

November 9, 2024

New Paradigms in Gastrointestinal Surgery and Medicine

# New Insights in Diverticular Disease: Antibiotics, Colorectal Cancer, and Bleeding

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*Staff Gastroenterologist*

VA Pittsburgh Healthcare System



# Disclosures

- No financial conflicts of interest to disclose
- This presentation does not necessarily represent the views of the U.S. Department of Veterans Affairs or the United States Government



# Objectives

1. To describe **evolving clinical recommendations** for the management of diverticular diseases.
2. To discuss the **clinical research** underlying new recommendations.



# Overview

1. Should we treat uncomplicated diverticulitis with antibiotics?
2. Should we order colonoscopies to evaluate for colorectal cancer after diverticulitis?
3. Can we prevent recurrent diverticular bleeding?



# Antibiotics

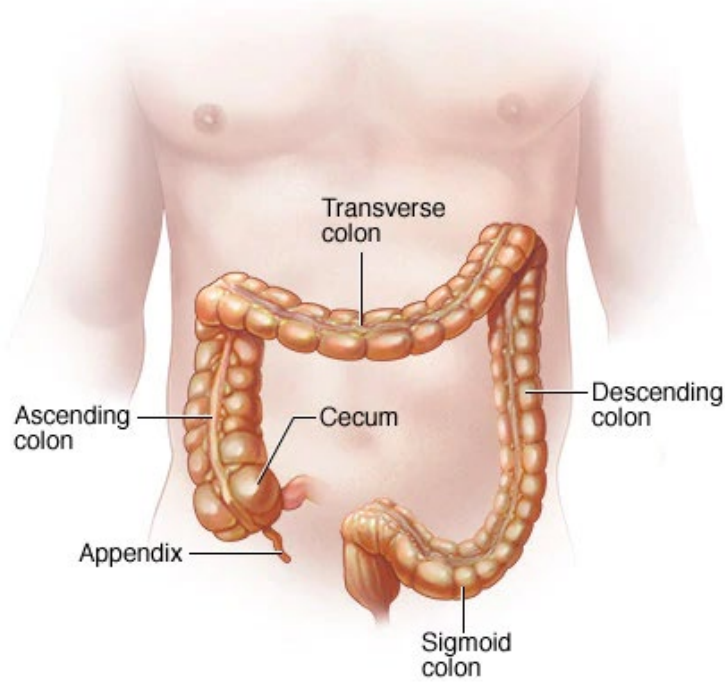
Should we treat uncomplicated diverticulitis with antibiotics?

1. **Antibiotics** → 2. Colonoscopy → 3. Bleeding

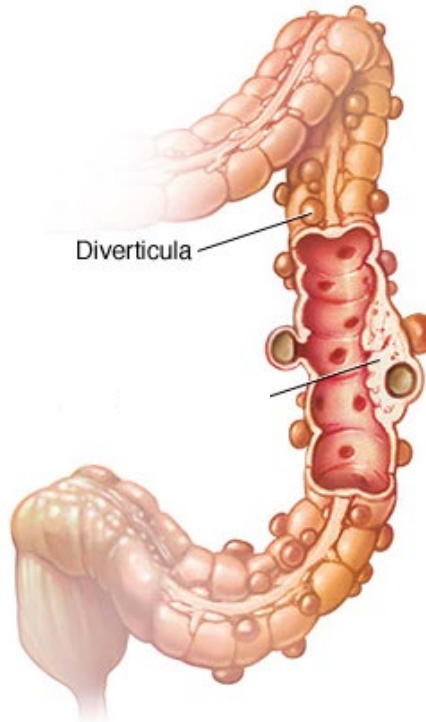


# Colonic diverticulosis

Normal colon



Colon with diverticulosis

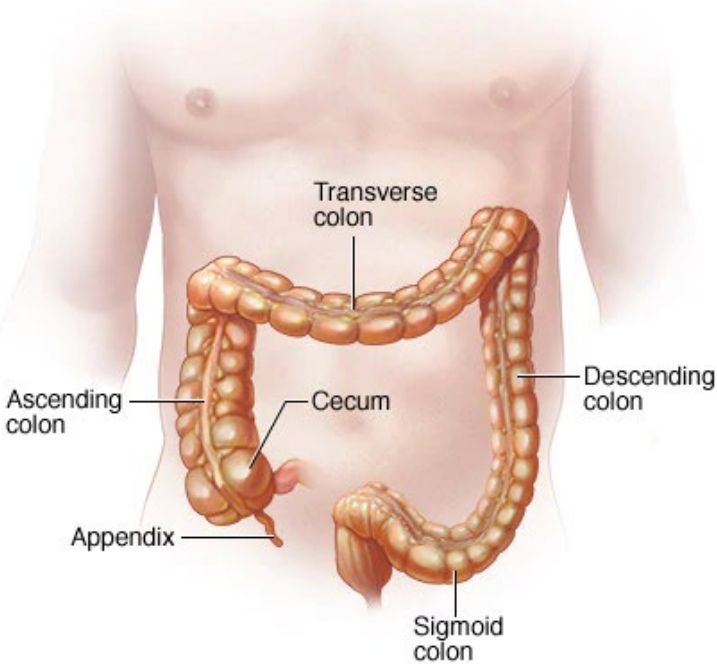


60% of individuals older than 60

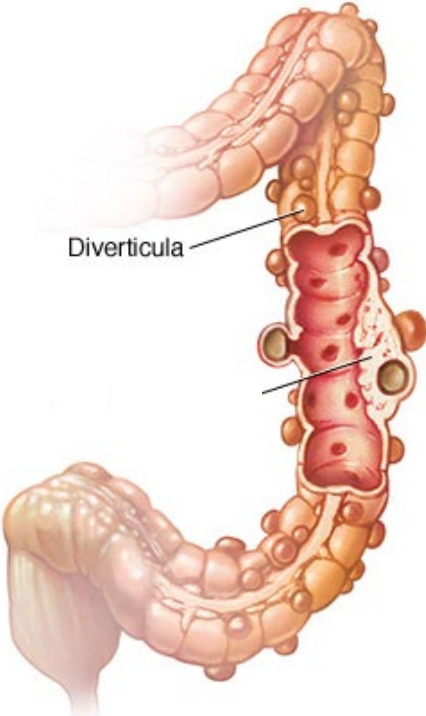


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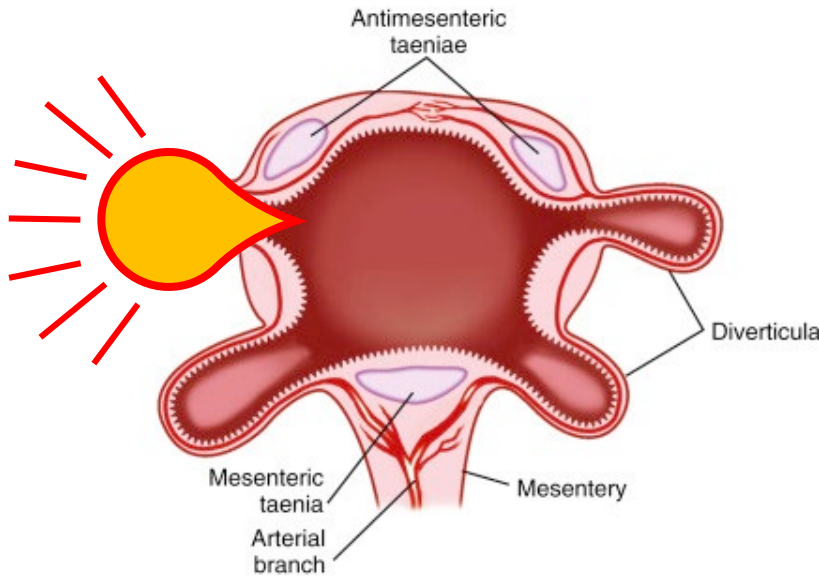
Normal colon



Colon with diverticulosis



Diverticulitis



60% of individuals older than 60

5% of individuals with diverticulosis

Left and middle images: Mayo Foundation for Medical Education and Research; Right image: Sleisenger and Fordtran, ed. 10, 2016



