Second-generation distal attachment cuff improves adenoma detection rate: meta-analysis of randomized controlled trials

Short Title: Second-generation cuff vs standard colonoscopy

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Abstract:

Background and Aims: Multiple randomized controlled trials (RCT) using the second-generation distal attachment cuff device (Endocuff Vision) have reported conflicting results in improving adenoma detection rate (ADR) compared with standard high definition colonoscopy without distal attachment. We conducted a systematic review and meta-analysis of RCTs to compare outcomes between second-generation cuff colonoscopy (CC) versus colonoscopy without distal attachment (SC).

Methods: An electronic literature search was performed using PubMed, Google Scholar, Embase, and Cochrane Library through May 2020. The primary outcome was reporting of ADR and secondary outcomes included polyp detection rate (PDR), mean withdrawal time, mean adenomas per colonoscopy (APC), sessile serrated lesion detection rate (SDR), and adverse events. Pooled rates and risk ratios with 95% confidence intervals were reported.

Results: Eight RCTs with 5695 patients were included in final analysis. There were 2862 patients (mean age 62.8 years, 52.9% males) in CC group and 2833 patients (mean age 62.6 years, 54.2% males) in the SC group. Compared with SC, use of CC was associated with a significant improvement in ADR: 49.8% vs 45.6% (RR, 1.12; p=0.02); PDR, 58.1% vs 53% (RR, 1.12; p=0.009) and APC (p<0.01). Furthermore, use of CC had a 0.93 min lower mean withdrawal time (p < 0.01) when compared with SC. The difference in ADR was larger in the screening/surveillance population (6.5%; p= 0.02) and when used by endoscopists with ADR < 30% (9.4%; p= 0.03).

Conclusion: The results of this meta-analysis of randomized trials show a significant improvement in ADR and APC with shorter withdrawal times using the second-generation cuff device compared with standard colonoscopy.

Keywords: Endocuff vision; Endocuff; Colonoscopy; ADR

Introduction:

Despite steadily decreasing trends in the incidence of colorectal cancer over the last 5 years, colorectal cancer still ranks second in the United States for cancer related mortality[1]. Colonoscopy, as a screening procedure, is a useful tool in detecting tumors at an earlier and more treatable stage and also facilitates the timely removal of precancerous lesions or adenomas[2]. Adenoma detection rate (ADR) has been proposed as a benchmark and a reportable colonoscopy quality measure by the Centers for Medicare and Medicaid Services[3–6]. ADR has been shown to be inversely associated with the risk of interval colorectal cancer[3,4]. ADR can be improved by technique or devices that improve mucosal exposure, or by tools that highlight flat colonic lesions.

A number of distal attachments have been tested to improve ADR including a transparent cap, cuff or rings. The cuff is attached to the tip of the colonoscope, and the fingers are used to flatten colonic folds and lead to increase mucosal visualization. Although a number of studies and analyses have been published, they had mostly used the first-generation cuff (Endocuff, UK) [7–13]. More recently, a second-generation cuff (Endocuff Vision; Olympus America, Center Valley, Pa, USA) has been evaluated in several RCTs showing divergent results in improving ADR. Compared with the first-generation device, the Endocuff Vision has only one row of flexible arms that are softer, 2 mm longer and available in 4 different sizes for different type of colonoscopes. The aim of this systematic review and meta-analysis was to compare the outcomes of cuff colonoscopy (CC) using the more recent and widely available second-generation device with standard high-definition white-light colonoscopy (SC) without any distal attachment.

Methods:

This systematic review and meta-analysis along with the eligibility criteria and analyses were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[14] **(Supplementary table 1)**.

Search strategy:

A comprehensive electronic literature search was conducted in PubMed/ MEDLINE, Google Scholar, EMBASE, Cochrane and major conference proceedings to identify eligible articles, from the beginning of indexing for each database through May 10, 2020. The following text words and Medical Subject Heading/ Entrée terms were for search: "Endocuff vision," "Endocuff," "distal attachment," "adenoma detection rate," "ADR," "adenoma," "polyp detection rate," "PDR," "screening," "surveillance," "withdrawal," and "adverse events" **(Supplementary table 2).**

Inclusion/ Exclusion criteria:

The retrieved articles were screened for eligibility by 2 independent reviewers (H.P. and V.T.) and any disagreement was resolved by consensus with a third author (P.S.). The inclusion criteria for this analysis were (1) Studies reporting ADR using CC and SC, (2) prospective enrollment of patients undergoing colonoscopy, and (3) randomized study design. Exclusion criteria were (1) studies not reporting ADR for either CC or SC in same study, (2) studies including patients with polyposis syndrome and inflammatory bowel disease, (3) retrospective studies, prospective single-arm studies, case reports and case series, and (4) studies conducted using the first-generation cuff device.

Data extraction and quality assessment:

The following data were extracted from each study in each group: study author, study design, age, gender, number of patients, ADR, total number of adenomas, polyp detection rate (PDR), sessile serrated lesion detection rate (SDR), advanced adenoma detection rate (A-ADR), proximal and distal ADR (P-ADR, D-ADR), cecal intubation rates (CIR), ileal intubation rate (IIR), mean adenomas per colonoscopy (APC), withdrawal times and adverse events.

Definitions and outcomes:

ADR was defined as the number of patients with at least one adenoma (tubular, villous or tubulo-villous adenoma based on histopathology) divided by the total number of patients. PDR was defined as number of patients with at least one polyp divided by the total number of patients. SDR was defined as the number of patients with at least one sessile serrated lesion (sessile serrated or traditional serrated adenoma) divided by the total number of patients. A-ADR was defined as the total number of patients with at least one advanced adenoma (adenoma ≥ 10 mm in size, villous features or high-grade dysplasia). P-ADR was the number of patients with adenoma in the proximal colon (cecum, ascending colon, hepatic flexure, and transverse colon) divided by the total number of patients. D-ADR was the number of patients with adenoma in the distal colon (splenic flexure, descending colon, sigmoid colon, and rectum) divided by the total number of patients. APC was the number of adenomas detected in total divided by the number of patients who underwent colonoscopy. CIR was the proportion of patients who had a successful intubation of the cecum. Mean withdrawal time (MWT) was calculated by the time measured from reaching the cecum until examination of the colon was complete with withdrawing of the scope and termination of the procedure, excluding the time required for polypectomy. Serious adverse events recorded during

the procedure included the incidence of bleeding and perforation.

The primary outcome of interest was comparing the ADR between the CC and SC groups. The secondary outcomes were as follows: PDR, SDR, A-ADR, P-ADR, D-ADR, APC, CIR, IIR, MWT and rate of adverse events. If there was moderate-high heterogeneity, subgroup and sensitivity analyses were performed as follows: (1) outcomes for screening and surveillance patients only; (2) outcomes for screening and surveillance patients after excluding the U.K. Bowel Cancer Screening Program (BCSP) FOBT positive patients (FOBT+); and (3) comparison of ADR between the 2 groups for studies reporting < 30%, <40%, <50% and > 50% ADR in the SC group (control arm).

