



**EVIDENCE-BASED GI**  
AN ACG PUBLICATION

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# EVIDENCE-BASED GI

## *An ACG Publication*

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*February 2023*

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# Dupilumab, an Anti-Interleukin-4/12 Monoclonal Antibody, for Eosinophilic Esophagitis: Revising the Treatment Paradigm



Dr Afrin Kamal  
Guest Contributor



Dr Philip Schoenfeld  
Editor-in-Chief

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<sup>2</sup>Chief (Emeritus), Gastroenterology Section, John D. Dingell VA Medical Center, Detroit, MI.

This summary reviews Dellon ES, Rothenberg MH, Collins I, et al. Dupilumab in Adults and Adolescents with Eosinophilic Esophagitis. *N Engl J Med* 2022; 387: 2317-30.

Correspondence to Philip Schoenfeld, MD, MEd, MSc. Editor-in-Chief. Email: [EBGI@gi.org](mailto:EBGI@gi.org)

## STRUCTURED ABSTRACT

**Question:** Are weekly subcutaneous injections of dupilumab (Dupixent; Regeneron Pharmaceuticals, Tarrytown, NY), an anti-interleukin-4/12 monoclonal antibody, superior to placebo for inducing histologic remission and symptomatic improvement in swallowing for eosinophilic esophagitis (EoE) in adults and adolescents ( $\geq 12$  to  $< 18$  years old)?

**Design:** To assess induction of remission at 24 weeks, 2 multi-center, double-blind, placebo-controlled randomized controlled trials (RCTs) were conducted (Part A and Part B). A single multi-center, active treatment extension study through week 52 was also performed (Part C). Randomization was stratified for age (adolescent [ $\geq 12$  years and  $< 18$  years old] vs adults [ $\geq 18$  years old]) and current use of proton pump inhibitors (PPIs).

**Setting:** Ninety-six centers across Australia, Canada, Europe, and the United States, with the US accounting for the majority (n = 63) of sites.

**Patients:** Eligible patients were: (a)  $\geq 12$  years old; (b) had a confirmed EoE diagnosis based on  $> 15$  eosinophils per high power field (hpf) after 8 weeks of

high-dose PPI therapy; and, (c)  $>10$  on Dysphagia Symptom Questionnaire (DSQ; range 0-84 with higher scores identifying more severe and/or more frequent dysphagia). Study patients were allowed to continue on stable doses of PPI and/or stable food elimination diets at study entry, but could not start PPI or food elimination diets after study entry.

**Interventions/Exposure:** In Part A, patients were randomized 1:1 to dupilumab 300 mg subcutaneous (subq) weekly vs placebo subq weekly for 24 weeks. In Part B, patients were randomized 1:1:1 to dupilumab 300 mg subq weekly vs dupilumab 300 mg subq every 2 weeks vs placebo subq every 2 weeks. In Part C, where data is only available from patients who participated in Part A, all patients were treated with dupilumab 300 mg subq weekly for an additional 28 weeks (52 weeks total), regardless of whether they originally received dupilumab or placebo during Part A.

**Outcome:** Co-primary endpoints were histologic remission, defined as  $\leq 6$  eosinophils per hpf) and change from baseline in DSQ. Multiple secondary endpoints were also evaluated, including absolute change from baseline in the endoscopic reference scoring system, EREFS, which stands for edema, rings, exudates, furrows, and strictures (range 0-18 with higher scores indicating more severe endoscopic findings).

**Data Analysis:** Histologic remission and binary secondary endpoints were analyzed with Cochran-Mantel-Haenszel test, and absolute changes in the DSQ and continuous secondary endpoints were analyzed with analysis of covariance. Safety analysis was performed for any patient who received at least 1 dose of study medication (dupilumab or placebo).

**Funding:** Sanofi and Regeneron Pharmaceuticals, manufacturers of dupilumab.

**Results:** Patients in Part A (n=81) and Part B (n=240) had EoE for mean of 5-5.6 years with mean peak eosinophil count of 87-89, mean DSQ score of 33-37, mean EREFS score of 6.3-7.2, and 36%-41% were on food elimination diet at screening. Histologic remission was significantly more common with dupilumab 300 mg subq weekly vs placebo in Part A (60% vs 5%) and Part B (59% vs 6%) (**Table 1**). Dupilumab 300 mg subq weekly also produced significantly larger reductions from baseline in dysphagia symptoms per DSQ in Part A (68% vs 27%) and Part B (62% vs 38.5%). Although histologic remission was significantly more common with dupilumab 300 mg subq every 2 weeks vs placebo in Part B, it did not produce a statistically significant decrease in DSQ scores vs placebo. Reduction in EREFS score was also greater with dupilumab 300 mg subq weekly vs placebo in Part A (-3.2 vs -0.3) and Part B (-4.5 vs -0.6). In Part C, where all patients from Part A received dupilumab 300 mg subq weekly for an additional 28 weeks, histologic remission and reduction in DSQ was sustained among patients who originally received dupilumab and similar rates of histologic remission and



reduction in DSQ were observed in patients switched from placebo to dupilumab. No significant differences in adverse events occurred.

