2019: we have included this RCT already
18. Shibuya et al. Continuation of antithrombotic therapy may be associated with a high incidence of colonic post-polypectomy bleeding. Digestive Endoscopy. 29(3):314-321, 2017.
    * Considered for several PICOs, but it is impossible to extract 2x2 data for events/non-events in patients with continued vs interrupted specific antithrombotic agents (i.e., with clean denominators). See 1st column of Table 5
19. Fujita et al. Safety of gastrointestinal endoscopic biopsy in patients taking antithrombotics. Digestive Endoscopy. 27(1):25-9, 2015.
    * Note: provides additional results for other PICOs too
    * Indirectness: intervention limited to endoscopic biopsies; excluded emergency endoscopy and therapeutic endoscopy; excluded patients with cessation of antithrombotics prior to endoscopy and/or heparin bridge therapy
    * n= 28 on **thienopyridine**; events (bleeding): 0/28
    * **Comparator (indirect): 3671 patients undergoing diagnostic endoscopy without antithrombotics**
    * No direct comparator of patients who interrupted thienopyridine

1. Namasivayam et al. The risk of endoscopic mucosal resection in the setting of clopidogrel use. ISRN Gastro 2014
   * Indirectness: intervention limited to esophageal EMR
   * EMRs (not patients) with recent clopidogrel alone = 17; bleeding =0, Ischemic events = 0
   * Unclear if **all** 17 EMRs were done after temporarily interruption of clopidogrel
   * **Comparator (indirect): 922 EMRs on patients who were not on anticoagulant or antiplatelet**
   * No direct comparator of patients who interrupted thienopyridine
2. Khubchandan et al. Optimal timing of anticoagulation pre-and post-colonoscopy with polypectomy. Techniques in Coloproctology 2011.
   * Note: additional results for other PICOs
   * Indirectness: intervention limited to colonic polypectomy
   * n= 17 on temporary interrupted **clopidogrel**. Events (bleeding): 1
   * No comparator of continued clopidogrel
3. Lee et al. Effect of sustained use of platelet aggregation inhibitors on post-endoscopic sphincterotomy bleeding. Digestive Endoscopy. 26 (6) (pp 737-744), 2014
   * Note: provides (indirect) results for PICO 14.B too
   * Indirectness: intervention limited to ERCP sphincterotomy; most results include both elective and urgent ERCPs
   * Did not report results stratified by antiplatelet agent (results for all agents are pooled together)
     1. **“Continued”** antiplatelet treatment = 132 (this includes 49 sustained users and 83 “non-sustained users” in whom therapy was interrupted <7 days prior to the procedure)
     2. **Interrupted** antiplatelet treatment = 29
4. Feagins et al. Low rate of postpolypectomy bleeding among patients who continue thienopyridine therapy during colonoscopy. Clinical Gastroenterology and Hepatology. 11 (10) (pp 1325-1332), 2013.

Population: N = 516 patients on thienopyridines undergoing elective colonoscopies

Intervention: n = 219 patients were receiving thienopyridines

Comparator: n = 297 patients were not

The comparator were patients who were not on thienopyridines

1. Feagins et al. The rate of post-polypectomy bleeding for patients on uninterrupted clopidogrel therapy during elective colonoscopy is acceptably low. Digestive Diseases and Sciences. 56 (9) (pp 2631-2638), 2011