Statistical analyses

The pooled proportions were calculated including the frequency of events over the total number of patients along with 95% confidence limits. Random-effects model described by DerSimonian and Laird was used for analysis. Risk ratios (RR) were calculated by comparison of the pooled proportions. A P-value <0.05 was considered statistically significant. The corresponding forest plots were constructed with the weights of individual studies representing the size of individual squares. Heterogeneity among the studies was assessed using the inconsistency index (I^2-statistic). I^2-values of 0% to 30%, 31% to 60%, 61% to 75% and 76% to 100% were reflective of low, moderate, substantial, and considerable heterogeneity, respectively. Comparison of APC and withdrawal times were performed by calculating the mean difference with standard error. Publication bias was

assessed by funnel plot and asymmetry was tested using the Rucker test. The number of patients needed to be treated (NNT) for detecting one additional patient with an adenoma was calculated as the inverse of the difference of ADR between the 2 groups. All analyses were performed using statistical software, Open Meta analyst (CEBM, Brown University, Rhode Island, USA) and Review Manager version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark).

Quality of evidence assessment

The risk of bias in individual studies was assessed using the Cochrane Collaboration tool[15]. The quality of body of evidence was assessed using the Grading of Recommendations, Assessment and Evaluation (GRADE) approach[16]. Two independent researchers (H.P. and V.T.) graded risk of bias, indirectness, inconsistency, imprecision and publication bias and the quality was deemed high, moderate, low, or very low using GRADEPro (GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc).

Results:

A total of 469 articles were retrieved based on the initial search and after exclusions, 21 studies were reviewed in detail, of which 8 RCTs were included in the final analysis (Figure 1) [12,13,17–22]. There were a total of 5695 patients: CC group (n=2862, 52.9% males, 62.8 +/- 2.9 years mean age) and SC group (n= 2833, 54.2% males, 62.6 +/- 3.4 years mean age). There was no difference in the proportion of males or mean age between the 2 groups. The indications for colonoscopy in most studies were varied (screening, surveillance and/or diagnostic) but 5 of the 8 studies[12,13,17,21,22] reported outcomes on screening and surveillance patients also. Of the 8 studies, 2 were from the United Kingdom (n= 2306)[12,13], and one each from France (n=2058)[21], United States (n= 200)[17],

Germany (n= 240)[19], Portugal (n= 170)[20], Thailand (n= 404)[22], and Australia (n= 320)[18]. Two studies were multicenter[13,17] and 6 of them were single-center experiences[12,18–22]. Six studies were in full text format[12,13,17–19,21] and 2 were abstracts[20,22]. Out of 4 studies that reported the information, endoscopists were experienced in all but one study (EVASTA)[19] in using CC before initiation of trial. Detailed characteristics of each study with their demographics are reported in **Table 1**. Risk of bias assessment using Cochrane Collaboration tool is provided in **Supplementary figure 1.**

Primary Outcome: ADR

All 8 studies reported ADR in the CC and SC groups (n= 5695 patients) and it was reported as the primary outcome in 4 of 8 studies[13,18,21,22] **(Table 2, Figure 2, Supplementary Table 3)**. The Rucker's coefficient for publication bias in these studies was p= 0.294, indicating no publication bias existed for primary outcome between the 8 studies **(Supplementary Figure 2)**. The pooled ADR in the CC group was 49.8% (95% CI, 42.3 – 57.3%) and in the SC group was 45.6% (95% CI, 36.3% – 54.8%). The use of CC was associated with a statistically significant ~4.2% improvement in ADR when compared with SC (RR, 1.12; 95% CI, 1.02 – 1.23; p= 0.02; I^2= 53%).

If ADR calculation was restricted to the subgroup of patients undergoing either screening or surveillance colonoscopies[12,13,17,21,22](n = 3294), the values were as follows: CC: 55.8% (95% CI, 46.7% – 64.9%) and SC: 49.3% (95% CI, 37.7% – 61%) (RR, 1.15; 95% CI, 1.03 – 1.28; p= 0.02; I^2= 59%) (**Figure 2; Supplementary Table 4**). The NNT was calculated at 24 for all 8 studies and 15 if calculation was restricted to only screening/ surveillance studies. Further sensitivity analysis for the average risk screening and the surveillance population, after excluding 2 studies that included

FOBT+ patients[12,13], yielded the following results: 51.7% vs 44.2% (RR, 1.21; 95% CI, 1.09 – 1.34; p= 0.0004; I^2= 3%; NNT 13), respectively for CC versus SC[17,21,22] **(Figure 2; Supplementary Table 5)**.

Further subgroup analysis of ADR based on the baseline ADR of endoscopists involved in the RCTs yielded the following results **(Supplementary Figure 3; Supplementary Table 5).** For operators with low baseline ADR< 30%, ie, the low detectors (n= 2378)[18,21]: 38.8% vs 29.4% (RR, 1.32; 95% CI, 1.18 – 1.48; p< 0.01; I^2= 0%); baseline ADR< 40% (n= 4150)[13,18,21]: 39.7% vs 31.9% (RR, 1.23; 95% CI, 1.09 – 1.39; p= 0.0009; I^2= 45%); baseline ADR< 50% (n= 4390)[13,18,19,21,22]: 41.4% vs 36.7% (RR,1.16; 95% CI, 1.03 – 1.31; p= 0.01; I^2= 51%); and baseline ADR> 50%, ie, the very high detectors (n= 901)[12,17,20]: 64% vs 60.8% (RR, 1.03; 95% CI, 0.93 – 1.14; p= 0.51; I^2= 0%). Thus, ADR improved in the CC group for detectors up to 50% but no difference was seen beyond that. The NNT further decreased to 11 for baseline ADR< 30%.

Restricting the analysis further to include only the 3 studies which reported withdrawal time[13,17,21], the ADR was higher with CC vs SC: 41% vs 33.5% (RR, 1.21; 95% CI, 1.08 – 1.36; p= 0.001; I^2= 0%), respectively (NNT 13). If the population was limited to screening/surveillance subgroup in those 3 studies, the difference in ADR was further higher with CC vs SC: 50.9% vs 40.9% (RR, 1.24; 95% CI, 1.14 – 1.35; p<0.0001; I^2= 0%), respectively (NNT 10) **(Supplementary Figure 4, Supplementary Table 5)**.

Secondary Outcomes:

Sessile Serrated Lesion Detection Rate (SDR): Five studies reported the SDR (n= 4520)[13,17,18,20,21] **(Table 2, Figure 3, Supplementary Table 3)**. The CC and SC groups had individual pooled rates of 8.8% (95% CI, 3.1%– 14.4%) and 6.1% (95% CI, 0.7 – 11.5%), respectively, with no statistically

significant difference in the SDR (RR, 1.21; 95% CI, 0.90 – 1.61; p= 0.20; I^2 = 18%). If analysis was restricted to the screening/surveillance population only (n= 2299)[13,17,21], the SDR was significantly higher in the CC group: 12.1% vs 8.3% (RR, 1.28; 95% CI, 1.01 – 1.64; p= 0.04; I^2 = 0%) for CC and SC, respectively **(Supplementary table 4)**.