A	Outcome (%)	Dupilumab 300 mg subq week (n= 42)	Placebo (n= 39)	Adjusted Treatment Difference (95% CI)
	Histologic Remission*	60%	5%	55% (40-71%)
	Decrease in DSQ**	-21.9	-9.6	-12.3 (-19.1 to -5.5)

B	Outcome (%)	Dupilumab 300 mg subq week (n= 80)	Placebo (n= 79)	Adjusted Treatment Difference (95% CI)
	Histologic Remission*	59%	6%	54% (41-66%)
	Decrease in DSQ**	-23.8	-13.9	-9.9 (-14.8 to -5.0)

**Table 1. Co-Primary Endpoint Outcomes of Part A and Part B Randomized Controlled trials.**

\*Histologic Remission:  $\leq 6$  eosinophils per high power field

\*\*Decrease in DSQ: Absolute numeric decrease in score on DSQ, which has a range of 0-84 with higher scores identifying more severe or more frequent dysphagia. In Part A, mean dysphagia score at baseline = 33.6 and was 36.7 at baseline in Part B.

CI, confidence interval ; DSQ, Dysphagia Symptom Questionnaire; subq, subcutaneous.

## COMMENTARY

### *Why Is This Important?*

The incidence and prevalence of EoE, an immune-mediated, chronic allergic inflammatory condition of the esophagus, has steadily risen as endoscopists began to routinely obtain biopsies from patients who presented with the characteristic symptoms of dysphagia or food impaction.<sup>1-2</sup> Although PPIs, swallowing corticosteroids from metered dose inhalers approved for asthma (e.g., Flovent, Pulmicort), and 6-food elimination diets (dairy, wheat, soy, eggs, nuts, and shellfish) were the mainstays of therapy, their efficacy is limited and marred by poor adherence.<sup>3-5</sup> Unfortunately, it's unlikely that

oral suspensions of budesonide will become available in the US in the near future since Takeda Pharmaceuticals discontinued its development program in 2022. Given these limitations, the introduction of dupilumab 300 mg subq weekly as the first FDA-approved treatment for EoE is a very welcome event.

Dupilumab is a monoclonal antibody that binds to the interleukin-4 receptor  $\alpha$ -subunit, which is shared by the cytokine IL-4 and IL-13 receptors. This inhibits the type 2 helper T-cell inflammation that involves T cells, mast cells, cytokines IL-4, IL-13, and IL-5, and eosinophils, which is associated with asthma, atopic dermatitis/eczema, chronic rhinosinusitis as well as EoE. This Phase 3 RCT clearly demonstrates its

efficacy for clinically important dysphagia symptoms and histologic remission, which is important since symptomatic improvement and histologic remission sometimes do not correlate. Importantly, these data also demonstrate improvement in the structural damage (e.g., rings, strictures) due to EoE inflammation based on the EREFS score.

Safety is very important with any new class of drugs. Although only approved for EoE since summer 2022, dupilumab has been FDA-approved for various eosinophilic-mediated inflammatory disorders since 2017, has extended safety data in these disorders, and is actually approved for use in pediatric patients as young as 6 months old with atopic dermatitis/eczema. Although eosinophil counts decrease with dupilumab use, no monitoring of complete blood cell counts, comprehensive metabolic profiles/liver function tests, or screening for opportunistic infections are recommended with dupilumab.

### ***Key Study Findings***

Histologic remission was significantly more common with dupilumab 300 mg subq weekly vs placebo in Part A (60 vs 5%) and Part B (59% vs 6%) (**Table 1**). Dupilumab 300 mg subq weekly also produced significantly larger reductions from baseline in dysphagia symptoms per DSQ in Part A (68% vs 27%) and Part B (62% vs 38.5%).

### ***Caution***

Study patients had already tried PPIs and failed to get histologic remission or

adequate relief of dysphagia, which is similar to other studies of EoE treatments. Approximately 40% had used or were using food elimination diets at the onset of trial, too. Therefore, the efficacy of dupilumab in treatment-naïve patients is unclear. Dupilumab is significantly more expensive than PPIs, food elimination diets or swallowing the content of corticosteroid metered dose inhalers. Although the 52-week data reported in this trial is longer than virtually any other trial, it's still a relatively short period of follow-up for a chronic, lifelong condition.

### ***My Practice***

First, we adhere to recently published quality indicators for the diagnosis and management of EoE.<sup>2</sup> Specifically, we obtain at least 6 biopsies from at least 2 esophageal levels in patients with dysphagia without a known etiology, and we also obtain these biopsies when endoscopically treating food impactions as long as it is medically safe. Approximately 3-4 months after initiating a specific therapy or changing therapies, we will order a repeat EGD to assess for histologic improvement since symptomatic response may not correlate with histologic remission. We also educate that this is a chronic condition and that maintenance therapy is needed even after clinicopathologic remission in order to minimize the risk of recurrent symptoms and fibrosis/stricturing in the esophagus.

Our standard approach is to educate patients about the risks and benefits of PPIs, food-elimination diets, swallowed corticosteroids from a metered dose



inhaler, and dupilumab. Generally, we recommend PPIs twice daily as initial therapy. If this is unsuccessful, then we utilize shared decision-making to choose between the other options. When using food-elimination diets, we start with 2-food elimination: dairy and wheat. One of us (AK) has had success with her patient population in Northern California, although it's been difficult for the other co-author (PS) to implement this in his midwestern Veteran population. Efficacy of topical corticosteroids may be facilitated with detailed instructions about how to swallow the contents of the inhaler, but adherence and clinicopathologic remission is variable. As the first FDA-approved treatment, dupilumab meets a clinically important need, especially in patients who have already failed alternative treatments, as long as insurance covers this medication and the patient commits to being adherent with weekly subq injections.

