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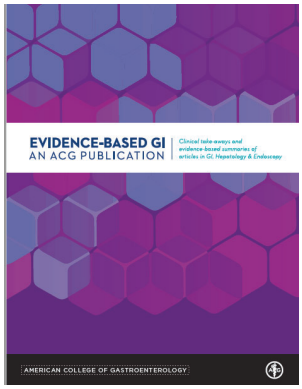


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## INDICATION

IBSRELA (tenapanor) is indicated for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in adults.

## IMPORTANT SAFETY INFORMATION

**WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS**

**IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration. Avoid use of IBSRELA in patients 6 years to less than 12 years of age. The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age.**

### CONTRAINDICATIONS

- IBSRELA is contraindicated in patients less than 6 years of age due to the risk of serious dehydration.
- IBSRELA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

### WARNINGS AND PRECAUTIONS

#### Risk of Serious Dehydration in Pediatric Patients

- IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).
- Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age.

#### Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients. If severe diarrhea occurs, suspend dosing and rehydrate patient.

### MOST COMMON ADVERSE REACTIONS

The most common adverse reactions in IBSRELA-treated patients (incidence ≥2% and greater than placebo) were: diarrhea (16% vs 4% placebo), abdominal distension (3% vs <1%), flatulence (3% vs 1%) and dizziness (2% vs <1%).

**Reference:** IBSRELA [prescribing information]. Waltham, MA: Ardelyx, Inc.; 2022.

**Please see Brief Summary of full Prescribing Information on the following page.**

ardelyx

**IBSRELA (tenapanor) tablets, for oral use**

**Brief Summary of Full Prescribing Information**

**WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS**

- **IBSRELA is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile rats administration of tenapanor caused deaths presumed to be due to dehydration [*see Contraindications (4), Use in Specific Populations (8.4)*].**
- **Avoid use of IBSRELA in patients 6 years to less than 12 years of age [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].**
- **The safety and effectiveness of IBSRELA have not been established in patients less than 18 years of age [*see Use in Specific Populations (8.4)*].**

## 1 INDICATIONS AND USAGE

IBSRELA is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

## 4 CONTRAINDICATIONS

IBSRELA is contraindicated in:

- Patients less than 6 years of age due to the risk of serious dehydration [*see Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].
- Patients with known or suspected mechanical gastrointestinal obstruction.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Risk of Serious Dehydration in Pediatric Patients

IBSRELA is contraindicated in patients below 6 years of age. The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established. In young juvenile rats (less than 1 week old; approximate human age equivalent of less than 2 years of age), decreased body weight and deaths occurred, presumed to be due to dehydration, following oral administration of tenapanor. There are no data available in older juvenile rats (human age equivalent 2 years to less than 12 years).

Avoid the use of IBSRELA in patients 6 years to less than 12 years of age. Although there are no data in older juvenile rats, given the deaths in younger rats and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4)*].

### 5.2 Diarrhea

Diarrhea was the most common adverse reaction in two randomized, double-blind, placebo-controlled trials of IBS-C. Severe diarrhea was reported in 2.5% of IBSRELA-treated patients [*see Adverse Reactions (6.1)*]. If severe diarrhea occurs, suspend dosing and rehydrate patient.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 1203 adult patients with IBS-C in two randomized, double-blind, placebo-controlled clinical trials (Trial 1 and Trial 2). Patients were randomized to receive placebo or IBSRELA 50 mg twice daily for up to 52 weeks. Demographic characteristics were comparable between treatment groups in the two trials [*see Clinical Studies (14)*].

Most Common Adverse Reactions

The most common adverse reactions reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo during the 26-week double-blind placebo-controlled treatment period of Trial 1 are shown in Table 1.

**Table 1: Most Common Adverse Reactions* in Patients With IBS-C in Trial 1 (26 Weeks)**

| Adverse Reactions | IBSRELA N=293 % | Placebo N=300 % |
|---|---|---|
| Diarrhea | 16 | 4 |
| Abdominal Distension | 3 | <1 |
| Flatulence | 3 | 1 |
| Dizziness | 2 | <1 |

*Reported in at least 2% of patients in IBSRELA-treated patients and at an incidence greater than placebo.

The adverse reaction profile was similar during the 12-week double-blind placebo-controlled treatment period of Trial 2 (610 patients: 309 IBSRELA-treated and 301 placebo-treated) with diarrhea (15% with IBSRELA vs 2% with placebo) and abdominal distension (2% with IBSRELA vs 0% with placebo) as the most common adverse reactions.

*Adverse Reaction of Special Interest – Severe Diarrhea*

Severe diarrhea was reported in 2.5% of IBSRELA-treated patients compared to 0.2% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 [*see Warnings and Precautions (5.2)*].

Patients with Renal Impairment

In Trials 1 and 2, there were 368 patients (31%) with baseline renal impairment (defined as eGFR less than 90 mL/min/1.73m$^2$). In patients with renal impairment, diarrhea, including severe diarrhea, was reported in 20% (39/194) of IBSRELA-treated patients and 0.6% (1/174) of placebo-treated patients. In patients with normal renal function at baseline, diarrhea, including severe diarrhea, was reported in 13% (53/407) of IBSRELA-treated patients and 3.5% (15/426) of placebo-treated patients. No other differences in the safety profile were reported in the renally impaired subgroup.

The incidence of diarrhea and severe diarrhea in IBSRELA-treated patients did not correspond to the severity of renal impairment.

Adverse Reactions Leading to Discontinuation

Discontinuations due to adverse reactions occurred in 7.6% of IBSRELA-treated patients and 0.8% of placebo-treated patients during the 26 weeks of Trial 1 and the 12 weeks of Trial 2. The most common adverse reaction leading to discontinuation was diarrhea: 6.5% of IBSRELA-treated patients compared to 0.7% of placebo-treated patients.

Less Common Adverse Reactions

Adverse reactions reported in less than 2% of IBSRELA-treated patients and at an incidence greater than placebo during the 26 weeks of Trial 1 and the 12 weeks of Trial 2 were: rectal bleeding and abnormal gastrointestinal sounds.

*Hyperkalemia*

In a trial of another patient population with chronic kidney disease (defined by eGFR from 25 to 70 mL/min/1.73m$^2$) and Type 2 diabetes mellitus, three serious adverse reactions of hyperkalemia resulting in hospitalization were reported in 3 patients (2 IBSRELA-treated patients and 1 placebo-treated patient).

