

# Optimal Care Forum for Evidence-Based Medicine

 Earn up to 1.00 CNE/CME credit per issue

|                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Claiming credit</b>      | For more information, visit <a href="https://optumhealtheducation.com/ebm-forum">optumhealtheducation.com/ebm-forum</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Activity description</b> | Practicing evidence-based medicine (EBM) is important in today's health care environment. This model of care offers clinicians a way to enrich quality, provide patient satisfaction, reduce costs and improve outcomes. A common implementation of EBM involves the use of clinical practice algorithms during medical decision-making to encourage optimal care. This widely recognized practice is designed to address the persistent problem of clinical practice variation with the help of actionable information at the point of care. These e-newsletters enable health care professionals to put new EBM into practice.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Learning objectives</b>  | <ul style="list-style-type: none"> <li>• Discuss and apply evidence-based guidelines to the diagnosis and management of uncomplicated diverticulitis in adults, with a focus on reducing low-value care, minimizing unnecessary antibiotic use, and promoting patient-centered, cost-effective treatment strategies.</li> <li>• Describe the emerging role of GLP-1 receptor agonists, particularly semaglutide, in the treatment of MASLD and MASH, including their impact on steatohepatitis resolution, fibrosis reduction, and associated metabolic outcomes, based on recent clinical trial evidence.</li> <li>• Assess the efficacy, safety and clinical potential of lorundrostat, a direct aldosterone synthase inhibitor, in the management of uncontrolled hypertension and compare its therapeutic profile with established fourth-line agents such as MRAs and amiloride.</li> <li>• Examine long-term neurological and mortality outcomes associated with GLP-1 RA therapy in obese patients with type 2 diabetes, and explore potential mechanisms underlying observed reductions in dementia, stroke and overall mortality.</li> <li>• Recognize current evidence-based strategies to assess cardiovascular and cerebrovascular risk, including the use of validated scoring systems for PFO-related stroke and coronary artery CTA for guiding preventive therapy to optimize individualized patient care and reduce unnecessary interventions.</li> </ul> |

## Accreditation statement

In support of improving patient care, this activity has been planned and implemented by Optum Health Education and Optum. Optum Health Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE) and the American Nurses Credentialing Center (ANCC) to provide continuing education for the health care team.



JOINTLY ACCREDITED PROVIDER™  
INTERPROFESSIONAL CONTINUING EDUCATION

## Credit designation statements

### Nurses

The participant will be awarded up to 1.00 contact hour(s) of credit for attendance and completion of supplemental materials. This activity is designated for 1.00 ANCC pharmacotherapeutic contact hours.

### Nurse practitioners

The American Academy of Nurse Practitioners Certification Program (AANPCP) accepts credit from organizations accredited by the ACCME and ANCC.

### Physicians

Optum Health Education designates this enduring activity for a maximum of 1.00 AMA PRA Category 1 Credit(s).™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

### American Board of Internal Medicine

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 Medical Knowledge MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. **Please note, by claiming ABIM points, you authorize Optum Health Education to share your attendance information with the ABIM.**

### Physician assistants

The American Academy of Physician Assistants (AAPA) accepts credit from organizations accredited by the ACCME.

### Attendance

A certificate of attendance will be provided to learners upon completion of activity requirements, enabling participants to register with licensing boards or associations that have not been pre-approved for credits. To apply for credit types not listed above, participants should use the procedure established by the specific organization with which they wish to obtain credit.

### Provided by

This activity is provided by Optum Health Education and Optum.

### Commercial support

No commercial support was received for this activity.

## Summary of diverticulitis management: 2025 JAMA Review and other key articles

Diverticular disease has been estimated to be present in up to 50% of people over age 60.<sup>1</sup> Symptomatic diverticulitis occurs in 1%–4%, or 180 per 100,000 people, resulting in hundreds of thousands of hospitalizations and billions of dollars in health care expenditures every year. As evidence for appropriate treatment has advanced, some of the care represented in these numbers is no longer indicated. Most (85%) cases of diverticulitis are uncomplicated, meaning there is no abscess, bowel obstruction, perforation or fistula. This article summarizes the 2025 *JAMA Review* on diverticulitis management and integrates findings from key recent peer-reviewed articles that address low-value care, unwarranted variation and unnecessary cost in the treatment of diverticulitis.