### ***For Future Research***

Longer-term data about efficacy, safety, and adherence with dupilumab in management of EoE patients would be welcome as well as data that identifies EoE patients that are most likely to achieve histologic remission and improvement in dysphagia with dupilumab. Cost-effectiveness and comparative RCTs of EoE treatments are also needed.

### ***Conflicts of Interest***

Dr. Kamal reports serving as an advisory board member for Castle Biosciences. Dr. Schoenfeld reports serving as an advisory board member for Sanofi Pharmaceuticals.

**Note:** The authors of the article published in the *New England Journal of Medicine* are active on social media. Tag them to discuss their work and this EBGJ summary!

@EvanDellon

@IkuoHirano

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# Endoscopic Sleeve Gastroplasty Is Effective for Patients With Obesity Who MERIT Intervention



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This summary reviews Dayyeh BKA, Bazerbachi F, Vargas EJ, et al. Endoscopic sleeve gastroplasty for treatment of class 1 and 2 obesity (MERIT): a prospective, multicentre, randomised trial. *Lancet* 2022; 400: 441–51.

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## STRUCTURED ABSTRACT

**Question:** Is endoscopic sleeve gastroplasty (ESG), a minimally invasive, endoluminal, organ-sparing bariatric procedure, safe and effective for patients with class 1 (body mass index [BMI] 30-<35 kg/m<sup>2</sup>) and class 2 obesity (BMI 35-<40 kg/m<sup>2</sup>)?

**Design:** Prospective, multicenter, unblinded, randomized clinical trial (RCT).

**Setting:** Nine academic and community centers (5 gastroenterology, 4 bariatric surgery) in the US.

**Patients:** Adult patients aged 21-65 years with BMI 30-40 kg/m<sup>2</sup> who had previously failed non-surgical weight loss methods. Patients with a history of gastroin-

testinal surgery or gastrointestinal inflammatory disease were excluded.

**Interventions/Exposure:** Lifestyle modifications included a low-calorie diet plan and physical activity counseling customized to the individual. ESG was performed by experienced proceduralists who underwent a standardized training program with a commercially available, full-thickness endoscopic suturing device (OverStitch; Apollo Endosurgery, Austin, TX). Patients were randomly assigned in a 1:1.5 ratio using stratified permuted blocks to either the ESG group (ESG + moderate-intensity lifestyle modifications) or the control group (moderate-intensity lifestyle modifications alone). At 52 weeks, participants in the control group who did not reach the target weight loss goal were offered crossover to receive ESG and followed for another 52 weeks.

**Outcomes:** The primary outcome was excess weight loss (EWL) at 52 weeks with ESG compared to lifestyle intervention alone. EWL was calculated as: (weight loss from initial to follow up divided by baseline excess weight) x 100. Baseline excess weight was defined as index weight minus ideal weight based on BMI of 25 kg/m<sup>2</sup>. Durability was evaluated in the primary ESG group for a total of 104 weeks. Secondary efficacy endpoints at 52 weeks were proportion of patients with 25% or more EWL, 5% or 10% more of total body weight loss (TBWL), and percentage of TBWL. The effect of ESG on obesity comorbidities was also assessed. Safety endpoints were evaluated using the Clavien-Dindo grade, which is a standardized and validated system to define and grade post-surgical events based on the therapy needed to address the adverse event.