## 7 DRUG INTERACTIONS

### 7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 [*see Clinical Pharmacology (12.3)*]. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with IBSRELA. Monitor for signs related to loss of efficacy and adjust the dosage of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with tenapanor (30 mg twice daily for five days, a dosage 0.6 times the recommended dosage), the peak exposure ($C_{max}$) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by approximately 50% to 65% compared to when enalapril was administered alone [*see Clinical Pharmacology (12.3)*].

Monitor blood pressure and increase the dosage of enalapril, if needed, when IBSRELA is coadministered with enalapril.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. Therefore, maternal use is not expected to result in fetal exposure to the drug. The available data on IBSRELA exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.1 times the maximum recommended human dose and in rabbits at doses up to 8.8 times the maximum recommended human dose (based on body surface area).

Data

*Animal Data*

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.1 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 8.8 times the maximum recommended human dose, based on body surface area).

In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 9.7 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

**8.2 Lactation**

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is minimally absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration [*see Clinical Pharmacology (12.3)*]. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IBSRELA and any potential adverse effects on the breastfed infant from IBSRELA or from the underlying maternal condition.

**8.4 Pediatric Use**

IBSRELA is contraindicated in patients less than 6 years of age. Avoid IBSRELA in patients 6 years to less than 12 years of age [*see Contraindications (4), Warnings and Precautions (5.1)*].

The safety and effectiveness of IBSRELA in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week-old rats approximate human age equivalent of less than 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

*Juvenile Animal Toxicity Data*

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats [post-natal day (PND) 5] at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups [*see Contraindications (4), Warnings and Precautions (5.1)*].

**8.5 Geriatric Use**

Of the 1203 patients in placebo-controlled clinical trials of IBSRELA, 100 (8%) were 65 years of age and older. No overall differences in safety or effectiveness were observed between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**10 OVERDOSAGE**

Based on nonclinical data, overdose of IBSRELA may result in gastrointestinal adverse effects such as diarrhea as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged [*see Warnings and Precautions (5.1)*].

**17 PATIENT COUNSELING INFORMATION**

Advise the patients to read the FDA-approved patient labeling (Medication Guide).

Diarrhea

Instruct patients to stop IBSRELA and contact their healthcare provider if they experience severe diarrhea [*see Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of IBSRELA in children, especially children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to store IBSRELA securely and out of reach of children [*see Contraindications (4), Warnings and Precautions (5.1)*].

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CRC SCREENING

# Quality Indicators for Colonoscopy: New Targets… But Will They Be Measured?

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Dr Philip Schoenfeld
*Editor-in-Chief*

This summary reviews Rex DK, Anderson JC, Butterly LF, et al. Quality Indicators for Colonoscopy. Am J Gastroenterol. 2024;119:1754-80 .

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**Keywords:** Colonoscopy, colorectal cancer, quality indicators

## STRUCTURED ABSTRACT

**Question:** What numeric indicators improve the efficacy of colonoscopy to decrease colorectal cancer (CRC), are measurable, and are associated with variable performance?

**Design**: This multi-society (American College of Gastroenterology [ACG] and American Society for Gastrointestinal Endoscopy [ASGE]) position statement updates the 2015 guidance based on new research. Literature searches of Pubmed (MEDLINE) from 2014-2022 were performed to identify relevant literature. For clinically relevant topics that were not amenable to formal evidence-based recommendations, key concepts based on expert consensus were presented.

**Patients**: Adults (≥ 18 years old) undergoing colonoscopy. While most quality indicators address colonoscopy performed for CRC screening or colon polyp surveillance among individuals ≥ 45 years old, several quality indicators (e.g., frequency of serious adverse events, cecal intubation rate, and adequate bowel

preparation rate) apply to all colonoscopies. New quality indicators for performance of colonoscopy in inflammatory bowel disease patients were added.

**Interventions/Exposure**: Multiple pre-procedure (e.g., adequate bowel preparation rate), intraprocedure (e.g., adenoma detection rate), and post-procedure (e.g., rate of recommending repeat screening or surveillance colonoscopy consistent with guidelines) were identified.

**Outcome:** Quality indicators were classified as outcome measures or process measures. Outcome measures impact quality of care but may require large amounts of data and/or long-term follow-up to quantify (e.g., rate of post-colonoscopy CRC). Process measures are usually surrogates for outcome measures that are more easily measured with less data and are recorded after each colonoscopy (e.g., colonoscopy withdrawal time).

**Data Analysis**: Selection of quality indicators, updates in performance targets, and strength of recommendations for each quality indicator were reached based on consensus among authors after review of relevant literature. An earlier (circa 2002) and more detailed version of grading framework[1] was again adapted to rate strength of recommendation for each quality indicator.

**Funding:** Supported by the ACG and ASGE.

**Results:** The 2024 ACG/ASGE Position Statement on Quality Indicators updates multiple definitions and performance targets from the 2015 version[2] (**Table 1**). A simpler definition of adenoma detection rate (ADR) was defined, which encompasses all CRC screening, colon polyp surveillance and diagnostic colonoscopies performed in individuals $\geq$ 45 years old (while excluding individuals undergoing colonoscopy for positive screening tests, IBD surveillance, or with an incomplete colonoscopy). Low sessile serrated lesion detection rate is associated with post-colonoscopy CRC, which is unsurprising since large, flat serrated lesions in the proximal colon may be a frequent source of this. Therefore, sessile serrated lesion detection rate (SSLDR) with a 6% target was added. Among "non-priority" intraprocedural quality indicators, a target ADR of $\geq$ 50% was set for colonoscopies performed for positive screening tests (e.g., fecal immunochemical test or multitarget stool DNA test) and the average withdrawal time in normal colonoscopies without biopsy was increased from $\geq$ 6 minutes to $\geq$ 8 minutes, partly based on randomized controlled trials (RCTs), demonstrating that this increases ADR. Also, based on RCT data demonstrating superior efficacy and safety of cold snare vs hot

snare, a new quality indicator targets 90% adherence with using cold snare to remove 4-9 mm polyps.