### 2025 JAMA Review highlights<sup>2</sup>

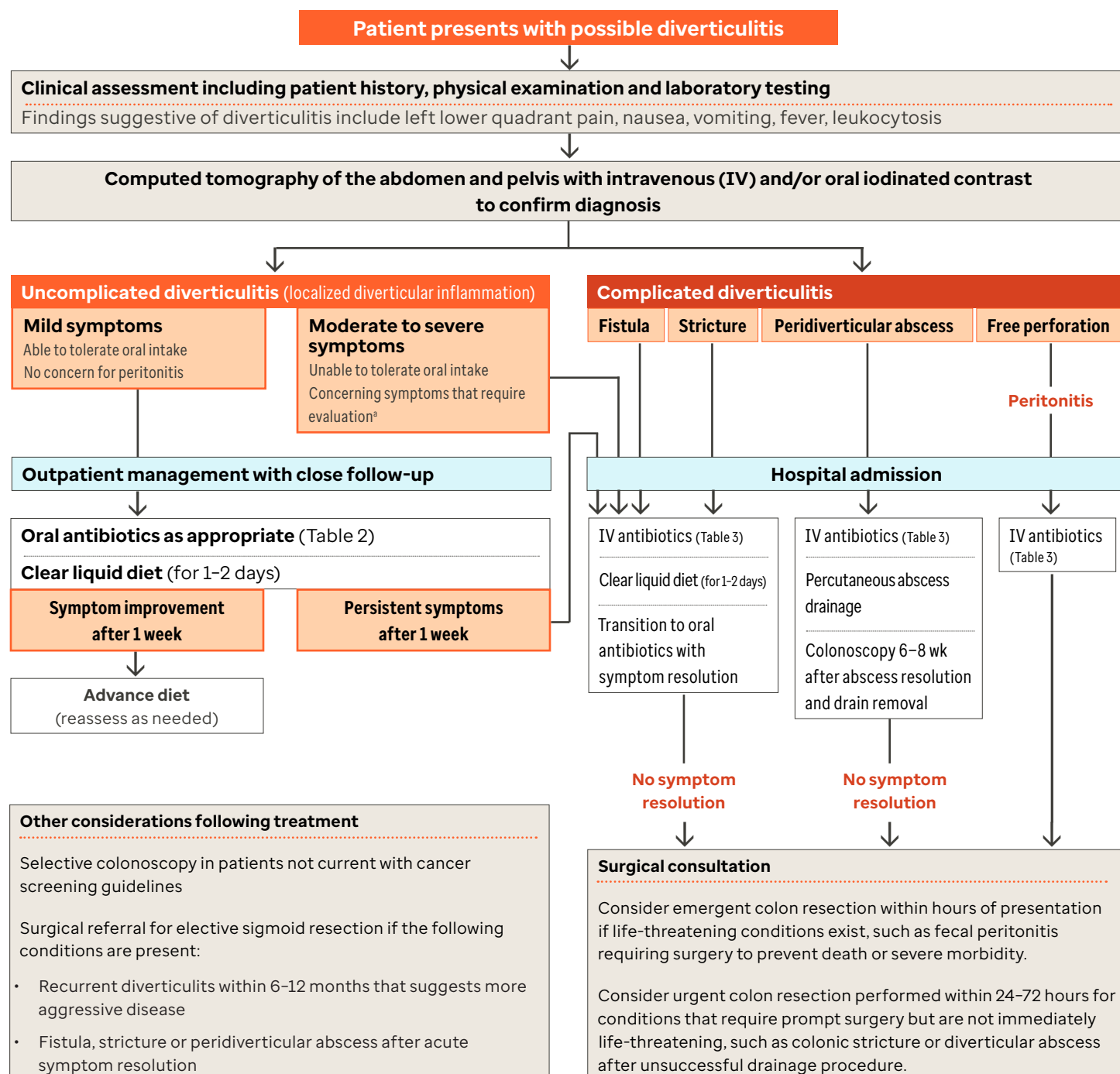
The authors searched the evidence of high-quality reports published between 2000 and 2025 to include 85 studies in the review. The included Figure 3 (reproduced below) summarizes the management algorithm. Findings of the review revealed the following:

- Diverticular disease is more prevalent in patients with diabetes mellitus, obesity or connective tissue disorders (for example, Marfan, Ehlers-Danlos, polycystic kidney disease)
- Observation alone is indicated if the following conditions are met:
  - Clinically suspected and CT-verified uncomplicated diverticulitis
  - Absence of systemic symptoms such as fever or chills
  - Adequate control of symptoms such as pain control with acetaminophen
  - Improving clinical picture over 24–48 hours
  - Ability to tolerate oral fluids
  - Immuno-competent patient without significant comorbidities
  - Age < 80 years

Abdominal ultrasound or MRI may alternatively have a role in confirming the diagnosis in those for whom CT is contraindicated or not available.

- Antibiotics are still considered first line for patients with worsening signs or symptoms, advanced age (> 79 years) or significant comorbidities (for example, CKD, cirrhosis, poorly controlled DM, and other conditions or medications that suppress the immune system).
- For patients who require antibiotics and can tolerate oral fluids, outpatient treatment is effective for the majority (95%) of patients with uncomplicated acute diverticulitis.
- In the 13%–40% of patients with recurrent diverticulitis, elective surgical resection after the acute phase may result in higher quality of life scores compared with those who are managed conservatively.

Figure 3. Management algorithm for complicated and uncomplicated diverticulitis



This algorithm has not been validated.

a. Concerning symptoms include persistent or worsening abdominal pain, moderate fever (38.3 °C to 38.9 °C [100.94 °F to 102.02 °F]), increased abdominal tenderness with guarding, and worsening leukocytosis.