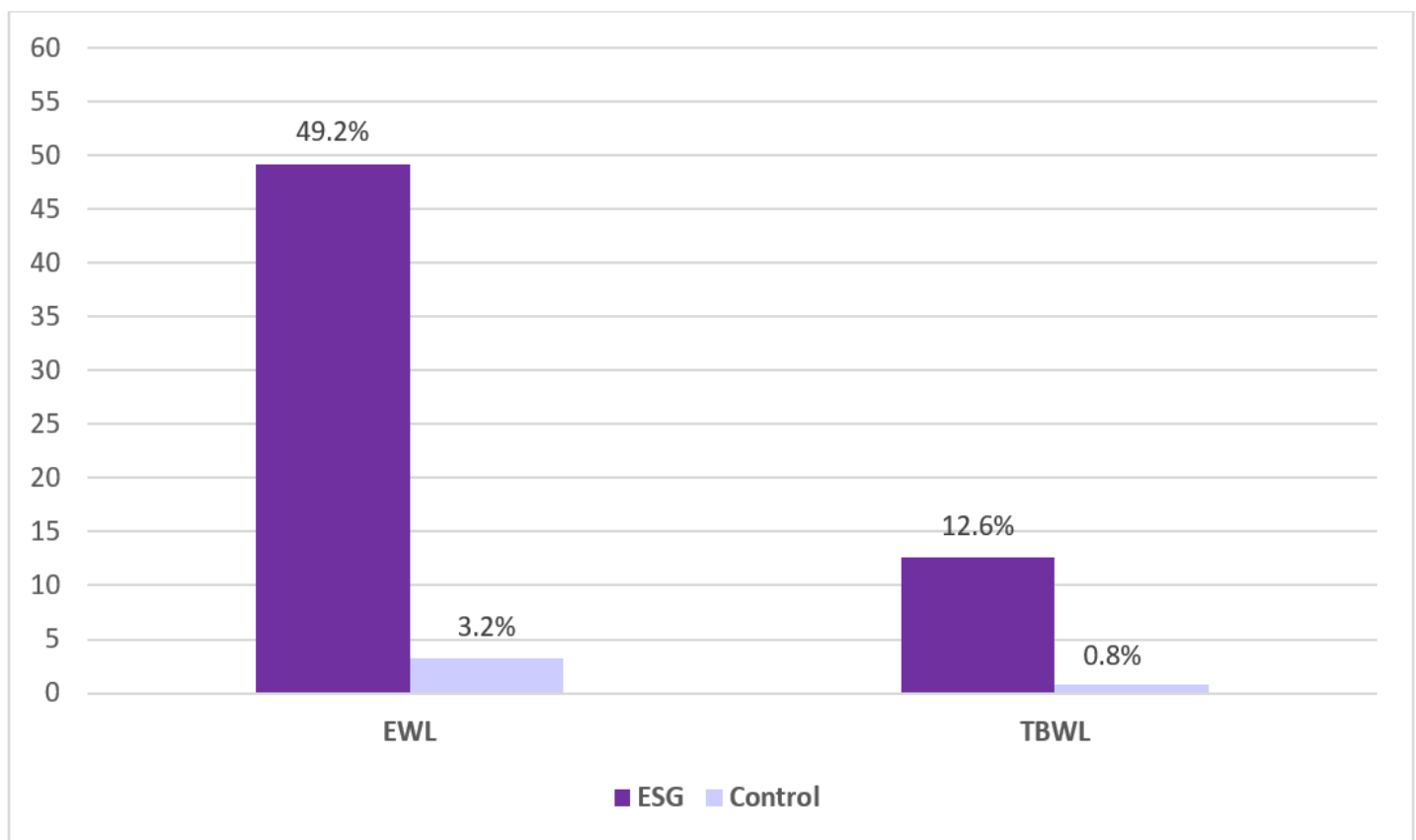
**Data Analysis:** Efficacy at 52 weeks was assessed on both a per-protocol basis (participants who completed the 52-week visit) and a modified intention-to-treat basis. The primary outcome (% EWL) was assessed using a linear mixed-effects regression model.

**Funding:** Mayo Clinic and Apollo Endosurgery (manufacturer of the OverStitch System) provided grant support to conduct research, but site investigators conducted the study and controlled data.

**Results:** Between December 20, 2017 and June 14, 2019, a total of 209 study patients (mean age 46-47; approximately 86% female; mean weight approximately 216 pounds/99kg) were randomly assigned to ESG (n=85) or control (n=124). The mean %EWL was 49.2% (SD 32.0) in the ESG group and lower at 3.2% (SD 18.6) in the control group ( $P < 0.001$ ). Similarly, TBWL at 52 weeks was higher with ESG compared to control (12.6% vs 0.8%,  $P < 0.0001$ ), which equates to approximately 27 pounds vs 2 pounds. On modified intention-to-treat analysis ad-

justed for age, sex, diabetes, hypertension, and BMI, participants in the ESG group had a mean difference of 44.7% EWL and 12.6% TBWL compared to the control group (**Figure 1**). For the secondary endpoint, 77% in the ESG group compared to 12% in control group achieved 25% or more EWL at 52 weeks. At 52 weeks, 9 patients in the ESG group did not meet the primary endpoint of 25% EWL and 5 of these underwent suture reinforcement. This consists of a repeat endoscopy with placement of additional sutures to shorten and tighten the stomach. Individuals who had crossover ESG achieved mean 44.1% EWL after 52 weeks, achieving similar success as the primary ESG group.

Among the 60 patients who had ESG and achieved  $\geq 25\%$  EWL, most (68%) maintained this at 104 weeks. Diabetes metrics (fasting glucose, hemoglobin A1C) and hypertension improved significantly in the ESG group but had minimal to negative change in the control group. There were 6 (4%) individuals who required hospital admission for medical management of expected post procedure accommodative gastrointestinal symptoms. There were 3 (2%) device-related or procedure-related adverse events including abscess managed endoscopically, upper GI bleed



**Figure 1.** Primary outcome results. Percent of excess weight loss (EWL) and mean total body weight loss (TBWL) at week 52. ESG, endoscopic sleeve gastroplasty.



## COMMENTARY

### *Why Is This Important?*

Obesity rates continue to rise in the United States affecting nearly half of individuals older than 20 years, of whom 10% meet criteria for severe obesity.<sup>1</sup> Obesity is a chronic disease and significant contributor to major morbidities such as heart disease, stroke, diabetes, and cancer. Despite the growing utilization of bariatric surgery, it still has failed to reach even a fraction of patients who would benefit from an intervention. Endoscopic approaches are an alternative option for individuals who either do not qualify for bariatric surgery due to anatomy/prior surgeries or severe comorbidities or who do not want surgery due to potential complications. It can also be a bridge to bariatric surgery.

