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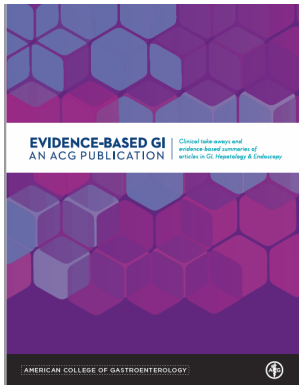

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CRC SCREENING

ADR Isn't the Only Game in Town: Proximal Serrated Lesion Detection Rates Predicts Interval Cancer Risk

Swati G. Patel, MD, MS

Associate Professor of Medicine

University of Colorado Anschutz Medical Center; Rocky Mountain Regional Veterans Affairs Medical Center, Denver, Colorado

This summary reviews: van Toledo DEFWM, IJspeert JEG, Bossuyt PMM, et al. Serrated polyp detection and risk of interval post-colonoscopy colorectal cancer: a population-based study. Lancet Gastroenterol Hepato 2022; 7 (8):747-54. https://pubmed.ncbi.nlm.nih.gov/35550250/

Correspondence to Swati G. Patel, MD, MS. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is a higher proximal serrated polyp detection rate (PSPDR) inversely associated with post-colonoscopy colorectal cancer (PC-CRC) risk?

Study Design: Population-based prospective cohort study.

Setting: Dutch fecal immunochemical test (FIT)-based colorectal cancer screening program linked with the Netherlands Cancer Registry.

Participants: Asymptomatic individuals aged 55-74 years who had a colonoscopy for positive FIT from January 2014 to December 2020 were included. Overall, 277,555 colonoscopies performed by 441 endoscopists were included (median 542 colonoscopies per endoscopist). Median age of patients was 68 and 58% were male.

Definitions: Positive FIT testing was defined with a cutoff of >15 μg Hb/g feces from January 2014 to mid-2014, then defined as > 47 μg Hb/g feces for the remainder of the study period. PSPDR was defined as the proportion of colonoscopies in which at least one serrated polyp proximal

to the descending colon was detected. Serrated polyp was defined as histologically proven hyperplastic polyp, traditional serrated adenoma, or sessile serrated lesion. PC-CRC was defined as a CRC case detected before the advised post-colonoscopy surveillance interval in the endoscopy report. If the recommended surveillance interval was not documented, Dutch national polyp surveillance guidelines were applied to determine the surveillance interval. PC-CRCs included adenocarcinoma, mucinous carcinoma, undifferentiated carcinoma or signet ring cell carcinomas located in the colon or rectum. Neuroendocrine tumors, lymphomas, small cell carcinomas and carcinoids were excluded.

Outcomes: The primary outcome was the association between endoscopists' individual PSPDR and their patients' risk for PC-CRC. Adenoma detection rate (ADR) and association with PC-CRC as well as correlation to PSPDR was also assessed.

Results: The overall PSPDR was 11.9% (IQR 8.3%-15.8%) and the ADR was 66.3% (IQR 61.4%-69.9%) in the asymptomatic, FIT+ patients. The median time from index colonoscopy to CRC or end of follow up was 36 months overall, and 33 months for those diagnosed with PC-CRC. Of the 277,555 patients included, 305 were diagnosed with PC-CRC. Fifty-seven percent of the PC-CRC cases were in men, 49% were located proximal to the descending colon and 58% were diagnosed at advanced stages. For each percentage point increase in PSPDR, the adjusted interval post-colonoscopy CRC hazard was 7% lower (hazard ratio [HR]= 0.93; 95% confidence interval [CI]: 0.90-0.95). Risk of PC-CRC was significantly lower in the fourth (HR 0.42, 95% CI 0.28-0.64) and fifth (0.35, 95% CI 0.21-0.55) highest performing quintiles, compared to the lowest performing quintile. The association between PSPDR and CRC remained significant for both advanced and non-advanced stages, proximal and distal tumors, and male and female patients. ADR was inversely related to interval cancer (HR 0.94, 95% CI 0.93 -0.96). The correlation between PSPDR and ADR was moderate (r=0.59). Endoscopists were defined as "high" or "low" performers based on having ADR above or below the median. Endoscopists with high PSPDR and high ADR had the lowest risk of PC-CRC. Compared with this high-performing group, there was a significant increase in PC-CRC for endoscopists with high ADR but low PSPDR (HR = 1.79; 95% CI: 1.22-2.63) as well as for endoscopists with low ADR but high PSPDR (HR = 1.97; 95% CI: 1.19-3.24).

Funding: None.