**Population:** N = 1967 patients undergoing colonoscopic polypectomy

**Intervention:** n = 118 patients on clopidogrel

**Comparator:** n = 1849 patients not on clopidogrel

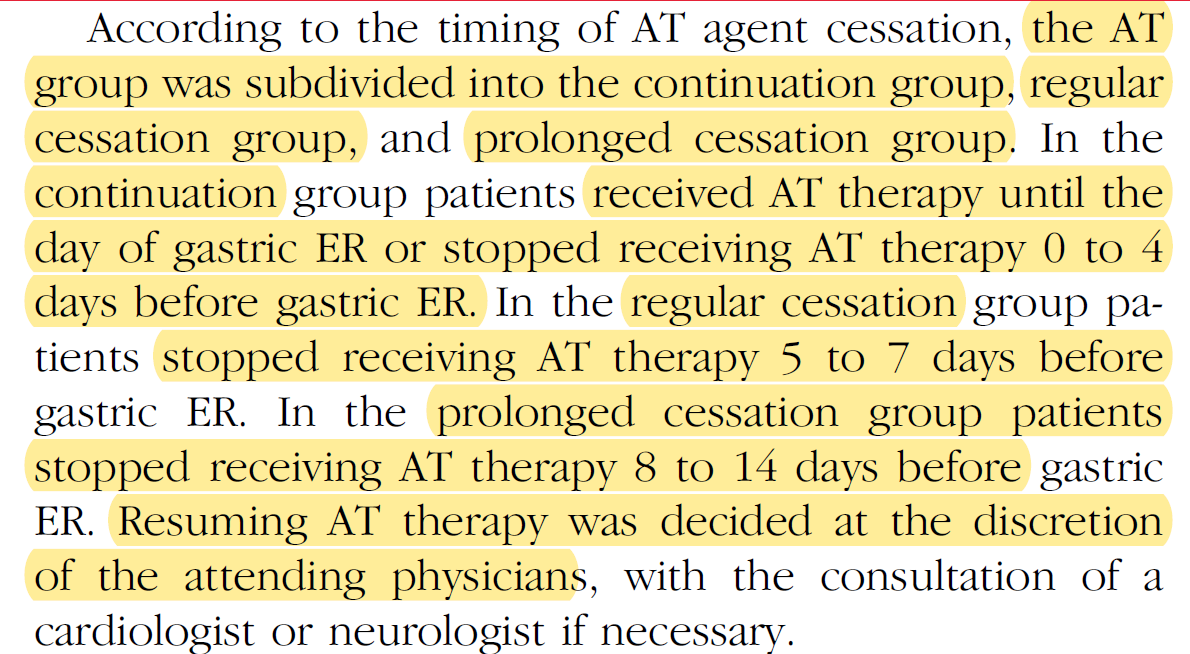
The comparator were patients who were not on thienopyridines

1. Friedland et al. Colonoscopy with Polypectomy in Patients Taking Clopidogrel. Gastroenterology Research. 2(4):209-212, 2009

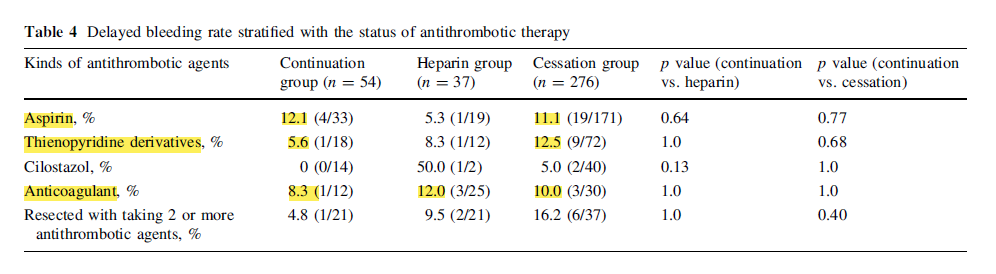
**Population**: N = 60 patients undergoing polypectomy

**Intervention:** n = 60 patients on clopidogrel, of which n = 10 were on DAPT with ASA

**Comparator:** No comparator group

1. So et al. Comparison of the effects of antithrombotic therapy on delayed bleeding after gastric endoscopic resection: a propensity score-matched case-control study. Gastrointestinal Endoscopy. 89 (2) (pp 277-285.e2), 2019.
   * Indirectness (population): intervention limited to endoscopic resection of gastric neoplasms
   * Indirectness: reported results
     1. according to patients being or not being on antithrombotic agents (all anticoagulants and all antiplatelets lumped together);
     2. by “continuation” (note: this also includes interruption 4 or less days prior to the procedure) vs. “regular cessation” vs. “prolonged cessation” with all antithrombotic agents lumped together. These categories are shown here:  
        