Among pre- and post-procedural quality indicators, the performance target for achieving adequate bowel preparation was increased from 85% to 90% and the definition was expanded to include providing an appropriate indication for timing of repeat screening or surveillance colonoscopy plus stating that bowel preparation was adequate. Use of Boston Bowel Preparation Scale (BBPS), which has been validated, provides visualization scores for proximal, transverse, and distal colon, and assesses quality of bowel preparation after intra-procedural washing and suctioning, is preferred vs the Aronchick scale (poor, fair, good, excellent). Finally, frequency of recommending an appropriate interval for next screening or surveillance colonoscopy remains at 90%. Although recent database studies suggest that endoscopists are improving their performance with this, the 90% threshold is frequently not attained.

| | Performance Target |
|---|---|
| Adenoma Detection Rate* | ≥ 35% |
| Sessile Serrated Lesion Detection Rate* | ≥ 6% |
| Rate of Using Recommended Screening and Surveillance Intervals | ≥ 90% |
| Bowel Preparation Adequacy Rate** | ≥90% |
| Cecal Intubation Rate with Photo Landmarks | ≥ 95% |

**Table 1.** Priority quality indicators for colonoscopy.

*ADR and SSLDR are calculated based on colonoscopies with at least one adenoma in individuals ≥ 45 years old for CRC screening, colon polyp surveillance, or diagnostic indication, while excluding patients undergoing colonoscopy for positive screening tests (e.g., FIT), IBD surveillance, or with an incomplete colonoscopy.

**Percentage of patients with adequate bowel preparation PLUS receiving recommended screening or surveillance interval for next colonoscopy.

ADR, adenoma detection rate; FIT, fecal immunochemical test; IBD, inflammatory bowel disease; SSLDR, sessile serrated lesion detection rate.

## COMMENTARY

### Why Is This Important?

This updated position statement makes substantial changes based upon a plethora of new research. This work identifies interventions to reduce post-colonoscopy CRC while minimizing adverse events. Many of these seminal studies, which were published in *JAMA, Annals of Internal Medicine*, and *The Lancet*, have been summarized in *Evidence-Based GI*, including research about simplifying the ADR calculation[3], the impact of higher ADRs on reducing post-colonoscopy CRC[4], a higher target ADR in FIT+ patients[5], the impact of low sessile serrated lesion detection rates on increasing post-colonoscopy CRC[6], the benefits of extending withdrawal time to increase ADR[7], the reduction in post-polypectomy bleeding when small adenomas are removed with cold snare instead of hot snare,[8] support for 10-year intervals after normal screening colonoscopy[9] and 7-10 year intervals after finding 1-2 small adenomas after high-quality colonoscopy,[10] while confirming that many endoscopists are not adherent with following those guideline recommendations.[11]

Ultimately, measuring quality indicators and providing feedback to endoscopists can be time-consuming. Therefore, the authors of the position statement identified "priority quality indicators" (**Table 1**), which are most clinically relevant to the efficacy and efficiency of colonoscopy to reduce CRC, are relatively easy to measure, and are subject to variable performance by individual endoscopists.

### *Key Study Findings*

Priority quality indicators are ADR $\geq$ 35% among individuals $\geq$ 45 years old getting colonoscopy for CRC screening, colon polyp surveillance or diagnostic indications. Sessile serrated lesion detection rate should also be monitored in the same group and be $\geq$ 6%. Bowel preparation should be adequate and accompanied by an appropriate recommendation for repeat screening or surveillance colonoscopy in $\geq$ 90% of individuals.

### *Caution*

Although an early, modified version of the GRADE framework[1] was adapted to rate strength of recommendation for each quality indicator, the authors' subjective opinions may influence assessments about the strength of recommendations and quality of evidence. A GRADE methodologist was not used to help produce this position statement, which might have been helpful and could be used in the future.

### *My Practice*

In my VA practice, our report cards provide feedback on all of the priority quality indicators except for sessile ser-

rated lesion detection rate. In the past, this report card was done manually and based on a sample of colonoscopies as opposed to my entire colonoscopy volume since its time-consuming. The VA has instituted the Veterans Affairs Endoscopy Quality Improvement Program (VA-EQuIP), a large ongoing national quality assurance program in the VA health care system, which utilizes informatics and natural language processing to automatically measure and report colonoscopy quality. Hopefully, this will simplify the process, and other large health systems are instituting similar programs.

Among the priority quality indicators, achieving adequate bowel preparation frequency of $\geq$ 90% might seem difficult in our patient population, which is an inner-city population with low socioeconomic levels and relatively low literacy levels. Nevertheless, we've achieved this performance target by creating a patient navigation system which provides information through multiple sources (e.g., mail, phone) at multiple times before colonoscopy as well as screening patients at high-risk for an inadequate bowel preparation and prescribing an enhanced bowel preparation that combines bisacodyl with 4 liters of polyethylene glycol.[12]

### *For Future Research*

There is appropriate original research data to support the priority quality indicators and most of the additional quality indicators with their associated performance targets. This is the first step. We need more and better implementation research about getting endoscopists to measure these quality indicators in their own practice as well as identifying interventions to improve the outcomes of poor performers. This will be especially important for adherence to recommended screening and surveillance intervals for repeat colonoscopy, which continues to lag performance targets.[13] Perhaps, simply providing feedback to endoscopists about this quality indicator through an automated system will be sufficient to improve performance, which has worked to improve ADR.[14]

## Conflict of Interest

Dr. Schoenfeld reports no relevant conflicts of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

# Decreasing Cirrhosis Risk in MASLD: Don't Drink Alcohol!

Dr Nicole Rich
*Associate Editor*

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LIVER

This article reviews Wong RJ, Yang Z, Cheung R *et al*. Impact of longitudinal alcohol use patterns on long-term risk of cirrhosis among US veterans with steatotic liver disease. Gastroenterology 2024; 166(6):1156-1165.

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**Keywords:** MASLD, cirrhosis, AUDIT-C, alcohol use

## STRUCTURED ABSTRACT

**Question:** What is the impact of long-term alcohol use on risk of cirrhosis among U.S. veterans with metabolic dysfunction-associated steatotic liver disease (MASLD)?