Mean Adenomas per Colonoscopy (APC): Seven studies reported the APC in the CC group and SC group **(Supplementary Table 3)**: 1.18 +/- 0.33 (n= 2680 patients) and 1.05 +/- 0.36 (n= 2695 patients) respectively[12,13,17,19–22]. The mean difference between the 2 groups was statistically significantly higher for the CC group detecting 0.13 more adenomas compared with SC group (Standard error, 0.009; 95% CI, 0.11 - 0.15; p < 0.0001).

Advanced Adenoma Detection Rate (AADR): Advanced adenoma detection rate was reported in only 3 of the 8 studies (n= 4361)[12,13,21] **(Table 2, Figure 3, Supplementary Table 3)**. The use of CC did not show any statistically significant increase in AADR when compared with the SC group: 11.4% (95% CI, 7.5 – 15.4%) vs 10.8% (95% CI, 6.5 – 15.2%), respectively; (RR, 1.11; 95% CI, 0.93 – 1.33; p= 0.499, I^2 = 0%).

Proximal and Distal Adenoma Detection Rate (P-ADR and D-ADR): The P-ADR and the D-ADR were reported by 3 of 8 studies[13,18,21]. The use of CC did not improve the P-ADR but improved D-ADR compared with SC **(Table 2, Figure 3, Supplementary Table 3)**: 29.9% (95% CI, 20.1% -39.7%) vs 25.5% (95% CI, 21.9% – 29%) (RR, 1.26; 95% CI, 0.94 – 1.68; p =0.12; I^2 = 81%) for P-ADR and 25.2% (95% CI, 23.2% – 27.3%) vs 18.2% (95% CI, 13.7% – 22.8%) (RR, 1.31; 95% CI, 1.09 – 1.58; p= 0.004; I^2 = 41%) for D-ADR respectively. In the screening/surveillance population from 2 studies (n= 2099)[13,21], again there was no difference in P-ADR between the CC and SC groups **(Supplementary**

Table 4): 39.9% (95% CI, 36.9% - 42.8%) vs 29.7% (95% CI, 20.7% – 38.6%); (RR, 1.24; 95% CI, 0.96 – 1.58; p= 0.09) but CC resulted in detection of more distal adenomas than SC: 32.1% (95% CI, 16.8% - 47.3%) vs 25.6% (95% CI, 10.3% – 40.9%) respectively; (RR, 1.26; 95% CI, 1.10 – 1.45; p< 0.01).

Polyp Detection Rate (PDR): Five studies reported the PDR (n = 4921)[12,13,18,19,21]**(Table 2, Figure 3, Supplementary Table 3)**. The PDR for CC was significantly higher than SC: 55.5% (95% CI, 47.4% – 63.6%) vs 49.8% (95% CI, 38.8% – 60.8%) (RR, 1.13; 95% CI, 1.03 – 1.23; p= 0.009; I^2 = 54%), respectively. When the analysis was restricted to only screening/surveillance population (n = 2630)[12,21], the difference was still significant and greater (**Supplementary table 4**): 62% (95% CI, 42% – 82%) vs 53.2% (95% CI, 30.7% – 75.7%) (RR, 1.14; 95% CI, 1.07 – 1.21; p<0.01), respectively.

Mean Withdrawal Time and other outcomes: The MWT was reported by 3 studies[13,17,21] and was significantly lower in the CC group (7.19 ± 0.62 minutes; 2015 patients) compared with the SC group (8.12 ± 0.30 minutes; 2015 patients) with a significant mean difference of 0.93 minute (SE, 0.02; 95% CI, 0.89 - 0.97; p < 0.0001) **(Table 2)**. For additional secondary outcomes including the CIR, IIR and Adverse Events there was no significant difference between the 2 groups. Table 2 reports for individual pooled rates and RR for all the detection endpoints.

Quality assessment by GRADE estimate:

The quality of evidence based on GRADE approach was found to be moderate for ADR for screening and surveillance population and low for ADR, PDR, SDR, A-ADR, APC, and MWT. **(Table 2, Supplementary table 6).** The level of evidence was downgraded by 2 levels primarily due to the following reasons: concerns for risk of bias as the endoscopists were not blinded to the study groups or outcomes and also due to the presence of indirectness due to different study populations

and indications for procedure. Overall, the quality of evidence based on the estimates was considered low.

Discussion:

This systematic review and meta-analysis of RCTs reports quality measure outcomes in patients undergoing colonoscopy using either a distal cuff attachment versus no attachment. The results including 8 RCTs[12,13,17–22] demonstrate a 4.2% increase in ADR (RR, 1.12; p= 0.02), a 5.1% increase in PDR (RR, 1.13; p= 0.009), a 0.13 increase in APC along with an approximate 1 minute shorter withdrawal time when the second generation cuff device was used compared with a standard colonoscopy without any distal attachment. The distal ADR was also significantly higher in the CC group by 7% (25.2% versus 18.2%), but there was no significant difference in the serrated lesion ADR, cecal intubation rates or the proximal ADR between the 2 groups. Prior meta-analyses have been published on the utility of distal attachment devices such as cap, and cuff; however, the cuff results were based primarily on the first-generation tip device.

The E-CAP study by Bhattacharya et al[12] was the first randomized study comparing CC and SC where all patients enrolled in the study were FOBT+ from the National BCSP in the United Kingdom. Contrary to the results of this meta-analysis, there was no significant difference in endpoints (ADR, APC, and PDR) between both of the groups from this study. One possible explanation could be the high baseline ADR of endoscopists (58.5%) in the United Kingdom study and higher ADR in FOBT+ patients compared with other populations[23], making it difficult to improve ADR further with the use of any distal attachment device. However, Karsenti et al[21] reported that the ADR with CC significantly improved in the high-detector group. However, the cut-off for high ADR in their study

was >/=25%, which overlaps with the low-detector group in prior meta-analyses and prior RCTs. Consequently, high-ADR endoscopists will probably not benefit from the use of CC or any other attachment device; this was shown in our current analysis based on baseline ADR. Stratifying studies into groups based on ADR from the SC arm (control arm) as <30%, <40%, <50% and ≥50%, we showed that operators with baseline ADR < 30%[18,21] benefit from the use of CC (NNT 11), whereas the very high baseline detectors (ADR> 50%)[12,17,20] did not (no or low heterogeneity in this population).

Rex et al,[17] in their study highlighted the significance of withdrawal times. As reported in prior studies, they suggested that CC helps reduce procedural times and technical success without compromising the endpoints for outcomes[24,25]. However, that study was not adequately powered to report significant difference in ADR, PDR, and APC. The current meta-analyses included 2 large studies[13 21] which constituted the majority of the patients. Ngu et al,[13] with a large sample size of 1772 patients, reported improved ADR, PDR, SDR, D-ADR, and APC but no difference in mean withdrawal time using CC **(Supplementary Table 3)**. Karsenti et al,[21] in a large cluster randomized cross over trial (n= 2058) reported close to a 10% improvement in ADR and significantly lower withdrawal times using CC. Given the differences in the above studies, our meta-analysis reports important results of improvement in ADR, and APC while reducing the mean withdrawal time in the CC compared with SC group.