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 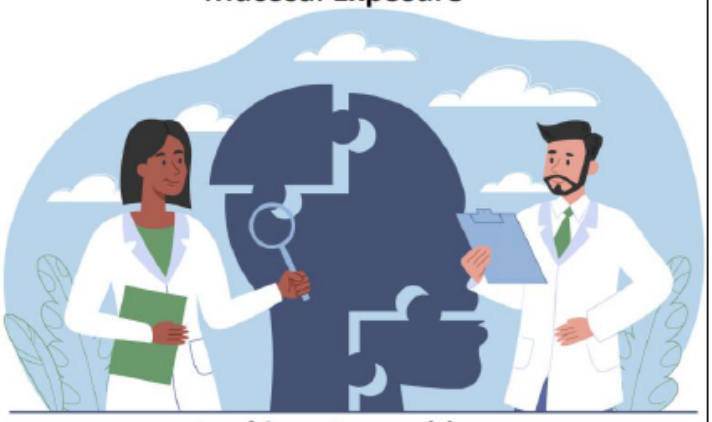
Looking at a problem</td><td colspan="2">Lesion Recognition
 
Seeing a problem</td></tr>
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❋ Irregular shape, indistinctive border
❋ Cloud-like surface
❋ Dilated, branching vessels
❋ Type II open pit pattern
❋ Small dark dots
❋ Similar color to surrounding mucosa</td></tr>
<tr><td colspan="2">Adjunct Devices
❋ Attachment devices
❋ Wide-angle colonoscopies</td><td colspan="2">Computer-aided detection systems</td></tr>
</table>

Figure 1. Techniques to improve lesion detection rate during colonoscopy.

COMMENTARY

Why Is This Important?

CRCs progressing through the serrated pathway account for a disproportionate number of PC-CRCs,[1] likely because serrated lesions are flatter, have similar color to surrounding mucosa, may have a mucus cap, and are more likely to be located in the ascending colon where the bowel preparation is more likely to be sub-optimal. Thus, they are more difficult to detect[2] and more likely to be incompletely resected[3] compared to conventional tubular adenomas. There is highly variable serrated lesion detection rates among endoscopists and only moderate correlation between serrated lesion detection rates and ADR,[4] thus leaving the question of whether ADR

alone is an adequate quality metric to assess risk of PC-CRC.

Key Study Findings

This is the first prospective cohort study to demonstrate an inverse association between proximal serrated lesion detection rates and the clinical outcome of interest in CRC screening—post-colonoscopy CRC. This finding was consistent regardless of CRC stage, anatomic location, or patient sex.

For each percentage point increase in PSPDR, the adjusted interval post-colonoscopy CRC hazard was 7% lower (HR = 0.93; 95% CI: 0.90-0.95).

This study reinforced that ADR is also inversely associated with PC-CRC risk, but only moderately correlated to serrated lesion detection rate. In other words, both are important to optimize since endoscopists with high ADR and low PSPDR demonstrated an increased hazard for PC-CRC (HR = 1.79; 95% CI: 1.22-2.63) versus high performers for both ADR and PSPDR.

Caution

It is important to note that the patients included in the study were referred for colonoscopy due to a positive FIT. Thus, the lesions detection rates are not generalizable to a screening population, thus cannot inform minimum detection rate benchmarks. In most healthcare systems, collection of PSPDR is a resource-intensive process that requires manual entry of colonoscopy data and pathology data. Although there are emerging ways to streamline this process into routine clinical care[5] or use natural language processing to automate data extraction,[6] these methods are not widely available, thus implementing PSPDR as an additional quality metric may not be feasible.

My Practice

This study confirms that serrated lesion detection rate is an important quality metric and although most techniques to improve ADR and serrated lesion detection are similar, serrated lesion detection requires special attention. To optimize lesion detection during colonoscopy, I take specific measures to maximize mucosal exposure and lesion recognition (**Figure**). Optimal mucosal exposure requires a high-quality bowel preparation, intentional inspection technique (fold examination, lumen distention), multiple passes in the right colon, and if available, adjunctive devices such as distal attachment caps, EndoCuff, or wide angle colonoscopes. Optimal lesion recognition requires high-definition equipment and special training in the endoscopic characteristics of adenomatous and serrated lesions. Serrated lesions tend to be

located in the right colon, have overlying mucous caps, an open pit pattern, and have a similar color as surrounding mucosa. Familiarity with classification systems such as the Workgroup SerrAted PolypS and Polyposis (WASP) criteria (indistinctive borders, irregular shape, cloud-like surface, dark spots) can be helpful. Finally, emerging technologies, such as computer-aided detection, can also help with lesion recognition.

For Future Research

Similar studies need to be conducted in average-risk screening populations to establish minimum benchmarks for serrated lesion detection rates. More work needs to be done in collaboration with informatics specialists to facilitate streamlined and automated collection and reporting of lesion detection rates.

Conflicts of Interest

Dr. Patel has no conflicts of interest.

Note

The authors of the article published in the journal *Lancet Gastroenterology and Hepatology* are active on social media. Tag them to discuss their work and this EBGI summary!
@defvantoledo
@pmmbossuyt
@arnebleijenberg
@Ieremier78

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EVIDENCE-BASED GI
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CRC SCREENING

Tiny Polyps—It's OK to Remove Polyps ≤3mm with Large or Jumbo Biopsy Forceps!