# Pathophysiology (traditional)

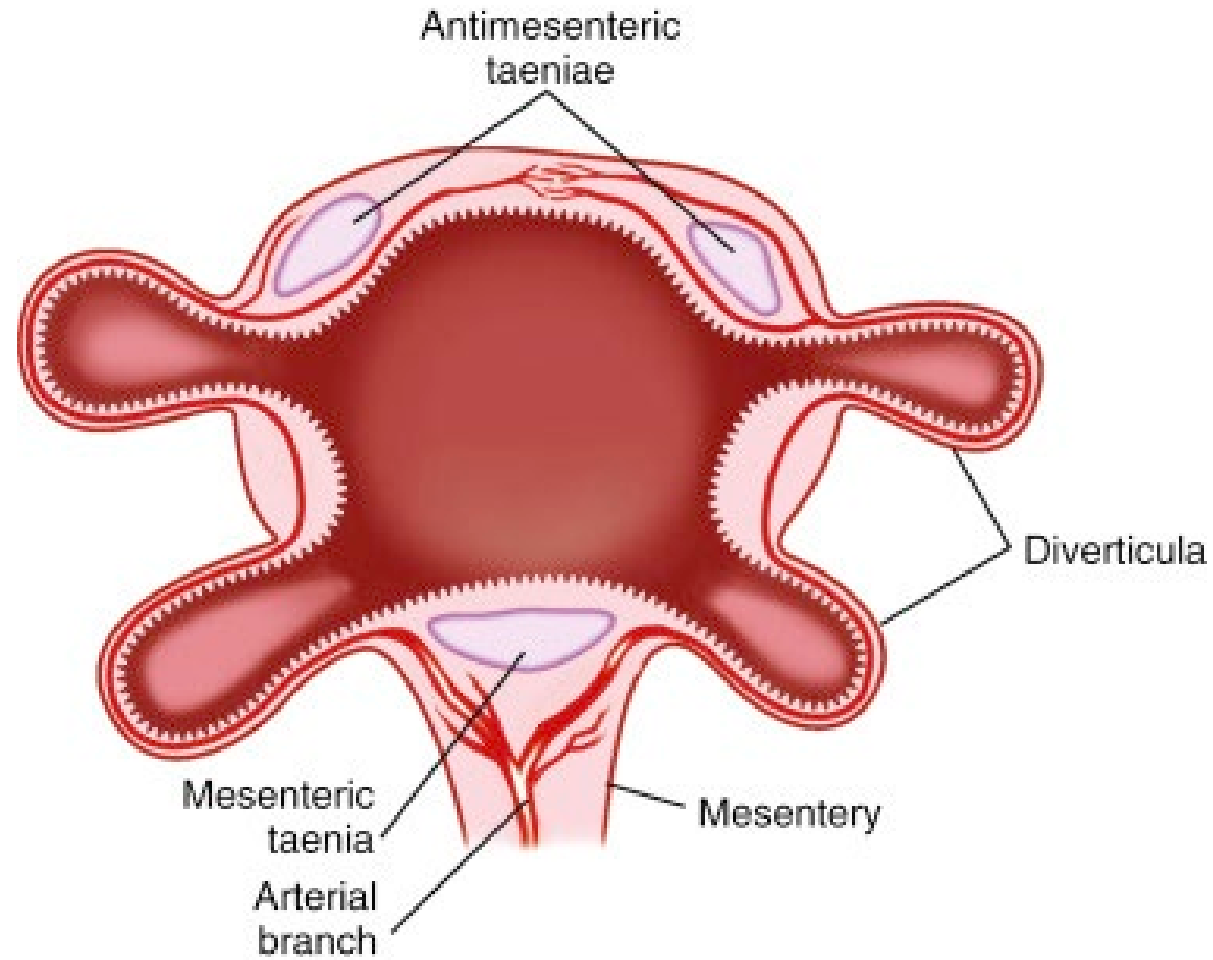


Image: Sleisenger and Fordtran, ed. 10, 2016





# Pathophysiology (traditional)

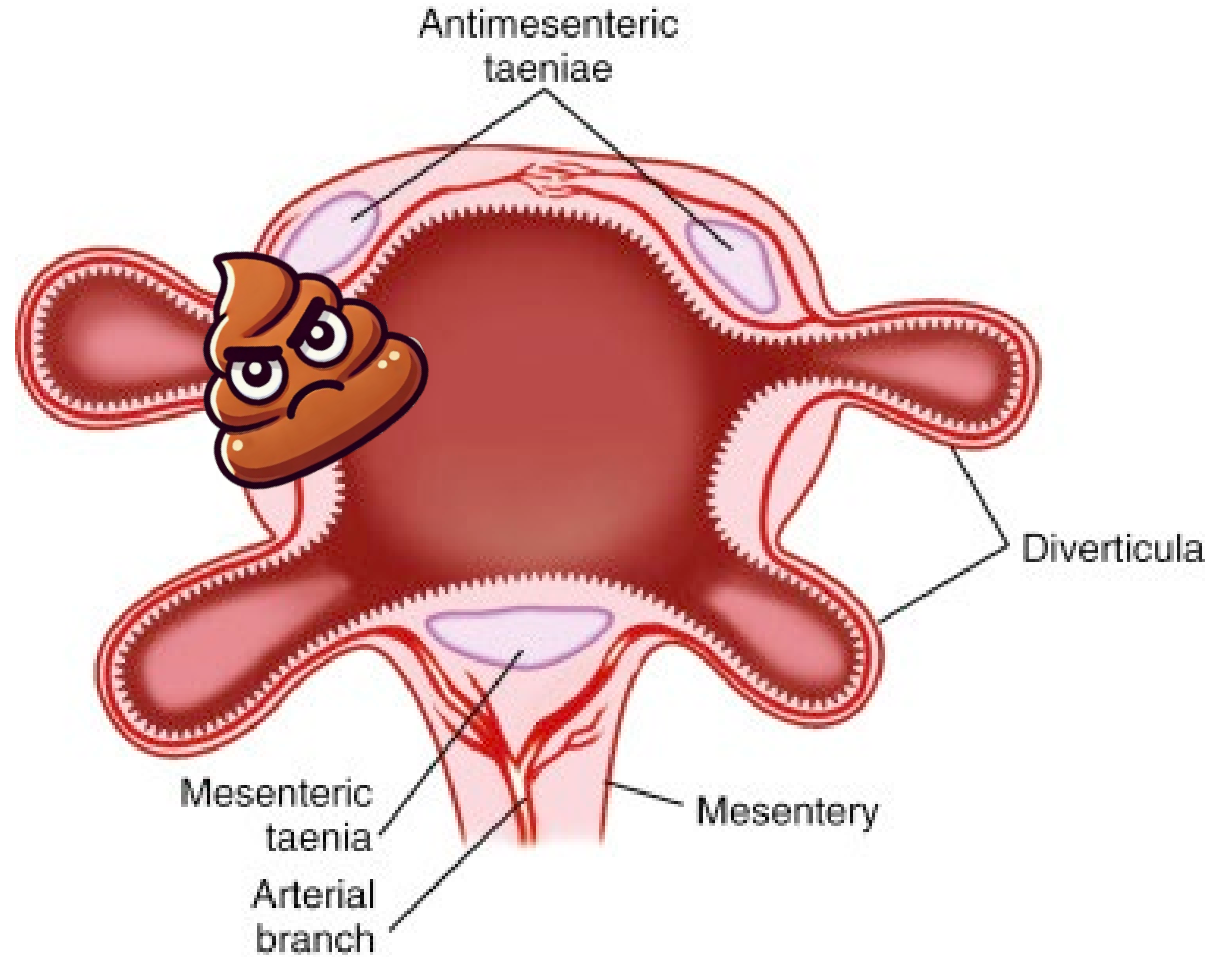


Image: Sleisenger and Fordtran, ed. 10, 2016 and DALL-E



# Pathophysiology (traditional)

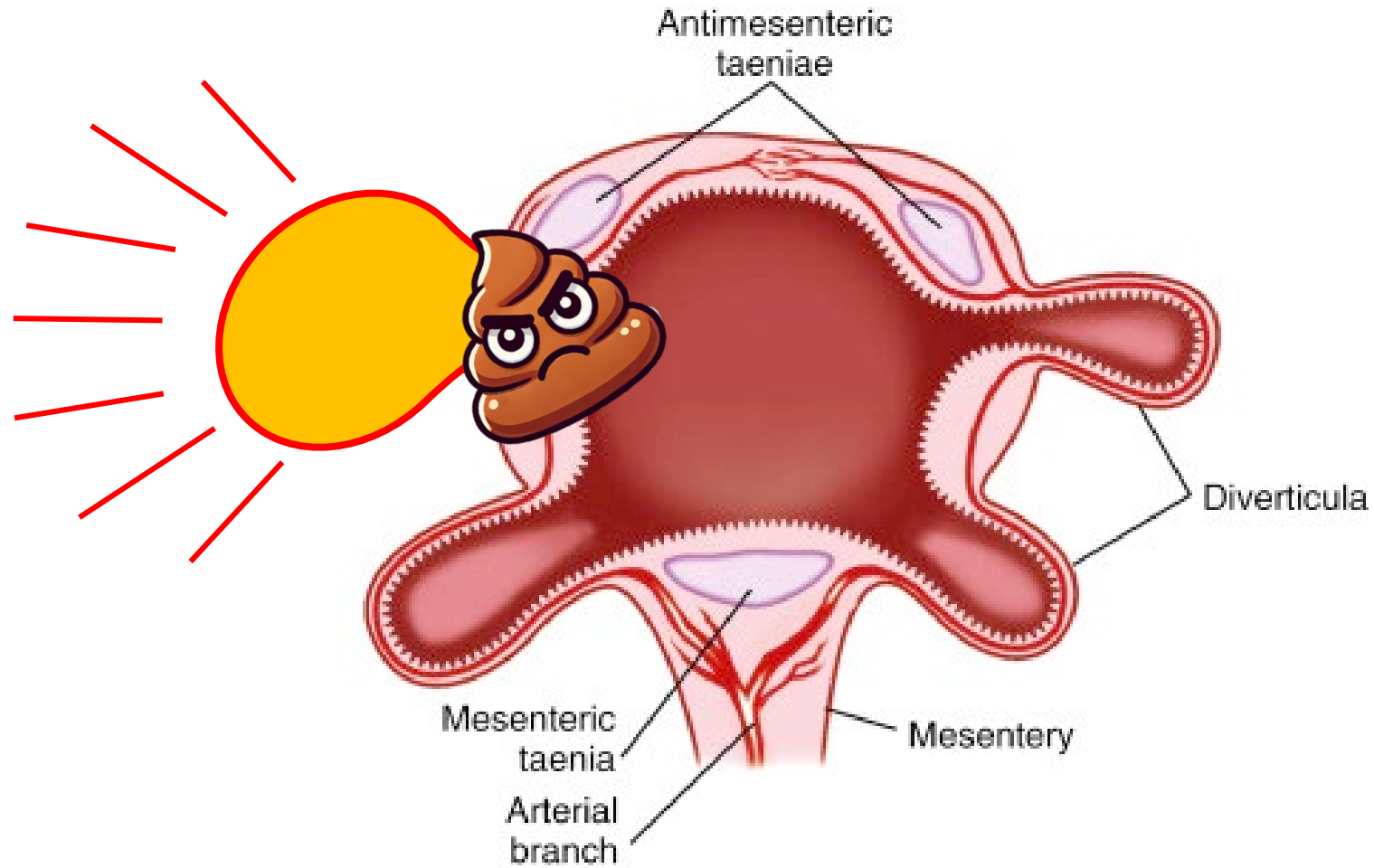


Image: Sleisenger and Fordtran, ed. 10, 2016 and DALL-E



# Clinical guidelines for antibiotics

1999

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## PRACTICE GUIDELINES

### Diagnosis and Management of Diverticular Disease of the Colon in Adults

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Neil H. Stollman, M.D., F.A.C.P., and Jeffrey B. Raskin, M.D., F.A.C.P., F.A.C.G., for and on behalf of the  
*Ad Hoc* Practice Parameters Committee of the American College of Gastroenterology\*  
*Division of Gastroenterology, University of Miami School of Medicine, Miami, Florida*

*Selected patients with mild diverticulitis*

*... can be treated as outpatients with*

*broad-spectrum oral antibiotics.*



# Pathophysiology (new paradigm)

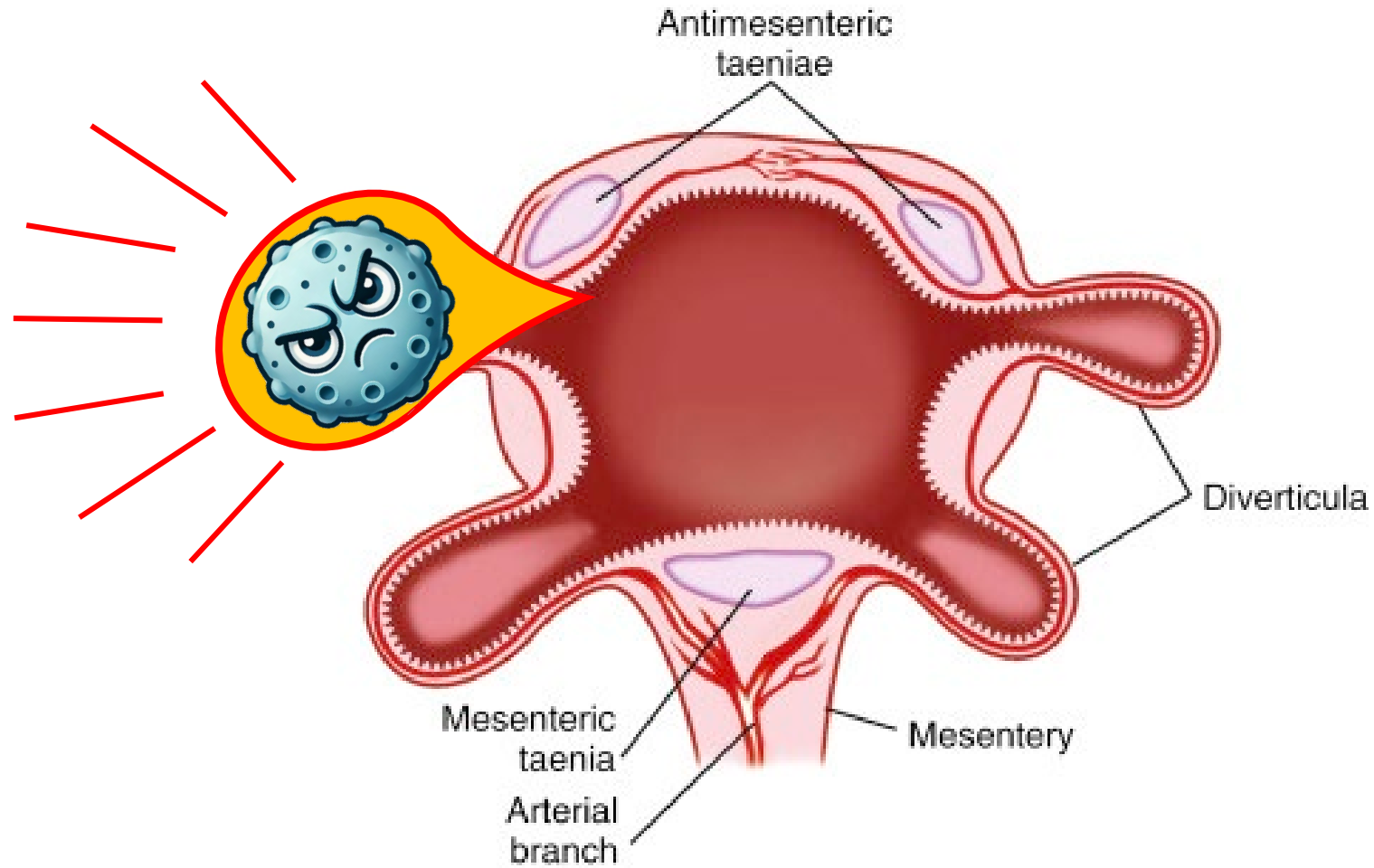


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*Selected patients with mild diverticulitis  
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2015

Gastroenterology 2015;149:1944–1949

## AGA SECTION

### American Gastroenterological Association Institute Guideline on the Management of Acute Diverticulitis



Neil Stollman,<sup>1</sup> Walter Smalley,<sup>2,3</sup> Ikuo Hirano,<sup>4</sup> and AGA Institute Clinical  
