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A prospective international multisite randomized controlled trial of water exchange with and without distal cap(s) in adenoma detection

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Abstract

Background Interval cancers are linked to a low adenoma detection rate (ADR), prompting calls for benchmark-guided ADR performance improvement. Although water exchange and a straight cap (CAP) have been reported to independently improve ADR, the effects of Daisycuff™ and Endocuff Vision® remained unknown. We hypothesized that selected cap(s) could increase ADR and related water exchange outcomes.

Methods Subjects were randomized to No cap, or CAP, Daisycuff™ and Endocuff Vision® at 7, 5 and 2 sites. The primary outcome was ADR. Outcomes were compared for No cap vs. the above randomized caps.

Results Demographic and historic data revealed adequate randomization. Despite variations in site-specific pretrial ADR, the aggregated data showed that the ADR of No cap (45.6%) exceeded the latest benchmark (35%). Each added cap increased the ADR, and the difference using Daisycuff™(52.8%) approached statistical significance (P=0.05). In the right colon, CAP and Daisycuff™ significantly increased ADR. In the left colon, Daisycuff™ significantly increased adenoma per colonoscopy. Factors that improved adenoma detection were consistent with published reports. Detection rates based on site, indication, sedation type, polyp size, shape and pathology in the No cap group were consistent with conventional data and were not influenced by the caps.

Conclusions The significantly higher right-colon ADRs with CAP and Daisycuff™ suggest potential clinical relevance for reducing interval cancers. Although water exchange with or without caps yields ADRs that surpass the benchmark, the positive findings for selected cap(s) need to be confirmed in order to enhance the options for further improvement of water exchange.

Keywords Water exchange colonoscopy, distal cap, adenoma detection rate

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Introduction

Data mining studies have reported an association between a low adenoma detection rate (ADR) and interval cancers diagnosed before the next recommended surveillance colonoscopy [1]. New modifications of conventional colonoscopy have been proposed, aimed at decreasing interval cancers by identifying and removing additional premalignant adenomas [2]. A benchmark ADR has been proposed to encourage and guide improvement

(e.g., with water exchange added to conventional colonoscopy) [3].

Looking behind folds increases the exposure of the mucosa [4]. A randomized controlled trial in conventional colonoscopy, reported by high detectors in the United States in 2012, showed that a distal straight cap (CAP) increased ADR by 13% (69% vs. 56%, P=0.009) [5]. An earlier Asian report, however, showed a contrary result (30.5% vs. 37.5%, P=0.018) [6], possibly due to residual feces lodged in the CAP interfering with mucosal inspection. No published ADR data existed for the Daisycuff™ or Endocuff Vision® in conventional or water exchange colonoscopy at the time of planning of this study protocol (2014-2016).

Adequate bowel cleanliness, coupled with an enhanced inspection technique, improves ADR [7]. Water exchange (the infusion and suction of water during colonoscope insertion) augments the removal of residual fecal debris, resulting in a cleaner colonic lumen for withdrawal inspection [8]. Three in-press randomized controlled trials in 2017 [9-11] showed that water exchange significantly increased ADR when compared with conventional colonoscopy. We postulated that CAP, which facilitates exposure of the mucosa, could increase ADR when added to water exchange.

Unpublished preliminary data suggest that Daisycuff™ [12] added to water exchange tends to increase ADR. Daisycuff™ was the initial planned controlled comparison. Insufficient compliance documentation in 2016, however, led to unexpected suspension of approval of Daisycuff™ by the local institution review boards at 2 of the 7 study sites. The commercially available Endocuff Vision® [13] was substituted to preserve the participation of coinvestigators committed to performing the comparison between water exchange with and without CAP.

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Conflict of Interest: None

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We tested the hypothesis that, in patients undergoing colonoscopy for screening, surveillance, or positive fecal immunochemical test (FIT+) or fecal occult blood test (FOBT+), ADR would be higher for water exchange with CAP than for water exchange with No cap. Daisycuff™ and Endocuff Vision® were included as comparative controls.

Patients and methods

This prospective, multicenter, randomized controlled trial was performed at 7 sites (3 in Asia, 1 in Europe, and 3 Veterans Affairs centers in the United States). The diversity of investigators, sites and patient mix aimed to maximize the generalizability of the results. Recruitment took place from July 2018 to October 2022, and was closed during the COVID-19 pandemic. The protocol was approved by Institutional Review Boards at each study site, and by the University of California at Los Angeles. It was registered with ClinicalTrials.gov (NCT03566615). Signed informed consent was obtained.

Inclusion criteria

Male and female patients (50-80 years old) who underwent colonoscopy for screening, surveillance or FIT+/FOBT+, and who expressed interest in participating in the study, were assessed for eligibility.

Exclusion criteria

Patients who declined to provide informed consent, or had known colonic obstruction, inflammatory bowel disease, active gastrointestinal bleeding or previous colonic resection, were excluded. Participants were allocated to 1 of the following study arms in a 1:1:1 ratio: No cap, CAP, and comparative control caps (Daisycuff™ and Endocuff Vision®). The statistician prepared the codes of computer-generated random numbers (variable block sizes of 3 and 6), with separate parallel randomization at each site, and the codes were placed inside opaque envelopes. Randomization was stratified by investigators, indication and patient sex. When the colonoscopist was ready to insert the colonoscope, the codes were revealed by the coordinator, who also assisted in recording the data.

Conscious sedation was used at all study sites. Based on subjects' preference, at the Dalin Tzu Chi Hospital, Chiayi, Taiwan, propofol was also used; and at the Presidio Ospedaliero CTO, Iglesias, Italy, sedation was available on demand. Water exchange with sterile water was used, as described previously [8-11]. Abdominal compression, changing patient position and stiffening of the colonoscope were applied as needed. After reaching the cecum, air insufflation was used to distend the colon. Mucosal inspection, biopsy (cold forceps), and polypectomy (hot or cold snare) were performed during withdrawal (>6 min). Because of a possible effect on the ADR,

a second look (being investigated elsewhere) [14] was not used to standardize comparisons.

Bowel preparation

A standardized local split-dose was used. Instructions were provided by the schedulers and research coordinators. Patients with diabetes, chronic constipation or a known history of poor bowel preparation were asked to refrain from solid food intake for extra days before colonoscopy.

Management of polyps

To optimize insertion time, all polyps were removed during withdrawal. Small polyps (size <7 mm) were biopsied with forceps. Polyps >7 mm were removed by snare (hot or cold). Very large polyps with features suggestive of malignancy were biopsied for diagnosis, with removal in the same session, or referred to a local interventionalist. All resected polyps underwent pathology assessment by local pathologists.

Fig. 1 shows the distal attachments inside the distended colon during withdrawal. CAP was a transparent straight cap (Disposable Distal Attachment; Olympus Medical Systems Corp., Tokyo, Japan) [5,6,15]. The comparative Daisycuff™ cap (Visualization Balloons LLC, West Caldwell, NJ) [12] was a ring with 10 "petals" distributed around the circumference. One Daisycuff™ was placed at the 20-cm mark and 1 at the distal tip (manufacturer's instruction). The colon was pleated on the instrument shaft. Endocuff Vision® (Olympus) [13] had a single row of 8 flexible arms. When the tip of the colonoscope was pressed against a fold, an enhanced view of the back side of the fold was obtained.

Study outcomes

The primary outcome was ADR, defined as the proportion of subjects with at least 1 adenoma of any size in any location, irrespective of the indications for the procedure [16,17]. ADR of the right colon (cecum to hepatic flexure) and left colon (transverse to rectum) were secondary outcomes.

Sample size calculation

The following ADRs were used in sample size estimates: water exchange with No cap (36%) [8], water exchange with CAP (48%) (unpublished pilot data), and water exchange with Daisycuff™ (45%) (unpublished pilot data). An on-line sample size calculator comparing 2 proportions (https://select-statistics.co.uk/calculators/sample-size-calculator-two-proportions/) was used. The sample size of 464 (No cap vs. CAP or Daisycuff™) was obtained. About 464 cases in each arm were adopted to detect a difference with a power of 80% and a 2-sided significance level of 0.05.

The sample size was not recalculated when the substitution of Endocuff Vision® for Daisycuff™ was made at 2 of the study sites.

Statistical analysis

In the intention-to-treat analytical phase, the adenoma data from all investigators were combined. Analysis of variance and pairwise tests were used. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, and continuous variables with Student's *t*-test, Kruskal-Wallis, or Mann-Whitney nonparametric test, as appropriate. Univariate and multivariate logistic regression analysis were used to assess factors associated with adenoma detection. Analyses were performed using R (version 4.4.1) and RStudio (version 2024.04.2) software for Windows. A P-value of <0.05 was the criterion of statistical significance. Confidence intervals (CI) were calculated.