Shria Kumar, MD, MSCE
Associate Editor

Shria Kumar, MD, MSCE

Assistant Professor, Division of Digestive and Liver Diseases, University of Miami Miller School of Medicine, Miami, Florida

This summary reviews: Wei MT, Louie CY, Chen Y, et al. Randomized Controlled Trial Investigating Cold Snare and Forceps Polypectomy Among Small POLYPs in Rates of Complete Resection: The TINYPOLYP Trial. Am J Gastroenterol 2022;117(8):1305-10. http://www.doi.org/10.14309/ajg.0000000000001799.

Correspondence to Shria Kumar, MD, MSCE. Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is cold forcep polypectomy (CFP) non-inferior to cold snare polypectomy (CSP) for complete resection of polyps ≤3 mm?

Design: Single-center, prospective randomized non-inferiority clinical trial.

Setting: Palo Alto Veterans Affairs Health Care System (VACHS), California, US.

Patients: Adults (age 18-80) who presented for outpatient screening, surveillance, or diagnostic colonoscopy from October 15, 2020 through October 19, 2021 were invited to participate. Patients were included if they had 1+ polyps ≤3 mm removed. Lastly, only neoplastic polyps (as confirmed by histopathology), such as adenomas, serrated adenomas, and cancers were included in the analysis.

Interventions: Upon encountering a polyp ≤3 mm (estimated by the endoscopist using open jaws of biopsy forceps or snare), the research

coordinator opened an envelope revealing whether the polypectomy would be performed via CSP (Exacto Cold Snare, Steris, US Endoscopy) or CFP with 2.4 mm diameter large forceps (Radial Jaw 4 Large Capacity with Needle, Boston Scientific). After the endoscopist completed the polypectomy and placed the polyp in an individual jar, 2 biopsies were then taken from the polypectomy margin and placed in a separate jar. (Figure 1). Each colonoscopy was video recorded, and the study team reviewed each colonoscopy video and measured the time of CSP or CFP, as well number of passes until completion of polypectomy.

Outcomes: Primary outcome was complete resection defined as absence of polyp tissue in both polypectomy site margin biopsies. Secondary outcomes included time required for polypectomy, number of cold forceps or snare attempts to remove polyp completely, use of hemostatic clips, and complications (such as perforation, bleeding, and post-polypectomy syndrome).

Data Analysis: The primary outcome, complete resection, was evaluated for non-inferiority. That is, to see if CFP is not significantly worse than CSP in achieving complete resection. (This is opposed to a superiority trial, where the authors would test if CFP is significantly better than CSP. The reason to do non-inferiority here is that CSP is considered a standard for polypectomy, so CFP will likely not be better, but before we recommend it, we should ensure it is not significantly worse).

Results: Overall, 179 patients were enrolled with 279 polypectomies performed (141 by CFP and 138 by CSP), although approximately 14% of specimens had normal colonic mucosa. There were no significant demographic or procedural (e.g., indication of procedure, sedation, bowel prep, or withdrawal time) differences between the CFP and CSP groups. There were no 30-day complications experienced in patients in either group.

Incomplete resection, defined as positive margin biopsies for polyp tissue, occurred in 1.7% (2/117 tubular adenomas, sessile serrated lesions or hyperplastic polyps) in both the CFP and CSP groups. CSP groups require a significantly longer time to perform compared to CFP: 42.3 vs 23.2 seconds, $P<0.001$. CFP was more likely to required piecemeal resection: 15.6 vs 3.6%, $P<0.001$. In a logistic regression adjusted for confounders, none of the factors (CFP or CSP, polyp size, polyp location,

time of polypectomy, piecemeal resection, polyp pathology, fellow involvement in polyp resection) were found to be statistically significant for predicting complete resection.

Funding: None

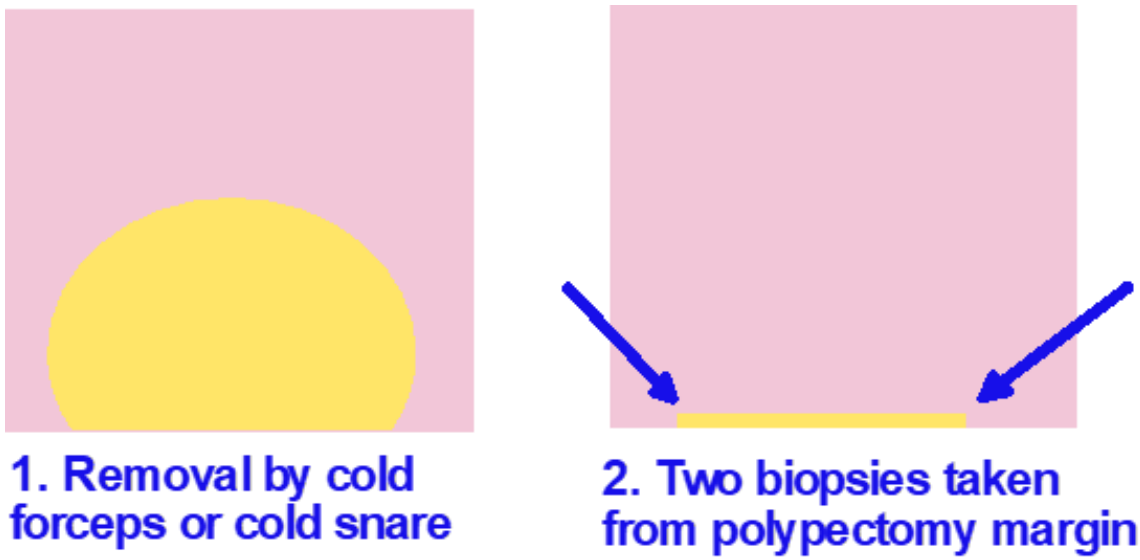

Figure 1: Study procedures

COMMENTARY

Why Is This Important?