**Design:** Retrospective cohort study

**Setting:** US veterans receiving care at all Veterans Affairs (VA) healthcare facilities between January 2010 and December 2017, with data captured in the VA Corporate Data Warehouse

**Patients:** Adult veterans aged >18 years with MASLD, based on the recent internationally-accepted definition. This requires presence of hepatic steatosis and 1 or more of the following metabolic comorbidities: 1) overweight or obese, defined as body mass index (BMI) >25 kg/m$^2$ in non-Asian people and >23 in

Asian people; 2) presence of diabetes, insulin resistance and/or use of anti-diabetes medications; 3) hypertension, blood pressure >130/85 mmHg and/or use of antihypertensive medications; 4) triglycerides >150 mg/dL, high-density lipoprotein (HDL) <40 mg/dL for men or <50 mg/dL for women and/or use of lipid-lowering medications. While the term MASLD does not encompass patients with significant alcohol use and/or possible concurrent alcohol-associated fatty liver disease (newly termed *metALD*), such patients were included in the study. Exclusion criteria included: 1) patients with known cirrhosis at baseline (including 12 months prior to MASLD diagnosis) or within 6 months after study entry; and 2) patients missing data on baseline alcohol use.

**Outcomes:** Primary outcome was development of incident cirrhosis, stratified by baseline alcohol use as defined by the Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score. This survey is routinely conducted as standard of care at VA healthcare facilities. High-risk alcohol use was defined as AUDIT-C score $\geq$3 for men and $\geq$4 for women, low-risk alcohol use as AUDIT-C score 1-2 for woman and 1-3 for men, and no alcohol use defined as AUDIT-C = 0. Cirrhosis was defined using ICD-9/10 codes and previously published algorithms to identify cirrhosis in the VA Corporate Data Warehouse. Longitudinal changes in alcohol use were assessed based on changes in AUDIT-C score on follow-up assessment. The secondary outcome was median overall survival, stratified by alcohol use (none, low-risk, and high-risk) with censoring at date of death or liver transplant.

**Data Analysis:** Risk of cirrhosis was presented as incidence per 100 person-years, stratified by baseline alcohol use categories and other demographic and clinical factors. Multivariable competing risks Cox proportional hazards models were used to evaluate the association between alcohol use and risk of cirrhosis.

**Funding:** None reported.

**Results:** Overall, 1,156,189 veterans with steatotic liver disease (SLD) were identified, with 54.2% reporting no alcohol use, 34.6% with low-risk alcohol use, and 11.2% with high-risk alcohol use at baseline. Median follow-up time was 9.1 years (interquartile range [IQR] 5.8 – 12.0 years), 9.7 years (IQR 6.7 – 12.1) and 9.3 years (IQR 6.3 – 11.9) for the no alcohol, low-risk, and high-risk groups, respectively. Incidence of cirrhosis among patients with SLD and high-risk alcohol use was 0.76 per 100 person-years (PY) compared to 0.42 per 100 PY in the low-risk group and 0.53 per 100 PY in the no alcohol group ($P < 0.001$) (**Figure 1**).

This corresponded to a 43% higher incidence of cirrhosis among patients with high-risk alcohol use compared to those with no alcohol use. This finding was consistent across subgroups. Cirrhosis incidence was highest in the high-risk alcohol group among both men and women, and across all racial and ethnic groups. Among patients with high-risk alcohol use, the highest risk of cirrhosis was observed among Hispanic patients (0.90 compared to 0.78 per 100 PY for White patients, 0.70 per 100 PY for Black patients, and 0.47 per 100 PY for Asian/Pacific Islander patients), men (0.78 vs 0.43 per 100 PY for women), and adults aged 40-59 years (0.96 vs 0.26 per 100 PY for those aged >60 years and 0.70 per 100 PY for those aged 18-29 years).

Among patients with high-risk alcohol use, those that decreased their intake during follow-up had a 39% lower risk of cirrhosis compared to those who did not change their alcohol intake (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.45- 0.83). However, very few patients received either pharmacologic or behavioral therapy for alcohol use during the study period: 1.7% of the no alcohol group, 1.4% of the low-risk alcohol group and 5.0% of the high-risk alcohol group. No significant difference in survival was observed between the 3 groups.