Results

A total of 3794 patients expressed interest in participation, and 2280 of them were deemed potentially eligible. Of these patients, 700 declined consent and 200 met the exclusion criteria (Fig. 2): thus, 1380 were consented and examined with water exchange. They were randomized to No cap (N=464), CAP (N=456) and comparative caps (N=460). Randomization distributed the subjects evenly (Supplementary Table 1): mean age 60 years, 30% female, body mass index 26-27 kg/m^2 and

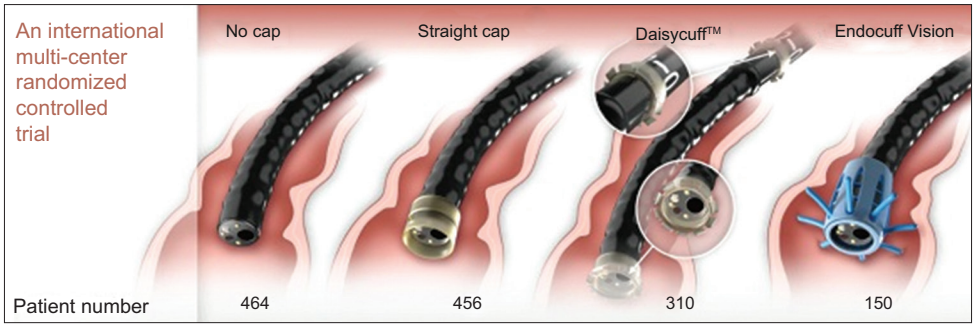

Figure 1 Distal attachments are depicted in the withdrawal view with distension of the colonic lumen. Straight cap is CAP

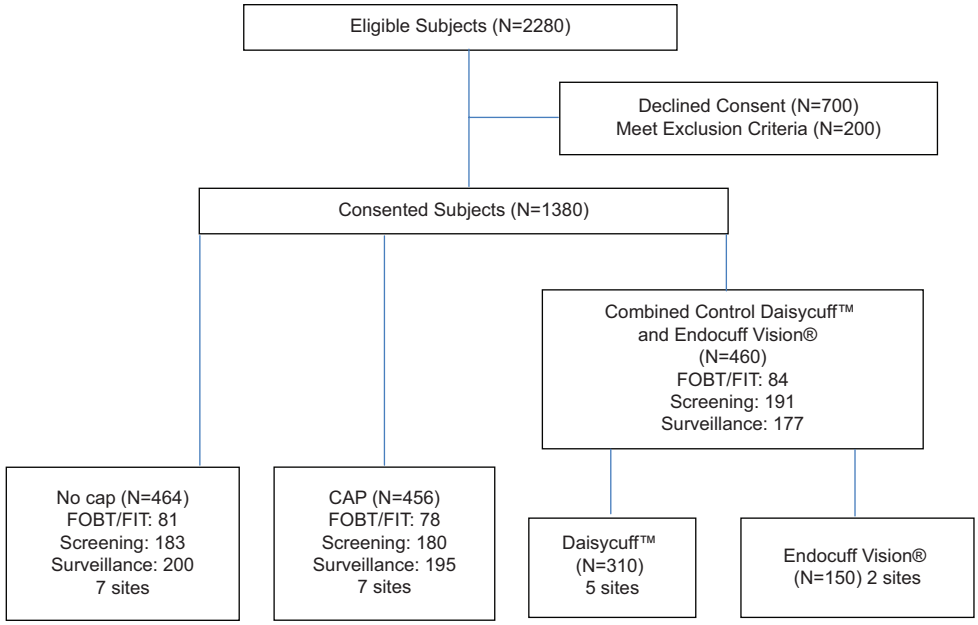

Figure 2 Study flow chart. A total of 3794 participants expressed interest when informed of the study. Of these, 1380 patients consented and were randomized.
**Missing data included 3 cases in the CAP group and 8 cases in the combined Daisycuff™ and Endocuff Vision® group.*
FIT, fecal immunochemical test; FOBT, fecal occult blood test; CAP, straight cap

smoking history 36%. The proportions of patients with a family history of colon cancer, specific medical history, self-reported abdominal discomfort, use of narcotic medication, prior colonoscopy, indications of colonoscopy, race and ethnic composition, household income, employment and education status were comparable.

The indications for colonoscopy in the current trial are shown in Table 1. Table 1 also shows some site-related variations in published historical water exchange ADRs, which reflected endoscopist experience, patient mix, procedural-related factors, or local institutional context. In keeping with the original design to assess aggregated data, the exact site identification is not displayed.

Table 2 shows procedural data. Water exchange was applied appropriately during insertion to the cecum with nearly equal mean volumes of water infused 852 (564) mL (n=452) and suctioned 818 (592) mL (n=450) in the No cap group. The other cap groups showed similar patterns. Cecal intubation failed in <5%. Poor bowel preparation was observed during withdrawal in <6%. The withdrawal time did not differ among the groups.

To ensure appropriate comparison by investigators, the groups that randomized similar caps were analyzed separately. Inclusion of all 7 sites maximized the number of patients in the No cap vs. CAP comparison. The ADR was 45.6±2.3% (No cap) and 49.6±2.3% (CAP) (P=0.227) (Table 3A); and CAP significantly increased the ADR in the right colon: 29.7±2.1% vs. 23.5±2%, (P=0.034; 95%CI -12.1% to -0.3%) (Table 3B). Data from the 5 sites that randomized No cap, CAP and Daisycuff™ showed Daisycuff™ to be marginally superior in terms of ADR: Daisycuff™ vs. No cap 52.8±2.8% vs. 44.9±2.8% (P=0.050; 95%CI -16% to 0.3%). Daisycuff™ significantly improved ADR in the right colon: 32.0±2.7% vs. 24.4±3.4% (P=0.027; 95%CI -15.4% to -0.6%) (Table 3C). In the left colon, Daisycuff™ had a significantly better adenoma per colonoscopy score (APC): 0.417±0.812 vs. 0.272±0.616 (P=0.012; 95%CI -0.259 to -0.031) (Table 3D).

Tables 3E and 3F show that Endocuff Vision® did not significantly change ADR or APC.

Several ADR differences were nearly significant. For example, overall ADR, Daisycuff™ (52.8%) vs. No cap (44.9%) (P=0.05; 95%CI -16% to 0.3%) (Table 3C); Endocuff Vision® 58.0±4% vs. No cap 47.0±4.1% (P=0.057; 95%CI -22.9% to 0.9%) (Table 3E); and Endocuff Vision® for both right colon ADR 32±3.8% vs. 22.5±3.4% (P=0.066; 95%CI -20.2% to 1.2%) and left colon ADR 47.3±4.1% vs. 35.8±3.9% (P=0.0422; 95%CI -23.3% to 0.2%) (Table 3F).

Table 4 shows a univariate and multivariate logistic regression analysis of the aggregated data. Long withdrawal time, alcohol history and older age were associated with high adenoma counts (APC≥3) in the multivariate logistic analysis (Table 4B).

Supplementary Table 2A shows site-related variations in study outcome ADR and Supplementary Table 2B shows ADR data by site which did not have significant effects on ADR.

Supplementary Tables 3A-C show ADR comparisons of No cap vs. respective caps based on colonoscopy indication. Only in the case of Endocuff Vision®, was the ADR of a FIT+ indication significantly higher than that of No cap 66.2% vs. 57.6% (P=0.026; 95%CI -0.372 to -0.012). Supplementary Table 4 shows that varying the mode of sedation did not affect the ADR of different caps, except that CAP had a significantly greater ADR compared with No cap (P=0.008; 95%CI 0.25-

Table 1 Site-related variations in historical baseline ADR and indications

Variations			Historical water exchange ADR	Indication (%)		
Site	# of endoscopists	# of subjects		FIT+/FOBT+	Screening	Surveillance
A	3	183	36%	4	12	81
B	2	151	44%	1	66	32
C	4	156	42%	3	14	83
D	2	249	29.4%	6	76	18
E	2	200	49.8%	45	19	36
F	3	247	49.3%	45	42	11
G	1	194	72%	7	40	53

Historical ADR was based on the following references: GIE 2010;**72**:693-700; Endoscopy 2010;**42**; AJG 2017;**112**:568; GIE 2017;**86**:192-201; Endoscopy 2017;**49**:456; JCG 2021
In keeping with the original design to assess aggregated data, the exact site identification is not reported. The historical data were prepared by de-identifying the site
ADR, adenoma detection rate; FIT, fecal immunochemical test; FOBT, fecal occult blood test

Table 2 Procedure-related characteristics by randomized group

Characteristics	No cap n=464	CAP n=456	Control Daisycuff™ & Endocuff Vision® n=460	P-value*
Insertion time, mean±SD, min	12.1±8.0 (n=453)	11.9±8.6 (n=448)	11.8±8.6 (n=442)	0.919
Water infused during insertion, mean±SD, mL	852±564 (n=452)	805±648 (n=446)	841±599 (n=446)	0.475
Water suctioned during insertion, mean±SD, mL	818±592 (n=450)	806±684 (n=446)	837±617 (n=445)	0.760
Withdrawal time, mean±SD, min	12.4±7.5 (n=453)	13.2±7.2 (n=447)	12.0±6.4 (n=439)	0.037**
Poor preparation	4 (0.9) %	5 (1.1) %	6 (1.3) %	0.810
Failed cecal intubation	2.4% (n=458)	2.2% (n=452)	4.1% (n=459)	0.173

*ANOVA (1-way analysis of variance); **On further scrutiny, the normality assumption (needed for ANOVA test) was not born out well in our data. Pairwise test was performed. No cap vs. CAP was 0.81 (95%CI -0.15 to 1.28) and No cap vs. control Daisycuff™ & Endocuff Vision® was -0.37 (95%CI -1.29 to 0.55); neither difference was statistically significant
CAP, straight cap; CI, confidence interval; SD, standard deviation

Table 3A ADR and APC: No cap vs. CAP (data from 7 sites). Data are mean and confidence interval

Variable	No cap (N=463)	CAP (N=456)	P (CAP vs. no CAP)
ADR	45.6±2.3%	49.6±2.3%	0.227 (-10.7%, 2.7%)
APC	0.991±1.522	1.119±1.637	0.222 (-0.333, 0.077)

0.463) in subjects with no sedation. Supplementary Tables 5-11 show that site, polyp size (large, diminutive, small), shape (sessile, flat, pedunculated) and pathology (serrated) did not affect the ADR of different caps. In the current trial there were only 3 polyps with high-grade dysplasia, a number too small for further analysis.