Up to 1 in 5 interval cancers can be attributed to incomplete resection of polyps[1,2], so complete resection is of the utmost importance. Therefore, the US Multi-Society Task Force on CRC and multiple other professional societies[3,4] recommend CSP over CFP, especially since CSP facilitates resection of a 2 mm rim of normal mucosa around the polypectomy site and is considered optimal polypectomy technique.

However, sometimes it's technically quite difficult to rotate the scope and place a tiny polyp in the 5 o'clock or 6 o'clock position for CSP. It's simply faster and easier to do CFP, and CFP ensures that the tissue specimen is retrieved, too. Note that the current US Multi-Society Task Force recommendations do permit CFP for tiny polyps when CSP is technically difficult. Furthermore, multiple non-US studies of "tiny" polyps $\leq$ 3 mm demonstrate complete resection rate in >90% with both CFP and CSP.[5-8] Unfortunately, these studies assessed very small numbers of tiny polyps, so the performance of this large RCT by the Stanford University/Palo Alto VAHCS group is commendable and helps resolve the potential discrepancy between guideline recommendations and scientific findings for polyps $\leq$3 mm.

Key Study Findings

This well-designed RCT is the largest trial to compare incomplete resection rates for CFP vs CSP in "tiny" polyps ≤3 mm.

Incomplete resection, defined as positive margin biopsies for polyp tissue, was rare and occurred in only 1.7% of polypectomies in both groups.

Caution

This is a single center study where 4 experienced endoscopists were aware they were participating in a clinical trial. Regardless, the investigators ensured blinding whenever possible in the study and attempted to objectively measure polyp diameter with snare tip or open biopsy forceps. The non-inferiority design of the study also bears mention. Non-inferiority trials are increasingly common, to demonstrate that a new modality has approximately the same efficacy ("it is not significantly worse") than an established modality. In general, a smaller sample size is often needed, making these trials more feasible. Given what we know about CSP, it is unlikely that CFP would show superiority when it comes to resection rates. Practically, we just need to know that it achieves complete resection at about the same rate as CSP, making a non-inferiority trial a reasonable study design here. Finally, and most importantly, large-capacity forceps (2.4 mm in diameter) were used, and these results should not be extrapolated to polypectomy performed with standard-size forceps. In fact, there is evidence that standard forceps size (2.2 mm) are inadequate for polypectomy.[9]

My Practice

This study supports my own practice. I rely on CSP for polyps >3 mm. However, for sessile polyps ≤3 mm, I often use jumbo-capacity CFP, taking care to ensure I remove all polypoid tissue, ideally *en bloc* or within one piece. The positioning, retrieval, and actual polypectomy for CFP is often more favorable than CSP. To measure size, I use the forceps jaw. The jumbo-sized forceps we use have a 2.8 mm jaw diameter, ensuring I can appropriately estimate the polyp size and switch to CSP if the polyp is larger than I had initially estimated (sizes may vary by company and product).

For Future Research

As the authors note, while this is the largest trial to date, it is still a single center study performed by 4 experienced endoscopists. Future US based studies should undertake to confirm the findings. Diminutive polyps are not strong risk factors for incomplete resection leading to future malignancy.[10] Accordingly, an emphasis on CSP (with its greater time and technical burdens) may not strongly mitigate future CRC, and could also be explored in future US-based studies. Conversely, it's also important to educate and incentivize endoscopists to

avoid forceps polypectomy considering that recent retrospective studies show that up to 24% of polyps 5-9 mm in diameter were still being removed with CFP.[11]

Conflict of Interest

Dr. Shria Kumar reports no conflicts of interest.

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EVIDENCE-BASED GI
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Tirzepatide For Obesity: "Mounting" Evidence for Substantial Weight Loss

Sonali Paul, MD, MS
Associate Editor

Sonali Paul, MD, MS

Assistant Professor of Medicine, Division of Gastroenterology, Hepatology & Nutrition, Pritzker School of Medicine, University of Chicago, Chicago, Illinois

OBESITY

This summary reviews: Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med 2022;387(3):205-216. https://pubmed.ncbi.nlm.nih.gov/35658024/

Correspondence to Sonali Paul, MD, MS, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Is tirzepatide, a glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist recently approved for Type II diabetes mellitus (DM), safe and effective for weight loss in conjunction with lifestyle interventions in obese individuals without DM?