     3. by type of antithrombotic agent (still too broad categories) but without stratifying patients according to continuation or interruption (see suppl Table 3)
   * The most direct analyses (without stratifying patients according to continuation or interruption):
     1. Suppl Table 3: **“one antiplatelet”** group (n= 281) vs. propensity score matched control, not on antithrombotics
     2. Suppl Table 3: **“two antiplatelet”** group (n= 57) vs. propensity score matched control, not on antithrombotics
     3. Last paragraph in Results: “Comparison of the DB rate according to the type of AT agent”: **Thienopyridines** (n=48) vs controls (8.3% vs 4.2%; P = 0.328). Also results for ASA. But the comparator is patients who had not been on AT.
   * Overall, no comparative results (with clean comparators) can be extracted for any PICO for our guideline
2. Sorbi D, Norton I, Conio M, Balm R, Zinsmeister A, Gostout CJ. Postpolypectomy lower GI bleeding: descriptive analysis. Gastrointest Endosc 2000; 51: 690–6.
   * Considered for PICO 15.
   * Describes 83 patients with post-polypectomy bleeding
   * 32.5% had taken ASA within 3 days of the presentation of the bleeding (unclear if they were on ASA at the time of polypectomy)
   * No comparative cohort, no comparative control group. Impossible to assess the contribution of ASA to the bleeding.
3. Hui et al. Risk of colonoscopic polypectomy bleeding with anticoagulants and antiplatelet agents: analysis of 1657 cases. Gastrointestinal Endoscopy. 59(1):44-8, 2004
   * Considered for PICO 15
   * In this paper the term “antiplatelet agent” includes NSAIDs too
   * intervention = colonic polypectomy
   * n= 127 with use of aspirin (and another 7 with use of aspirin and NSAID) within 1 week before colonoscopy. Events (bleeding): 6
   * The definition of exposure in this study does not fit to our PICO question: “use of aspirin within 1 week before colonoscopy” would be compatible with both continuous anticoagulation and temporary interruption of less than 7 days
4. Matsumura T, Arai M, Maruoka D, et al. Risk factors for early and delayed post-operative bleeding after endoscopic submucosal dissection of gastric neoplasms, including patients with continued use of antithrombotic agents. BMC Gastroenterol 2014;14:172.
   * Retrospective cohort study of patients on various antithrombotics who underwent gastric ESD.
   * It has been erroneously included in previous SRMAs. No data for any comparison can be extracted (previous SRMAs did different mistakes in their interpretation of the extractable data)
   * See comments in Evidence Profile #15 regarding the SRMAs by Dong and by Wu
5. Lee et al. Effect of sustained use of platelet aggregation inhibitors on post-endoscopic sphincterotomy bleeding. Digestive Endoscopy. 26 (6) (pp 737-744), 2014
   * Retrospective cohort study
   * Procedure limited to ERCP sphincterotomy; most results include both elective and urgent ERCPs
   * Did not report results stratified by antiplatelet agent
     1. “Continued” antiplatelet treatment = 132 (this includes 49 sustained users and 83 “non-sustained users” in whom therapy was interrupted <7 days prior to the procedure)
     2. Interrupted antiplatelet treatment = 29
   * However, it did not report results stratified by antiplatelet agent: 62% of patients were ASA-alone users, 19% were taking ASA plus clopidogrel, and 19% were taking other antiplatelet treatment
   * We cannot extract data for ASA-alone users
6. Fujita et al. Safety of gastrointestinal endoscopic biopsy in patients taking antithrombotics. Digestive Endoscopy. 27(1):25-9, 2015.
   * Procedure: limited to endoscopic biopsies; excluded emergency endoscopy and therapeutic endoscopy; excluded patients with cessation of antithrombotics prior to endoscopy and/or heparin bridge therapy
   * n= 105 on aspirin. Events (bleeding): 1/105
   * Comparator (indirect): 3671 patients undergoing diagnostic endoscopy without antithrombotics
   * Not compared to patients who interrupted ASA therapy
7. Khubchandan et al. Optimal timing of anticoagulation pre-and post-colonoscopy with polypectomy. Techniques in Coloproctology 2011.
   * colonic polypectomy
   * n= 416 on temporary interrupted aspirin. Events (bleeding): 4
   * Not compared to patients who did not interrupted ASA therapy
8. Oh et al. Continuous use of thienopyridine May be as safe as low-Dose aspirin in endoscopic resection of gastric tumors. Gut and Liver. 12 (4) (pp 393-401), 2018.
   * gastric ESD
   * n= 94 on cardiac aspirin. Events (bleeding): 12
   * Did not report separate results for ASA users according to continuation or interruption of ASA (reported such results for all antiplatelets grouped together)
   * n= 56 on thienopyridine. Events (bleeding): 2
   * Did not report separate results for thienopyridine users according to continuation or interruption of ASA (reported such results for all antiplatelets grouped together)
9. Feagins et al. Efficacy of Prophylactic Hemoclips in Prevention of Delayed Post-Polypectomy Bleeding in Patients with Large Colonic Polyps. Gastro 2019
   * This was an RCT, but for this guideline’s PICOs it can only provide observational (cohort)-type data at best. The randomization was about clipping vs not clipping.
   * The logistic regression analysis refers to the whole study population, not to the comparator we would need for our PICOs (e.g. warfarin with bridging was not compared to warfarin continuation or warfarin interruption without bridging)
   * “Patients taking aspirin were not advised to stop aspirin before or after the procedure” However, it is not reported how many patients eventually stopped aspirin on their own.
   * Table 4 allows extraction of unadjusted results (2x2), however, we don’t know how many patients used more than one drug.
   * Overall, we were unable to extract data for any PICO
10. Polmanee P et al. Outcomes of EUS-FNA in patients receiving antithrombotic therapy. Endoscopy International Open. 7 (1) (pp E15-E25), 2019.
    * Population: 908 patients undergoing EUS-FNA for pancreatic and non-pancreatic lesions
    * Intervention: n = 794 (84.6%) patients not on antithrombotic drugs
    * Comparator: n = 114 patients on continuous antithrombotic management ( 42 ASA, 10 clopidogrel, 2 ticlodipine, 10 warfarin, 40 others)
    * Outcome: 6 patients (0.7%) had significant GI bleeding; 4 in antithrombotic group and 2 in non-antithrombotic group.
    * 1 patient (0.9%) had a thromboembolic event.
    * Appears to be eligible for PICO 11, 12, 13, 15, but it is not: It is impossible to break down results per antithrombotic agent and per continuation, cessation, bridging.
11. Kawasaki K et al. Continuing use of antithrombotic medications for patients with bleeding gastroduodenal ulcer requiring endoscopic hemostasis: a case-control study. Scandinavian Journal of Gastroenterology. 52 (9) (pp 948-953), 2017
    * Population: N = 346 patients with endoscopically verified bleeding gastroduodenal ulcer requiring endoscopic hemostasis
    * Intervention: n = 173 patients taking antithrombotic medications (n = 91 on ASA)
    * Comparator: n = 173 patients not taking antithrombotic medications
    * Outcome:
      1. 24/173 patients (13.9%) had GI rebleeding episode in antithrombotic group
      2. 10/173 patients (5.8%) had GI rebleeding episode in control group
    * No thromboembolic events occurred during periendoscopic period.
    * Appears to be eligible for PICO 11, 12, 13, 15, but it is not: It is impossible to break down results per antithrombotic agent and per continuation, cessation, bridging
    * By the way, this was not a case-control study
12. Manocha D; Singh M; Mehta N; Murthy UK. Bleeding risk after invasive procedures in aspirin/NSAID users: polypectomy study in veterans. American Journal of Medicine. 125(12):1222-7, 2012
    * Population: N = 1174 patients undergoing colonoscopic polypectomy on ASA/NSAID
      1. Intervention: n = 502 patients on ASA and/or NSAIDs
      2. Comparator: n = 672 patients not on ASA and/or NSAIDs
    * Outcome: Overall postpolypectomy bleeding (%):
      1. ASA/NSAIDs group had 16/502 (3.2%)
      2. Control group had 20/672 (3%)
    * No mortality reported in either group.
    * Appears to be eligible for PICO 15, but it is not: Not only the comparator is too indirect, the intervention is indirect too (ASA is mixed with NSAIDs)
13. Rebello D., Bakhit M., McCarty T.R., Machan J.T., Nagar A., Moss S.F. Heparin bridge is associated with more post-polypectomy bleeding and emergency department visits among anticoagulated patients. Annals of Gastroenterology. 33 (1) (pp 73-79), 2020.
    * Design: single-center, retrospective cohort study
    * Population: N = 662 anticoagulated patients undergoing colonoscopy. 551 underwent polypectomy
    * Intervention: n = 192 patients had heparin bridge therapy (warfarin 183, DOACs 9)
    * Comparator: n = 470 patients had no bridge therapy (warfarin 401, DOACs 69)
    * Outcome:
      1. PPB occurred in 24/192 patients (13%) of bridged patients and 27/470 patients (5.7%) of non-bridged patients.
      2. Thrombotic events occurred in 5.2% of the bridged patients and 2.6% in the non-bridged patients.
    * EXCLUDED: did not report separate results for patients on warfarin; only reported outcomes for the mixed population of warfarin and DOAC users
14. Shimodate et al. Post-polypectomy bleeding in hot-snare polypectomy of colonic polyps under continued warfarin or short interruption of direct oral anticoagulants. International Journal of Colorectal Disease. 34(10):1705-1712, 2019
    * Population: N = 344 patients undergoing hot-snare polypectomy on DOACs or Warfarin
    * Intervention: n = 212 patients interrupted AC, of which; n = 139 interruption with heparin bridging (HB group) and n = 73 interrupted based on JGES guideline (FG group)
    * Comparator: n = 132 patients without interruption of ACs
    * Outcome:
      1. PPB in HB group was 12.9% versus 9.6% in FG group.
    * exclude (the comparator is not eligible)
15. Li et al. Colonoscopic post-polypectomy bleeding in patients on uninterrupted clopidogrel therapy: A systematic review and meta-analysis. Exp Ther Med. 2020 May;19(5):3211-3218.
    * Serious methodological limitations (one of the two “RCTs” (Feagins CGH 2013) is in fact a retrospective observational study, RCTs and observational studies were pooled together, the x-axis in the forest plot was inverted, RR was used for case-control studies, the assessment of study quality has serious mistakes, adjusted data were not use, etc.). However, we checked the studies included in this SRMA.
    * Feagins CGH 2013 is not an RCT as the authors of the systematic review stated. It is a prospective cohort study, that compared patients who did not discontinue thienopyridine for more than 2 days, vs. those who were not taking thienopyridines at all. Some patients were on ASA. Not eligible for PICO 14 or 14b.
    * Feagins DDS 2011: retrospective cohort study (not a case-control study as its own authors and the SR authors stated). Compared patients who did not discontinue thienopyridine vs. those who were not taking thienopyridines at all.
    * Grossman GEI 2010: abstract publication. Case-control study. Compared clopidogrel use vs non-use.
    * Singh GIE: retrospective cohort study (not a case-control study as the SR authors stated). Compared patients who did not discontinue thienopyridine vs. those who were not taking thienopyridines at all.
    * Chan Gastro 2019: we have included this RCT already