Discussion

The procedure characteristics indicated that water exchange was appropriately applied (Table 2). Despite site-specific variations in published baseline water exchange ADR (Table 1), the aggregated data confirmed the efficacy of the novel method: i.e. the ADR in all study groups of water exchange, with or without selected cap (Table 3), surpassed the benchmark (35%) [16]. A more comprehensive metric that may be less prone to variability and reflects more thorough mucosal inspections is APC [18], which measures the average number of adenomas found per procedure. The proposed benchmarks are 0.46-0.50 for men and 0.13-0.20 for women [18]. Our APC data surpassed the benchmark (Table 3): No cap 0.991±1.522, CAP 1.119±1.637, Daisycuff™ 1.094±1.473 and Endocuff Vision® 1.313±1.618.

Logistic regression analysis revealed several factors correlated with high APC (Table 4), confirmed their importance [19-21], and enhanced the credibility of the novel cap findings. There were variations in site-specific pretrial ADR (Table 1) and current ADR outcomes (Supplementary Table 2A) and a lack of site-based cap effects on ADR (Supplementary Table 2B). There was a lack of significant influence of colonoscopy indications on ADR, except for the FIT+ indication (Supplementary Tables 3A-C). These variations were evened out by the inclusion of multiple investigators, whose outcome data were aggregated to yield the above benchmark ADR and APC (Table 3).

Table 3B ADR and APC in right vs. left colon – No cap vs. CAP (data from 7 sites)

Variable	No Cap (N=463)	Cap (N=456)	No Cap	CAP	P (CAP vs. no CAP)
Right colon ADR	No Cap	CAP	23.5±2%	29.7±2.1%	0.034 (-12.1%, -0.3%)
Left colon ADR	No Cap	CAP	35.4±2.2%	37.7±2.3%	0.480 (-8.7%, 4.2%)
Right colon APC	No Cap	CAP	0.65±1.198	0.692±1.159	0.594 (-0.194, 0.111)
Left colon APC	No Cap	CAP	0.341±0.773	0.427±0.788	0.095 (-0.187, 0.015)

Table 3C ADR and APC analysis of 5 sites that randomized No cap vs. CAP vs. Daisycuff™

Variable	No Cap (N=312)	CAP (N=311)	P (CAP vs. no Cap)	Daisycuff™ (N=309)	P (Daisycuff™ vs. No Cap)
ADR	44.9±2.8%	48.9±2.8%	0. 299 (-12.3%, 4%)	52.8±2.8%	0.050 (-16%, 0.3%)
APC	0.981±1.47	1.035±1.435	0.639 (-2.1e-05, 7.12e06)	1.094±1.473	0.618 (-0.288, 0.171)

Table 3D ADR and APC in right vs. left colon – No cap vs. CAP vs. Daisycuff™ (data from 5 sites)

Variable	No Cap (N=312)	Cap	No Cap	Cap	P (Cap vs. No Cap)
Right colon ADR	No Cap (N=312)	CAP (N=311)	24.4±2.4%	29.4±2.6%	0.134 (-12.6%, 1.9%)
Right colon ADR	No Cap (N=312)	Daisycuff™ (N=309)	24.4±3.4%	32.0±2.7%	0.027 (-15.4%, -0.6%)
Left colon ADR	No Cap (N=312)	CAP (N=311)	35.3±2.7%	35.5±2.7%	0.953 (-8%, 7.5%)
Left colon ADR	No Cap (N=312)	Daisycuff™ (N=309)	35.3±2.7%	36.2±2.7%	0.797 (-8.9%, 6.9%)
Right colon APC	No Cap (N=312)	CAP (N=311)	0.708±1.253	0.668±1.1016	0.657 (-0.139, 0.220)
Right colon APC	No Cap (N=312)	Daisycuff™ (N=309)	0.708±1.253	0.676±1.012	0.727 (-0.148, 0.211)
Left colon APC	No Cap (N=312)	CAP (N=311)	0.272±0.616	0.368±0.746	0.083 (-0.203, 0.012)
Left colon APC	No Cap (N=312)	Daisycuff™ (N=309)	0.272±0.616	0.417±0.812	0.012 (-0.259, -0.031)

Table 3E ADR and APC analysis of 2 sites that randomized No cap vs. CAP vs. Endocuff Vision®

Variable	No Cap (N=151)	CAP (N=144)	P (CAP vs. No Cap)	Endocuff Vision® (N=150)	P (Endocuff Vision® vs. No Cap)
ADR	47.0±4.1%	50.7±4.2%	0.528 (-15.8%, 8.4%)	58.0±4%	0.057 (-22.9%, 0.9%)
APC	1.103±1.629	1.299±1.997	0.181 (0.704, 0.133)	1.313±1.618	0.945 (0.433, 0.404)

Table 3F ADR and APC in right vs. left colon – No cap vs. CAP vs. Endocuff Vision® (data from 2 sites)

Location	No cap	Cap	ADR or APC No cap	ADR or APC Cap	P (Cap vs. No CAP)
Right colon ADR	No cap (N=151)	CAP (N=144)	22.5±3.4%	30.6±3.8%	0.119 (-18.8%, 2.7%)
Right colon ADR	No cap (N=151)	Endocuff Vision® (N=150)	22.5±3.4%	32±3.8%	0.066 (-20.2%, 1.2%)
Left colon ADR	No cap (N=151)	CAP (N=144)	35.8±3.9%	42.4±4.1%	0.246 (-18.4%, 5.2%)
Left colon ADR	No cap (N=151)	Endocuff Vision® (N=150)	35.8±3.9%	47.3±4.1%	0.0422 (-23.3%, 0.2%)
Right colon APC	No cap (N=151)	CAP (N=144)	0.53±1.07	0.743±1.423	0.148 (-0.503, 0.076)
Right colon APC	No cap (N=151)	Endocuff Vision® (N=150)	0.53±1.07	0.747±1.07	0.099 (-0.475, 0.042)
Left colon APC	No cap (N=151)	CAP (N=144)	0.483±1.012	0.556±0.859	0.509 (-0.287, 0.143)
Left colon APC	No cap (N=151)	Endocuff Vision® (N=150)	0.483±1.012	0.567±0.901	0.452 (-0.301, 0.134)

P-values are based on logistic regression with cap type as independent variable. Data are mean±standard deviation. Bracketed numbers show 95% confidence intervals. Right colon (cecum, ascending, hepatic); left colon (transverse, descending, sigmoid, rectum). In the right colon, CAP and Daisycuff™ significantly increased ADR. In the left colon, Daisycuff™ significantly increased APC

ADR, adenoma detection rate; APC, adenoma per colonoscopy. No cap, water exchange only. CAP, straight cap

Table 4A Univariate logistic regression analysis with adenoma per colonoscopy as dependent variable and individual covariates as independent variables

Significant associations		P-value
Long withdrawal time	High counts	<0.001
Alcohol history		<0.001
Older age		<0.001
Easy examination as assessed by colonoscopist		0.009
Diabetes		0.003
Use of supine position	Low counts	0.003

Univariate logistic regression with high/low counts as dependent variable and individual covariates as independent variables. High counts (number of adenomas ≥3 per colonoscopy)

Table 4B Multivariate logistic regression

Predictors	Odds Ratio (OR)	95%CI for the OR	P-value
Withdrawal time	1.113	(1.088, 1.141)	<0.001
Alcohol use*	2.059	(1.371, 3.054)	<0.001
Age	1.026	(1.004, 1.048)	0.0184
Diabetes	1.417	(0.956, 2.073)	0.077
Use of supine position	0.718	(0.479, 1.059)	0.101
Assessment: Easy	1.278	(0.214, 24.528)	0.8266
Assessment: Somewhat difficult	1.228	(0.203, 23.696)	0.8515
Assessment: Very difficult	1.364	(0.213, 26.89)	0.7815