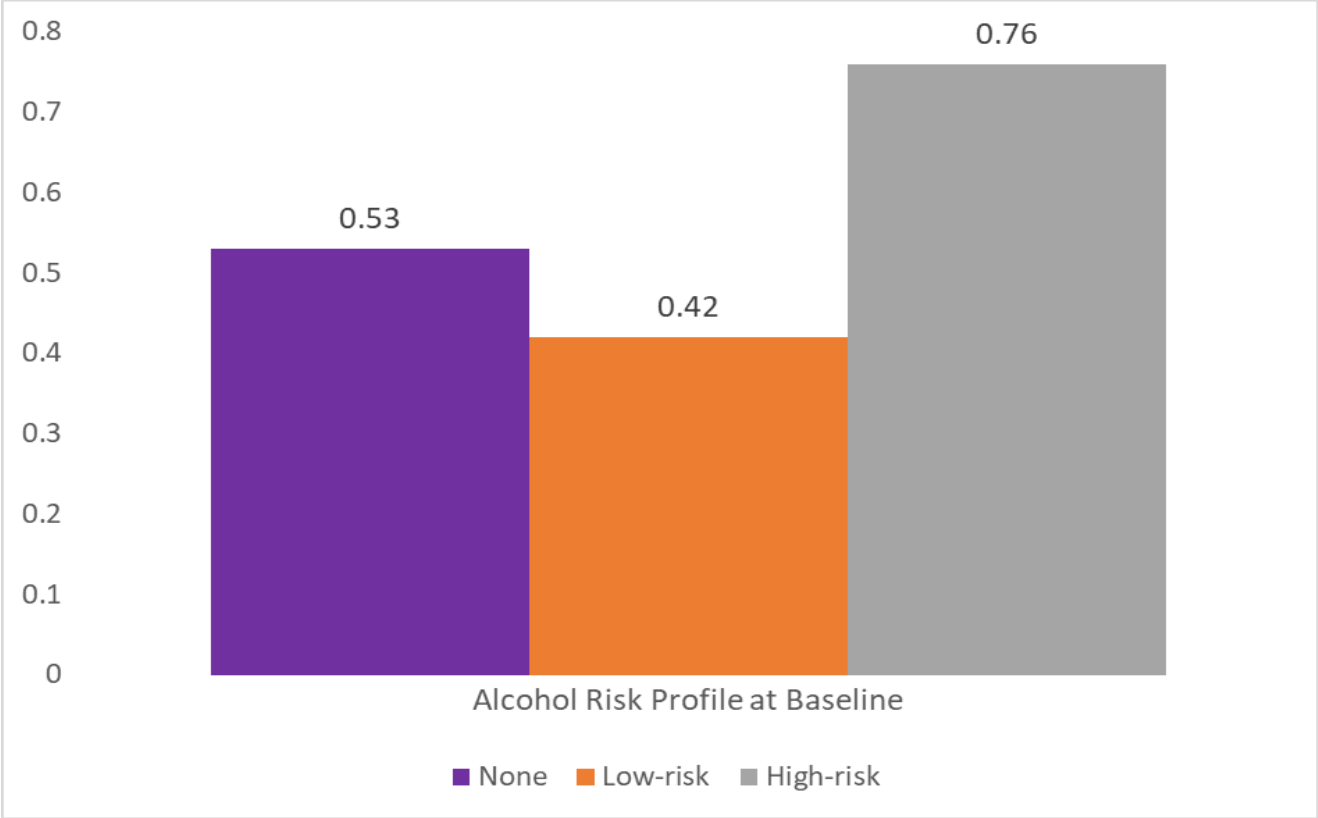


**Figure 1:** Cirrhosis incidence per 100 person-years.

## COMMENTARY

### Why Is This Important?

MASLD is now the most common liver disease globally and the fastest increasing indication for liver transplant in the US.[1,2] Alcohol use is also highly prevalent (and increasing in recent years[3]) among the general population in the US,[4] including those with SLD. It has been surmised that moderate to heavy alcohol use in patients with MASLD may lead to increased rates of (and more rapid) disease progression. However, data are conflicting on the magnitude of the impact of concurrent alcohol use on progression to cirrhosis and decompensating events (e.g., development of ascites, hepatic encephalopathy, variceal hemorrhage) among patients with MASLD. Further, most patients with MASLD and alcohol-related liver disease (ALD) are asymptomatic and only an estimated 20%-35% will progress to advanced fibrosis or cirrhosis.[5, 6] Accurate risk estimates are needed to quantify the harmful effect of alcohol in MASLD to better equip clinicians when counseling patients with this highly common condition about the risks of continued alcohol consumption and the benefits of abstinence.

This large, nationwide cohort study comprising >1.1 million patients with AUDIT-C survey data provides important data on the harmful impact of alcohol use in MASLD. Identification of patients with MASLD at higher risk of developing cirrhosis may help identify patients at greatest need of intervention, including linkage to care for behavioral and pharmacologic treatment of alcohol use disorder (AUD).

### Key Study Findings

In a nationwide cohort of over 1.1 million veterans with steatotic liver disease, 1 in 9 patients reported concurrent high-risk alcohol use, which was associated with 43% higher risk of cirrhosis compared to those with low-risk or no alcohol use. Among patients with high-risk alcohol use, those that decreased their intake during follow-up had a 39% lower risk of cirrhosis compared to those who did not change their alcohol intake (HR 0.61, 95% CI 0.45-0.83).

### Caution

The primary limitations of this study are those inherent to retrospective cohort studies, particularly the possibility of recall and misclassification biases. The AUDIT-C, which was used to risk stratify alcohol use in this study is self-reported and prone to recall bias. Additionally, the misclassification of MASLD is common and often results in patients with ALD being incorrectly diagnosed as MASLD when alcohol consumption is not disclosed or underestimated, as well as patients with "true" MASLD being incorrectly diagnosed as ALD. However, the results in this study were consistent after sensitivity analyses were performed excluding patients with AUDIT-C scores >8 and those

with an ICD-9/10 code for ALD. This study also used *International Classification of Diseases, Ninth/Tenth Revision* (ICD-9/10) codes to ascertain the outcome of incident cirrhosis which may also result in misclassification. Notably, there is no specific code for MASLD-associated cirrhosis; the new ICD-10 code for MASLD, K76.0, does not specify liver disease severity and/or presence of cirrhosis.

This study evaluated overall survival (which was similar between the 3 groups, possibly due to inadequate follow-up time) but did not assess the outcome of major adverse liver outcomes (MALO), an important clinical endpoint increasingly being reported in MASLD trials. Finally, we should remain cautious when generalizing this study's results to women and racial and ethnic minority groups given the predominantly male, non-Hispanic white veteran population.

## My Practice

In my practice, in accordance with the 2019 AASLD Alcohol-Related Liver Disease and 2023 AASLD MASLD Practice Guidance documents, I advise patients with MASLD (and/or other chronic liver diseases) that any amount of alcohol, even mild or moderate use, has not been determined to be "safe" and advise complete abstinence.[7, 8] The AASLD also recommends that all patients in both inpatient and outpatient settings should be routinely screened for alcohol use with validated questionnaires, such as the AUDIT-C.[9] A nonjudgmental, compassionate and motivational interviewing approach can center the patient's concerns regarding alcohol cessation and treatment. For patients reporting unhealthy or hazardous alcohol use, I recommend counseling either online or in-person (e.g., Alcoholics Anonymous or other support groups) and offer referrals to behavioral health/psychiatry services for consideration of the full range of treatment options, including pharmacologic therapy. The study by Wong et al found that less than 5% of patients with MASLD receive treatment for alcohol use disorder, including those with high-risk alcohol use. Inadequate treatment of AUD among patients with chronic liver disease may partly result from the discomfort of primary care and gastroenterology/hepatology providers regarding prescribing relapse prevention medications and monitoring for their effectiveness and side effects. Integrated, multidisciplinary care models can improve ALD outcomes by addressing patients' medical, social and psychological concerns but are not widely available.[10]

I also counsel patients with MASLD, metALD and ALD on lifestyle modifications for healthy weight loss (when applicable) as well as behavioral, pharmacologic and surgical therapies for treatment of obesity. Patients should also be advised to consult with their primary care provider regarding diabetes control and cardiac risk factor modification.

## For Future Research

Further studies are needed to confirm these results in other populations (including women and racial and ethnic minority groups). Moreover, improving our ability to distinguish between patients with MASLD, ALD and metALD (using the new nomenclature) will be crucial when assessing prognosis and the efficacy of therapeutics for these conditions in the future.

## Conflicts of Interest

Dr. Rich has no relevant conflicts of interest.

**Note:** An author of this study are active on social media. Tag them to discuss their work and this EBGI summary.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

# A PPI a Day Keeps the GI Bleed Away in the ICU



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This summary reviews Cook D, Deane A, Lauzier F et al. Stress ulcer prophylaxis during invasive mechanical ventilation. NEJM 2024; 391(1):9-20 .

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Keywords: GI bleeding, stress ulcer prophylaxis, intensive care

## STRUCTURED ABSTRACT

**Question:** Does 40 mg intravenous pantoprazole daily reduce the risk of clinically important upper gastrointestinal (GI) bleeding in mechanically ventilated patients without increasing all-cause mortality or other adverse events?