In order to minimize the influence of the outcomes from non-screening or non-surveillance procedures, we performed a subgroup analysis based on indications for colonoscopy including patients undergoing a screening or surveillance colonoscopy (n = 3234)[12,13,17,21,22]. There was a

statistically significant improvement in ADR,[12,13,17,21,22] SDR,[13,17,21] and D-ADR[13,21]. The NNT based on the ADR for this subgroup was 15. An interesting observation was the significant increase in the SDR in this subgroup with the use of CC over SC: 12.1% vs 8.3% (RR, 1.28; p= 0.04). However, there was still a high heterogeneity in this subgroup for the primary outcome ADR (I^2= 59%). Thus, we performed a further sensitivity analysis by excluding 2 studies that included FOBT+ population and found persistent improvement in the ADR with minimal heterogeneity (I^2= 3%) further reducing the NNT to 13.

Finally, our results show that an attachment with flexible arms at the tip of the endoscope did not translate into increased adverse events. Prior meta-analysis with the first-generation cuff compared with SC by Chin et al have shown more adverse events and specifically mucosal abrasions when compared with SC[26]. On the contrary, studies with the second-generation device have not shown similar results and our meta-analysis reaffirms these results.

The strength of the current analysis lies in the inclusion of only RCTs with more than 5500 patients. This meta-analysis specifically focuses on all outcomes for only second-generation cuff device compared with screening colonoscopy which have not been reported before. The majority of outcomes reported in our study had only mild or moderate heterogeneity. The potential reasons for heterogeneity include studies being performed in different countries with different patient populations, varying expertise and experience of endoscopists, variations in bowel preparation and withdrawal time. In case of moderate to high heterogeneity, we have performed further subgroup and sensitivity analyses to successfully identify and reduce or eliminate the heterogeneity for most outcomes. However, there are limitations to the study. The endoscopists in both groups were not

blinded, which is common to most endoscopic studies designed for assessment of external attachments. Data on polyp size, adenoma miss rate and cancer outcomes were limited because there were no follow-up data in these studies, and we could not perform an analysis for these outcomes. There were different scales used for grading the quality of bowel preparation across different studies, making it difficult to generalize the outcomes, but individual studies did not have significant difference in bowel preparation between both the groups, thus the results from our analysis holds good, even if we were unable to analyse outcomes based on the bowel preparation. One study reported industry funding for the RCT thereby making it difficult to eliminate funding bias[13].

In conclusion, the use of the second-generation cuff distal attachment device was associated with a significant improvement in adenoma detection rate, adenomas per colonoscopy, a reduction in the mean withdrawal time without any increase in adverse events compared with standard high-definition colonoscopy without any distal attachment. The benefit in ADR was more pronounced in patients undergoing screening and/or surveillance colonoscopy and for endoscopists with baseline low ADR. Future studies with stratification of outcomes based on polyp size and evaluation of cost-effectiveness are needed.

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Table 1. Study Characteristics with demographics and indications:

Study, Year	Duration	Type of study and Center	Number of Patients (CC; SC)	Mean Age, Years (CC; SC)	Males, % (CC; SC)	Primary Outcome	Screening +/- Surveillance population % (CC; SC)	Pretrial experience of using EV
Bhattacharya et al, 2017	2015-2016	Parallel, 1 center	266; 265	68; 67	60.9; 67.9	MPP	100; 100 (FOBT+)	NA
Ngu et al, 2018	2014-2016	Parallel, 7 centers	888; 884	61.7; 62.1	57.1; 56.8	ADR	45.4; 44.6	20 Procedures
Rex et al, 2019	2017-2018	Parallel, 2 centers	101; 99	62.7; 61.7	56.4; 42.4	Withdrawal time	100; 100	Highly experienced
Jacob et al, 2019	2016-2017	Parallel, 1 center	182; 138	NA	56.7; 59.3	ADR	NA	4 Procedures
Von Figura et al, 2019	2017-2019	Parallel, 1 center	118; 122	63.6; 65.3	51.7; 62.3	Polypectomy duration	45.8; 38.5	None
*Costa Santos et al, 2019	2018-2019	Parallel, 1 center	81; 89	62.4 (total)	57.4 (total)	Mean SSL per colonoscopy	100; 100	NA
Karsenti et al, 2020	2017-2018	Cluster-randomized, cross-over, 1 center	1026; 1032	59.2; 57.4	47.4; 49	ADR	64.3; 62.2	NA
*Vanduangden et al, 2020	NA	Parallel, 1 center	200; 204	NA	NA	ADR	100; 100	NA

CC: Cuff Colonoscopy; SC: Standard Colonoscopy; ADR: Adenoma Detection Rate; EV: Endocuff Vision; MPP: Mean Polyp per Patient; SSL: Sessile Serrated Lesion; FOBT: Fecal Occult Blood Test

*Abstracts

Table 2. Outcomes of Meta-analysis comparing Cuff Colonoscopy and Standard Colonoscopy

Outcomes (Number of Studies)	CC % (95% CI)	SC % (95% CI)	Risk Ratio (95% CI; P value; I^2)	Quality of Evidence per GRADE
ADR (8)	49.8 (42.3 – 57.3)	45.6 (36.3 – 54.8)	1.12 (1.02 – 1.23; 0.02; 53%)	Low
PDR (5)	58.1 (49 .5 – 66.8)	53 (40.7 – 65.4)	1.13 (1.03 – 1.23, 0.009, 54%)	Low
SDR (5)	8.8 (3.1 – 14.4)	6.1 (0.7 – 11.5)	1.21 (0.90 – 1.61; 0.20; 18%)	Low
AADR (3)	11.4 (7.5 – 15.4)	10.8 (6.5 – 15.2)	1.11 (0.93 – 1.33; 0.49, 0%)	Low
P-ADR (3)	29.9 (20.1 -39.7)	25.5 (21.9 – 29)	1.26 (0.94 – 1.68; 0.12; 81%)	NA
D-ADR (3)	25.2 (23.2 – 27.3)	18.2 (13.7 – 22.8)	1.31 (1.09 – 1.58; 0.004; 41%)	NA
IIR (3)	50 (21.9 - 78.1)	58.7 (22.6 - 94.8)	0.83 (0.68 – 1.02; 0.07; 81%)	NA
CIR (7)	97.8 (96.4 – 99.2)	98.7 (97.7 – 99.7)	0.99 (0.98 – 1.01; 0.46; 68%)	NA
Adverse Events (7)	0.4 (0 – 0.7)	0.6 (0 – 1.1)	0.70 (0.35 – 1.38; 0.66; 0%)	NA