1. Hui APT 2002 2 (Hui CK, Lai KC, Yuen MF, Wong WM, Lam SK, Lai CL. Does withholding aspirin for one week reduce the risk of post-sphincterotomy bleeding? Aliment Pharmacol Ther 2002; 16: 929–36)
   * Retrospective cohort study
   * Over an 11-year period, 240 patients on ASA underwent endoscopic sphincterotomy
     1. 124 (51.7%) continued to take aspirin until the day of endoscopic sphincterotomy (Group 1)
     2. 116 (48.3%) had their aspirin discontinued for 1 week before endoscopic sphincterotomy (Group 2)
   * Outcome: Delayed post-sphincterotomy bleeding (timing of assessment was not stated)
     1. Mild = hemoglobin drop of less than 3 g/dL and no need for blood transfusion
     2. Moderate = transfusion of four units or less with no angiographic intervention or surgery
     3. Severe = transfusion of five units or more in those requiring intervention (angiographic or surgical)
     4. We included moderate and severe, pooled together, as outcome
        1. Continued aspirin: 3/124
        2. Interrupted aspirin 4/116
   * Analysis not adjusted for differences in the procedure between the two groups (only “repeat cannulation” was assessed, but not any of: indication for ERCP, urgent vs elective procedure, reason for sphincterotomy, size of sphincterotomy, type of current used, sphincteroplasty, pre-cut, other interventions such as stone extraction, stent insertion, individual endoscopist skill, etc.)
   * The denominators (number of patients who had ERCP with/without sphincterotomy) were not reported: it is possible that under similar circumstances, patients on aspirin were less likely to have sphincterotomy
   * Indirectness concern: there is a mention that patients in NSAIDs were excluded, but it is not clear if all patients were on aspirin monotherapy or if some patients were taking a second antithrombotic agent.
   * **Excluded** because clean data for patients on ASA monotherapy could not be extracted, as the patients may have been on other anti-thrombotics. Dr. Laine contacted the author who said he didn’t know and that it was possible.
2. Igarashi SE 2017 14 (Igarashi K., Takizawa K., Kakushima N., Tanaka M., Kawata N., Yoshida M., Ito S., Imai K., Hotta K., Ishiwatari H., Matsubayashi H., Ono H. Should antithrombotic therapy be stopped in patients undergoing gastric endoscopic submucosal dissection? Surgical Endoscopy. 31 (4) (pp 1746-1753), 2017).