Guidelines Committee

<sup>1</sup>Alta Bates Summit Medical Center, Oakland, California; <sup>2</sup>Department of Medicine, Division of Gastroenterology, Hepatology,  
and Nutrition, Vanderbilt University School of Medicine; <sup>3</sup>VA Tennessee Valley Healthcare System, Nashville, Tennessee; and  
<sup>4</sup>Division of Gastroenterology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

*... antibiotics should be used selectively,  
rather than routinely, in patients with  
acute uncomplicated diverticulitis.*



# What changed?

- Three non-U.S. randomized control trials of antibiotics versus no antibiotics for treatment of uncomplicated diverticulitis
- ~1300 patients assessed

	Antibiotic treated	Not antibiotic treated	RR
<b>Abscess, perforation, or fistula within 30 days</b>	1.5%	1.3%	0.89 (95% CI 0.30 – 2.62)



# What changed?

- Three non-U.S. randomized control trials of antibiotics versus no antibiotics for treatment of uncomplicated diverticulitis
- ~1300 patients assessed

	Antibiotic treated	Not antibiotic treated	RR
Abscess, perforation, or fistula within 30 days	1.5%	1.3%	0.89 (95% CI 0.30 – 262)
Recurrent diverticulitis within 30 days	23.8%	24.0%	1.01 (95% CI 0.81 – 1.25)





**Cochrane  
Library**

Cochrane Database of Systematic Reviews

## Antibiotics for uncomplicated diverticulitis (Review)

Dichman ML, Rosenstock SJ, Shabanzadeh DM

*Cochrane Database of Systematic Reviews* 2022, Issue 6. Art. No.: CD009092.