P-values are based on logistic regression. OR, odds ratio; CI, confidence interval
In univariate logistic regression analysis several factors were correlated with high adenoma detection (Table 4A). They confirmed literature reports of their importance. Such confirmation enhanced the credibility of the novel cap findings. Multivariate logistic regression analysis shows comparable results except that the use of the supine position was no longer significant.
*Alcohol produces acetaldehyde, a carcinogenic metabolite that causes deoxyribonucleic acid damage, impairs deoxyribonucleic acid repair, and disrupts methylation. Alcohol and its metabolites induce oxidative stress, generating reactive oxygen species that further damage deoxyribonucleic acid and cellular structures. Alcohol disrupts 1-carbon metabolism and folate pathways, leading to epigenetic dysregulation and aberrant gene expression. Alcohol alters the gut microbiome and increases intestinal permeability, promoting inflammation, bacterial translocation, and local immunosuppression. Chronic alcohol exposure impairs immune surveillance and promotes a proinflammatory environment, both of which facilitate neoplastic transformation

The effect of sedation type on ADR is variable. No significant difference was shown in ADR between conscious vs. deep sedation (50% vs. 54%; P=0.394) [22], and between moderate vs. deep sedation (35.9% vs. 37.3%; P=0.82) [23]. A study that included 196 endoscopists and 52,506 patients revealed that the anesthesia state did not enhance the ADR [24]. Some findings even suggested that the ADR may be higher for endoscopy without anesthesia [25]. While the use of propofol-based anesthesia was associated with better patient satisfaction and pain levels, ADR was not enhanced [26]. In the current study, sedation type had no significant impact on the effect of caps on ADR (Supplementary Table 4), except that the analysis of data from 5 sites found that CAP showed a significantly higher ADR than No cap in unsedated subjects (P=0.008; 95%CI 0.25-0.463).

Large colon polyps (>10 mm in size) account for about 5% of all colon polyps. Their presence indicates a higher risk of cancer development. The prevalence of large polyps was reported to be in the range of 6-7% [27]. The earliest water exchange report described 16.7% of patients with large (>10 mm) polyps [8]. The current study found the following large polyp detection rates (Supplementary Table 5): No cap (8.6%), CAP (8.6%), Daisycuff™ (6.9%), Endocuff Vision® (14.4%), all higher than the values reported by Leiberman *et al* [27]. The current data show that the detection rates of diminutive and small polyps were consistent with reported data [27-30]. The detection rate of diminutive and small polyps was not affected by the caps (Supplementary Tables 6 and 7).

The proportion of flat polyps varies by study. One report indicated that 24.2% of polyps could be flat [29]. While not the most common shape, flat polyps are important, because they are harder to find and remove completely during a colonoscopy and may carry a higher risk of containing cancer or high-grade dysplasia. The detection rates of flat polyps (Supplementary Tables 8 and 9) in the present study were comparable to published data, and were not affected by the caps.

Serrated polyps have variable definitions, which continue to evolve. The sessile serrated polyp detection rate has been reported at 3.3-5.1% [31]. One review reported a sessile serrated polyp detection rate of 2.5% (1.5-3.8%) [32] and another 3.3% (2.2-4.8%) [33]. A serrated polyp detection rate of 3% was linked to the development of interval cancers and considered as minimum cutoff point of competency, but striving for higher rates is critical for reducing interval colorectal cancer risk and improving colonoscopy quality [34]. The detection rates of serrated polyps in the current study were of a comparable order of magnitude (Supplementary Table 10): No cap (3.02%), CAP (4.4%), Daisycuff™ (5.57%), Endocuff Vision® (2.05%). The study methods provided benchmark performance but did not appear to modify the detection rates. The proportion of colon polyps with dysplasia varies, but studies show that roughly 20-30% have high-grade dysplasia [30]. We found only 3 mentions of "high-grade dysplasia" in our data, insufficient for further analysis.

This study was carried out by endoscopists at sites with a record of improving ADR using water exchange [8-11]. There were nearly equivalent mean volumes of water infused and suctioned during insertion (Table 2). Compared with the first description of water exchange, the mean procedure time improved (decreased) from 56 min [9] to ~25 min (Table 2). All withdrawals exceeded 9 min [35] and were close to 13 min [19]. The CAP protruded 2 mm beyond the tip of the colonoscope, restricted peripheral vision and possibly prolonged the withdrawal time, although the difference did not reach significance (Table 2).

In a recent meta-analysis, pooled ADRs in studies with and without a second forward view were 26% and 18%, respectively (significant difference); pooled advanced ADRs were 3.7% and 2.5% (no significant difference) [14]. In the current study a second look was not used to avoid confounding the ADR findings.

The ADR benchmark served as a key quality indicator [3], and as an aspirational goal for low detectors. Variability in ADR in control groups of randomized controlled trials necessitated standardization of clinical, methodological and technical parameters for comparisons [36]. We analyzed 6 trials (2010-2017) that compared gas (air or CO_2) insufflation (n=2699) and water exchange (n=2708). The sites were community hospitals in Mainland China (n=6), Taiwan (n=2), Europe (n=5), and Veterans Affairs centers in the United States (n=3). Water exchange showed significantly better ADR compared with air insufflation (27.4% vs. 20.9%, P=0.001) [37]. The demographics of the current study (Supplementary Table 1) mimicked those of the pooled data [37]. The No cap ADR of 45.6% (7 sites) and 44.9% (5 sites) exceeded that (27.4%) in the pooled data [37]. Only 1 site (22.7%) (Supplementary Table 2) was below the pooled data. While endoscopist experience, patient mix or local variations might have accounted for the difference, the current result of total procedure time of about 25 min (Table 2), decreased from 56 min when water exchange was first described (8) indicated that the performance of the water exchange method had improved and become more efficient.

When the entire cohort in the CAP and the No cap groups were evaluated (data from 7 sites), even though CAP did not significantly increase ADR, the CAP ADR (49.3%) exceeded the new benchmark of 35% [16]. It was plausible that the insertion cleaning of water exchange optimized the ADR results of CAP, resolving the conflicting data [5,6] due to the interference of residual fecal matter lodged in the CAP [6].

The data of the 5 sites that randomized No cap, CAP and Daisycuff™ showed that the effect of Daisycuff™ (52.8% vs. 44.9%) was nearly significantly P=0.05 (-16%, 0.3%). A study using larger samples is needed to overcome a type II error. A plausible underlying mechanism for high ADR could be as follows. With 2 Daisycuff™ holding onto the pleated colon at 2 separate points (20 cm apart) along the shaft of the colonoscope, there was a smaller "bowstring effect" [38]. On withdrawal, there was less "fly-off" of the fold compressed by the Daisycuff™ at the tip. A more controlled and stable fold exposure was provided for inspection. The more stable inspection resulted in a higher ADR and APC (Table 3C).

When the data from 2 sites were analyzed, the lack of a significant effect of Endocuff Vision® P=0.057 (-22.9%, 0.9%) could be a type II error. Reports from the United Kingdom and Canada showed that Endocuff Vision® increased ADR (without water exchange) from 36.2% to 40.9% (P=0.02) [39], and from 46.7% to 54.6% (P=0.001) [40], respectively. A third international report, however, showed that Endocuff Vision® did not significantly improve ADR (41.1% vs. 35.5%; P=0.125) [41]. The ADR of 58.0% and APC of 1.313 suggest that water exchange optimized the performance of Endocuff Vision® in adenoma detection (Table 3E).

Historical data showed that water exchange increased adenoma [11] and flat polyp [42] detection rates, as well as decreasing the adenoma miss rate [43] in the right colon. Now, CAP (Table 3B) and Daisycuff™ (Table 3D) significantly increased the right colon ADR. The higher proportion of interval than non-interval cancers residing in the right colon [44] suggests that water exchange combined with CAP or Daisycuff™ may have the potential to preferentially attenuate interval cancers in the right colon. The current novel findings deserve further study for confirmation. The enhancement of APC in the left colon by Daisycuff™ (Table 3D) adds to its potential utility.

The strengths of the current study included multi-national, multi-site and multi-investigator design, effective randomization, intention-to-treat analysis, a low (<6%) proportion of poor bowel preparation, and a high (>95%) cecal intubation rate. The novel results in the exploratory assessment of Daisycuff™ and Endocuff Vision® in water exchange colonoscopy open new avenues for investigation into approaches to enhance the performance of water exchange colonoscopy.

The limitations included no definitive outcome data to support the proposed hypothesis that selected cap(s) improved the overall ADR performance of water exchange. In addition, some data were missing from the aggregated data file, while the uneven number of subjects randomized to each arm, as a result of the limited access to Daisycuff™ and the substitution of Endocuff Vision® at 2 study sites, precluded an explanation of the difference in outcome between sites. Only unblinded investigators with expertise in water exchange participated in the study. Fold exposure and interval cancers were not evaluated. The average insertion time was long (~12 min) and could remain as a disincentive in routine clinical practice. Despite the limitations, interesting pilot data (Daisycuff™ and Endocuff Vision®) were obtained.