**Table 2. Oral antibiotic regimens for the treatment of uncomplicated acute diverticulitis<sup>a,b,c</sup>**

|                          | <b>Amoxicillin-clavulanate</b>                                        | <b>Cefalexin + metronidazole</b>                              | <b>Ciprofloxacin + metronidazole</b>                                                       | <b>Trimethoprim-sulfamethoxazole + metronidazole</b>                       |
|--------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| <b>Dose</b>              | 875 mg/125 mg twice daily                                             | 1g g times daily + 500 mg 3 times daily                       | 500 mg twice daily + 500 mg 3 times daily                                                  | 160 mg/800 mg double-strength tablet twice daily + 500 mg 3 times daily    |
| <b>Adverse effect, %</b> | Nausea (16), diarrhea (10), rash (5–8), liver enzyme elevation (0.04) | Nausea (2–3), diarrhea (2–7), stomach pain (rare), rash (1.5) | GI upset (4.8), taste disturbance (15.5), tendinitis (0.14–0.4), neuropathy (3) rash (1.8) | GI upset (3.7), rash (7.3), hypersensitivity (3–6), photosensitivity (1–5) |
| <b>Efficacy, %</b>       | 86–89                                                                 | 75–100                                                        | 74–94                                                                                      | Limited data                                                               |

Abbreviation: GI, gastrointestinal.

- a. Broad-spectrum oral antibiotic regimens for treatment of acute diverticulitis against gram-negative rods and anaerobic bacteria. When possible, the selection of antibiotics should be guided by local resistance patterns and patient allergies. For all antibiotics, consult local formulary for appropriate use and dosing in specific populations – for example, hepatic impairment, kidney impairment, pregnancy and breastfeeding, and administering intravenous antibiotics. A longer course may be needed based on clinical assessment. For intravenous antibiotics: Duration of antibiotics depends on improvement in symptoms. Review within 48 hours or after scanning and consider de-escalating to oral antibiotics where possible.
- b. In uncomplicated diverticulitis, antibiotics can be withheld in immunocompetent and stable patients. Antibiotics are indicated in unstable patients with uncomplicated diverticulitis and patients with complicated diverticulitis.
- c. Appropriate for patients who are stable and can tolerate oral intake. If intolerant, proceed to intravenous antibiotics. For all regimens, treatment should be 4 to 7 days' duration.

**Table 3. Intravenous Antibiotic Regimens for the Treatment of Complicated Acute Diverticulitis<sup>a,b</sup>**

|                                        | <b>Ceftriaxone + metronidazole</b>                                             | <b>Imipenem-cilastatin</b>                      | <b>Meropenem</b>                                                                                | <b>Piperacillin-tazobactam</b>                                                                                             |
|----------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| <b>Dose</b>                            | 1–2 g once daily + 500 mg 3 times daily                                        | 500 mg every 6 h                                | 1 g every 8 h                                                                                   | 3.375–4.5 g every 6 h                                                                                                      |
| <b>Duration (days)</b>                 | 7–14                                                                           | 7–14                                            | 7–14                                                                                            | 7–14                                                                                                                       |
| <b>Adverse Effects (%)<sup>c</sup></b> | GI upset (1.5), neutropenia (2), diarrhea (2–10), infusion reactions (0.5–2.5) | GI upset (2–10), seizures (1.5), rash (0.3–3.7) | Seizures (<1), nausea (1–4), hypersensitivity (1–2), <i>Clostridioides difficile</i> risk (1–6) | GI upset (0.9), allergic reactions (1.3), <i>C. difficile</i> risk (3–10), GI upset (2–10), seizures (1.5), rash (0.3–3.7) |
| <b>Disease Severity<sup>b</sup></b>    | Complicated (clinically stable)                                                | Complicated (clinically unstable)               | Complicated (clinically unstable)                                                               | Complicated (clinically unstable)                                                                                          |
| <b>Efficacy (%)</b>                    | 75–100                                                                         | 81                                              | 70–96                                                                                           | 86–89                                                                                                                      |

Abbreviation: GI, gastrointestinal.

- a. Broad-spectrum intravenous antibiotic regimens for treatment of acute diverticulitis against gram-negative rods and anaerobic bacteria. When possible, the selection of antibiotics should be guided by local resistance patterns and patient allergies. For all antibiotics, consult local formulary for appropriate use and dosing in specific populations – for example, hepatic impairment, kidney impairment, pregnancy and breastfeeding, and administering intravenous antibiotics. A longer course may be needed based on clinical assessment. For intravenous antibiotics, duration of antibiotics depends on improvement in symptoms. Review within 48 hours or after scanning and consider de-escalating to oral antibiotics when possible.
- b. Uncomplicated diverticulitis is defined as the presence of inflammation of colonic diverticula only. Complicated diverticulitis is inflammation of colonic diverticula that is associated with one or more of the following: perforation, abscess formation, fistula (eg, colovesical, colovaginal), or bowel obstruction.
- c. Incidence of adverse drug reaction obtained from the World Health Organization at <https://vigiaccess.org/>.