DOI: [10.1002/14651858.CD009092.pub3](https://doi.org/10.1002/14651858.CD009092.pub3).

## Quality of Evidence Low

- Heterogeneity
  - ▶ Different observation protocols
  - ▶ Different inclusion criteria
- Selection bias
- Imprecision





# DINAMO Randomized Control Trial, Spain 2021

480 patients with CT-confirmed diverticulitis treated with  
ibuprofen + acetaminophen +/- amoxicillin-clavulanic acid

	Antibiotic treated	Not antibiotic treated
Re-hospitalization	5.8%	3.3%
Emergency department visit	6.7%	7.0%
Poor pain control at 2 days	5.7%	2.3%

All endpoints met the non-inferiority margin



# Barriers to adoption

**With mounting evidence that uncomplicated diverticulitis can be safely treated without antibiotics, why are we still using them in North America?**

- Not all practitioners may be aware of the growing body of literature.
- Patients have come to expect to have diverticulitis treated with antibiotics.
- Physicians may also be concerned about the medicolegal ramifications.

**Alexander T. Hawkins, MD, MPH, FACS**

Colorectal Surgeon, Vanderbilt University



# Clinical guidelines for antibiotics

2020

2021

Gastroenterology 2021;160:906–911

## CLINICAL PRACTICE GUIDELINES

### The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Treatment of Left-Sided Colonic Diverticulitis

Jason Hall, M.D., M.P.H.<sup>1</sup> • Karin Hardiman, M.D., Ph.D.<sup>2</sup> • Sang Lee, M.D.<sup>3</sup>  
Amy Lightner, M.D.<sup>4</sup> • Luca Stocchi, M.D.<sup>5</sup> • Ian M. Paquette, M.D.<sup>6</sup>  
Scott R. Steele, M.D., M.B.A.<sup>4</sup> • Daniel L. Feingold, M.D.<sup>7</sup> • Prepared on behalf of  
the Clinical Practice Guidelines Committee of the American Society of Colon and  
Rectal Surgeons

*Selected patients with uncomplicated  
diverticulitis can be treated without  
antibiotics (**strong recommendation  
based on high-quality evidence**)*

## CLINICAL PRACTICE UPDATES

### AGA Clinical Practice Update on Medical Management of Colonic Diverticulitis: Expert Review



Anne F. Peery,<sup>1</sup> Aasma Shaukat,<sup>2</sup> and Lisa L. Strate<sup>3</sup>

*Antibiotic treatment can be used selectively,  
rather than routinely, in immunocompetent  
patients with mild uncomplicated  
diverticulitis.*



# Clinical guidelines for antibiotics

## What is the definition of uncomplicated?

Gastroenterology 2021;160:906–911

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*Antibiotic treatment can be used selectively, rather than routinely, in immunocompetent patients with mild uncomplicated diverticulitis.*



# Takeaways

- Several recent randomized control trials indicate that uncomplicated diverticulitis can be treated without antibiotics.

*The studies have limitations, but it is unlikely that significantly better studies will be performed.*

- Subspecialty guidelines accept new treatment paradigm.

*More guidance on the definition of “uncomplicated” is needed.*

- We need to educate patients and front-line providers about the new treatment paradigm.



# Colonoscopy

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Should we order colonoscopies to evaluate for colorectal cancer after diverticulitis?

1. Antibiotics → 2. Colonoscopy → 3. Bleeding



# Clinical guidelines for colonoscopy after diverticulitis

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*A colonic evaluation is indicated after  
resolution of a clinically diagnosed  
case of presumptive diverticulitis to  
exclude other diagnostic considerations  
such as colonic neoplasia.*



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*A colonic evaluation is indicated after resolution of a clinically diagnosed case of presumptive diverticulitis to exclude other diagnostic considerations such as colonic neoplasia.*

- Legacy from when diverticulitis was diagnosed by physical examination and/or barium enema.
- CT diagnosis has become ubiquitous and image resolution has improved.





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- Colorectal cancer screening has become a cornerstone of American preventative healthcare.



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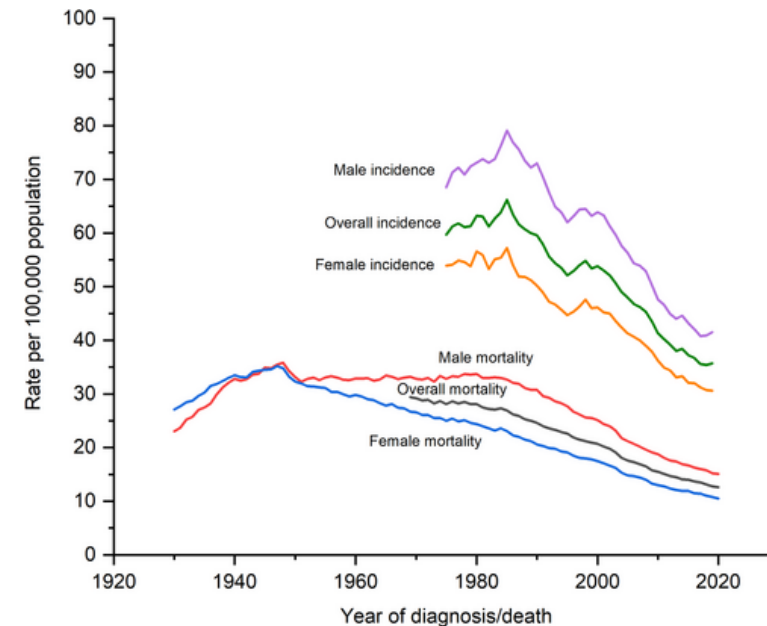
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*A colonic evaluation is indicated after resolution of a clinically diagnosed case of presumptive diverticulitis to exclude other diagnostic considerations such as colonic neoplasia.*

- CRC incidence has declined by 25% since 1999



RL Siegel et al. *CA Cancer J Clin* 2023



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*The AGA suggests that colonoscopy be performed ... to exclude the misdiagnosis of a colonic neoplasm **if a high-quality examination of the colon has not been recently performed.***



# Is there evidence for the change in recommendation?

## Routine colonoscopy after left-sided acute uncomplicated diverticulitis: a systematic review CME

Lidewine Daniels, MD,<sup>1</sup> Çağdaş Ünlü, MD,<sup>1</sup> Thomas R. de Wijkerslooth, MD, PhD,<sup>2</sup>  
Evelien Dekker, MD, PhD,<sup>2</sup> Marja A. Boermeester, MD, PhD<sup>1</sup>

Amsterdam, the Netherlands

GASTROINTESTINAL ENDOSCOPY Volume 79, No. 3 : 2014

- 8 studies with cumulative ~1800 patients diagnosed from 2000 – 2010
- **1.5%** colorectal cancer prevalence among patients with diverticulitis vs. **0.7%** colorectal cancer prevalence among U.S. population



# Newer evidence

GASTROINTESTINAL ENDOSCOPY Volume 91, No. 3 : 2020

## Prevalence of colorectal cancer and advanced adenoma in patients with acute diverticulitis: implications for follow-up colonoscopy

Shahrzad Tehranian, MD,<sup>1,\*</sup> Matthew Klinge, MD,<sup>1,\*</sup> Melissa Saul,<sup>2</sup> Michele Morris,<sup>3</sup>  
Brenda Diergaarde, PhD,<sup>4,5</sup> Robert E. Schoen, MD, MPH<sup>1</sup>

Pittsburgh, Pennsylvania, USA

- Identified ~1000 cases of CT-confirmed diverticulitis at UPMC Presbyterian + Shadyside
- ~500 had subsequent colonoscopy at UPMC
- Colorectal cancer prevalence **2.7%** vs. 1.5% in prior systematic review