Design: Phase 3 randomized, double-blind, placebo-controlled trial.

Setting: Nine countries in North and South America, Asia, and Europe.

Patients: Overall, 2,539 adults (mean age 44.9 years) with either body mass index (BMI) $\geq$ 30 or BMI $\geq$ 27 and at least 1 weight-related condition (hypertension, obstructive sleep apnea, cardiovascular disease, or dyslipidemia) were included in the study. Participants were approximately 71% White, 67% women, 41% prediabetic, and mean body weight of 104.8 kg and BMI 38.0. Key exclusion criteria included a history of DM and those with a change in body weight of more than 5 kg within 90 days of enrollment.

Exposure/Intervention: Once weekly subcutaneous tirzepatide (5mg,

10 mg, or 15 mg) vs placebo randomized into a 1:1:1:1 ratio plus lifestyle intervention (defined as individual counseling sessions to improve adherence to healthy balanced meals with 500 calorie deficit per day and at least 150 minutes of physical activity per week) for 72 weeks. Initial tirzepatide dose was 2.5 mg once weekly and increased by 2.5 mg every 4 weeks to reach maintenance dosing (20 weeks for 15 mg once weekly dosing).

Outcome: Co-primary endpoints were percentage change in weight from baseline and weight reduction of $\geq$ 5% or more at week 72.

Data Analysis: Intention-to-treat analysis reported.

Funding: Eli Lilly, manufacturer of tirzepatide, designed and oversaw the study including data collation and analysis.

Results: Mean percentage change in weight was -15.0% (95% confidence interval [CI] -15.9 to -14.2) with 5 mg weekly tirzepatide doses, -19.5% (95% CI -20.4 to -18.5) with 10 mg doses, and -20.9% (95% CI -21.8 to -19.9) with 15 mg doses compared to -3.1% (95% CI -4.3 to -1.9) with placebo at 72 weeks (**Figure 1**). These differences were statistically significant ($P < 0.001$) for all doses compared to placebo.

Eighty-five percent of participants (95% CI 82 to 89), 89% (95% CI 86 to 92), and 91% (95% CI 88 to 94) of participants achieved weight reduction of $\geq$ 5% with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, compared to 35% (95% CI 30 to 39) with placebo ($P < 0.001$ for all comparisons compared to placebo). Additionally, 50% (95% CI, 46 to 54) of participants on 10mg group and 57% (95% CI, 53 to 61) in the 15 mg groups had body weight reduction of $\geq$ 20% compared with only 3% (95% CI 1 to 5) in the placebo group ($P <0.001$ for all comparisons with placebo).

Importantly, tirzepatide also improved cardiometabolic parameters (including waist circumference, systolic and diastolic blood pressure, fasting insulin, and lipid levels) and mean reduction in total body fat mass (33.9% with tirzepatide compared to 8.2% with placebo). Ninety-five percent of patients with prediabetes had improved glucose levels (compared to 62% in placebo). Gastrointestinal side effects (nausea, vomiting, diarrhea) were more common in the tirzepatide group vs placebo and occurred in the setting of higher doses.