**Design:** Investigator-initiated, randomized, placebo-controlled, multicenter, triple-blinded trial (REVISE trial) conducted between July 2019 to October 2023.

**Setting:** Sixty-eight hospitals in 8 countries (Australia, Brazil, Canada, England, Kuwait, Pakistan, Saudi Arabia and the United States).

**Patients:** Adults undergoing invasive mechanical ventilation in the intensive care unit (ICU).

**Intervention:** Participants received single daily dose of 40 mg pantoprazole IV or an identical placebo until discontinuation of invasive ventilation or 90 day threshold or occurrence of a pre-specified adverse event.

**Outcomes:** The primary efficacy outcome was clinically important upper GI bleeding defined as overt GI bleeding with evidence of hemodynamic compromise or leading to endoscopic/angiographic/surgical intervention in the ICU, occurring up to 90 days after randomization. The primary safety outcome was all-cause mortality at 90 days. Secondary outcomes included ventilator-associated pneumonia, treatment with renal-replacement therapy, ICU and hospital mortality, patient-important upper GI bleeding (i.e. receipt of at least one blood transfusion, vasopressors, receipt of diagnostic endoscopy, CT angiography, or surgery, outcomes of death, disability, or prolonged hospitalization). Tertiary outcomes included total number of red blood cell transfusions, peak serum creatinine level, duration of mechanical ventilation, hospital and ICU length of stay.

**Data Analysis:** Cox proportional-hazards analyses were performed for the primary efficacy and safety outcomes after adjusting for receipt of acid suppression before hospitalization. Outcomes were reported as hazard ratios and 95% confidence intervals along with absolute risk differences and Kaplan-Meier curves. Mortality outcomes were adjusted for baseline illness severity using the Acute Physiology and Chronic Health Evaluation (APACHE) II score. For the primary outcomes, subgroup analyses were also performed for: use of acid suppression before hospitalization, diagnosis on ICU admission, SARS-CoV-2 status, and sex.

**Funding:** The trial was funded by grant support from the Canadian Institutes of Health Research (CIHR), CIHR Accelerating Clinical Trials Fund, National Health and Medical Research Council of Australia, National Institute of Health Research (NIHR) in the United Kingdom, NIHR Clinical Research Network, CIHR Gold Leaf Award, Physicians Services of Ontario, and the Hamilton Association for Health Sciences Organizations.

**Results:** During the study period, 4,821 patients were randomized with baseline characteristics similar between both trial arms. Pantoprazole or placebo was administered for a median of 5 days (interquartile range 3-10 days). Clinically important upper GI bleeding occurred significantly less in pantoprazole-treated patients vs placebo-treated patients (**Table 1**): 1% vs 3.5%, respectively; hazard ratio = 0.30, 95% confidence interval [CI], 0.19-0.47, $P<0.001$. Patient-important GI bleeding was also less frequent in pantoprazole-treated patients vs placebo-treated

patients: 1.5% vs 4.2%, respectively; hazard ratio=0.36; 95% CI 0.25-0.53, *P*<0.001.

| | Pantoprazole arm | Placebo arm | Hazard Ratio (95% CI) |
|---|---|---|---|
| **Clinically important upper GI bleeding** | 25/2,385 (1.0%) | 84/2,377 (3.5%) | 0.3 (0.19-0.47) |
| **90-day mortality** | 696/2,390 (29.1%) | 734/2,379 (30.9%) | 0.94 (0.85-1.04) |
| **Ventilator-associated pneumonia** | 556/2,394 (23.2%) | 567/2,381 (23.8%) | 1.0 (0.89-1.12) |
| ***Clostridioides difficile* infection** | 28/2,385 (1.2%) | 16/2,377 (0.7%) | 1.78 (0.96-3.29) |
| **Patient important upper GI bleeding** | 36/2,385 (1.5%) | 100/2,377 (4.2%) | 0.36 (0.25-0.53) |
| **New renal replacement therapy** | 146/2,385 (6.1%) | 142/2,380 (6.0%) | 1.04 (0.83-1.31) |

**Table 1.** Efficacy and safety outcomes.

## COMMENTARY

### *Why Is This Important?*

Recent randomized trials investigating the benefits of proton pump inhibitor (PPI) prophylaxis among patients on mechanical ventilation in the ICU have shown different results with regards to outcomes of mortality and GI bleeding [1]. The PEPTIC trial (Proton Pump Inhibitors vs Histamine-2 Receptor Blockers for Ulcer Prophylaxis Treatment in the Intensive Care Unit) trial did not show any difference in in-hospital mortality among ICU patients receiving either PPI or H2RB [2]. Another multicenter trial (SUP-ICU) comparing pantoprazole prophylaxis to placebo showed that there was no difference in mortality at 90 days, and no difference in the number of clinically

important events, including GI bleeding, between both groups [3]. However, some of these studies reported composite outcomes. Importantly, these landmark trials suggested that stress ulcer prophylaxis with PPIs may increase mortality among severely ill patients requiring mechanical ventilation and could not exclude an increased risk of ventilator-associated pneumonia and *C. difficile* infection [2]. This potential gap in knowledge led current guidelines to offer only conditional or weak recommendations to use stress ulcer prophylaxis with PPIs in mechanically-ventilated patients.

Cook *et al* definitively address these issues in their large, multicenter, REVISE trial by conducting a rigorously designed RCT with an adequate sample size to overcome the limitations of the prior trials. [4] They are to be congratulated for this huge effort, which clearly demonstrate the benefits of PPI prophylaxis while also demonstrating their safety in this setting, even among patients with higher baseline severity of illness.

### *Key Study Findings*

Stress ulcer prophylaxis 40 mg Pantoprazole IV daily was superior to placebo for lowering rates of clinically important upper GI bleeding (1% vs 3.5%, 95% CI 1.6 to 3.3%) in mechanically ventilated patients without any difference in 90-day mortality (29.1% vs 30.9%, HR = 0.94; 95% CI 0.85-1.04).

Importantly, subgroup analysis did not show an increased risk of death in the most severely ill patients receiving pantoprazole and in the subgroup of patients receiving PPI prior to hospitalization. Also, no difference was observed in infection-related adverse events, including ventilator associated pneumonia and *C. difficile* infection.