ADR: Adenoma Detection Rate; PDR: Polyp Detection Rate; SDR: Sessile Serrated Lesion Detection Rate; AADR: Advanced ADR; P-ADR: Proximal ADR; D-ADR: Distal ADR; CDR: Cancer Detection Rate; CIR: Cecal Intubation Rate; AE: Adverse Events; CC: Cuff Colonoscopy; SC: Standard Colonoscopy

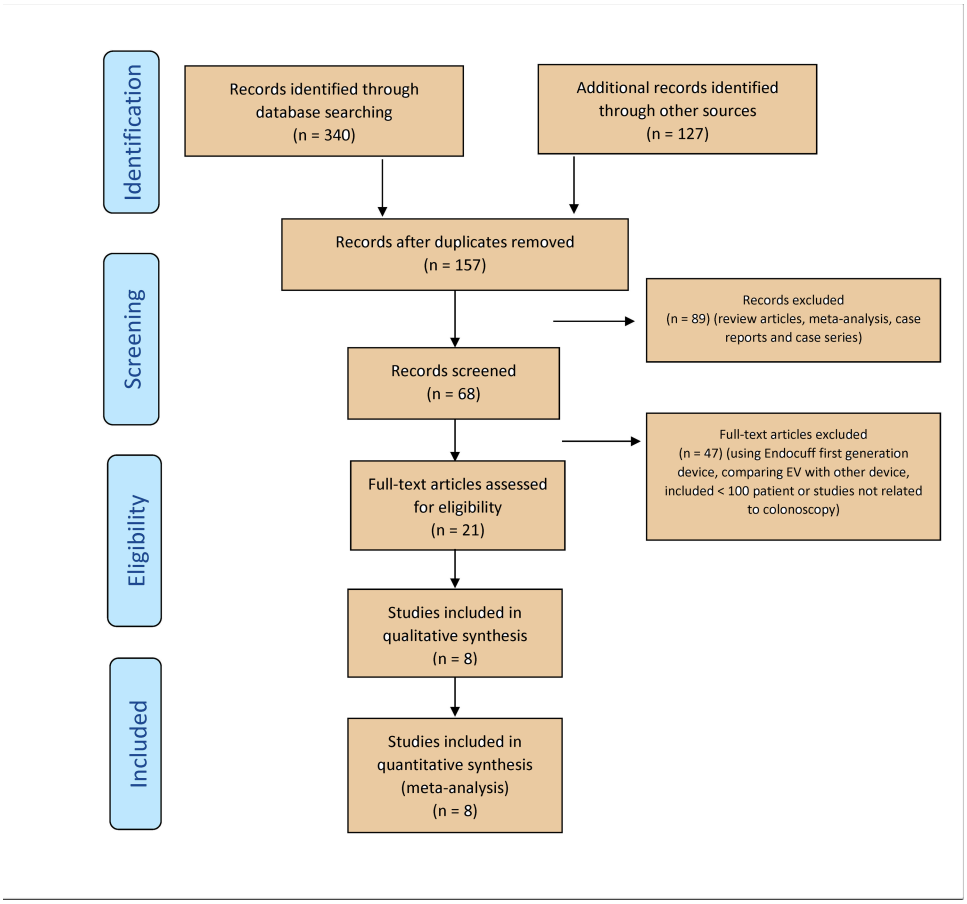
FIGURE LEGEND:

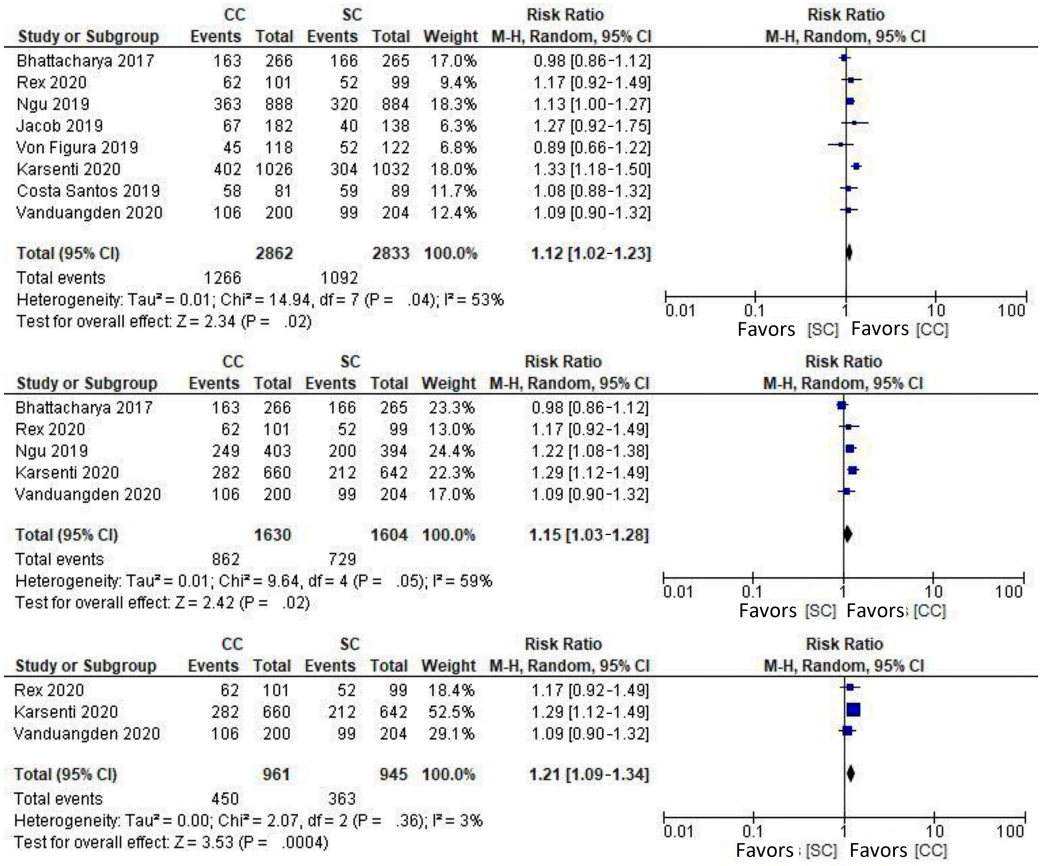
Figure 1: PRISMA Flowchart of study selection process