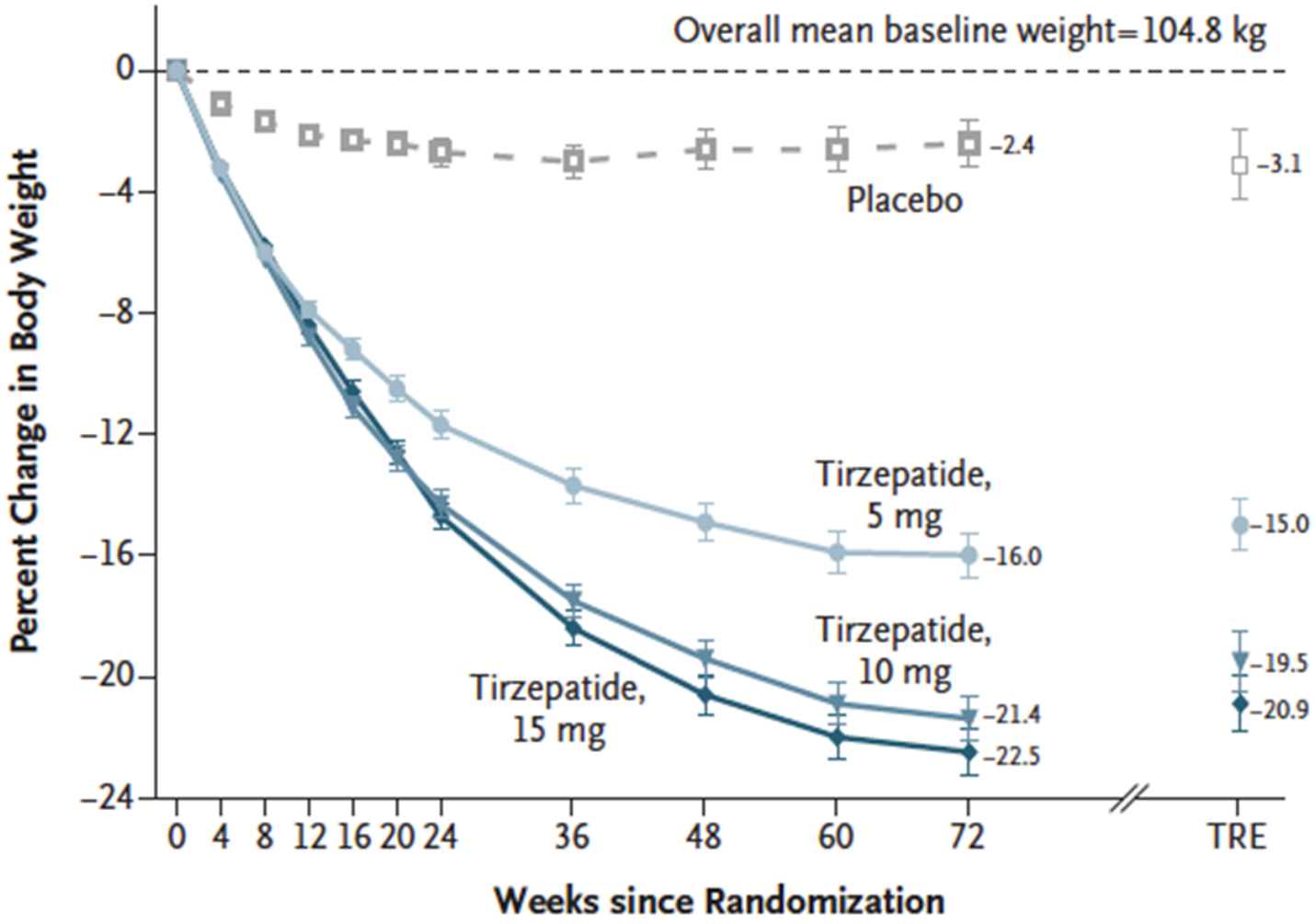

Figure 1: Percent change in body weight

COMMENTARY

Why Is This Important?

Obesity is a global health epidemic resulting in myriad complications including type 2 diabetes, cardiovascular disease, and nonalcoholic fatty liver disease (NAFLD) among many others. Treatments that result in significant weight loss can improve obesity related morbidity and outcomes. These data indicate that tirzepatide is far superior in weight loss as compared to currently available weight loss medications. Older anti-obesity medications currently approved by the FDA include orlistat, phentermine, phentermine-topiramate, naltrexone-bupropion, and liraglutide, and have an average placebo-adjusted weight reduction of 3% to 8.6%.[1] A more recently approved GLP-1 receptor agonist, semaglutide 2.4 mg, resulted in a placebo-adjusted weight reduction of 12.4% (and up to 20% in up to a third of patients in that trial).[2] Comparatively, tirzepatide—even at the lowest dose of 5 mg—had mean placebo adjusted weight reduction of 11.9% and 36.2% of participants receiving 15 mg dosing achieved weight reduction of 25% or more, comparative to bariatric surgery which results 25 to 30% weight

reduction at 1-2 years.[3] These data reinforce the importance that this drug will have in the future of obesity management.

Key Study Findings

Tirzepatide achieved greater mean reduction in body weight of 15% to 21% compared to only 3% in placebo

Caution

GI adverse events, specifically nausea, diarrhea, and constipation, occurred more frequently with tirzepatide compared to placebo, although only a small percentage of patients discontinued treatment because of adverse events (4.3%, 7.1%, 6.2% of participants receiving 5 mg, 10 mg, and 15 mg tirzepatide doses respectively compared to 2.6% receiving placebo). Additionally, tirzepatide is only currently FDA approved for diabetes and the expectation is it will be approved within the coming year for weight loss. However, insurance coverage and cost remain to be determined. Importantly, any anti-obesity medication should be coupled with counseling from a dietitian on reduced calorie diets and increased physical activity. Finally, the majority of trial participants were White women; further study in other patients' populations is needed.

My Practice

In my hepatology practice, which includes many NAFLD patients, most obese and overweight patients with 1 additional risk factor are prescribed semaglutide 2.4 mg weekly, which was recently approved by the FDA for obesity. Also, there is some data to also show efficacy in non-alcoholic steatohepatitis (NASH).[2] However, insurance often dictates which medications are covered and therefore prescribed. Tirzepatide is approved for patients with diabetes and is being used "off-label" for weight loss in some endocrinology practices.

Until tirzepatide is approved for weight loss and is widely covered from an insurance perspective, bariatric surgery also remains a pillar for the treatment of obesity. Additionally, from a NAFLD perspective, each of these anti-obesity medications is paired with important lifestyle interventions and counseling from a registered dietician.

For Future Research

Better data across all racial/ethnic groups, in men, and in obese diabetic patients are needed. From a GI and hepatology perspective, previous data has shown that tirzeptide can improve NASH-related biomarkers in those with T2DM.[4] Tirzepatide is currently being studied in the treatment of NASH in current phase 3 clinical trials (ClinicalTrials.gov Identifier: NCT04166773) and will likely play an role in the future.