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Clinical Gastroenterology and Hepatology 2024;22:2125–2133

## Follow-Up Colonoscopy for Detection of Missed Colorectal Cancer After Diverticulitis

Walker D. Redd,<sup>1</sup> Jennifer L. Holub,<sup>2</sup> Hazel B. Nichols,<sup>3</sup> Robert S. Sandler,<sup>1,4</sup> and Anne F. Peery<sup>1,4</sup>

- Identified ~90,000 colonoscopies for diverticulitis follow-up from GIQuIC
  - **0.3%** colorectal cancer prevalence
- Compared to 4,500,000 screening colonoscopies
  - **0.3%** colorectal cancer prevalence



# Remaining questions

- What is the rate of colorectal cancer among patients with diverticulitis who completed colonoscopy outside of the health system?
- What is the rate of colorectal cancer among patients with diverticulitis who did not complete colonoscopy within the recommended time frame?
- Can post-diverticulitis colonoscopy be delayed based on time from last high-quality colonoscopy?
  - *No study has directly assessed this.*



# Clinical guidelines for colonoscopy after diverticulitis

2022

CLINICAL GUIDELINE



## Colonoscopy for Diagnostic Evaluation and Interventions to Prevent Recurrence After Acute Left-Sided Colonic Diverticulitis: A Clinical Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Itziar Etxeandia-Ikobaltzeta, PharmD, PhD; Jennifer S. Lin, MD, MCR; Nick Fitterman, MD; Tatyana Shamliyan, MD, MS; and Timothy J. Wilt, MD, MPH; for the Clinical Guidelines Committee of the American College of Physicians\*

*Ann Intern Med.* 2022;175:416-431. doi:10.7326/M21-2711

*ACP suggests that clinicians refer patients for a colonoscopy after an initial episode of complicated **left-sided** colonic diverticulitis in patients **who have not had recent colonoscopy** (conditional recommendation; low-certainty evidence).*





2022

## CLINICAL GUIDELINE



### Colonoscopy for Diagnostic Evaluation and Interventions to Prevent Recurrence After Acute Left-Sided Colonic Diverticulitis: A Clinical Guideline From the American College of Physicians

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*ACP suggests that clinicians refer patients for a colonoscopy after an initial episode of complicated left-sided colonic diverticulitis in patients who have not had recent colonoscopy (conditional recommendation; low-certainty evidence).*

- Relationship between diagnosed diverticulitis and colorectal cancer is biologically plausible.
- The epidemiologic data aren't perfect.
- But we probably won't get significantly better studies soon.



2022

## CLINICAL GUIDELINE



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- Clinical judgement for subsequent colonoscopy is appropriate based on:

- Prior colonoscopy results
- Characteristics of diverticulitis diagnosis
  - ▶ Certainty
  - ▶ Uncomplicated vs complicated



# Bleeding

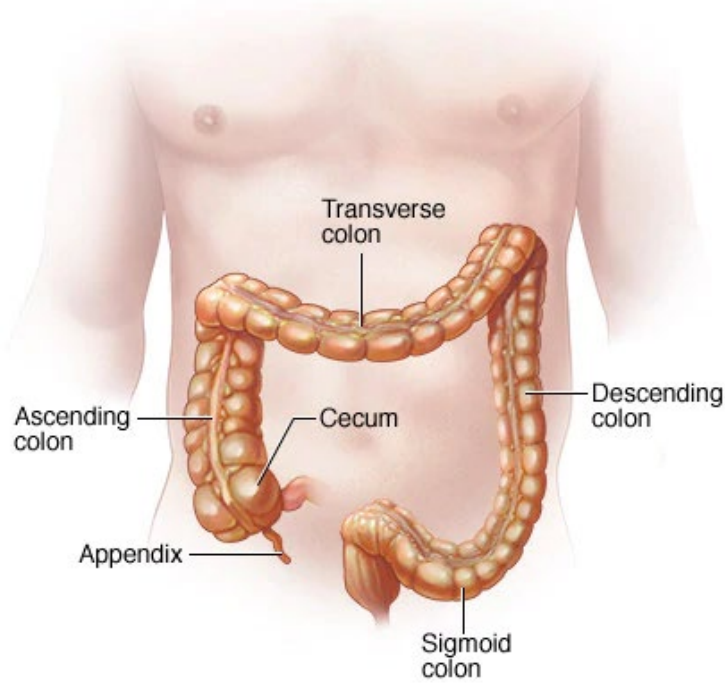
Can we prevent recurrent diverticular bleeding?

1. Antibiotics → 2. Colonoscopy → **3. Bleeding**

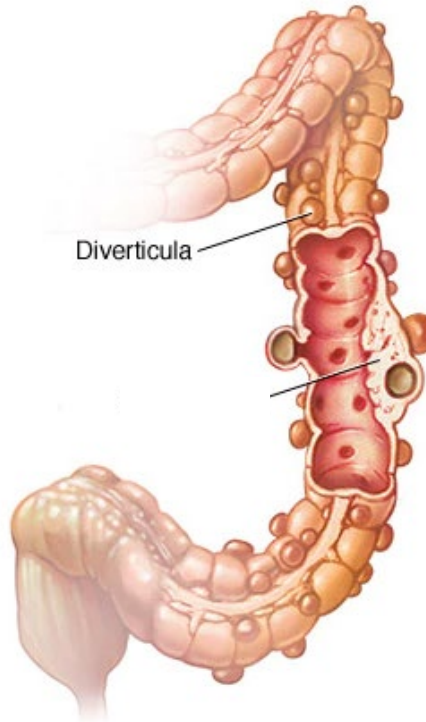


# Colonic diverticulosis

Normal colon



Colon with diverticulosis

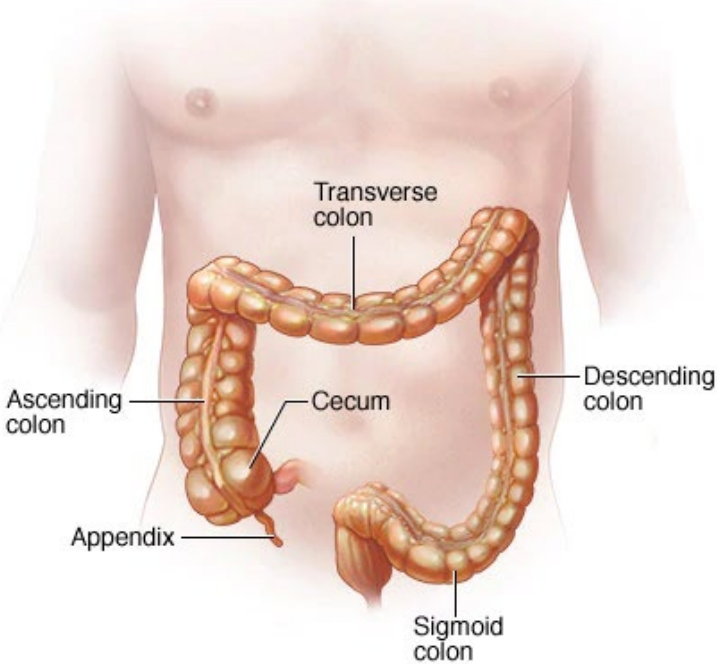


60% of individuals older than 60

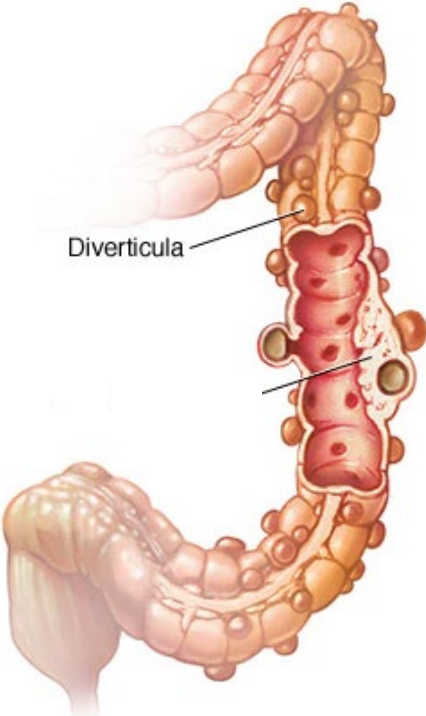


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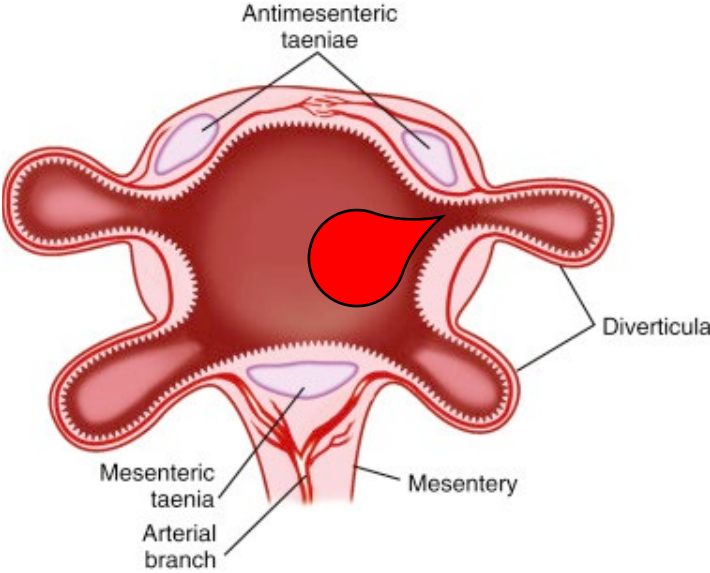
Normal colon



