



## To clip or not to clip: still no closure for all

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*Comment on:* Feagins LA, Smith AD, Kim D, *et al.* Efficacy of prophylactic hemoclips in prevention of delayed post-polypectomy bleeding in patients with large colonic polyps. *Gastroenterology* 2019;157:967-76.e1.

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Colonoscopy reduces both the incidence and mortality associated with colorectal cancer through the early recognition and removal of precancerous adenomatous polyps (1,2). While endoscopic mucosal resection (EMR) has largely replaced surgery as the first-line therapeutic approach for the removal of most colon polyps (3,4), polypectomy can be associated with adverse events, with bleeding being the most commonly encountered (5). Post-polypectomy bleeding can occur either during the procedure or post-operatively. Delayed post-polypectomy bleeding (DPPB), which typically presents within 10 days after resection, has been estimated to occur in the range of 3–12%; depending on several risk factors, including both patient and polyp characteristics (6–11). Prophylactic endoscopic clip closure of the post-resection mucosal defect has been previously proposed to be of benefit, primarily based on findings from retrospective case series (9). More recent higher quality randomized controlled trials have not consistently shown a reduction in DPPB from routine clip closure attempt after EMR; with data suggesting the highest benefit following complete closure and for lesions located in the right colon (6,12). Therefore, whether this practice truly reduces the risk of DPPB remains a topic of debate.

The current study by Feagins *et al.* is a randomized clinical trial evaluating the efficacy of prophylactic clip placement in the prevention of DPPB after endoscopic resection of colon polyps  $\geq 1$  cm in size (13). Patients scheduled to undergo elective colonoscopy were enrolled from 4 Veterans Affairs (VA) Medical Centers during the 7-year study period. Patients were randomized to prophylactic clip placement or no prophylactic clip placement in a 1:1 ratio. The primary outcome was the

occurrence of clinically important DPPB, which the authors defined as rectal bleeding within 30 days after polypectomy requiring repeat colonoscopy, associated with hemodynamic instability, requiring blood transfusion or a drop of hemoglobin by 2 g/dL or more. The study was designed as an equivalence study, with an estimated required sample size of 1,622 patients, based on an expected DPPB rate set at 1.5%.

A total of 1,098 patients with polyp(s)  $\geq 1$  cm were enrolled in the study and randomized to either prophylactic clip placement (n=547) or no clip placement (n=551) following polypectomy. The study was terminated prior to reaching the sample size goal of 1,622 due to funding restraints. Final analysis included 680 polyps in 530 in the clip group and 706 polyps in 520 in the no-clip group. There were no significant baseline differences in age, body mass index, gender, procedure indication, or use of antithrombotic agents between the two groups.

Overall, polyp characteristics were similar in patients randomized to clip versus no-clip in terms of morphology or pathology. There were similar numbers of polyps  $> 2$  cm in both groups (14.9% clip group *vs.* 17% *vs.* no-clip group, respectively,  $P=0.22$ ). Most polyps were removed with hot snare polypectomy (97.1% clip group *vs.* 96.6% no-clip group;  $P=0.79$ ), and approximately only a one third with an injection-lift technique (32.2% clip groups *vs.* 32.7% no-clip group;  $P=0.75$ ). For patients randomized to clip placement, complete closure was achieved in 98.4% of all cases and 90.3% of polyps  $> 2$  cm.

In all, Feagins *et al.* reported important DPPB in 12 of 530 (2.3%) patients randomized to clip placement and 15 of 520 (2.9%) with no clip placement (relative risk =0.79; 95%

CI: 0.37–1.66). Given the study's early termination due to lack of funding and the higher actual DPPB rates compared to the originally estimated rate set at 1.5%, the study was underpowered and therefore did not meet the a priori equivalence criteria. On multiple logistic regression analysis, significant predictors of DPPB included the use of warfarin with bridging (adjusted OR 7.34; 95% CI: 2.22–24.3), thienopyridines (adjusted OR 5.79; 95% CI: 2.25–14.9), larger polyp size ( $P=0.04$ ), and proximal polyp location ( $P=0.03$ ). Based on their results, the authors concluded that routine clip placement after resection of polyps  $\geq 1$  cm does not affect the rate of important DPPB when compared to no clip placement.