Conflicts of Interest

Dr. Paul has no conflicts of interest.

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EVIDENCE-BASED GI
AN ACG PUBLICATION

Prophylactic Rifaximin Decreases Post-TIPS Hepatic Encephalopathy

Philip Schoenfeld, MD, MSEd, MScEpi, FACG

Chief Emeritus-Gastroenterology Section, John D. Dingell VA Medical Center, Detroit, Michigan

Philip Schoenfeld, MD, MSEd, MScEpi, FACG
Editor-in-Chief

LIVER

This summary reviews: Bureau C, Thabut D, Jezequel C, et al. The Use of Rifaximin in the Prevention of Overt Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt. Ann Intern Med 2021; 174: 633-40.

Correspondence to Dr. Philip Schoenfeld, Editor-in-Chief. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does rifaximin 600mg bid prevent overt hepatic encephalopathy (HE) after transjugular intrahepatic portosystemic shunt (TIPS) compared to placebo?

Design: Multi-center, double-blind, placebo-controlled randomized controlled trial. Randomization stratified based on presence or absence of prior episode of overt HE and to Child-Pugh class (A + B or C).

Setting: Twelve tertiary care centers in France. Patients were recruited by expert hepatologists at each site.

Patients: Included patients were: (a) ≥ 18 years old; and, (b) planning to have elective TIPS for intractable ascites or to prevent variceal rebleeding due to cirrhosis. Exclusion criteria included recurrent or persistent overt HE, hepatocellular carcinoma beyond Milan criteria, or Child-Pugh score > 12.

Interventions/Exposure: Rifaximin 600 mg twice a day vs identical placebo tablets, starting 2 weeks prior to scheduled TIPS and continued

for 168 days post-TIPS. All patients were treated with 10 mm covered stents. Prophylaxis for overt HE with lactulose was not allowed, but could be used for episodes of overt HE.

Outcome: The primary endpoint was cumulative incidence of overt HE, defined by West Haven modified criteria, which also defines isolated asterixis as Grade 2 overt HE. Predetermined secondary endpoints included duration and severity of initial overt HE episode, transplant-free survival at 168 days post-TIPS, and incidence of cirrhosis-related complications. Scheduled follow -up occurred every 28 days to asses for overt HE and minimal HE using the Psychometric Hepatic Encephalopathy Score.

Data Analysis: Modified intention-to-treat analysis (defined as patients who did undergo scheduled TIPS) was performed for the primary and secondary endpoints. Safety analysis performed for any patient who received study medication.

Funding: French Public Health Ministry.

Results: From October 2013 through June 2016, 197 patients were randomized; 194 received at least 1 dose of study medication (safety analysis), and 186 had TIPS placed (modified ITT analysis for efficacy). Study patients were primarily male (77%), mean age of 60 years old, had alcohol-related liver disease (86%), and had intractable ascites as indication for TIPS (81%). Thirteen percent had prior overt HE episodes. For the primary endpoint, the incidence of overt HE was significantly lower in rifaximin-treated patients vs placebo-treated patients: 34% vs 53%, respectively, odds ratio (OR) 0.48; 95% confidence interval (CI): 0.27-0.87. (**Figure 1**) If isolated asterixis is not graded as overt HE, then rifaximin-treated patients still have lower incidence of overt HE: 20% vs 40%, respectively, $P = 0.010$. In post hoc analysis of 162 patients without prior overt HE episodes, the incidence of overt HE during 168 days follow-up trended lower in rifaximin-treated patients: 35% vs 51%, stratified log-rank $P = 0.070$. There were no significant differences in transplant-free survival, cirrhosis-related complications, incidence of minimal HE, or adverse events based on the safety analysis.