Colon with diverticulosis



Diverticular hemorrhage



60% of individuals older than 60



1% of individuals with diverticulosis

Left and middle images: Mayo Foundation for Medical Education and Research; Right image: Sleisenger and Fordtran, ed. 10, 2016



# Risk of recurrent diverticular hemorrhage

**Those who have one diverticular hemorrhage were presumed to be at increased risk for a 2<sup>nd</sup> diverticular hemorrhage**

Estimated cumulative incidence varied widely: 13.8 – 47.4%

- All available incidence estimates were from institutional cohorts
- Maximum cohort size: 123 patients

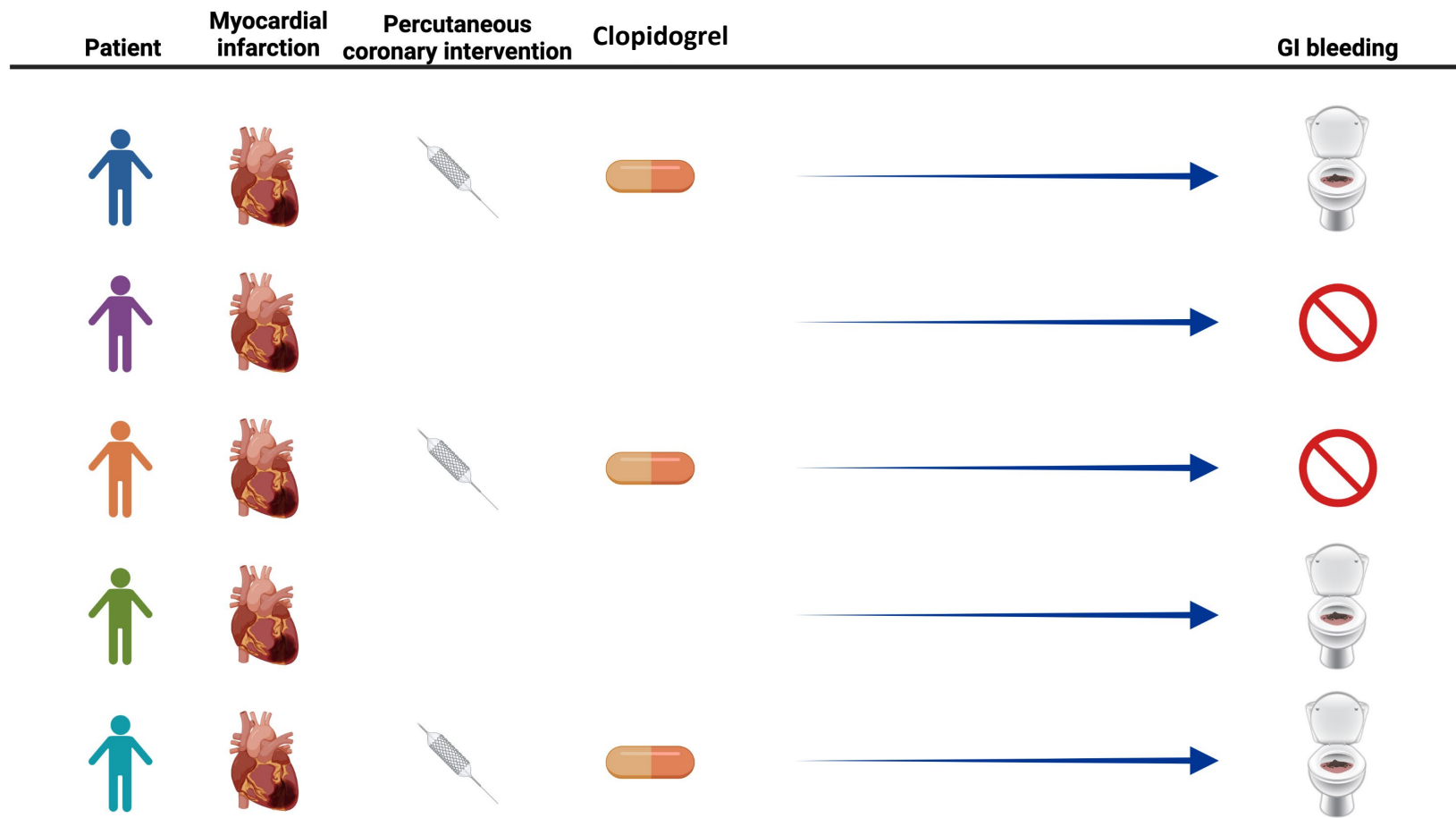


# Risk factors and characteristics

	<u>Estimate</u>	<u>95% CI</u>
Aspirin	HR 1.70	1.21 – 2.39
NSAIDs	HR 1.74	1.15 – 2.64
Obesity	RR 3.19	1.45 – 7.00
Hypertension	OR 6.6	2.1 – 20.5

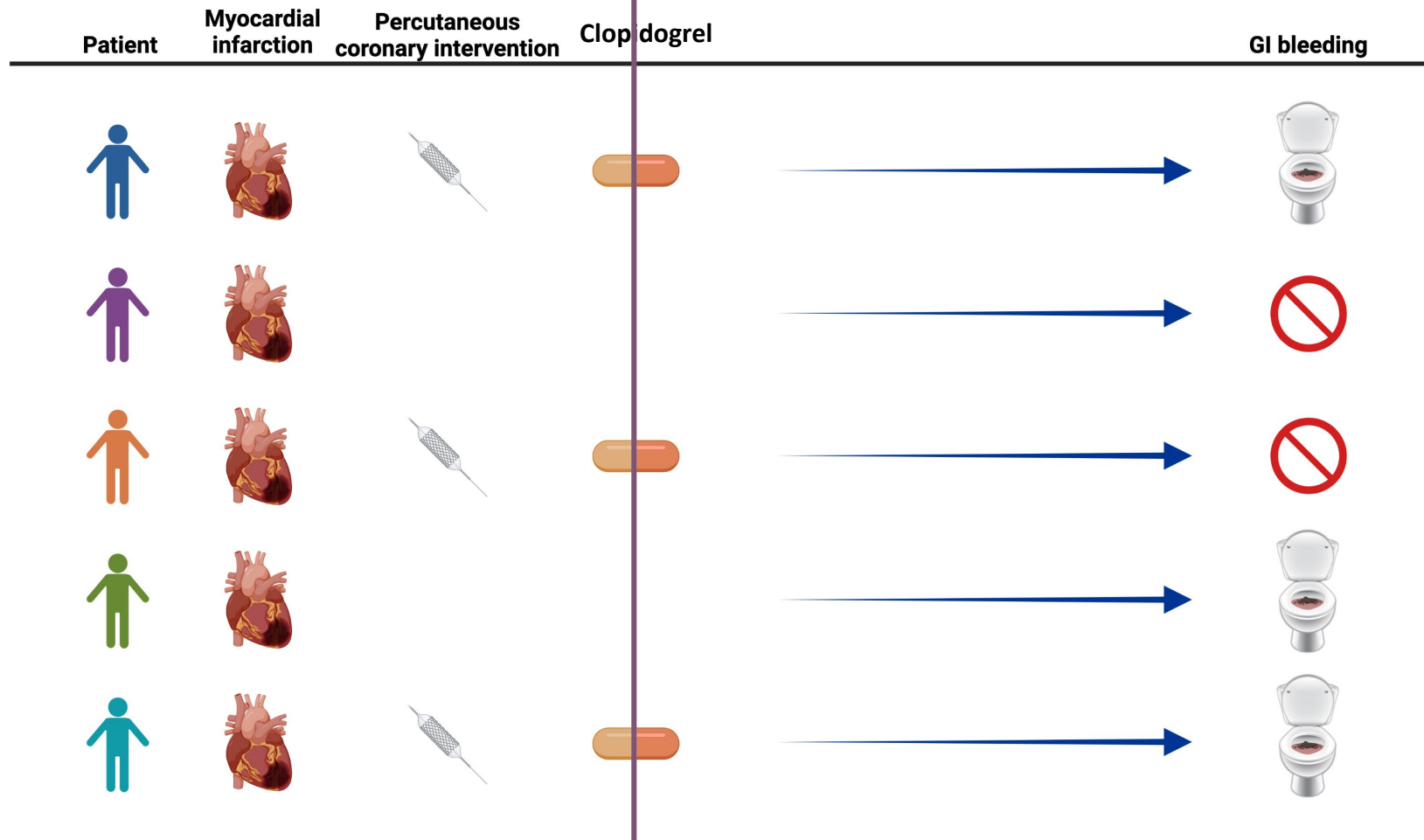
**Limited data on risk from  
anticoagulants and  
antiplatelets**