Feagins and colleagues should be commended for this study; specifically, for the daunting task of undertaking a randomized trial requiring such a large sample size in an attempt to address a clinically important question: the role of prophylactic clipping after endoscopic resection of polyps  $\geq 1$  cm in size. Overall, their results demonstrated that the rate of delayed bleeding in these patients was relatively low, ranging between 2% to 3%, irrespective of clip placement. However, additional observations beyond this conclusion should be made with caution, as this study was marred by some of the same issues that have yielded conflicting results in prior publications (9,10,14–18). For one, as conceded by the authors, the study was vastly underpowered for equivalence analyses, as they would have needed 2,752 cases for their intention-to-treat evaluation. Hence, demonstration of equivalence between prophylactic clipping vs no clipping on the incidence of DPPB was not achieved, and only suggested by simulated data.

Several additional issues deserve further consideration, many of which are acknowledged and discussed by the authors themselves. It is well recognized that the risk of bleeding is innately different between sessile and pedunculated polyps. Indeed, prophylactic mechanical hemostasis has been shown to be effective in reducing the risk of bleeding in pedunculated polyps  $>10$  mm in size, and this practice is currently advocated by GI societal guidelines (19). The impact of polyp morphology on DPPB is unclear and the inclusion of both sessile and pedunculated polyps in this study limits the interpretability of their findings. Another significant limitation of this study was the inclusion of various endoscopic resection techniques (e.g., biopsy forceps, cold or hot snare polypectomy, and EMR) for polyp removal. DPPB has often been attributed to thermal energy induced injury of the underlying resection defect. Hence, submucosal lifting prior to endoscopic resection

is recommended for the removal of larger polyps as to minimize deep thermal injury (19). Furthermore, with the increasing number of studies supporting the safety and efficacy of cold snare resection for polyps up to 10 mm, data is also beginning to emerge on the potential role of cold snare resection for larger polyps as well (20,21). Yet, in this study by Feagins *et al.*, most polyps in both groups (~97%) were removed with hot snare polypectomy, with lift prior to resection performed in only one third of the patients and cold snare resection in only 2.5%. Lastly, the study did not control and failed to report the electrocautery settings used during polypectomy, a factor that has been shown to impact the risk of DPPB (22).

So should we consider prophylactic clipping after the endoscopic resection of large colon polyps? The answer is it depends. In this particular issue, polyp size does matter. Previous studies have already shown no preventive effect of clip placement following endoscopic resection of polyps  $\leq 20$  mm in size (16,17). The prohibitive large number of cases needed for analysis as shown in this trial further emphasizes the low rate of DPPB associated with resection of polyps between 10–20 mm in size and supports the unlikely benefit of prophylactic clip closure in this cohort. Conversely, clip closure may be indicated in selected cases of non-pedunculated polyps  $\geq 20$  mm, as a meta-analysis and the two recently published randomized clinical trials have shown a reduction in DPPB rates from 7–12% to 3–5% with clip closure (6,12,23). In the North American study (12), the protective effect appeared to be restricted to polyps located in the proximal colon, which is concordant results with prior studies (10,11), including the one by Feagins and colleagues identifying proximal colon location as a predictor for DPPB.

At first glance, the results of these studies would appear to be practice changing; supporting routine clip closure following endoscopic resection of polyps  $\geq 20$  mm, particularly in the right colon. However, there are also some considerations worthy of discussion. In many cases, clip closure following resection of large lesions can be technically challenging if not impossible even in the hands of expert endoscopists, as shown by the high number of failed closures in these recent studies (6,12). Importantly, additional data is necessary to identify factors associated with failed complete closure, as partial closure may not be effective and possibly even harmful (6,24). Lastly, formal cost-effectiveness analysis is necessary as to better delineate how many clips and in what scenarios this becomes a clinically effective and cost-conscious strategy.

In summary, at present time, endoscopic clipping should not be routinely recommended following resection of colorectal polyps. Clipping may be considered in selected cases for higher-risk scenarios, such as patients on antithrombotic medications, particularly if such therapy needs to be restarted as soon as possible after EMR. While clip closure may be beneficial following endoscopic resection of selected proximal colon lesions > 20 mm in size, the decision to proceed mandates a case-by-case assessment of all pertinent endoscopist-, patient-, and procedural-related factors.

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### Footnote

*Conflicts of Interest:* PV Draganov is a consultant for Boston Scientific, Cook Medical and Olympus. D Yang is a consultant for Boston Scientific, Lumendi and US Endoscopy. C Jacobs has no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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