### Additional key peer-reviewed articles (2020–2025)

1. *JAMA Surgery* (2024): Management of Diverticulitis: A Review<sup>3</sup>
  - Highlights safe avoidance of antibiotics and surgery in uncomplicated cases
  - Up to 80% of patients with complicated diverticulitis can be treated successfully with antibiotics plus or minus percutaneous drainage, and without surgery
  - Highlights the need for shared decision-making for elective surgery to prevent recurrence
2. *Journal of Trauma and Acute Care Surgery* (2025): Evidence-Based, Cost-Effective Management of Acute Diverticulitis<sup>4</sup>
  - Provides another algorithm to evaluate appropriate treatment paths for patients with acute diverticulitis
  - Supports CT-based stratification and outpatient care
  - Recommends avoiding antibiotics in the Modified Hinchey Classification 0–1a cases (mild clinical diverticulitis and confined pericolic inflammation or phlegmon) unless comorbidities exist
3. *AHRQ Comparative Effectiveness Review* (2020)<sup>5</sup>
  - Systematic review of diagnosis, management and follow-up strategies
  - Supports non-antibiotic management in select patients
  - Evaluates effectiveness and safety of interventions
4. *BMC Emergency Medicine* (2022): Non-Antibiotic Management<sup>6</sup>
  - Real-world cohort study comparing antibiotic vs. non-antibiotic protocols
  - Found no difference in recurrence or complications
  - Non-antibiotic protocols reduced unnecessary antibiotic use

### Summary of themes across studies

| Theme                 | Key findings                                                                                                     |
|-----------------------|------------------------------------------------------------------------------------------------------------------|
| Low-value care        | Avoiding antibiotics and surgery in uncomplicated cases is safe and effective.                                   |
| Unwarranted variation | Treatment decisions should be based on established risk factors and take into consideration patient preferences. |
| Cost of care          | Outpatient and non-antibiotic management significantly reduce unnecessary costs and resource use.                |

**Bottom line for primary care:** Contemporary management of diverticulitis is more conservative and patient-tailored. Most patients with uncomplicated diverticulitis can be managed outpatient with close follow-up, using supportive care and selective antibiotics. This approach is supported by multiple high-level studies and reflected in current guidelines. It leads to similar (or better) outcomes while reducing exposure to antibiotics, lowering costs and improving patient convenience.

As always, clinical judgement is key – identify those who truly need intervention (antibiotics, admission or surgical referral) and manage others with a lighter touch. This nuanced strategy not only benefits individual patients but also advances our broader goal of value-based health care in the management of common conditions like diverticulitis.

## Semaglutide for MASLD and MASH

Accumulating data supports the use of the GLP-1 receptor agonists (RA) class for patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). In an earlier phase II trial, the effects of semaglutide were investigated in patients with biopsy-defined MASH and liver fibrosis (stages 1, 2 and 3). A significantly higher percentage of patients who received semaglutide compared to placebo had resolution of steatohepatitis with no worsening of fibrosis (59% vs. 17%).<sup>7</sup> Now, based on an interim analysis of a phase III trial published in the *New England Journal of Medicine* (NEJM) in June 2025, the FDA has approved the use of semaglutide for treatment of MASLD/MASH.<sup>8</sup> This publication was a planned interim analysis of the first 800 patients at week 72 of the study.

All patients had biopsy-proven disease that included both MASH and fibrosis stages 2 or 3 and were randomized to semaglutide 2.4 mg once weekly vs placebo. Approximately 73% of the patients were obese, and 56% had DM2, with 14% of the patients having MASLD that was not related to obesity or diabetes. After 72 weeks, resolution of steatohepatitis without worsening of fibrosis occurred in 62.9% in the semaglutide group and in 34.3% in the placebo group (estimated difference, 28.7 percentage points). A reduction in liver fibrosis without worsening of steatohepatitis was reported in 36.8% of the patients in the semaglutide group and in 22.4% of those in the placebo group (estimated difference 14.4 percentage points). Results for the 3 secondary outcomes were as follows:

- Combined resolution of steatohepatitis and reduction in liver fibrosis was reported in 32.7% of the patients in the semaglutide group and in 16.1% of those in the placebo group.
- Mean change in body weight was -10.5% with semaglutide and -2.0% with placebo.
- Improvement curve for liver fibrosis had begun to level off at 24 weeks while the curve for MASH was not shown.

Therefore, it will be important to see how much further resolution there will be in both steatohepatitis and fibrosis at trial conclusion.

## Lorundrostat efficacy and safety in patients with uncontrolled hypertension

We know from the Pathway studies published in *The Lancet*<sup>9</sup> that mineralocorticoid receptor antagonists (MRA) and amiloride are the most effective fourth drugs in patients whose hypertension remains uncontrolled on a 3-drug regimen that includes a thiazide, ACE/ARB and amlodipine. A new class of antihypertensives is under development by multiple pharmaceutical companies. These drugs are direct inhibitors of aldosterone synthetase. They work similarly to the MRAs. However, by directly impacting synthesis rather than blocking receptor binding, they could potentially be more potent. A recent study looked at lorundrostat in patients with uncontrolled hypertension.<sup>10</sup>