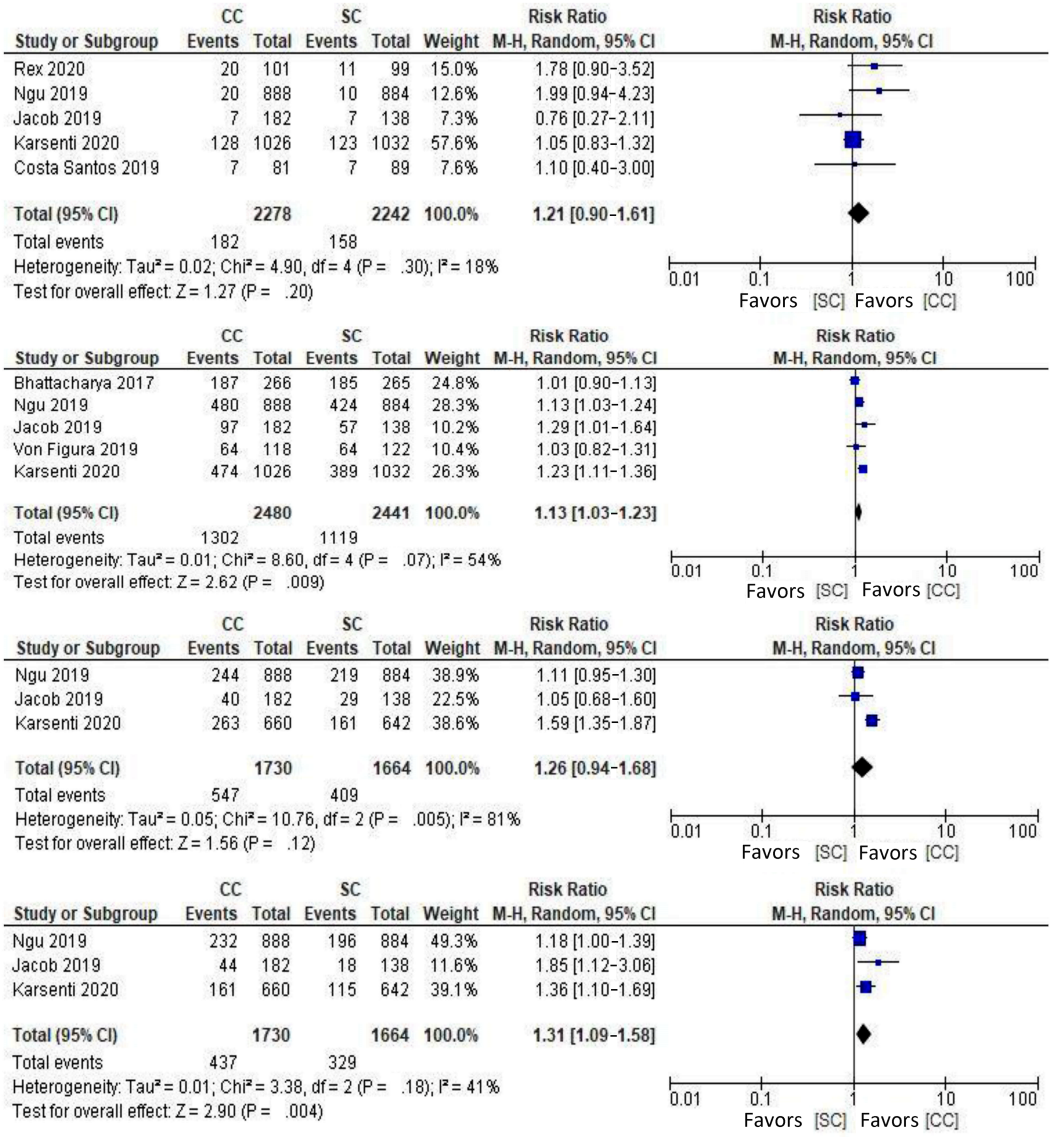
Figure 2: Comparison of ADR between Cuff assisted Colonoscopy and Standard Colonoscopy in form of Risk Ratio Forest Plot. A, All 7 RCTs. B, 5 RCTs Reporting Screening/Surveillance Population. C, Exclusion FOBT+ population from the screening/surveillance subgroup

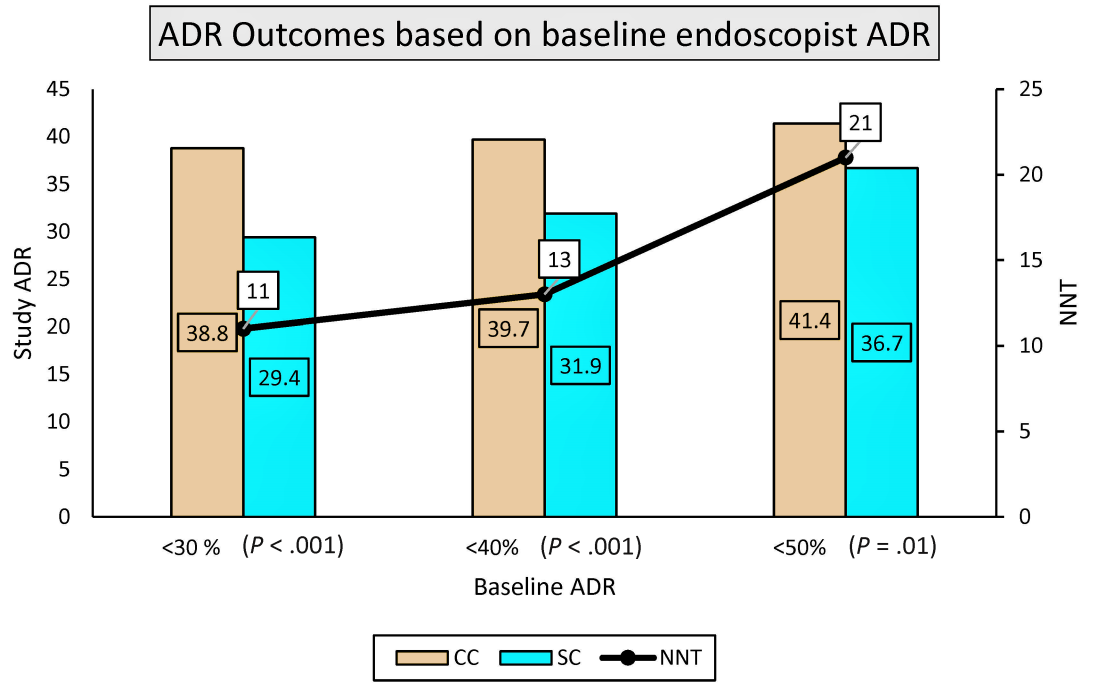
Figure 3: Comparison of outcomes between Cuff-assisted Colonoscopy and Standard Colonoscopy in form of Risk Ratio Forest Plot. A, PDR. B, SDR. C, P-ADR. D, D-ADR.