ESG utilizes full thickness suturing along the greater curvature to create a tubular stomach that mimics a surgical sleeve but preserves the fundus. ESG is mainly considered in patients with BMI of 30-40 kg/m<sup>2</sup>, but can be an option for individuals with a higher BMI >40 kg/m<sup>2</sup> or BMI 27-30 with comorbid illness, especially if refractory to pharmacotherapy. It is performed using the OverStitch endoscopic suturing system which was FDA approved in July 2022 for ESG and endoscopic bariatric revision in patients with BMI 30-50 kg/m<sup>2</sup>. ESG has been performed worldwide and consistently demonstrated improvement in TBWL of 15%-20%. In a meta-analysis of 1,772 patients who had ESG, participants achieved a mean

TBWL at 6, 12, and 18-24 months of 15.1%, 16.5%, and 17.2%.<sup>3</sup> Five year durability data from Sharaiha et al showed a mean TBWL of 15.9%.<sup>4</sup> ESG has also yielded improvements in metabolic parameters including hemoglobin A1c, liver enzymes, serum triglyceride, and systolic blood pressure.<sup>5</sup>

This study by Abu Dayyeh et al is the first randomized trial to demonstrate efficacy outcomes with ESG and lifestyle modifications compared to lifestyle changes alone for patients with obesity. Not only did patients achieve and maintain meaningful weight loss, but they also had marked improvement in their metabolic comorbidities. This landmark trial establishes ESG as the main player in our endoscopic obesity treatment armamentarium at the present time.

### *Key Study Findings*

In this RCT of ESG with lifestyle interventions compared to lifestyle interventions alone, the ESG group had significantly greater and meaningful weight loss.

The mean %EWL was 49.2% (SD 32.0) in the ESG group and lower at 3.2% (SD 18.6) in the control group ( $P<0.001$ ). Similarly, TBWL at 52 weeks was higher with ESG compared to control (12.6% vs 0.8%,  $P<0.0001$ ), which equates to approximately 27 pounds vs 2 pounds.

The ESG group also had improvement in their metabolic comorbidities. ESG



was overall very safe with a 2% rate of device or procedure related serious adverse events. Durability of ESG was also demonstrated. Of the 60 patients who achieved their goal weight of >25% EWL at 1 year, 41 (68%) had sustained weight loss using the same definition at 2 years.

### ***Caution***

This study still does not answer the question of how ESG compares to laparoscopic sleeve gastrectomy. Future comparative studies will be useful to determine patient characteristics that may predict success and to help patients make informed decisions based on effectiveness and safety profile. Additionally, this trial only provides data out to 2 years and at the 1-year mark, suture reinforcement was offered. More robust long-term data will be important to show durability of ESG and guide practice on when a repeat endoscopy with tightening may be indicated.

### ***My Practice***

I (JK) work with a multidisciplinary group that includes a bariatric surgeon, registered dietician, obesity medicine specialist, psychologist, health/behavior coach, and pharmacist. This team-based comprehensive approach is critical to implement a multitargeted intervention. In our Veteran's Affairs setting, this is accomplished through the MOVE! weight loss program for veterans. Like the workup for bariatric surgery, potential candidates should undergo a thorough medical, psychological and lifestyle evaluation to ensure there are no other conditions that would interfere with their post procedure lifestyle and

diet. Ideally these individuals have good functional status and can exercise. One of the most important keys to success is a motivated patient who is ready and willing to follow instructions and stay engaged with the team. Although I typically require patients to complete and "fail" a full lifestyle intervention program prior to consideration for ESG as they do for bariatric surgery, this article with a crossover design suggests that this approach is likely only causing a detrimental delay for patients without improved outcomes. These results also reinforce the limited success with lifestyle/diet alone and suggest we may need to be more aggressive up front with an endoscopic intervention, surgical intervention, or effective weight loss medications such as GLP-1 agonists. Indeed, for patients who do not achieve at least 5% TBWL in the first month after ESG or even show signs of weight regain, I add on weight loss pharmacotherapy to augment response.

### ***For Future Research***

ESG is becoming mainstream with more and more gastroenterologists and surgeons being trained daily. Its popularity is expected to continue to grow as insurance companies recognize its value and provide reimbursement. Alternative technologies for gastric remodeling procedures that are being evaluated are the primary obesity surgery endoluminal (POSE), which employs a similar concept as ESG but utilizes full thickness plications with suture anchor pairs. Additional weight loss interventions such as intragastric balloons, the transpyloric shuttle, and new techniques, including duodenal mucosal resurfacing and meta-

bolic focused interventions, with different mechanisms of action are being developed as we learn more about the pathophysiology of obesity and concomitant metabolic disorders. Clearly, there are millions of Americans with obesity that cannot be reached through surgery alone. Refining algorithms for a comprehensive approach to obesity care will require collaboration from all members of the healthcare team, the institution and payors, industry partners, and researchers. Additionally, endoscopic therapies may play a larger role in the growing obesity epidemic in children and adolescents.

### *Conflict of Interest*

Dr. Kolb reports no potential conflict of interest. Dr. Chiang is an employee of Medtronic.

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# Early Colonoscopy for Acute Lower GI Bleeding Usually Is Not the Answer



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This article reviews Shiratori, Y, Ishii N, Aoki T, et al. Timing of colonoscopy in acute lower GI bleeding: a multi-center retrospective cohort study. *Gastrointest Endosc* 2023 Jan;97(1):89-99.e10.

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## STRUCTURED ABSTRACT

**Question:** Is early colonoscopy (<24 hours) beneficial to reduce re-bleeding or other clinically important outcomes compared to colonoscopy performed electively (24-48 hours) or late (48-120 hours) for patients hospitalized with an acute lower gastrointestinal bleed (LGIB)?

**Design:** Multicenter, retrospective study of patients who underwent a colonoscopy within 120 hours of admission for a LGIB.