Patients with systolic blood pressure (BP) between 130 and 180 mm Hg were enrolled after stabilization with the above noted 3-drug regimen. Of the 285 patients, 188 were treated with lorundrostat (half each in fixed dose and dose-adjusted regimens) and 94 patients received placebo. At 12 weeks, relative to the placebo group that had a 7 mm Hg reduction in systolic BP, the fixed and adjusted groups on lorundrostat had reductions of 15 mm and 14 mm Hg on 24-hour continuous ambulatory BP monitoring. These results are consistent with those seen in the above-mentioned Pathway study. Black and white patients had similar BP reductions. A potassium level above 6.0 mmol per liter occurred in 5 participants (5%) in the stable-dose group, 7 (7%) in the dose-adjustment group, and no participants in the placebo group. The small decline in eGFR commonly observed when treatment with MRAs is initiated was also seen here. These transient reductions are thought to be related to the lowering of intraglomerular pressure and may signify a therapeutic effect rather than indicating harm.



## GLP-1 RA use and long-term CNS outcomes in obese patients with diabetes

With the widespread use of this drug class, there is increasing interest in both on-target effects. A recent retrospective propensity matched cohort analysis looked at the new onset of neurological diagnoses in patients on tirzepatide (GLP-1 RA/GIP combination) or semaglutide compared to patients on other drugs for DM2.<sup>11</sup> Approximately 30,000 GLP-1 RA users were propensity score matched with 30,000 patients using other drugs for DM2 and followed for 7 years. The median age was 58 years.

Over the 7 years of follow-up, the GLP-1 RA group had a 37% lower risk of dementia (although the absolute risk reduction was only 0.33%). There was no reduction in the risk of mild cognitive impairment. There was a 19% lower risk of stroke (absolute risk reduction 3.5%). There was a 30% lower risk of overall mortality in the GLP-1 RA group (absolute risk reduction 2.4%). There was no reduction in the risk of Parkinson's disease.

Since dementia, stroke and overall mortality are all increased in DM2 and the metabolic syndrome, the underlying mechanism of the GLP-1 RA benefit might be an improvement in insulin resistance, systemic inflammation and overall metabolic status. This aligns with the observation that the risk of Parkinson's disease was unaffected by GLP-1 RA use.



## Patent foramen ovale and the risk of stroke

A recent review of patent foramen ovale (PFO) and stroke was published in *JAMA* and forms the data source for this article.<sup>12</sup> Evaluating the benefit of PFO closure in younger patients who present with cryptogenic stroke and are found to have a PFO has been very difficult. This is largely related to the fact that PFO is found in 25% of the general population. However, in younger patients (< 60 years of age) who present with cryptogenic TIA or stroke, the rate of PFO is 50%. As studies of PFO closure have accrued and long-term outcomes documented in these younger individuals, a clearer picture of who is likely to benefit from PFO closure is emerging.

The 2 potential reasons for PFO resulting in cryptogenic stroke are:

1. Embolic tissue moving from right to left across a PFO, causing cerebral embolism
2. Potentially in situ thrombus formation around the interatrial tunnel, giving rise to a cerebral embolism

There are 2 main structural factors that contribute to the probability of cryptogenic stroke arising from a PFO. One is a large shunt through the PFO, and the other is an atrial septal aneurysm. These can both be documented with an echocardiogram or bubble study.

In addition to the above specifics of the PFO, the associated clinical factors are critical to the decision-making in terms of who might benefit from PFO closure. Age and stroke related comorbidities associated with an increased stroke risk (predominantly HTN, tobacco use, hyperlipidemia and DM2) are pivotal. Although PFO could be a potential etiology of cryptogenic stroke in patients over age 60, the risks of age- and stroke-related comorbidities eclipse PFO as the likely cause of stroke such that PFO closure in this age group is not likely to diminish the risk of recurrent stroke. Other clinical factors that increase the likelihood of PFO being etiologically related to a stroke are a cortical infarct on imaging, Valsalva maneuver being temporally related to stroke onset, and other risk factors or the diagnosis of DVT and/or hypercoagulability.

To assist in determining the probability of a cryptogenic stroke being caused by a PFO, 2 scores have been developed and validated.

- The first is the RoPE score. It was developed from an analysis of 8 databases that included 3,023 patients with cryptogenic stroke who were systematically evaluated for PFO. The RoPE score includes 6 clinical characteristics (age, history of stroke or TIA, diabetes, hypertension, smoking, cortical infarct on imaging) and ranges from 0 to 10. (Table 1 top). This has high utility in associating a cryptogenic stroke with PFO. For example, among patients in the lowest RoPE score category (score < 3, older patients with multiple stroke risk factors), the prevalence of PFO was 23%, like that in the general population, suggesting a PFO-attributable fraction near zero. However, the prevalence of PFO in patients with cryptogenic stroke and a RoPE score of 9 or 10 was 77%, suggesting a 90% likelihood that the stroke was attributable to a PFO.
- The second score is an extension of the RoPE score. The PFO-Associated Stroke Causal Likelihood (PASCAL) uses the RoPE score and adds to it the high-risk anatomical features defined by echo (atrial septal aneurysm or large right to left shunt through the PFO). Based on the PASCAL classification system, PFO is considered the “probable,” “possible” or “unlikely” cause of an otherwise cryptogenic stroke (Table 1 bottom).