* Retrospective cohort study (this article reports the results of 2 studies; we will not include the data from the case-control study)
* Patients undergoing gastric ESD. In Japan
* Compared continued ASA vs. interrupted with heparin bridging vs. interrupted (without heparin bridging). We did not include the “interrupted with heparin bridging” group.
* **There was serious indirectness concern: some of the patients in the results that we extracted were not on aspirin monotherapy, i.e., some patients they were taking aspirin plus 1 or more additional antithrombotics, and it is not clear if they discontinued all antithrombotics vs discontinued aspirin and continued the other antithrombotics.** For the outcome of thrombotic events, we included in the nominator only the 2 patients who had been on aspirin monotherapy, but the denominators were “not clean” (i.e., they included patients on aspirin plus other antithrombotics)
* **We attempted to extract data for PICO 14b and 15 (see below data for PICO 15), but after extensive discussions the panel agreed to exclude this study because it could not provide clean data.**
* **Delayed bleeding** (at 4 weeks) was defined as the cases that required emergent hemostasis after gastric ESD with an apparent sign of bleeding, such as melena, hematemesis.
* **Thrombotic events** (at 4 weeks) were defined as arterial thromboembolism, including stroke, transient ischemic attack, and systematic embolism.
* Note: this study is not eligible for the PICOs on warfarin or DOACs because the those two were not assessed separately
* 
* Delayed bleeding
  + ASA interruption: 19/171
  + ASA continuation: 4/33
* Thrombotic events
  + ASA interruption: 2/171
  + ASA continuation: 0/33