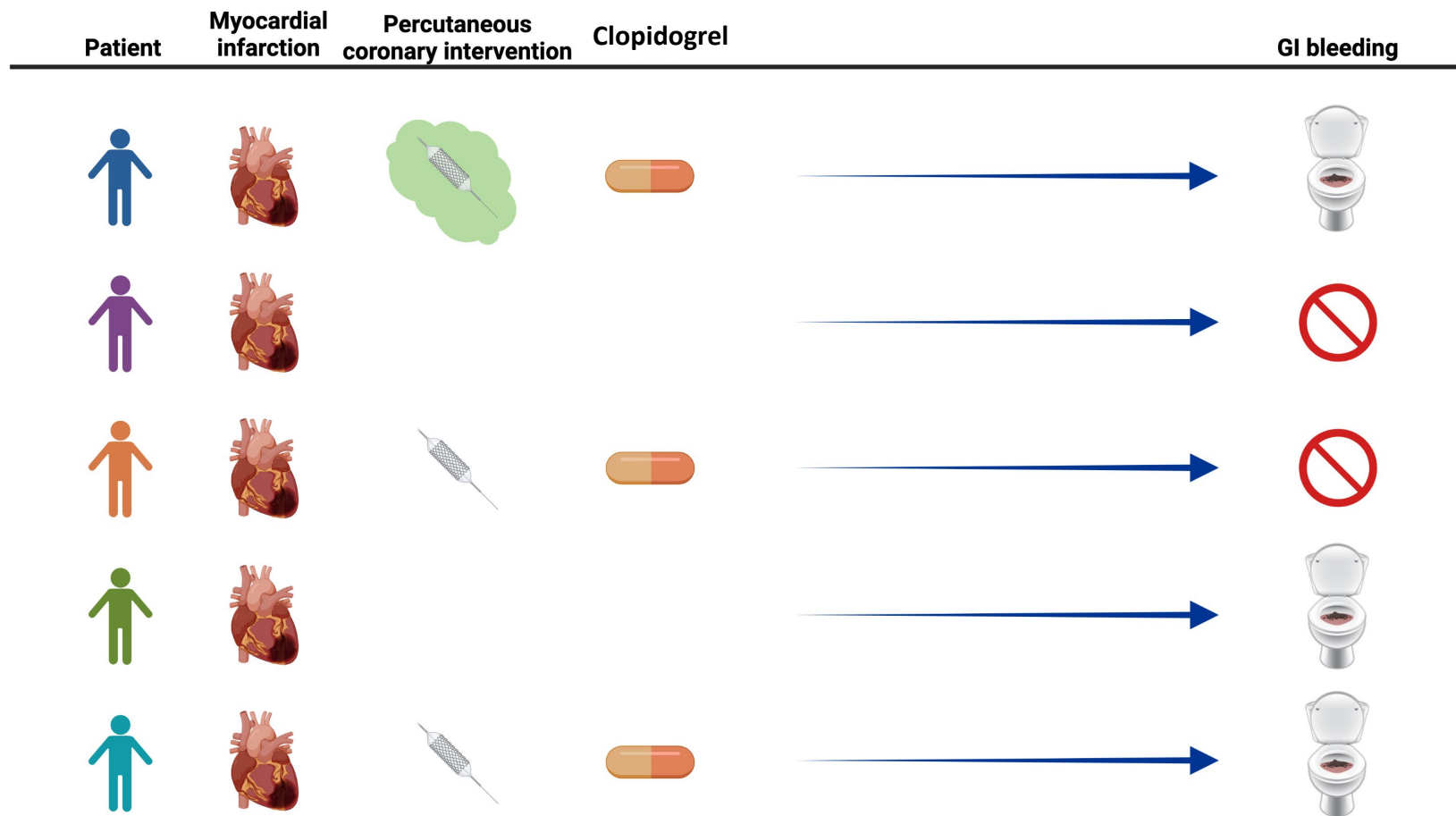
# Exposure assessment



	GI bleeding	No GI bleeding
Clopidogrel	2	1
No clopidogrel	1	1

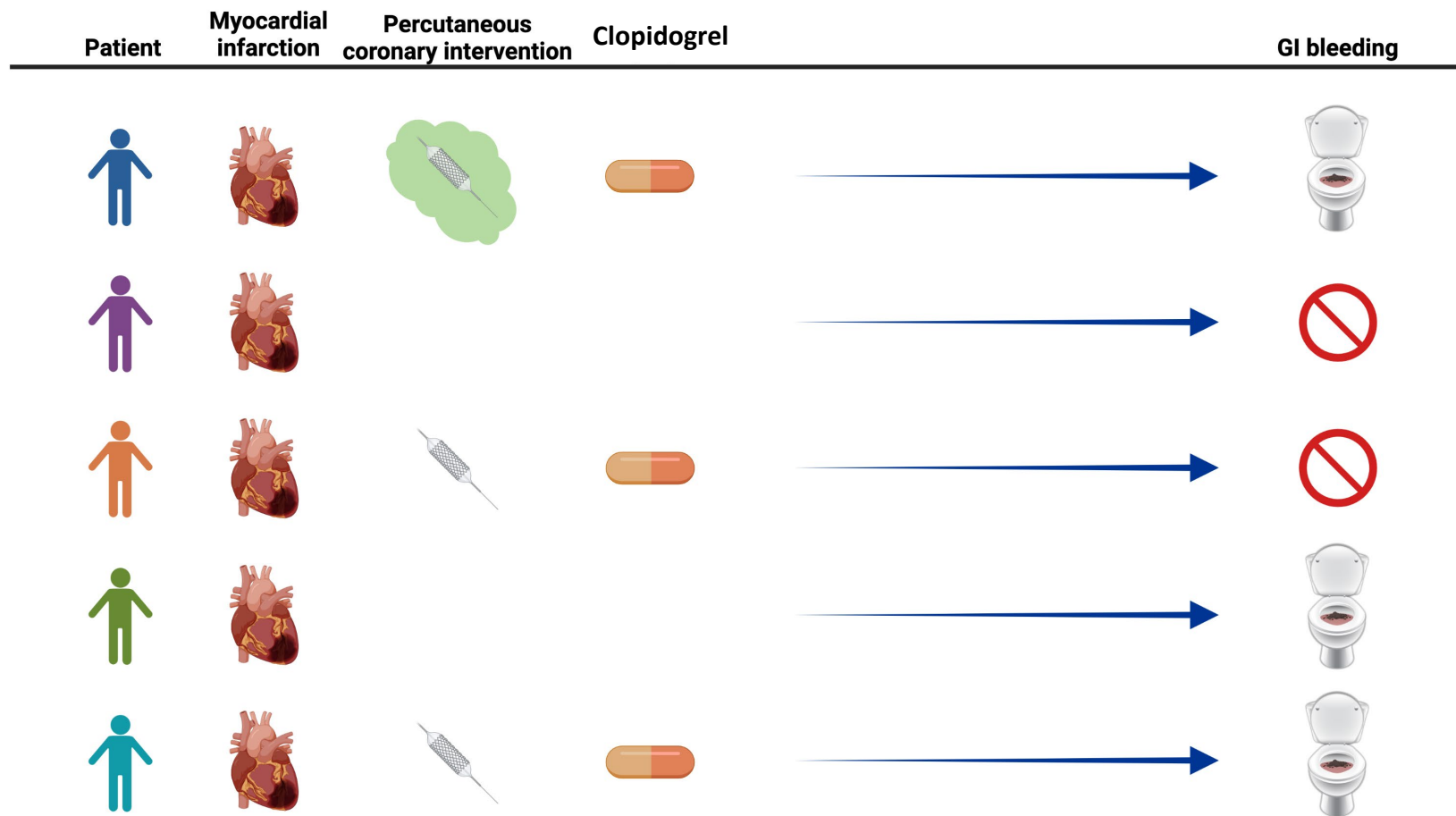
**RR = 1.3**





	GI bleeding	No GI bleeding
Clopidogrel	2	1
No clopidogrel	1	1