In summary, this study confirmed the efficacy of water exchange, in that the ADR and APC in all study groups surpassed the benchmarks. CAP and Daisycuff™ significantly increased ADR in the right colon. Daisycuff™ produced a nearly significant increase in overall ADR. In conclusion, the significantly higher ADR in the right colon when CAP and Daisycuff™ were compared with No cap suggested that they hold the promise of reducing interval cancers in the right colon. The nearly significantly higher ADR comparing Daisycuff™ and No cap and other comparisons with No cap deserve to be reevaluated with larger samples. Confirmation of the significant positive findings of selected cap(s) may support their role in performance improvement. The combination of water exchange with these selected caps is new, and the findings should be confirmed in further studies before their use is recommended for performance improvement to increase ADR and APC.

Summary Box

What is already known:

- A low adenoma detection rate (ADR) has been linked to interval cancer
- Water exchange and the distal attachment of a straight cap (CAP) independently increased ADR
- Whether the addition of a CAP would increase the ADR of water exchange colonoscopy was unknown
- At the time of protocol planning, there were no published data on the impact of Daisycuff™ or Endocuff Vision® on the ADR of water exchange colonoscopy. These devices were employed for comparison

What the new findings are:

- Contrary to the proposed hypothesis, the addition of a CAP did not significantly increase ADR further
- Water exchange with or without distal cap(s) maintained high ADR and high adenoma per colonoscopy (APC), surpassing benchmarks
- The addition of Daisycuff™ increased ADR almost significantly
- CAP and Daisycuff™ significantly increased the right colon ADR
- In the left colon, Daisycuff™ significantly increased APC

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Supplementary material

Supplementary Table 1 Demographic variables, medical history and socioeconomic characteristics

Variable name	No cap	CAP	Daisycuff™ & Endocuff Vision®
Number of cases	464	456	460
Demographic variables			
Age (years)	62.3±8.0 (n=463)	61.8±7.6 (n=455)	61.4±7.6 (n=459)
Sex	Female: 153 (33%) Male: 311 (67%)	missing: 1 (0.2%) Female: 141 (30.9%) Male: 314 (68.9%)	Female: 146 (31.7%) Male: 314 (68.3%)
Body mass index (kg/m^2)	26.4±5.6 (n=464)	27.0±17.1 (n=455)	26.6±5.1 (n=459)
Smoking history	18±38% (n=464)	15±36% (n=455)	14±35% (n=460)
Mean blood pressure (mm Hg)	96±13 (n=377)	97±13 (n=379)	96±13 (n=372)
Medical History			
History of cancer	5±22% (n=464)	9±28% (n=455)	5±22% (n=460)
Arthritis history	14±35% (n=464)	13±33% (n=455)	15±36% (n=460)
Diabetes history	15±36% (n=464)	19±39% (n=455)	17±37% (n=460)
Asthma history	4±19% (n=464)	3±17% (n=455)	4±9% (n=460)
Chronic obstructive pulmonary disease history	2±15% (n=464)	2±12% (n=455)	4±19% (n=460)
Alcohol history	13±34% (n=464)	14±35% (n=455)	13±34% (n=460)
Heart disease	7±25% (n=464)	10±31% (n=455)	9±28% (n=460)
Depression	10±29% (n=464)	9±28% (n=455)	10±31% (n=460)
Abdominal surgery	18±38% (n=464)	19±40% (n=455)	18±39% (n=460)
Other	13±34% (n=464)	16±37% (n=455)	13±33% (n=460)
Family history of colon cancer	16±37% (n=464)	17±37% (n=455)	16±36% (n=460)
Prior colonoscopy	61±49% (n=459)	59±49% (n=452)	59±49% (n=456)
Colonoscopy indication	FOBT/FIT: 81 (17.5%) Screening: 183 (39.4%) Surveillance: 200 (43.1%)	missing: 3 (0.7%) FOBT/FIT: 78 (17.1%) Screening: 180 (39.5%) Surveillance: 195 (42.8%)	missing: 8 (1.7%) FOBT/FIT: 84 (18.3%) Screening: 191 (41.5%) Surveillance: 177 (38.5%)
Race	missing: 2 (0.4%) Native American/ Alaska native: 2 (0.4%) African American: 34 (7.3%) Asian: 223 (48.1%) Hawaiian/Pacific Islander: 2 (0.4%) other: 1 (0.2%) White: 200 (43%)	missing: 3 (0.7%) Native American/ Alaska native: 1 (0.2%) African American: 25 (5.5%) Asian: 222 (48.7%) Hawaiian/Pacific Islander: 6 (1.3%) other: 2 (0.4%) White: 197 (43%)	missing: 1 (0.2%) Native American/ Alaska native: 1 (0.2%) African American: 24 (5.2%) Asian: 220 (47.8%) Hawaiian/Pacific Islander: 3 (0.7%) other: 5 (1.1%) White: 206 (45%)
Hispanic	5.3% (22.4%) (n=378)	6.4% (24.4%) (n=377)	6.4% (24.6%) (n=373)
Narcotic medication	missing: 1 (0.2%) no: 437 (94.2%) yes: 26 (5.6%)	missing: 3 (0.7%) no: 438 (96.1%) yes: 15 (3.3%)	missing: 1 (0.2%) no: 440 (95.7%) yes: 19 (4.1%)
Self-reported abdominal discomfort	missing: 1 (0.2%) mild: 73 (15.7%) moderate: 12 (2.6%) no: 378 (81.5%)	missing: 2 (0.4%) mild: 72 (15.8%) moderate: 9 (2%) no: 373 (81.8%)	missing: 3 (0.7%) mild: 69 (15%) moderate: 10 (2.2%) no: 378 (82.2%)

(*Contd...*)

Supplementary Table 1 (*Continued*)

Variable name	No cap	CAP	Daisycuff™ & Endocuff Vision®
Self-reported severe pain	no: 463 (99.8%) yes: 1 (0.2%)	no: 455 (99.8%) yes: 1 (0.2%)	no: 455 (98.9%) yes: 5 (1.1%)
Patient guess of method	missing: 277 (59.7%) Water exchange without cap: 102 (22%) With Daisycuff™ or Endocuff Vision® 41 (8.8%) With CAP: 44 (9.5%)	missing: 268 (58.8%) Water exchange without cap: 101 (22.1%) With Daisycuff™ or Endocuff Vision® 40 (8.8%) With CAP: 47 (10.3%)	missing: 272 (59.1%) Water exchange without cap: 91 (19.8%) With Daisycuff™ or Endocuff Vision® 56 (12.2%) With CAP: 41 (8.9%)
	Socioeconomic characteristics		
Household income	missing: 116 (25%) 0-14.9K: 123 (26.5%) 15-29.9K: 104 (22.4%) 30-59.9K: 73 (15.7%) 60-89.9K: 20 (4.3%) 90K+: 28 (6%)	missing: 106 (23.2%) 0-14.9K: 131 (28.7%) 15-29.9K: 93 (20.4%) 30-59.9K: 79 (17.3%) 60-89.9K: 25 (5.5%) 90K+: 22 (4.8%)	missing: 112 (24.3%) 0-14.9K: 129 (28%) 15-29.9K: 93 (20.2%) 30-59.9K: 72 (15.7%) 60-89.9K: 25 (5.4%) 90K+: 29 (6.3%)
Employment	missing: 11 (2.4%)	missing: 3 (0.7%)	missing: 4 (0.9%)
Disabled	183 (39.4%)	172 (37.7%)	184 (40.0%)
Employed	28 (6.0%)	35 (7.7%)	31 (6.7%)
Retired	32 (6.9%)	39 (8.5%)	37 (8.0%)
Unemployed	210 (45.3%)	207 (45.4%)	204 (44.3%)
Education	missing: 6 (1.3%)	missing: 3 (0.7%)	missing: 10 (2.2%)
11th grade or lower	128 (27.6%)	114 (25.0%)	131 (28.5%)
high school or GED	139 (30.0%)	148 (32.5%)	135 (29.3%)
College/vocational training	46 (9.9%)	44 (9.6%)	44 (9.6%)
2-yr college degree	48 (10.3%)	42 (9.2%)	48 (10.4%)
4-yr college degree	75 (16.2%)	70 (15.3%)	61 (13.3%)
Professional or grad school	22 (4.7%)	35 (7.7%)	31 (6.7%)

Data are presented as mean±standard deviation, or as number (percent). "missing" indicates missing data.
ANOVA (analysis of variance). P-values were >0.05, indicating adequate randomization of the study groups. They are omitted from this Table
GED, General Educational Development; CAP, straight cap

Supplementary Table 2A Site-related variations in study outcome adenoma detection rate (ADR)

Site	# of endoscopists	# of subjects	Study outcome ADR	P-value
A	3	183	51.4%	Reference
B	2	151	22.7%	<0.001
C	4	156	71.9%	0.001
D	2	249	40.6%	0.0261
E	2	200	64.8%	0.0079
F	3	247	41.3%	0.0385
G	1	194	58.8%	0.1493