### *Caution*

Overall, the REVISE trial is a large, adequately powered trial that addresses limitations from earlier trials which have led to varying results. The authors allude to the lack of patient-reported disability outcomes and the absence of data on microbiome modification in the setting of PPI prophylaxis. While their findings indicate that PPI use does not reduce risk of death in the subgroup of patients who are severely ill, it does underscores the impact of other patient factors such as previous health status on mortality outcomes in this group of patients.

### *My Practice*

In my hospital, the decision to initiate stress ulcer prophylaxis is usually made by the intensive care team. Based on the available research, stress ulcer prophylaxis is appropriate in mechanically-ventilated patients with lower severity of illness (i.e., APACHE II score $< 25$) [5]. The decision to initiate prophylaxis in patients with higher illness severity (i.e., APACHE II score $\geq 25$) may be individualized. Patients with higher illness severity with concurrent dual

antiplatelet therapy or combination anticoagulation are at higher risk of clinically important bleeding and most likely should get prophylaxis, although this group of patients were excluded from the REVISE study.

### *For Future Research*

The REVISE trial was adequately powered to compare the major outcomes of efficacy and safety separately, not as composite outcomes and the conclusion that stress ulcer prophylaxis reduces the risk of upper GI bleeding in patients undergoing mechanical ventilation is based on robust data. The safety results with regards to all-cause mortality and infection-related complications are also reassuring.

Practically, it is common for ICU patients to be on twice a day PPI dosing and the REVISE trial data cannot be extrapolated to those patients, particularly among the subgroup of severely ill patients (APACHE II score ≥ 25) on mechanical ventilation. Also, patients on dual antiplatelet and combination antiplatelet and anticoagulation therapy are a unique group that was excluded from these landmark trials because of their high-risk for clinically important bleeding.

### *Conflict of Interest*

Dr. Okafor reports no conflicts of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

# A Laser Ruler To Hit The Mark On Polyp Size



Timothy Yen, MD
*Associate Editor*

## Timothy Yen, MD

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This summary reviews Taghiakbari M, Djinbachian R, Haumesser C, et al. Measuring size of colorectal polyps using a virtual scale endoscope or visual assessment: A randomized controlled trial. Am J Gastroenterol. 2024 Jul 1;119(7):1309-1317.

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**Keywords**: polyp, adenoma, size, polypectomy

## STRUCTURED ABSTRACT

**Question:** Is a laser-based measurement tool more accurate than endoscopists' visual assessment in measuring polyp size during colonoscopy?

**Design:** Prospective randomized controlled trial with 1:1 allocation.

**Setting:** Single academic medical center in Montreal, Canada from 9/2022-1/2023 with high-definition colonoscopies performed by 4 gastroenterologists plus 1 trainee.

**Patients:** Patients aged 45-80 years old who were undergoing outpatient screening, surveillance or diagnostic colonoscopies with at least 1 colorectal polyp with *en bloc* polypectomy. Patients with coagulopathy/significant thrombocytopenia, inflammatory bowel disease, inpatients, or ASA classification > 3 were excluded.

**Interventions:** They evaluated a laser-based measurement system, or virtual scale endoscopy (VSE), integrated into a high-definition endoscope/

colonoscope with options for both linear ruler and circular scale (ELUXEO system; Fujifilm, Tokyo, Japan) **(Figure 1).** The control was standard visual assessment (VA). Colonoscopists were instructed not to use any other tools (biopsy forceps, snare, etc.) to estimate size of a polyp, and were asked to report the measure before use of any such tools. Polyps were then removed *en bloc* only using snare (no forceps) and measured manually using a digital caliper *ex vivo* after removal as the gold standard (Figure 1). Research personnel manually measuring polyp diameter with digital calipers were not blinded to intra-procedure assessment of polyp size by VSE or endoscopist visual assessment. If the polyp was fractured or damaged during suctioning, which may have altered polyp diameter, then it was excluded.

**Outcomes:** The primary outcome was relative accuracy of measurement of virtual scale endoscopy vs endoscopists' visual assessment. Secondary outcomes included over- vs under-measurement of size by a variety of metrics (mean normalized difference, discrepancy percent) and effect of the size of the polyp on accuracy.

**Data Analysis:** Descriptive statistics of mean, median, frequency, $X^2$ or Fisher exact test were used. T-tests were used to determine whether size measurements were accurate compared to gold standard. Relative accuracy (% of true polyp size) and generalized estimating equation methods were used to measure accuracy of the methods.

**Funding:** The study was supported by a research grant from Fujifilm.

**Results:** Among 230 study patients undergoing colonoscopy**,** mean age was 64; male sex 51%-54%; indication for colonoscopy was screening in 25%-28% and surveillance in 48%-50%. In the VSE group, 204 polyps were identified. In the endoscopist' visual assessment, 166 polyps were identified. However, only 6%-8% of these polyps were $\geq$ 10 mm based on caliper measurement, and 38%-42% of polyps in both groups were excluded from digital caliper assessment for various reasons and were not included in data analysis.

Overall, relative accuracy in size measurement was 84.0% with VSE compared to 68.4% with endoscopists' visual assessment alone ($P < 0.001$). Relative accuracy significantly increased with polyp size with visual assessment alone but not with VSE. Under-sizing of small (6-9 mm) polyps as diminutive (1-5) polyps was less frequent with VSE than with visual assessment (13.5% vs 57.1%, $P = 0.0005$). There was no oversizing of diminutive/small polyps (1-9mm) as large polyps ($\geq$10 mm), and no statistically significant under-sizing of large polyps, although sample size was quite limited. Both arms showed >90% agreement with USMSTF guidelines. In terms of exact size estimation, VSE was more accurate than visual assessment alone by a variety of metrics.