**Table 1. Calculation of the RoPE score and PASCAL classification<sup>a</sup>**

| Characteristic                                    |                                       | Points             |
|---------------------------------------------------|---------------------------------------|--------------------|
| <b>RoPE score calculator<sup>b</sup></b>          |                                       |                    |
| No history of hypertension                        |                                       | 1                  |
| No history of diabetes                            |                                       | 1                  |
| No history of stroke or transient ischemic attack |                                       | 1                  |
| Nonsmoking                                        |                                       | 1                  |
| Cortical infarct on imaging                       |                                       | 1                  |
| Age, years                                        |                                       |                    |
| 18-29                                             |                                       | 5                  |
| 30-39                                             |                                       | 4                  |
| 40-49                                             |                                       | 3                  |
| 50-59                                             |                                       | 2                  |
| 60-69                                             |                                       | 1                  |
| ≥70                                               |                                       | 0                  |
| Total RoPE Score (sum of individual points)       |                                       | X                  |
| <b>PASCAL classification system<sup>c</sup></b>   |                                       |                    |
| High RoPE score (≥7)                              | High-risk PFO feature (LS and/or ASA) | PFO-related stroke |
| Absent                                            | Absent                                | Unlikely           |
| Absent                                            | Present                               | Possible           |
| Present                                           | Absent                                | Possible           |
| Present                                           | Present                               | Probable           |

Abbreviations: ASA, atrial septal aneurysm (defined as ≥10 mm of excursion from midline); LS, large shunt (defined in the database as >20 bubbles in the left atrium on transesophageal echocardiogram); PASCAL, PFO-Associated Stroke Causal Likelihood; PFO, patent foramen ovale; RoPE, Risk of Paradoxical Embolism.

d. Adapted with permission from Neurology.<sup>38</sup>

e. The RoPE score assesses the probability that a PFO discovered in the setting of an otherwise cryptogenic stroke was pathogenically related to the stroke rather than an incidental finding. The RoPE score ranges from 0 to 10, with scores of 0 to 3 indicating a negligible likelihood that the stroke is attributable to the PFO and a score of 10 indicating an approximately 90% probability that the stroke is attributable to the PFO.

f. PASCAL combines the RoPE score with the presence or absence of high-risk PFO features to determine the likelihood that the PFO was causally related to the index stroke.

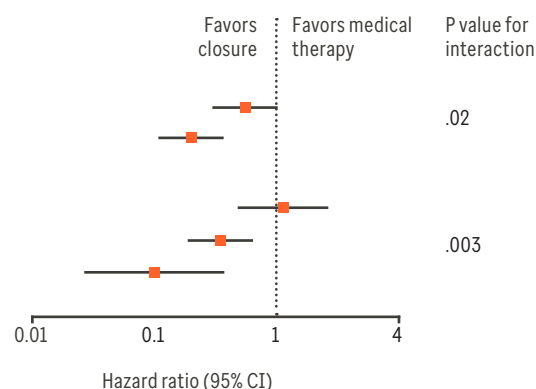
So how best to put all this information to use? The first 3 large RCTs comparing PFO closure/aspirin therapy to medical treatment of stroke showed no reduction in recurrent stroke rate. However, the RESPECT trial 6-year follow-up data showed a rate of recurrent ischemic stroke of 3.6% in the PFO closure group versus 5.8% in the medical therapy group (hazard ratio 0.55). Three subsequent trials also showed benefit, and a meta-analysis of all 6 trials reported a lower rate of recurrent ischemic stroke with PFO closure (2%) versus medical therapy alone (4.6%) (relative risk, 0.44 at a median follow-up of 57 months). Based on these results, guidelines now recommend PFO closure in selected patients (predominantly those patients aged < 60 years with cryptogenic stroke).

Figure 3B shows the absolute risk reduction for recurrent stroke as a function of PASCAL score at 2.1% for both probable and possible PFO-related etiology, compared to -0.7% for the low probability group. The NNT to prevent recurrent stroke was 47 in both the probable and possible categories. It should be noted that PFO closure is associated with new onset atrial fibrillation at a rate of ~3.7%, although this is often transient. However, any strokes related to periprocedural atrial fibrillation would have contributed to the stroke rates reported in the PFO closure group. For those patients not undergoing PFO closure in the probable and possible related categories, across the 6 studies in the aforementioned meta-analysis, anticoagulation was associated with a lower risk of recurrent stroke (3.2%), compared to antiplatelet therapy (5.5%). There is not adequate RCT data to determine which, if any, patients over age 60 may benefit from PFO closure.