1. **Yousfi AJG 2004** (Yousfi M, Gostout CJ, Baron TH et al. Postpolypectomy lower gastrointestinal bleeding: potential role of aspirin. Am J Gastroenterol 2004; 99: 1785–9)
   * + Excluded
     + Case control study: 81 patients with post-polypectomy bleeding matched (for age, gender, history of CAD) with 81 patients with uneventful polypectomy
     + Indirectness of the exposure: this study did not compare patients who continued vs interrupted ASA for 5-7 days. Instead compared those who used ASA within 3 days of colonoscopy (this group could include patients who interrupted ASA for 2 days) vs. those who did not use ASA within 3 days of colonoscopy (this group would include patients who were never on ASA (different population, likely healthier, with healthier vessels) as well as patients who discontinued ASA for 3 days or longer). Furthermore, it is not clear that dual antiplatelet therapy was excluded.
     + High risk of bias
       - the cases were derived from two databases, and the controls from a different third database (unknown timeframe)
       - Used retrospective evaluation of medical records to establish ASA exposure
       - Did not adjust for factors that affect bleeding risk post-polypectomy, even though there was an obvious imbalance in the total number of polyps removed: in the cases, the number of polyps removed was twice the number in controls. The imbalance in such an important factor is so large, that it makes it possible for the results to reverse direction if the results are appropriately adjusted - of course, a “protective effect” of ASA for post-polypectomy bleeding is implausible biologically and would simply mean that strong residual confounding (for example, the endoscopists may have acted differently when they scoped and removed polyps in patients on ASA vs patients not on ASA). We cannot do the statistical adjustment ourselves because we would need access to individual raw data.
     + Indirectness of the polypectomy technique: 85% and 88% hot polypectomy in each group, although >95% of the polyps were ≤ 10 mm (this approach is not applicable to current practice; nowadays, most of these polyps would have been removed by cold snaring)