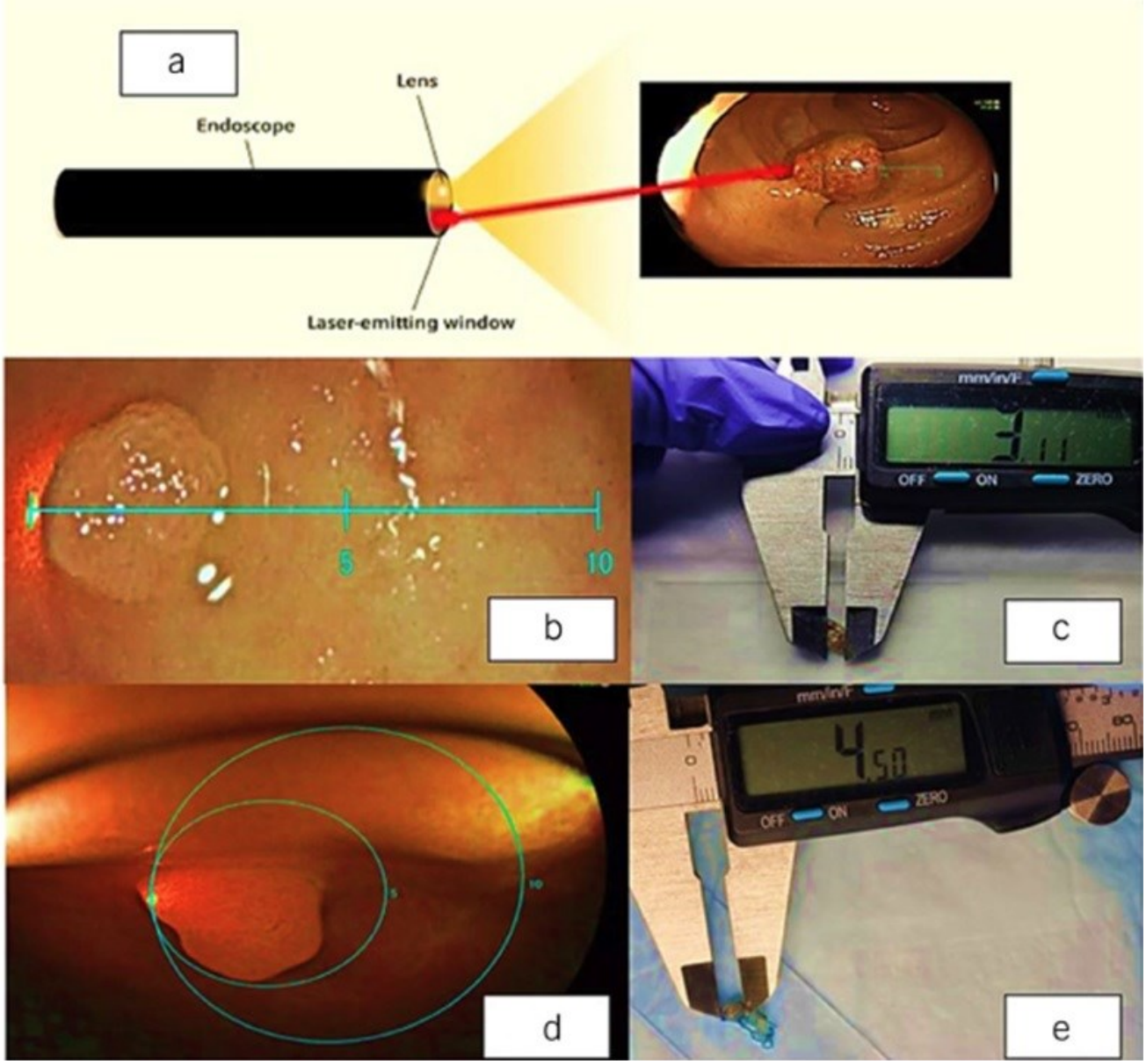


**Figure 1.** Visual laser endoscopy tool (images a, b, d) and measurement of polyp size with calipers after polypectomy and suctioning through colonoscope.

## COMMENTARY

### *Why Is This Important?*

Multiple studies demonstrate that endoscopists' visual assessment of polyp diameter is variable, suboptimal and subject to bias including overestimation of polyp size.[1-4] Interventions are needed to improve accuracy of polyp sizing for both individual patient care, as well as minimization of colonoscopy over- and under utilization. For example, removing a single 8-9 mm adenoma typically would warrant a 7-10 year interval, compared to 3 years for a 10-11 mm adenoma.

Multiple artificial intelligence (AI) tools can be used intra-procedure to facilitate polyp detection and have demonstrated particular benefit for helping trainees identify polyps. It seems possible or

even likely that new artificial intelligence (AI) tools will facilitate real-time measurement of polyp diameter during colonoscopy, although additional research is needed before widespread implementation.

### *Key Study Findings*

Overall, the laser-based, Virtual Scale Endoscopy tool was more accurate than the endoscopists' visual assessment.

The endoscopists in this study tended to show more undersizing at baseline/control, although there was no significant difference between arms at the 10 mm threshold with the assistance of the VSE tool. Of note, 20% of polyps ≥10 mm were undersized as <10 mm in this study of 4 endoscopists.

### *Caution*

Much of the variability in studies finding excess over- vs under- estimation of polyp size is likely influenced by practice, financial and legal contexts. In this study (and many others), endoscopists are fully aware that their practices are being studied and may inherently behave differently (i.e. Hawthorne effect).

This study was limited by lack of blinding. In the future, similar studies should insure that research personnel only enter the procedure room after polypectomy is completed, so that they are blinded from endoscopists' visual assessment or VSE measurement when doing digital caliper measurement of the specimen. Study results were also limited by the high percentage of polyps (38%-42%), which were not included in data analysis for various reasons, but primarily because the specimen was fractured or damaged during suctioning or because the polyp was removed piecemeal. In the future, similar studies might need to rely further on insuring *en bloc* resection with the time-consuming practice of basket extraction to minimize fracturing or damaging the specimen.

### *My Practice*

The accuracy of the laser-based Virtual Scale Endoscopy tool has been recently studied in Europe with similar findings.[5] Of note, that study also measured duration required to make the VSE measurement (median 17 seconds, range 12-22 seconds), which may be difficult to use when short on time or if there are many polyps[5]. Until this technology becomes a standard feature of high definition colonoscopes, I attempt to optimize my visual assessment of polyp diameter by using the width of the snare catheter sheath (approximately 2.5 mm) at the base of the polyp. This is not as variable as the dimensions of an opened snare, useful for estimation for both diminutive vs small as well as at the 10 mm threshold (4 times the sheath width), and does not require special or additional tools. Our group utilized this concept in an education-focused intervention to improve polyp sizing accuracy.[6]

### *For Future Research*

Although AI technologies such as the VSE may be superior to endoscopists' visual assessment of polyp size, its cost-effectiveness remains unclear. Future research should focus on the 10 mm (or larger) sizes of polyps, and its role as a quality metric in appropriate classification of advanced colorectal polyps.

### *Conflict of Interest*

Dr. Yen has no financial conflicts of interest.

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