**Figure 3. Recurrent Ischemic Stroke Heterogeneity of Treatment Effect (HTE) Analyses for RoPE and PASCAL**

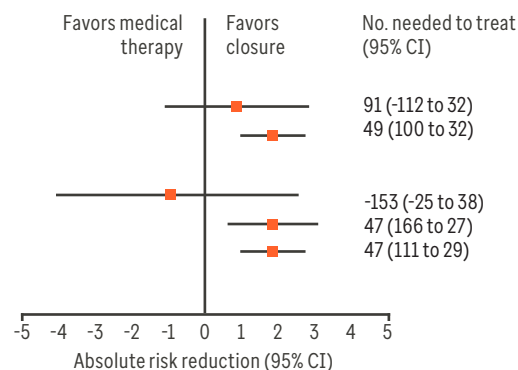
**A. Hazard ratios of the primary outcome of recurrent ischemic stroke**

|                          | Device, overall events/No. of patients | Medical therapy, overall events/No. of patients | Hazard ratio (95% CI) |
|--------------------------|----------------------------------------|-------------------------------------------------|-----------------------|
| <b>RoPe categories</b>   |                                        |                                                 |                       |
| < 7                      | 29/700                                 | 41/704                                          | 0.61 (0.37 to 1.00)   |
| ≥ 7                      | 11/1189                                | 41/1147                                         | 0.21 (0.11 to 0.42)   |
| <b>PASCAL categories</b> |                                        |                                                 |                       |
| Unlikely                 | 17/293                                 | 11/254                                          | 1.14 (0.53 to 2.46)   |
| Possible                 | 19/897                                 | 46/914                                          | 0.38 (0.22 to 0.65)   |
| Probable                 | 3/700                                  | 25/683                                          | 0.10 (0.03 to 0.35)   |



**B. Absolute risk reductions of the primary outcome of recurrent ischemic stroke**

|                          | Device, 2-y events/No. (%) | Medical therapy, 2-y events/No. (%) | Absolute risk reduction at 2 y (95% CI) |
|--------------------------|----------------------------|-------------------------------------|-----------------------------------------|
| <b>RoPe categories</b>   |                            |                                     |                                         |
| < 7                      | 20/700 (2.9)               | 27/704 (4.0)                        | 1.1 (-0.9 to 3.1)                       |
| ≥ 7                      | 7/1189 (0.6)               | 28/1147 (2.6)                       | 2.1 (1.0 to 3.1)                        |
| <b>PASCAL categories</b> |                            |                                     |                                         |
| Unlikely                 | 11/293 (4.1)               | 8/254 (3.4)                         | -0.7 (-4.0 to 2.6)                      |
| Possible                 | 13/897 (1.5)               | 31/914 (3.6)                        | 2.1 (0.6 to 3.6)                        |
| Probable                 | 2/700 (0.3)                | 16/683 (2.5)                        | 2.1 (0.9 to 3.4)                        |



Statistically significant heterogeneous treatment effects of patent foramen ovale (PFO) closure were seen for patients subgrouped both by Risk of Paradoxical Embolism (RoPE) score and by PFO-Associated Stroke Causal Likelihood (PASCAL). The hazard ratios observed by RoPE strata correspond very closely to anticipated relative event rate reductions shown in Table 1. Patients classified as PASCAL "unlikely" do not benefit from PFO closure. The hazard ratios in this figure are adjusted for age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or transient ischemic attack, smoking status, index event (stroke vs transient ischemic attack), atrial septal aneurysm, shunt size and superficial infarction on neuroimaging. Two-year absolute risk reductions are calculated as differences in Kaplan-Meier event rates at 2 years.

Republished from JAMA.<sup>59</sup>

## CCTA versus cardiac risk scoring for changing lifestyle behaviors and preventive therapy

Abundant literature now supports the use of coronary artery CTA (CCTA) over ischemia testing for most patients with stable chest pain. This approach reduces unnecessary heart catheterizations by 75% and unnecessary coronary stenting by 25%–40%.<sup>13,14</sup> Added to this body of literature is a new sub-study of the SCOT-HEART trial designed to determine the impact of CCTA on healthy lifestyle behaviors, acceptance of recommended treatments, and modification of risk factors as compared with guideline-directed cardiovascular risk scoring.<sup>15</sup>

Four hundred patients were examined, half who underwent CCTA and half with treatment recommendations based on risk scoring. In the CCTA group, compared with cardiovascular risk scoring, fewer participants were recommended preventive therapy after CCTA, - 51% versus 75%, as the absence of plaque in many patients in the CCTA group precluded the need for pharmacotherapy. On the other hand, acceptance of recommendations was higher in the CCTA group (77% versus 46%), likely due to the participant knowledge of the existence of coronary artery atheroma. There was also greater use of antiplatelet therapy in the CCTA group versus those in the risk scoring group (40% versus 0.5%), likely related to the clinician recommendation in the presence of observed coronary atheroma.

Ischemia testing is typically negative in patients with significant coronary atheroma when there is an absence of any flow-limiting stenoses. On the other hand, CCTA adds the opportunity to both intensify therapy and improve patient compliance in the presence of non-flow-limiting plaque and avoid pharmacotherapy in the absence of atheroma. This has been shown in the primary SCOT-HEART trial<sup>16</sup> to reduce MACE by about 40% at 5 years post CCTA. These results add to the existing body of literature supporting the move away from ischemia testing and towards CCTA.