**Setting:** Forty-nine hospitals in Japan.

**Patients:** Patients were from the CODE-BLUE-J study<sup>1</sup> of people hospitalized with acute LGIB at 49 participating hospitals in Japan. Exclusion criteria included: patients who had prior LGIB; patients who did not receive a colonoscopy (or received it after 120 hours); patients who had post-procedural bleeding, colorectal cancer, or other neoplasms; patients with an upper GI bleed; or those who had bleeding after a colorectal surgery. A total of 6,270 patients were identified.

**Exposures:** Patients were identified to have undergone early (within 24 hours), elective (24-48 hours), or late (48-120 hours) colonoscopy.

**Outcomes:** Primary outcome was 30-day rebleeding rate, defined as a significant quantity of fresh blood loss or passage of wine-colored stools after colonoscopy, associated with any of the following: systolic blood pressure <100 mm Hg, pulse rate  $\geq$  100 beats/min, or >2 g/dL decrease in hemoglobin. Secondary outcomes included: (a) stigmata of recent hemorrhage, defined as the presence of active bleeding, detection of vessel or adherent clot; (b) 30-day mortality; (c) need for interventional radiology or surgery during the admission and after colonoscopy; (d) blood transfusion; and, (e) length of hospital stay, measured in days.

**Statistical Analysis:** This was a retrospective study that used inverse probability of treatment weighting to adjust for baseline characteristics. They then created propensity scores to account for covariates that would predict timing of colonoscopy, and performed inverse probability of treatment weighting to adjust for baseline characteristics among groups. The purpose of these steps is to mimic a randomized control trial in a retrospective study – where the baseline covariates are balanced between the arms of the study (in this case, early, elective, or late colonoscopy).

**Results:** Patients were identified to have undergone early (n=4,133), elective (n=1,137), or late (n=1,000) colonoscopy. Compared to both the elective and late groups, the early group had increased rate of identification of stigmata of recent hemorrhage, more endoscopic therapies performed, and a shorter length of hospital stay. However, the early group also had a higher 30-day rebleeding rate. There were no significant differences in the requirement for interventional radiology or surgery procedures, mortality, and transfused packed red blood cells among the groups. The findings are summarized in **Table 1**.

A subgroup analysis based on shock index (which reflects hemodynamic stability) and performance status (which reflects level of functioning, higher performance status is worse) found a benefit in early colonoscopy. Early colonoscopy had a significantly lower intervention or surgery requirement in the shock index  $\geq$ 1 cohort (odds ratio [OR] 0.27; 95% confidence interval [CI], 0.10-0.72) compared with late colonoscopy. There was an interaction with performance status, with markedly divergent odds of rebleeding among those with poor performance status ( $\geq$ 3), in early vs late (ref) colonoscopy: performance status 0-2: OR 2.48, 95% CI, 1.90-3.24 and performance status  $\geq$ 3: OR 0.46, 95% CI, 0.16-1.28.

**Funding:** Research support was provided by the Ministry of Health, Labor and Welfare, Japan, JSPS KAKENHI, Smoking Research Foundation, Takeda Science



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	Rebleeding (OR; 95% CI)	Stigmata of recent hemorrhage (OR; 95% CI)	30-day mortality (OR; 95% CI)	Radiology or surgical intervention (OR; 95% CI)	Blood transfusion needed (OR; 95% CI)	Length of stay (OR; 95% CI)
Early vs elective (ref)	1.35; 1.127-1.62	1.79; 1.52-2.09	1.052; 0.44-2.53	1.02; 0.68-1.54	-0.302; 0.66-0.06	-0.820; 1.50 to -0.14
Elective vs late (ref)	1.712; 1.29-2.28	1.51; 1.19-1.91	1.362; 0.43-4.37	0.98; 0.58-1.66	0.433; 0.00-0.87	-0.65; 1.75-0.45
Early vs late (ref)	2.26; 1.75-2.91	2.56; 2.09-3.14	1.63; 0.58-4.59	0.96; 0.62-1.48	0.06; 0.28-0.39	-1.30; 0.04 to -0.55

**Table 1:** Odds ratios of outcomes between colonoscopy timing. CI, confidence interval; OR, odds ratio.

## COMMENTARY

### *Why Is This Important?*

Acute LGIBs pose a dilemma – as gastroenterologists, we know that colonoscopy plays an important role in diagnosis of the LGIB etiology, but that endoscopic therapy is limited. Previously, the 2016 ACG guideline<sup>2</sup> recommended a rapid bowel purge following hemodynamic resuscitation with colonoscopy performed within 24 hours to improve diagnostic and therapeutic yield. This contrasted with the British Society of Gastroenterology and the European Society of Gastrointestinal Endoscopy guidelines, which do not recommend early colonoscopy.<sup>3,4</sup> This lack of consensus was driven by conflicting literature prior to 2016.<sup>5</sup> While systematic reviews and meta-analyses have found at least higher rates of stigmata of recent hemorrhage and endoscopic intervention when colonoscopy is performed within 24 hours,<sup>6-8</sup> 2 recent small randomized controlled trials (RCTs) have found no improvement in rebleeding or mortality with early colonoscopy.<sup>9-10</sup>

These data led to an updated 2023 American College of Gastroenterology (ACG) guideline: “we recommend performing a nonemergent inpatient colonoscopy, as performing an urgent colonoscopy within 24 hours has not been shown to improve clinical outcomes.”<sup>11</sup> Nevertheless, confirmatory data is needed. The authors of the present study note the difficulty in performing RCTs for acute LGIBs—particularly as it relates to sample size and ensuring populations are representative of what is seen in the real-world, but also the limitations in observational studies, which can lack granularity. This well-designed study attempts to correct for the shortcomings of both by mimicking a RCT with observational data, and its findings provide further support for the new ACG guideline recommendation.