Supplementary Table 2B ADR data by site

Outcome variable: Overall ADR by site

Site	No cap	CAP	Daisycuff™	Endocuff Vision®	P (No cap vs. CAP)	P (No cap vs. Daisycuff™)	P (No cap vs. Endocuff Vision®)
A	55.74% (N=61)	45.16% (N=62)	53.33% (N=60)		0.321 (-0.086, 0.298)	0.934 (-0.17, 0.218)	
B	15.69% (N=51)	23.53% (N=51)	28.57% (N=49)		0.454 (-0.251, 0.095)	0.189 (-0.31, 0.052)	
C	63.46% (N=52)	73.58% (N=53)	78.43% (N=51)		0.364 (-0.297, 0.095)	0.146 (-0.342, 0.043)	
D	35.37% (N=82)	42.17% (N=83)	44.05% (N=84)		0.461 (-0.228, 0.092)	0.325 (-0.247, 0.073)	
E	66.67% (N=66)	60% (N=70)		68.25% (N=63)	0.53 (-0.11, 0.243)		0.997 (-0.193, 0.161)
F	31.71% (N=82)	41.1% (N=73)		51.19% (N=84)	0.295 (-0.258, 0.07)		0.017 (-0.354,0.036)
G	54.55% (N=66)	60.32% (N=63)	61.54% (N=65)		0.628 (-0.244, 0.128)	0.526 (-0.254, 0.114)	

Outcome variable: ADR in right colon by site

Site	No cap	CAP	Daisycuff™	Endocuff Vision®	P (No cap vs. CAP)	P (No cap vs. Daisycuff™)	P (No cap vs. Endocuff Vision®)
A	26.23% (N=61)	25.81% (N=62)	35% (N=60)		1 (-0.155, 0.164)	0.396 (-0.268, 0.092)	
B	13.73% (N=51)	11.76% (N=51)	12.24% (N=49)		1 (-0.129, 0.169)	1 (-0.132, 0.161)	
C	25% (N=52)	30.19% (N=53)	35.29% (N=51)		0.707 (-0.242, 0.138)	0.356 (-0.299, 0.093)	
D	3.66% (N=82)	13.25% (N=83)	10.71% (N=84)		0.053 (-0.192, 0)	0.146 (-0.16, 0.019)	
E	18.18% (N=66)	24.29% (N=70)		23.81% (N=63)	0.51 (-0.213, 0.091)		0.569 (-0.212, 0.1)
F	7.32% (N=82)	20.55% (N=73)		17.86% (N=84)	0.03 (-0.254, -0.011)		0.07 (-0.217, 0.006)
G	25.76% (N=66)	26.98% (N=63)	23.08% (N=65)		1 (-0.177, 0.152)	0.878 (-0.136, 0.189)	

Outcome variable: ADR in left colon by site

Site	No cap	CAP	Daisycuff™	Endocuff Vision®	P (No cap vs. CAP)	P (No cap vs. Daisycuff™)	P (No cap vs. Endocuff Vision®)
A	13.11% (N=61)	14.52% (N=62)	11.67% (N=60)		1 (-0.15, 0.122)	1 (-0.117, 0.146)	
B	1.96% (N=51)	13.73% (N=51)	6.12% (N=49)		0.066 (-0.239, 0.004)	0.581 (-0.139, 0.056)	
C	32.69% (N=52)	41.51% (N=53)	50.98% (N=51)		0.464 (-0.291, 0.115)	0.093 (-0.39, 0.024)	
D	17.07% (N=82)	18.07% (N=83)	23.81% (N=84)		1 (-0.136, 0.116)	0.377 (-0.202, 0.067)	
E	34.85% (N=66)	37.14% (N=70)		33.33% (N=63)	0.92 (-0.199, 0.153)		1 (-0.164, 0.194)
F	20.73% (N=82)	27.4% (N=73)		33.33% (N=84)	0.434 (-0.214, 0.081)		0.099 (-0.272, 0.02)
G	21.21% (N=66)	20.63% (N=63)	26.15% (N=65)		1 (-0.14, 0.152)	0.646 (-0.21, 0.111)	

Bracketed numbers show 95% confidence intervals. In keeping with the original design to assess aggregated data, the exact site identification is not reported. The historical data were prepared by de-identifying the site. Analyzed by site, the caps did not have significant effects on ADR

Supplementary Table 3A Adenoma detection rate (ADR) for No cap vs. CAP (data from 7 sites) based on indication

Indications	No cap	CAP	P (CAP vs. No cap)
ADR screening	35.2% (N=182)	41.7% (N=180)	0.204 (-0.171, 0.041)
ADR surveillance	54.5% (N=200)	54.4% (N=195)	0.978 (-0.098, 0.101)
ADR FIT+	46.9% (N=81)	55.1% (N=78)	0.301 (-0.25, 0.085)

Supplementary Table 3B ADR analysis of 5 sites that randomized No cap vs. CAP vs. Daisycuff™, based on indication

Indications	No cap	CAP	P (CAP vs. No cap)	Daisycuff™	P (Daisycuff™ vs. No cap)
ADR screening	33.3% (N=132)	39.7% (N=136)	0.279	43.1% (N=144)	0.034 (-0.168, 0.004)
ADR surveillance	53.9% (N=165)	57.1% (N=163)	0.570	64.1% (N=145)	0.098 (-0.219, 0.024)
ADR FIT+	46.7% (N=15)	41.7% (N=12)	0.795	50% (N=16)	0.069 (-0.217, 0.013)

Supplementary Table 3C ADR analysis of 2 sites that randomized No cap vs. CAP vs. Endocuff Vision® based on indication

Indications	No cap	CAP	P (CAP vs. No cap)	Endocuff Vision®	P (Endocuff Vision® vs. No cap)
ADR screening	40% (N=50)	47.7% (N=44)	0.451	48.9% (N=47)	0.377 (-0.307, 0.128)
ADR surveillance	57.1% (N=35)	40.6% (N=32)	0.179	61.3% (N=31)	0.732 (-0.309, 0.226)
ADR FIT+	46.9% (N=66)	57.6% (N=66)	0.223	66.2% (N=68)	0.026 (-0.372, -0.012)

Bracketed numbers show 95% confidence intervals. Endocuff Vision® showed a significantly higher ADR than No cap in the patients who were FIT+ (66.2% vs. 57.6%), P=0.026 (-0.372, -0.012)

Supplementary Table 4 Effect of mode of sedation on the adenoma detection rate (ADR) of different caps, based on data from 7 sites (A), 5 sites (B), or 2 sites (C)

A.

ADR (7 sites)

Group	No cap	CAP	P (95%CI of diff in ADR)
No sedation	40.24% (N=169)	45.56% (N=169)	0.379 (-0.165, 0.058)
Minimal sedation	48.84% (N=43)	60% (N=45)	0.403 (-0.341, 0.118)
Conscious sedation	45.93% (N=209)	48.51% (N=202)	0.671 (-0.127, 0.076)
On demand sedation	50% (N=4)	55.56% (N=9)	-
Full sedation with propofol	65.71% (N=35)	56.67% (N=30)	0.623 (-0.177, 0.358)

B.

ADR (5 sites)

Group	No cap	CAP	Daisycuff™	P (No cap vs. CAP)	P (No cap vs. Daisycuff™)
No sedation	34.94% (N=83)	41.18% (N=85)	43.53% (N=85)	0.008 (0.25, 0.463)	0.129 (0.308, 0.524)
Minimal sedation	56.76% (N=37)	58.33% (N=36)	62.86% (N=35)	0.511 (0.396, 0.725)	0.405 (0.409, 0.74)
Conscious sedation	46.88% (N=192)	50% (N=190)	55.61% (N=187)	0.427 (0.397, 0.542)	1 (0.43, 0.57)
On demand sedation	(N=0)	(N=0)	(N=0)	-	-
Full sedation with propofol	(N=0)	(N=1)	(N=2)	-	-

C.