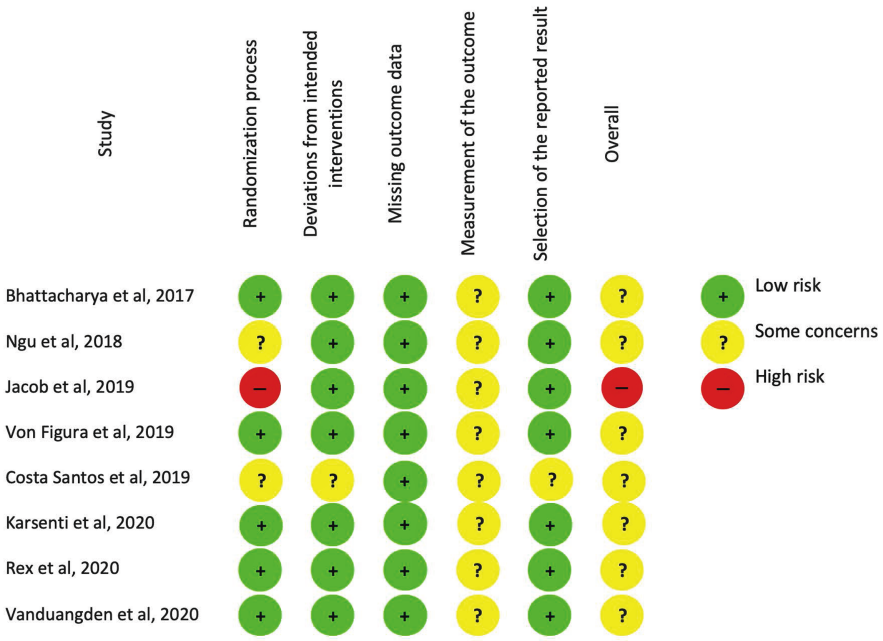
Figure 4: Graphical comparison of ADR between Cuff-assisted colonoscopy and Standard colonoscopy based on baseline endoscopist ADR

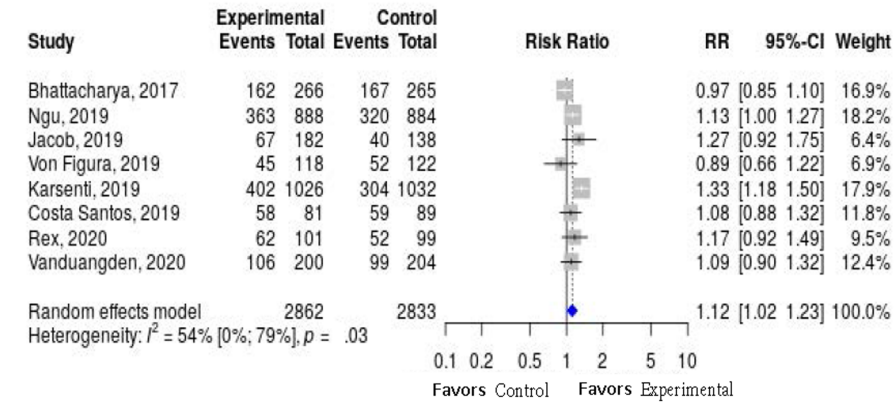

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 340)
Additional records identified through other sources (n = 127)
Records after duplicates removed (n = 157)
Records excluded (n = 89) (review articles, meta-analysis, case reports and case series)
Records screened (n = 68)
Full-text articles excluded (n = 47) (using Endocuff first generation device, comparing EV with other device, included < 100 patient or studies not related to colonoscopy)
Full-text articles assessed for eligibility (n = 21)
Studies included in qualitative synthesis (n = 8)
Studies included in quantitative synthesis (meta-analysis) (n = 8)


CC
SC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Bhattacharya 2017 163 266 166 265 17.0% 0.98 [0.86-1.12]
Rex 2020 62 101 52 99 9.4% 1.17 [0.92-1.49]
Ngu 2019 363 888 320 884 18.3% 1.13 [1.00-1.27]
Jacob 2019 67 182 40 138 6.3% 1.27 [0.92-1.75]
Von Figura 2019 45 118 52 122 6.8% 0.89 [0.66-1.22]
Karsenti 2020 402 1026 304 1032 18.0% 1.33 [1.18-1.50]
Costa Santos 2019 58 81 59 89 11.7% 1.08 [0.88-1.32]
Vanduangden 2020 106 200 99 204 12.4% 1.09 [0.90-1.32]
Total (95% CI) 2862 2833 100.0% 1.12 [1.02-1.23]
Total events 1266 1092
Heterogeneity: Tau² = 0.01; Chi² = 14.94, df = 7 (P = .04); I² = 53%
Test for overall effect: Z = 2.34 (P = .02)
0.01 0.1 1 10 100
Favors [SC] Favors [CC]
CC
SC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Bhattacharya 2017 163 266 166 265 23.3% 0.98 [0.86-1.12]
Rex 2020 62 101 52 99 13.0% 1.17 [0.92-1.49]
Ngu 2019 249 403 200 394 24.4% 1.22 [1.08-1.38]
Karsenti 2020 282 660 212 642 22.3% 1.29 [1.12-1.49]
Vanduangden 2020 106 200 99 204 17.0% 1.09 [0.90-1.32]
Total (95% CI) 1630 1604 100.0% 1.15 [1.03-1.28]
Total events 862 729
Heterogeneity: Tau² = 0.01; Chi² = 9.64, df = 4 (P = .05); I² = 59%
Test for overall effect: Z = 2.42 (P = .02)
0.01 0.1 1 10 100
Favors [SC] Favors [CC]
CC
SC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Rex 2020 62 101 52 99 18.4% 1.17 [0.92-1.49]
Karsenti 2020 282 660 212 642 52.5% 1.29 [1.12-1.49]
Vanduangden 2020 106 200 99 204 29.1% 1.09 [0.90-1.32]
Total (95% CI) 961 945 100.0% 1.21 [1.09-1.34]
Total events 450 363
Heterogeneity: Tau² = 0.00; Chi² = 2.07, df = 2 (P = .36); I² = 3%
Test for overall effect: Z = 3.53 (P = .0004)
0.01 0.1 1 10 100
Favors [SC] Favors [CC]