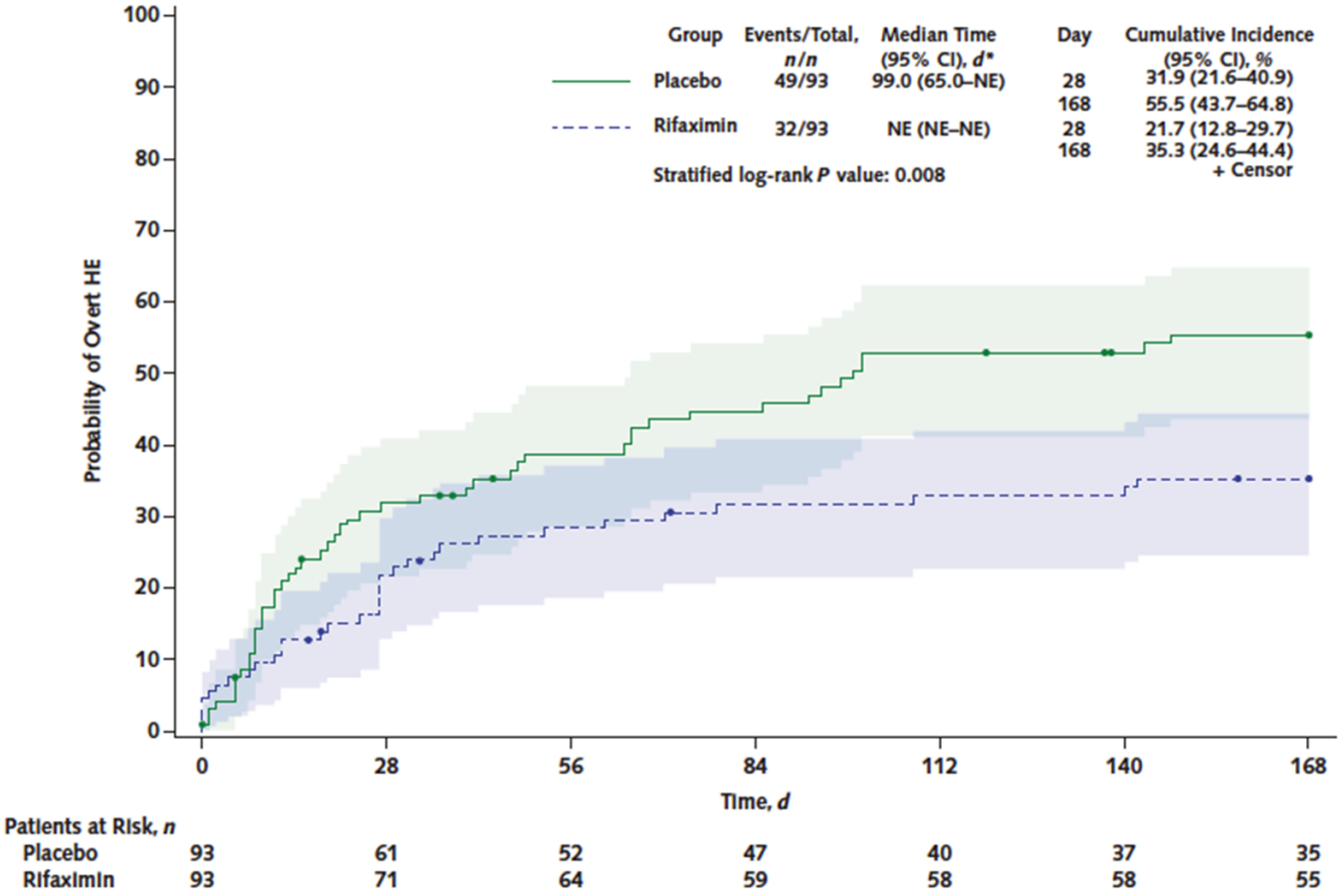

Figure 1: Incidence of overt hepatic encephalopathy procedures

COMMENTARY

Why Is This Important?

Since the introduction of covered stents for TIPS has reduced shunt dysfunction, the primary complication of TIPS is overt HE episodes, which occur in up to 50% of cirrhotic patients after TIPS and which usually lead to hospitalization. Although this is a frequent complication, prophylaxis against HE was not recommended in the 2014 American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) joint guideline on HE[1], primarily due to a lack of data. At that time, only one RCT[2] assessed this issue by randomizing 75 post-TIPS patients to rifaximin, lactulose, or no treatment and showed no difference in overt HE 1 month post-TIPS.

This well-designed RCT overcame these limitations by enrolling a larger sample size and following patients for almost 6 months post-TIPS. The investigators should be commended for their excellent study design and diligence to address this important issue.

Key Study Findings

For the primary endpoint, the cumulative incidence of overt HE was significantly lower in rifaximin-treated patients vs placebo-treated patients: 34% vs 53%, respectively, OR 0.48; 95% CI: 0.27-0.87.

Caution

Prophylactic use of lactulose use was not permitted, even among the 13% of patients who had a prior episode of overt HE, which is the standard of care in the US.

My Practice

Although this study demonstrated a significant reduction in cumulative incidence of overt HE, the most recent 2022 North American guidance on TIPS management[3] does not recommend routine HE prophylaxis with rifaximin pending further RCT data. The authors expressed concern that lactulose was not provided to the 13% of patients with prior overt HE episodes.

As a general gastroenterologist, I relied on several transplant hepatology colleagues for guidance on this issue. They assess each patient for additional HE risk factors (advanced age, Child-Pugh score) and make an individualized decision about using rifaximin (or lactulose) as prophylaxis for overt HE. Although rifaximin is more convenient to use than lactulose, cost and lack of insurance coverage sometimes limit its use. Nevertheless, based on the current RCT, rifaximin has clearly demonstrated efficacy for this indication while RCT data for lactulose efficacy is lacking.

For Future Research

Additional confirmatory studies will be needed, including in the US, before guidelines routinely recommend rifaximin (or lactulose) treatment post-TIPS. It's also unclear if HE prophylaxis should continue indefinitely after TIPS, especially since several study patients experienced overt HE shortly after discontinuing rifaximin at 168 days post-TIPS.

Conflict of Interest

Dr. Schoenfeld reports being an advisory board member and consultant for Salix Pharmaceuticals.

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