ADR (2 sites data)

Group	No cap	CAP	Endocuff Vision®	P (No cap vs. CAP)	P (No cap vs. Endocuff Vision®)
No sedation	45.35% (N=86)	50% (N=84)	63.24% (N=68)	0.45 (0.347, 0.564)	1 (0.395, 0.605)
Minimal sedation	0% (N=6)	66.67% (N=9)	63.64% (N=11)	-	0.505 (0.309, 0.91)
Conscious sedation	35.29% (N=17)	25% (N=12)	39.13% (N=23)	0.332 (0.153, 0.614)	0.149 (0.067, 0.572)
On demand sedation	50% (N=4)	55.56% (N=9)	33.33% (N=9)	1 (0.15, 0.85)	1 (0.227, 0.847)
Full sedation with propofol	65.71% (N=35)	55.17% (N=29)	66.67% (N=36)	0.091 (0.477, 0.803)	0.71 (0.36, 0.73)

Bracketed numbers show 95% confidence intervals. In the current study there were no significant differences in the impact of sedation types on the effect of caps on ADR, except that CAP showed a significantly higher ADR than No cap in the unsedated subjects in the 5-site analysis P=0.008 (CI 0.25, 0.463)

Supplementary Table 5A Adenoma detection rate (ADR) for No cap vs. CAP (7 sites) based on size (large polyps)

Large (≥10 mm) polyp detection rate	No cap (N=463)	CAP (N=456)	P (CAP vs. No cap) 95%CI for diff.
All locations	9.9±1.4%	10.3±1.4%	0.852 (-4.5%, 3.7%)
Right colon	3.9±0.9%	4.2±0.9%	0.83 (-3%, 2.5%)
Left colon	6.9±1.2%	7.5±1.1%	0.749 (-4.1%, 3%)

Supplementary Table 5B ADR analysis of 5 sites that randomized No cap vs. CAP vs. Daisycuff™, based on size (large polyps)

Large (≥10 mm) polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap 95%CI for diff
All locations	No cap (N=312)	CAP (N=311)	9.6±1.7%	7.4±1.5%	0.316 (-2.4%, 6.9%)
	No cap (N=312)	Daisycuff™ (N=305)	9.6±1.7%	9.4±1.7%	0.922 (-4.6%, 5.1%)
Right colon	No cap (N=312)	CAP (N=311)	4.8±1.2%	4.5±1.2%	0.849 (-3.3%, 3.9%)
Right colon	No cap (N=312)	Daisycuff™ (N=305)	4.8±1.2%	4.4±1.2%	0.87 (-3.3%, 3.8%)
Left colon	No cap (N=312)	CAP (N=311)	5.8±1.3%	3.5±1%	0.187 (-1.4%, 5.9%)
Left colon	No cap (N=312)	Daisycuff™ (N=305)	5.8±1.3%	6.1±1.4%	0.842 (-4.4%, 3.7%)

Supplementary Table 5C ADR analysis of 2 sites that randomized No cap vs. CAP vs. Endocuff Vision® based on size (large polyps)

Large (≥10 mm) polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	No cap (N=151)	CAP (N=142)	10.6±2.5%	16.7±3%	0.131 (-14.6%, 2.4%)
	No cap (N=151)	Endocuff Vision® (N=146)	10.6±2.5%	16±3%	0.170 (-13.7%, 2.9%)
Right colon	No cap (N=151)	CAP (N=142)	2±1.1%	3.5±1.5%	0.438 (-5.9%, 2.9%)
Right colon	No cap (N=151)	Endocuff Vision® (N=146)	10.6%	14.38%	0.09 (-9.1%, 1.1%)
Left colon	No cap (N=151)	CAP (N=142)	9.3±2.4%	16±3.1%	0.086 (-14.9%, 1.5%)
Left colon	No cap (N=151)	Endocuff Vision® (N=146)	9.3±2.4%	11.3±2.6%	0.557 (-9.6%, 5.5%)

Bracketed numbers show 95% confidence intervals. In the current study there were no significant differences in the impact of caps on the detection rate of large polyps

Supplementary Table 6A Detection rate of diminutive (5 mm) polyps (data from 7 sites)

Diminutive polyp detection rate	No cap (N=463)	CAP (N=453)	P (CAP vs. No cap) 95%CI for diff.
All locations	60.9±2.3%	65.1±2.2%	0.193 (-10.6%, 2.3%)
Right colon	33.7±2.2%	39.3±2.3%	0.076 (-12.1%, 0.8%)
Left colon	48.2±2.3%	51.2±2.3%	0.356 (-9.7%, 3.6%)

Supplementary Table 6B Detection rate of diminutive (5 mm) polyps (5 sites data)

Diminutive polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=312)	CAP (N=311)	64.7±2.7%	69.5±2.6%	0.211 (-12.4%, 3%)
	None (N=312)	Daisycuff™ (N=305)	64.7±2.7%	68±2.7%	0.396 (-11%, 4.5%)
Right colon	None (N=312)	CAP (N=311)	34.9±2.7%	41.8±2.8%	0.078 (-14.8%, 1.1%)
Right colon	None (N=312)	Daisycuff™ (N=305)	34.9±2.7%	41.1±2.8%	0.114 (-14.1%, 1.8%)
Left colon	None (N=312)	CAP (N=311)	52.6±2.8%	55.9±2.8%	0.397 (-11.5%, 4.8%)
Left colon	None (N=312)	Daisycuff™ (N=305)	52.6±2.8%	54.7±2.8%	0.595 (-10.3%, 6%)

Supplementary Table 6C Detection rate of diminutive (5 mm) polyps (2 sites data)

Diminutive polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=151)	CAP (N=142)	53±4.1%	55.6±4.1%	0.657 (-14.6%, 9.5%)
	None (N=151)	Endocuff Vision® (N=146)	53±4.1%	60.7±4%	0.179 (-19.5%, 4.1%)
Right colon	None (N=151)	CAP (N=142)	31.1±3.8%	34±3.9%	0.595 (-14.3%, 8.5%)
Right colon	None (N=151)	Endocuff Vision® (N=146)	31.1±3.8%	37.3±3.9%	0.257 (-17.6%, 5.2%)
Left colon	None (N=151)	CAP (N=142)	39.1±4%	41±4.1%	0.739 (-13.8%, 10%)
Left colon	None (N=151)	Endocuff Vision® (N=146)	39.1±4%	44.7±4.1%	0.326 (-17.4%, 6.2%)

Bracketed numbers show 95% confidence intervals. In the current study there were no significant differences in the impact of caps on the detection rate of diminutive polyps

Supplementary Table 7A Detection rate of small (6-9 mm) polyps (data from 7 sites)

Small polyp detection rate	No cap (N=463)	CAP (N=453)	P (CAP vs. No cap) 95%CI for diff.
All locations	20.3±1.9%	21.8±1.9%	0.588 (-6.9%, 4%)
Right colon	7.8±1.2%	10.1±1.4%	0.216 (-6.2%, 1.6%)
Left colon	15.1±1.7%	15.8±1.7%	0.768 (-5.6%, 4.2%)

Supplementary Table 7B Detection rate of small (6-9 mm) polyps (data from 5 sites)

Small polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=312)	CAP (N=311)	22.1±2.3%	21.9±2.3%	0.94 (-6.5%, 7%)
	None (N=312)	Daisycuff™ (N=305)	22.1±2.3%	20.7±2.3%	0.67 (-5.4%, 8.2%)
Right colon	None (N=312)	CAP (N=311)	10.3±1.7%	11.3±1.8%	0.688 (-6.2%, 4.2%)
Right colon	None (N=312)	Daisycuff™ (N=305)	10.3±1.7%	10±1.7%	0.926 (-4.7%, 5.2%)
Left colon	None (N=312)	CAP (N=311)	15.1±2%	16.1±2.1%	0.727 (-7%, 5%)
Left colon	None (N=312)	Daisycuff™ (N=305)	15.1±2%	14.2±2%	0.771 (-5.1%, 6.7%)

Supplementary Table 7C Detection rate of small (6-9 mm) polyps (data from 2 sites)

Small polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=151)	CAP (N=142)	16.6±3%	21.5±3.4%	0.278 (-14.6%, 4.7%)
	None (N=151)	Endocuff Vision® (N=146)	16.6±3%	22.7±3.4%	0.183 (-15.7%, 3.5%)
Right colon	None (N=151)	CAP (N=142)	2.6±1.3%	7.6±2.2%	0.062 (-10.7%, 0.7%)
Right colon	None (N=151)	Endocuff Vision® (N=146)	2.6±1.3%	7.3±2.1%	0.073 (-10.2%, 0.9%)
Left colon	None (N=151)	CAP (N=142)	15.2±2.9%	15.3±3%	0.991 (-8.3%, 8.2%)
Left colon	None (N=151)	Endocuff Vision® (N=146)	15.2±2.9%	16.7±3%	0.734 (-10.4%, 7.5%)

Bracketed numbers show 95% confidence intervals. In the current study there were no significant differences in the impact of caps on detection the rate of small polyps

Supplementary Table 8A Detection rate of sessile polyps (data from 7 sites)

Sessile polyp detection rate	No cap (N=463)	CAP (N=453)	P (CAP vs. No cap) 95%CI for diff.
All locations	35.2±2.2%	36.9±2.3%	0.588 (-8.1%, 4.7%)
Right colon	20.7±1.9%	24.8±2%	0.139 (-9.7%, 1.5%)
Left colon	26.8±2.1%	23.1±2%	0.195 (-2.1%, 9.5%)

Supplementary Table 8B Detection rate of sessile polyps (data from 5 sites)

Sessile polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=312)	CAP (N=311)	46.8±2.8%	47.9±2.8%	0.78 (-9.3%, 7%)
	None (N=312)	Daisycuff™ (N=305)	46.8±2.8%	45±2.8%	0.651 (-6.3%, 10%)
Right colon	None (N=312)	CAP (N=311)	28.2±2.5%	31.5±2.6%	0.367 (-10.8%, 4.2%)
Right colon	None (N=312)	Daisycuff™ (N=305)	28.2±2.5%	30.1±2.6%	0.604 (-9.4%, 5.6%)
Left colon	None (N=312)	CAP (N=311)	36.2±2.7%	31.2±2.6%	0.185 (-2.7%, 12.8%)
Left colon	None (N=312)	Daisycuff™ (N=305)	36.2±2.7%	30.7±2.6%	0.149 (-2.3%, 13.2%)