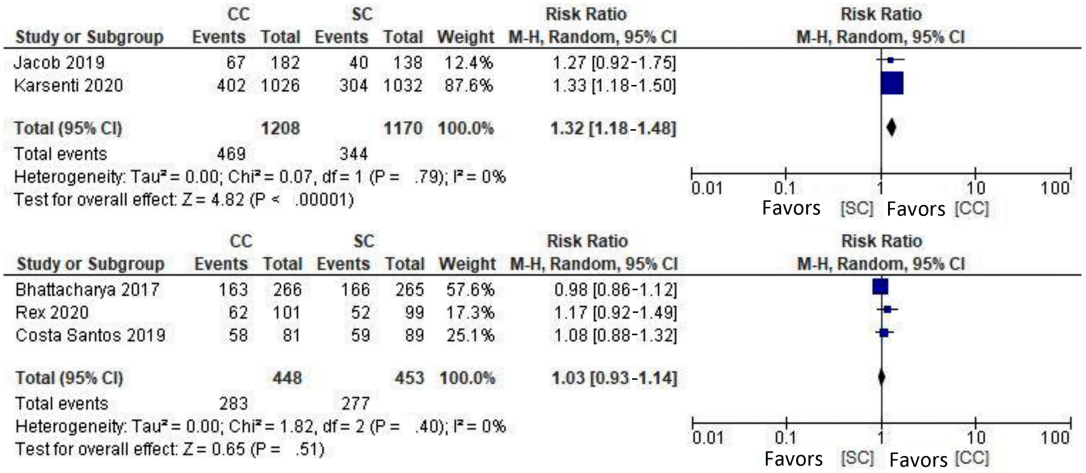

CC
SC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Rex 2020 20 101 11 99 15.0% 1.78 [0.90-3.52]
Ngu 2019 20 888 10 884 12.6% 1.99 [0.94-4.23]
Jacob 2019 7 182 7 138 7.3% 0.76 [0.27-2.11]
Karsenti 2020 128 1026 123 1032 57.6% 1.05 [0.83-1.32]
Costa Santos 2019 7 81 7 89 7.6% 1.10 [0.40-3.00]
Total (95% CI) 2278 2242 100.0% 1.21 [0.90-1.61]
Total events 182 158
Heterogeneity: Tau² = 0.02; Chi² = 4.90, df = 4 (P = .30); I² = 18%
Test for overall effect: Z = 1.27 (P = .20)
0.01 0.1 1 10 100
Favors [SC] Favors [CC]
CC
SC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Bhattacharya 2017 187 266 185 265 24.8% 1.01 [0.90-1.13]
Ngu 2019 480 888 424 884 28.3% 1.13 [1.03-1.24]
Jacob 2019 97 182 57 138 10.2% 1.29 [1.01-1.64]
Von Figura 2019 64 118 64 122 10.4% 1.03 [0.82-1.31]
Karsenti 2020 474 1026 389 1032 26.3% 1.23 [1.11-1.36]
Total (95% CI) 2480 2441 100.0% 1.13 [1.03-1.23]
Total events 1302 1119
Heterogeneity: Tau² = 0.01; Chi² = 8.60, df = 4 (P = .07); I² = 54%
Test for overall effect: Z = 2.62 (P = .009)
0.01 0.1 1 10 100
Favors [SC] Favors [CC]
CC
SC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Ngu 2019 244 888 219 884 38.9% 1.11 [0.95-1.30]
Jacob 2019 40 182 29 138 22.5% 1.05 [0.68-1.60]
Karsenti 2020 263 660 161 642 38.6% 1.59 [1.35-1.87]
Total (95% CI) 1730 1664 100.0% 1.26 [0.94-1.68]
Total events 547 409
Heterogeneity: Tau² = 0.05; Chi² = 10.76, df = 2 (P = .005); I² = 81%
Test for overall effect: Z = 1.56 (P = .12)
0.01 0.1 1 10 100
Favors [SC] Favors [CC]
CC
SC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Ngu 2019 232 888 196 884 49.3% 1.18 [1.00-1.39]
Jacob 2019 44 182 18 138 11.6% 1.85 [1.12-3.06]
Karsenti 2020 161 660 115 642 39.1% 1.36 [1.10-1.69]
Total (95% CI) 1730 1664 100.0% 1.31 [1.09-1.58]
Total events 437 329
Heterogeneity: Tau² = 0.01; Chi² = 3.38, df = 2 (P = .18); I² = 41%
Test for overall effect: Z = 2.90 (P = .004)
0.01 0.1 1 10 100
Favors [SC] Favors [CC]


ADR Outcomes based on baseline endoscopist ADR
Study ADR
NNT
45
40
35
30
25
20
15
10
5
0
25
20
15
10
5
0
38.8
29.4
11
39.7
31.9
13
41.4
36.7
21
<30 % (P < .001)
<40% (P < .001)
<50% (P = .01)
Baseline ADR
CC
SC
NNT


Study
Randomization process
Deviations from intended interventions
Missing outcome data
Measurement of the outcome
Selection of the reported result
Overall
Bhattacharya et al, 2017
Ngu et al, 2018
Jacob et al, 2019
Von Figura et al, 2019
Costa Santos et al, 2019
Karsenti et al, 2020
Rex et al, 2020
Vanduangden et al, 2020
Low risk
Some concerns
High risk

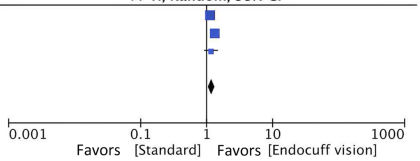


Test for funnel plot asymmetry (Rucker): p= .294 (may be falsely significant if < 10 studies)


CC
SC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Jacob 2019 67 182 40 138 12.4% 1.27 [0.92-1.75]
Karsenti 2020 402 1026 304 1032 87.6% 1.33 [1.18-1.50]
Total (95% CI) 1208 1170 100.0% 1.32 [1.18-1.48]
Total events 469 344
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = .79); I² = 0%
Test for overall effect: Z = 4.82 (P < .00001)
0.01 0.1 1 10 100
Favors [SC] Favors [CC]
CC
SC
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Bhattacharya 2017 163 266 166 265 57.6% 0.98 [0.86-1.12]
Rex 2020 62 101 52 99 17.3% 1.17 [0.92-1.49]
Costa Santos 2019 58 81 59 89 25.1% 1.08 [0.88-1.32]
Total (95% CI) 448 453 100.0% 1.03 [0.93-1.14]
Total events 283 277
Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 2 (P = .40); I² = 0%
Test for overall effect: Z = 0.65 (P = .51)
0.01 0.1 1 10 100
Favors [SC] Favors [CC]

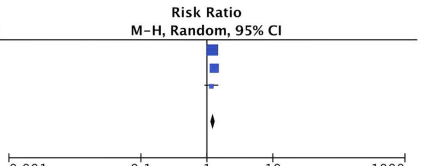
Study or Subgroup	Endocuff vision Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Ngu 2019	363	888	320	884	41.8%	1.13 [1.00-1.27]	2019
Karsenti 2020	402	1026	304	1032	40.7%	1.33 [1.18-1.50]	2020
Rex 2020	62	101	52	99	17.5%	1.17 [0.92-1.49]	2020
Total (95% CI)		**2015**		**2015**	**100.0%**	**1.21 [1.08-1.36]**	
Total events	827		676				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.72$, df = 2 (P = .16); $I^2 = 46\%$
Test for overall effect: Z = 3.27 (P = .001)



Study or Subgroup	Endocuff vision Events	Total	Standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Ngu 2019	249	403	200	394	49.3%	1.22 [1.08-1.38]	2019
Karsenti 2020	282	660	212	642	37.9%	1.29 [1.12-1.49]	2020
Rex 2020	62	101	52	99	12.8%	1.17 [0.92-1.49]	2020
Total (95% CI)		**1164**		**1135**	**100.0%**	**1.24 [1.14-1.35]**	
Total events	593		464				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.68$, df = 2 (P = .71); $I^2 = 0\%$
Test for overall effect: Z = 4.83 (P < .00001)



List of Abbreviations-

ADR – Adenoma Detection Rate

APC – Mean Adenomas Per Colonoscopy

A-ADR – Advanced Adenoma Detection Rate

CC – Cuff Colonoscopy

CIR – Cecal Intubation Rate

D-ADR – Distal Adenoma Detection Rate

EV – Endocuff Vision

IIR – Ileal Intubation Rate

MWT – Mean Withdrawal Time

NNT – Number Needed to Treat

PDR – Polyp Detection Rate

P-ADR – Proximal Adenoma Detection Rate

RCT - Randomized Controlled Trial

RR – Risk Ratio

SC – Standard Colonoscopy

SDR – Sessile Serrated Lesion Detection Rate