### *Key Study Findings*

Compared to both the elective (24-48 hours) and late group (48-120 hours), the early group (within 24 hours)



demonstrated increased rate of identification of stigmata of recent hemorrhage, more endoscopic therapies were performed, and length of hospital stay was shorter. However, early colonoscopy was associated with higher 30-day rebleeding compared to both the elective and late groups. There were no significant differences in the requirement for interventional radiology or surgery procedures, mortality, and transfused PRBCs among the groups.

Subgroup analyses showed that those with moderate or severe shock or those with poor performance status may benefit from early colonoscopy. Specifically, early colonoscopy in the moderate-severe shock group led to fewer additional procedures by radiology or surgery, and there was a non-significant decrease in rebleeding rate for the poor performance status group.

### ***Caution***

Given the retrospective nature of this study, there are some methodologic limitations that could not be overcome. The authors use propensity scores and inverse probability of treatment weighting to overcome the lack of randomization in study design. Although this could still lead to bias and can be susceptible to unmeasured confounders, the authors do an excellent job of showing the findings for the observed, imputed, and weighted imputed data. Also, they excluded anyone who did not receive a colonoscopy, which may reflect an exclusion bias itself. Lastly, it's hard to understand why the early group had a higher rebleeding rate, and

particularly why those with poor performance status may benefit from early colonoscopy.

### ***My Practice***

The updated ACG guidelines reflect my practice well. I generally recommend colonoscopy for hospitalized patients—but like the new guidelines, I consider whether the bleeding has stopped based on the patient's hemodynamic status and response to resuscitation. Among those persons who have undergone a computed tomography (CT) angiogram in the emergency room with evident extravasation, I recommend interventional radiology evaluation and embolization urgently. Otherwise, I recommend resuscitation, ideally holding anticoagulants, and a nonurgent inpatient colonoscopy. This study really bolsters that approach for me, but also highlights a new area of interest, that those with moderate-severe shock or poor performance status may be served by early colonoscopy. Personally, these subgroups may be similarly or better served by early CT angiogram and I am more apt to send them for CT angiogram (if their creatinine allows) than urgently perform a colonoscopy with attempts at rapid bowel purge.

### ***For Future Research***

I would like to see further evaluation of the authors' finding that those with poor performance status or high shock index can benefit in terms of early colonoscopy. In particular, I would want to know if CT angiogram provides the same (or greater) benefit in these groups, and if it is a more cost-effective

approach. That the early group also had higher rebleeding rates similarly suggests that CT angiogram may be an appropriate first step for durable hemostasis. Parsing these out could identify which subgroups of patients warrant early colonoscopy, which is especially critical given the resource intensive nature of colonoscopy.

### ***Conflicts of Interest***

Dr. Kumar reports no conflicts of interest.

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# Direct-Acting Antiviral Therapy for Hepatitis C Virus Decreases All-Cause Mortality and Decompensated Cirrhosis: Treat (Virtually) Everyone



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This summary reviews Ogawa E, Chien N, Kam L, et al. Association of Direct-Acting Antiviral Therapy with Liver and Nonliver Complications and Long-term Mortality in Patients with Chronic Hepatitis C. *JAMA Intern Med* 2023; 183(2):97-105.

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## STRUCTURED ABSTRACT

**Question:** Are direct-acting antiviral agents (DAA) associated with decreased mortality and decreased liver outcomes (e.g., decompensated cirrhosis, hepatocellular carcinoma) among individuals with hepatitis C virus (HCV)?

**Design:** A retrospective cohort study from January 2014 to March 2021.

**Setting:** Optum Clinformatics Data Mart database of administrative claims from individuals with commercial and Medicare Advantage Health Plans.

**Patients:** Patients infected with HCV.

**Interventions/Exposure:** Treatment with DAAs.

**Outcome:** Primary endpoints were: (1) incidence of liver outcomes, including hepatocellular carcinoma (HCC) and decompensated cirrhosis; and (2) all-cause mortality. Secondary endpoints were incidence of non-liver outcomes, including non-liver

cancer, chronic kidney disease, cardiovascular disease, and diabetes.