1. Tănase I, Păun S, Stoica B, Negoii I, Gaspar B, Beuran M. Epidemiology of diverticular disease – systematic review of the literature. *Chirurgia (Bucur)*. 2015;110(1):9-14.
2. Brown RF, Lopez K, Smith CB, Charles A. Diverticulitis: A Review. *JAMA*. Published online July 24, 2025. doi:10.1001/jama.2025.10234
3. Sacks OA, Hall J. Management of Diverticulitis: A Review. *JAMA Surg*. 2024;159(6):696-703. doi:10.1001/jamasurg.2023.8104
4. Inaba K, Biffi WL, Costantini TW et al. Evidence-based, cost-effective management of acute diverticulitis. An algorithm of the Journal of Trauma and Acute Care Surgery emergency general surgery algorithms work group. *J Trauma Acute Care Surg*. 2025;99(1):24-28. doi:10.1097/TA.0000000000004663
5. Balk EM, Adam GP, Cao W et al. *Management of Colonic Diverticulitis*. Rockville (MD): Agency for Healthcare Research and Quality (US); October 2020
6. Azhar N, Aref H, Brorsson A et al. Management of acute uncomplicated diverticulitis without antibiotics: compliance and outcomes -a retrospective cohort study. *BMC Emerg Med*. 2022;22(1):28. Published 2022 Feb 21. doi:10.1186/s12873-022-00584-x
7. Newsome PN, Buchholtz K, Cusi K et al. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med*. 2021;384(12):1113-1124. doi:10.1056/NEJMoa2028395
8. Sanyal AJ, Newsome PN, Kliers I et al. Phase 3 Trial of Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis. *N Engl J Med*. 2025;392(21):2089-2099. doi:10.1056/NEJMoa2413258
9. Williams B, MacDonald TM, Morant S et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386(10008):2059-2068. doi:10.1016/S0140-6736(15)00257-3
10. Laffin LJ, Kopjar B, Melgaard C et al. Lorundrostat Efficacy and Safety in Patients with Uncontrolled Hypertension. *N Engl J Med*. 2025;392(18):1813-1823. doi:10.1056/NEJMoa2501440
11. Lin HT, Tsai YF, Liao PL, Wei JC. Neurodegeneration and Stroke After Semaglutide and Tirzepatide in Patients With Diabetes and Obesity. *JAMA Netw Open*. 2025;8(7):e2521016. Published 2025 Jul 1. doi:10.1001/jamanetworkopen.2025.21016
12. Kent DM, Wang AY. Patent Foramen Ovale and Stroke: A Review. *JAMA*. Published online July 28, 2025. doi:10.1001/jama.2025.10946
13. Chang, H, Lin, F, Gebow, D et al. Selective Referral Using CCTA Versus Direct Referral for Individuals Referred to Invasive Coronary Angiography for Suspected CAD: A Randomized, Controlled, Open-Label Trial. *J Am Coll Cardiol Img*. 2019 Jul, 12 (7\_Part\_2) 1303-1312. <https://doi.org/10.1016/j.jcmg.2018.09.018>
14. DISCHARGE Trial Group, Maurovich-Horvat P, Bosserdt M et al. CT or Invasive Coronary Angiography in Stable Chest Pain. *N Engl J Med*. 2022;386(17):1591-1602. doi:10.1056/NEJMoa2200963
15. McDermott M, Khaing PH, Meah MN et al. CT Angiography, Healthy Lifestyle Behaviors, and Preventive Therapy: A Nested Substudy of the SCOT-HEART 2 Randomized Clinical Trial. *JAMA Cardiol*. 2025;10(8):841-850. doi:10.1001/jamacardio.2025.1763
16. SCOT-HEART Investigators, Newby DE, Adamson PD et al. Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. *N Engl J Med*. 2018;379(10):924-933. doi:10.1056/NEJMoa1805971

**Kenneth Roy Cohen, MD, FACP**

Dr. Kenneth Cohen is an experienced physician leader, practicing internist and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of Optum Care. He served as chief medical officer from 1995 to 2020. He now serves as the executive director of Translational Research for Optum Care and co-leads the Optum Center for Research and Innovation. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship, New West Physicians was awarded the AMGA Acclaim award in 2015 and the CDC Million Hearts Hypertension Champion Award in 2017. He is a clinical associate professor of Medicine and Pharmacy at the University of Colorado School of Medicine and School of Pharmacy. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

**Joshua Jacobs, MD, FAAFP**

With over 20 years of clinical, academic and leadership experience regionally, nationally and internationally, Dr. Jacobs currently serves as primary care engagement lead national medical director for Optimal Care within Clinical Performance at Optum Care. He is a clinical professor of Family Medicine at the Washington State University College of Medicine. He graduated from Pomona College with honors and from the John A. Burns School of Medicine as a member of the Alpha Omega Alpha honor society.

**Access other Optimal Care evidence-based resources using the links or QR codes below.**



[Specialty Modules](#): CME-accredited foundational lectures for primary care that distill key evidence in core specialties that is actionable to promote high-value care and decrease low-value care.



[Clinician and Patient Content](#): A collection of evidence-based clinical algorithms and handouts providing actionable decision-support and assistance with shared decision-making.



[Grand Rounds](#): An Optimal Care CME-accredited series of live and on-demand sessions focused on aspects of care important to PCPs and their patients.