Supplementary Table 8C Detection rate of sessile polyps (data from 2 sites)

Sessile polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=151)	CAP (N=142)	11.3±2.6%	13.2±2.8%	0.612 (-10.1%, 6.2%)
	None (N=151)	Endocuff Vision® (N=146)	11.3±2.6%	15.3±2.9%	0.299 (-12.4%, 4.2%)
Right colon	None (N=151)	CAP (N=142)	5.3±1.8%	10.4±2.5%	0.107 (-11.9%, 1.7%)
Right colon	None (N=151)	Endocuff Vision® (N=146)	5.3±1.8%	11.3±2.6%	0.064 (-12.9%, 0.8%)
Left colon	None (N=151)	CAP (N=142)	7.3±2.1%	5.6±1.9%	0.546 (-4.5%, 8%)
Left colon	None (N=151)	Endocuff Vision® (N=146)	7.3±2.1%	8±2.2%	0.815 (-7.4%, 6%)

Bracketed numbers show 95% confidence intervals. In the current study there were no significant differences in the impact of caps on the detection rate of sessile polyps

Supplementary Table 9A Detection rate of flat polyps (data from 7 sites)

Flat polyp detection rate	No cap (N=463)	CAP (N=453)	P (CAP vs. No cap) 95%CI for diff.
All locations	25.3±2%	25.1±2%	0.94 (-5.6%, 6%)
Right colon	16.2±1.7%	16.3±1.7%	0.979 (-4.9%, 4.8%)
Left colon	13.2±1.6%	14.9±1.7%	0.441 (-6.5%, 2.9%)

Supplementary Table 9B Detection rate of flat polyps (data from 5 sites)

Flat polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=312)	CAP (N=311)	20.8±2.3%	20.9±2.3%	0.984 (-6.5%, 6.4%)
	None (N=312)	Daisycuff™ (N=305)	20.8±2.3%	19.1±2.2%	0.588 (-4.9%, 8.3%)
Right colon	None (N=312)	CAP (N=311)	13.5±1.9%	12.2±1.9%	0.643 (-4.3%, 6.8%)
Right colon	None (N=312)	Daisycuff™ (N=305)	13.5±1.9%	12.9±1.9%	0.849 (-5.1%, 6.2%)
Left colon	None (N=312)	Cap (N=311)	9.9±1.7%	14.5±2%	0.086 (-10%, 0.9%)
Left colon	None (N=312)	Daisycuff™ (N=305)	9.9±1.7%	10.4±1.7%	0.862 (-5.5%, 4.7%)

Supplementary Table 9C Detection rate of flat polyps (data from 2 sites)

Flat polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=151)	CAP (N=142)	34.4±3.9%	34±3.9%	0.941 (-10.8%, 11.7%)
	None (N=151)	Endocuff Vision® (N=146)	34.4±3.9%	37.3±3.9%	0.601 (-14.4%, 8.6%)
Right colon	None (N=151)	CAP (N=142)	21.9±3.4%	25±3.6%	0.524 (-13.5%, 7.2%)
Right colon	None (N=151)	Endocuff Vision® (N=146)	21.9±3.4%	26.7±3.6%	0.331 (-15.1%, 5.5%)
Left colon	None (N=151)	CAP (N=142)	19.9±3.2%	16±3.1%	0.384 (-5.5%, 13.3%)
Left colon	None (N=151)	Endocuff Vision® (N=146)	19.9±3.2%	22±3.4%	0.649 (-12%, 7.7%)

Bracketed numbers show 95% confidence intervals. In the current study there were no significant differences in the impact of caps on the detection rate of flat polyps

Supplementary Table 10A Detection rate of pedunculated polyps (data from 7 sites)

Pedunculated polyp detection rate	No cap (N=463)	CAP (N=453)	P (CAP vs. no Cap) 95%CI for diff.
All locations	35.2±2.2%	36.9±2.3%	0.588 (-8.1%, 4.7%)
Right colon	20.7±1.9%	24.8±2%	0.139 (-9.7%, 1.5%)
Left colon	26.8±2.1%	23.1±2%	0.195 (-2.1%, 9.5%)

Supplementary Table 10B Detection rate of pedunculated polyps (data from 5 sites)

Pedunculated polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=312)	CAP (N=311)	46.8±2.8%	47.9±2.8%	0.78 (-9.3%, 7%)
	None (N=312)	Daisycuff™ (N=305)	46.8±2.8%	45±2.8%	0.651 (-6.3%, 10%)
Right colon	None (N=312)	CAP (N=311)	28.2±2.5%	31.5±2.6%	0.367 (-10.8%, 4.2%)
Right colon	None (N=312)	Daisycuff™ (N=305)	28.2±2.5%	30.1±2.6%	0.604 (-9.4%, 5.6%)
Left colon	None (N=312)	CAP (N=311)	36.2±2.7%	31.2±2.6%	0.185 (-2.7%, 12.8%)
Left colon	None (N=312)	Daisycuff™ (N=305)	36.2±2.7%	30.7±2.6%	0.149 (-2.3%, 13.2%)

Supplementary Table 10C Detection rate of pedunculated polyps (data from 2 sites)

Pedunculated polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=151)	CAP (N=142)	11.3±2.6%	13.2±2.8%	0.612 (-10.1%, 6.2%)
	None (N=151)	Endocuff Vision® (N=146)	11.3±2.6%	15.3±2.9%	0.299 (-12.4%, 4.2%)
Right colon	None (N=151)	CAP (N=142)	5.3±1.8%	10.4±2.5%	0.107 (-11.9%, 1.7%)
Right colon	None (N=151)	Endocuff Vision® (N=146)	5.3±1.8%	11.3±2.6%	0.064 (-12.9%, 0.8%)
Left colon	None (N=151)	CAP (N=142)	7.3±2.1%	5.6±1.9%	0.546 (-4.5%, 8%)
Left colon	None (N=151)	Endocuff Vision® (N=146)	7.3±2.1%	8±2.2%	0.815 (-7.4%, 6%)

Bracketed numbers show 95% confidence intervals. In the current study there were no significant differences in the impact of caps on the detection rate of pedunculated polyps

Supplementary Table 11A ADR No cap vs. CAP (data from 7 sites) serrated histology

Serrated polyp detection rate	No cap	CAP	P (CAP vs. No cap) 95%CI for diff.
All locations	3.02±0.8%	4.4±1%	0.277 (-4.1%, 1.3%)
Right colon	2.2±0.7%	3.5±0.9%	0.222 (-3.7%, 1%)
Left colon	1.1±0.5%	1.5±0.6%	0.545 (-2.1%, 1.2%)

Supplementary Table 11B ADR analysis of 5 sites that randomized No cap vs. CAP vs. Daisycuff™, serrated histology

Serrated polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=463)	CAP (N=456)	3.5% (1%)	6.4% (1.4%)	0.138 (-6.6%, 0.8%)
	None (N=463)	Daisycuff™ (N=305)	3.5% (1%)	5.5% (1.3%)	0.304 (5.7%, 1.6%)
Right colon	None (N=312)	CAP (N=311)	3.2% (1%)	5.1% (1.2%)	0.234 (-5.4%, 1.5%)
Right colon	None (N=312)	Daisycuff™ (N=305)	3.2% (1%)	3.9% (1.1%)	0.648 (-3.9%, 2.6%)
Left colon	None (N=312)	CAP (N=311)	0.6% (0.5%)	2.2% (0.8%)	0.115 (-3.8%, 0.6%)
Left colon	None (N=312)	Daisycuff™ (N=305)	0.6% (0.5%)	2.3% (0.8%)	0.112 (-3.8%, 0.5%)

Supplementary Table 11C ADR analysis of 2 sites that randomized No cap vs. CAP vs. Endocuff Vision® serrated histology

Serrated polyp detection rate	No cap	Cap	No cap	Cap	P (Cap vs. No cap) 95%CI for diff
All locations	None (N=151)	CAP (N=142)	2% (1.1%)	No data	-
	None (N=151)	Endocuff Vision® (N=146)	2% (1.1%)	2.05%	1.0 (-3.3%, 3.2%)
Right colon	None (N=151)	CAP (N=142)	-	-	-
Right colon	None (N=151)	Endocuff Vision® (N=146)	-	-	-
Left colon	None (N=151)	CAP (N=142)	2% (1.1%)	-	-
Left colon	None (N=151)	Endocuff Vision (N=146)	2% (1.1%)	1.3% (0.9%)	0.659 (-2.9%, 4.2%)

Bracketed numbers show 95% confidence intervals. In the current study there were no significant differences in the impact of caps on the detection rate of serrated polyps