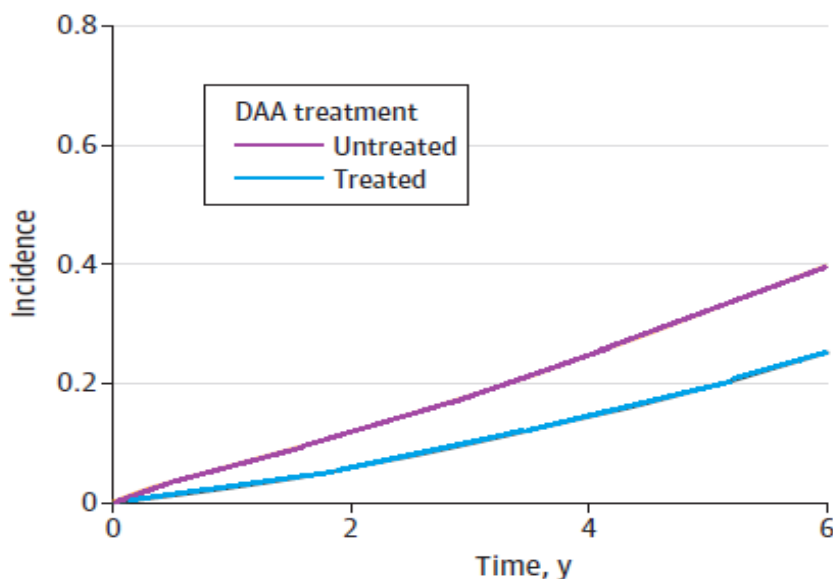
**Data Analysis:** Cumulative HCC incidence and mortality was calculated with the Kaplan-Meier method. Log-rank test was used to compare differences between DAA-treated HCV patients and non-treated patients. Cox proportional hazards regression was used to estimate adjusted hazard ratios (aHRs).

**Funding:** Stanford Center for Population Health Sciences and the National Institute of Health.

**Results:** A total of 245,596 patients with HCV (mean age 59; 59% men; 57% White; 17% Black) were included in data analysis, with 17% receiving at least 1 prescription for DAA and 83% with no prescriptions. Compared to untreated patients, patients receiving DAAs were slightly older (59.9 years vs 58.5 years), male (61.6% vs 58.5%), and had compensated cirrhosis (44% vs 29%).

The incidence (per 1,000 person-years) was significantly lower in DAA-treated patients vs untreated patients for developing decompensated cirrhosis (28.2 vs 40.8), HCC among the sub-group with compensated cirrhosis (20.1 vs 41.8), and all-cause mortality (36.5 vs 64.7). The difference in all-cause mortality was demonstrated in sub-groups of individuals without baseline cirrhosis, with compensated cirrhosis at baseline, and with decompensated cirrhosis at baseline (**Figure 1**).

In multi-logistic regression analysis, DAA treatment was independently associated with a decreased risk of decompensated cirrhosis (aHR 0.36; 95% confidence interval [CI]: 0.35-0.38), HCC (aHR 0.73; 95% CI: 0.68-0.77), diabetes (aHR 0.74; 95% CI: 0.70-0.77), and all-cause mortality (aHR 0.43; 95% CI: 0.42-0.45).



**Figure 1.** All-cause mortality among patients with hepatitis C virus treated with direct-acting antiviral agents (DAAs) vs untreated (total cohort).  $P < .001$ .



## COMMENTARY

### *Why Is This Important?*

HCV is a public health crisis. Over 2.4 million Americans are estimated to be infected with HCV, and Centers for Disease Control and Prevention data indicate that acute HCV infection has increased 400% from 2010 to 2020 with the highest infections rates among 20–39-year-olds. However, as many as 40% are unaware that they are infected.<sup>1</sup> Yet, the severe morbidity and mortality due to HCV can be decreased with the breakthrough antiviral agents approved in the past 10 years. Oral DAA regimens of 8-12 weeks are over 95% effective at eradicating HCV and extremely well-tolerated. This success has been demonstrated regardless of prior treatment failure, presence of cirrhosis, advanced age, or comorbidities. Thus, treatment is appropriate for virtually all populations unless they already have a very short life expectancy.

Unfortunately, only a minority of HCV-infected individuals have been treated and as many as 40% of these individuals are unaware that they are even infected. This has led to recommendations from the American Association for the Study of Liver Disease and the Infectious Disease Society of America for universal HCV screening and DAA treatment for all infected patients. The importance of these recommendations is affirmed by this excellent study from Ogawa et al, which estimates efficacy of DAAs when

prescribed in a large, insured community-based group of patients. Specifically, the adjusted risk reduction for all-cause mortality was greater than 50% and decompensated cirrhosis was greater than 60% when DAAs were prescribed.

### *Key Study Findings*

The incidence (per 1,000 person-years) was significantly lower in DAA-treated patients vs untreated patients for developing decompensated cirrhosis (28.2 vs 40.8), HCC among the sub-group with compensated cirrhosis (20.1 vs 41.8), and all-cause mortality (36.5 vs 64.7).

### *Caution*

Achieving sustained virologic response was not a primary outcome of the study. However, given the efficacy of DAAs, most patients prescribed DAAs probably achieved sustained virologic response. Study patients had private insurance or Medicare Advantage and may differ from non-insured individuals. Consistent with large database studies, misclassification bias is possible despite using *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* and *ICD-10-CM* codes to identify outcomes.

### *My Practice*

At our Veterans Affairs Medical Center, we offer DAAs to all HCV-infected patients unless they have a very short life expectancy or if their mental illness/polysubstance abuse is so severe that establishing compliance with follow-up visits or adherence to medication is hopeless. Overall, our treatment approach has



become much more inclusive, and we actively seek to screen all veterans for HCV and actively pursue HCV-infected veterans to initiate treatment.

### ***For Future Research***

Further research should focus on expanding HCV screening, diagnosis, and treatment since the consequences of untreated HCV infection are clear and since DAAs have demonstrated their efficacy and safety.

### ***Conflict of Interest***

Dr. Schoenfeld reports no potential conflicts of interest.

**Note:** The authors of the article published in *JAMA Internal Medicine* are active on social media. Tag them to discuss their work and this EBGI summary!

@stanford\_gi

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