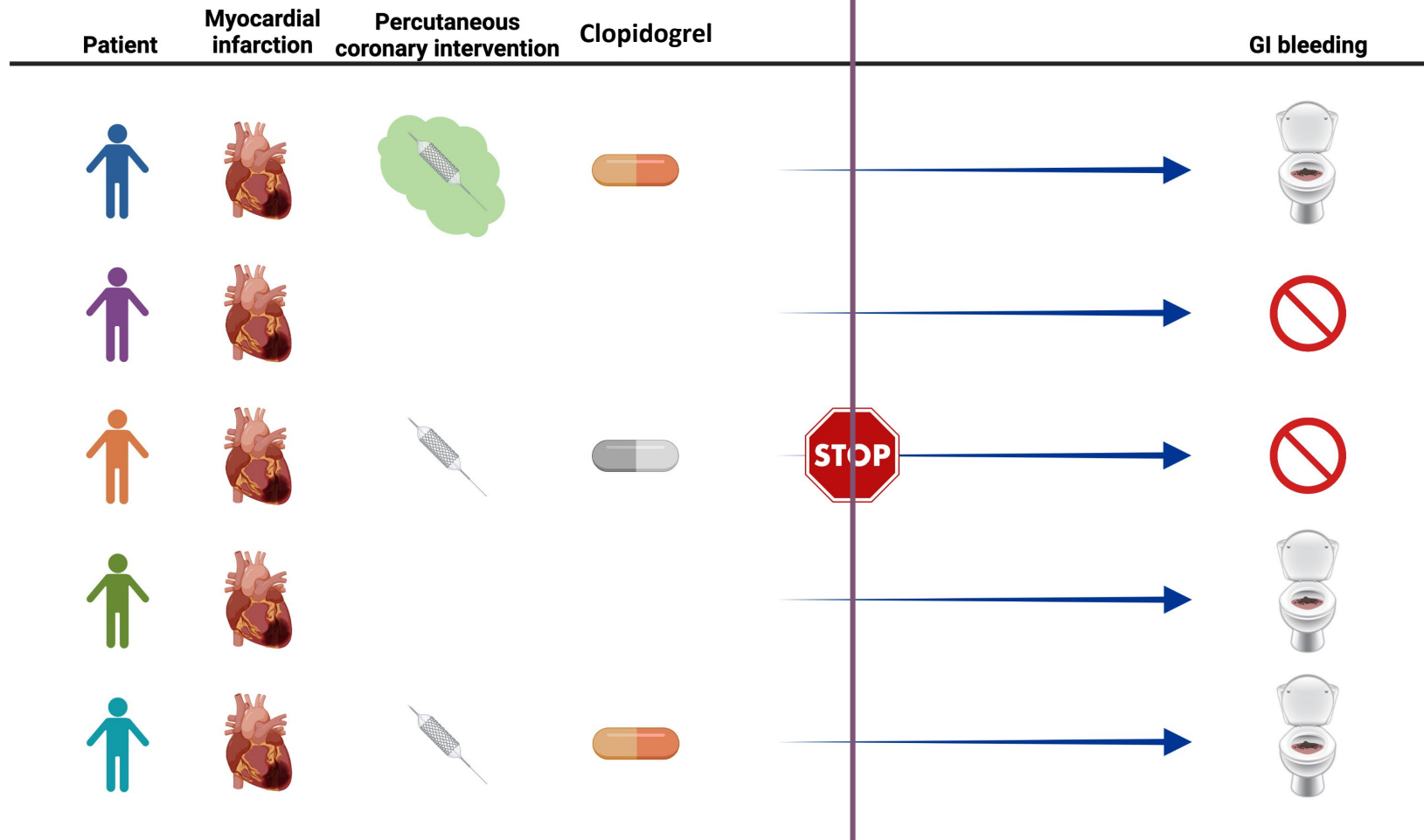




	GI bleeding	No GI bleeding
Clopidogrel	2	1
No clopidogrel	1	1



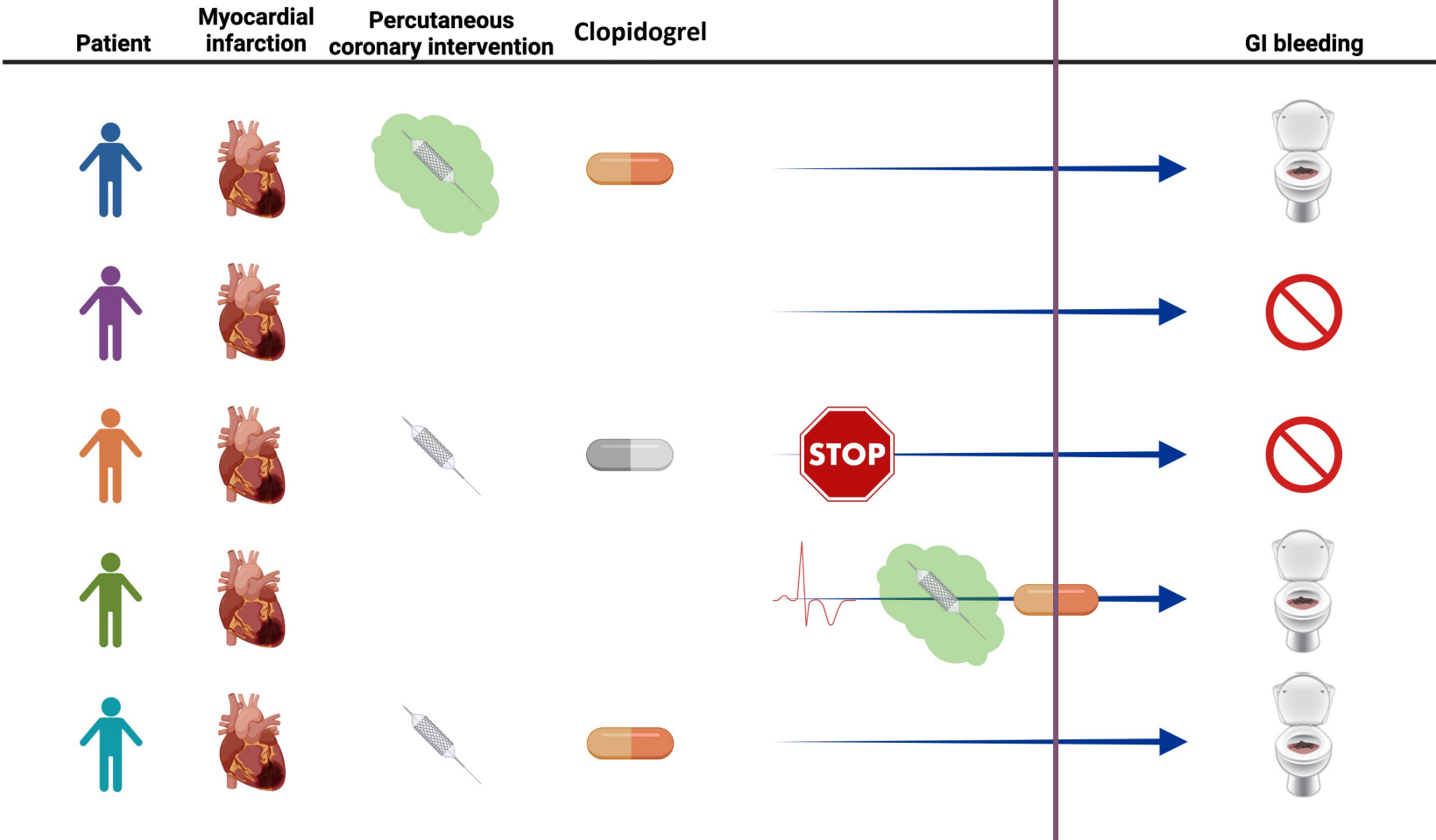
# Exposure assessment



	GI bleeding	No GI bleeding
Clopidogrel	2	0
No clopidogrel	1	2



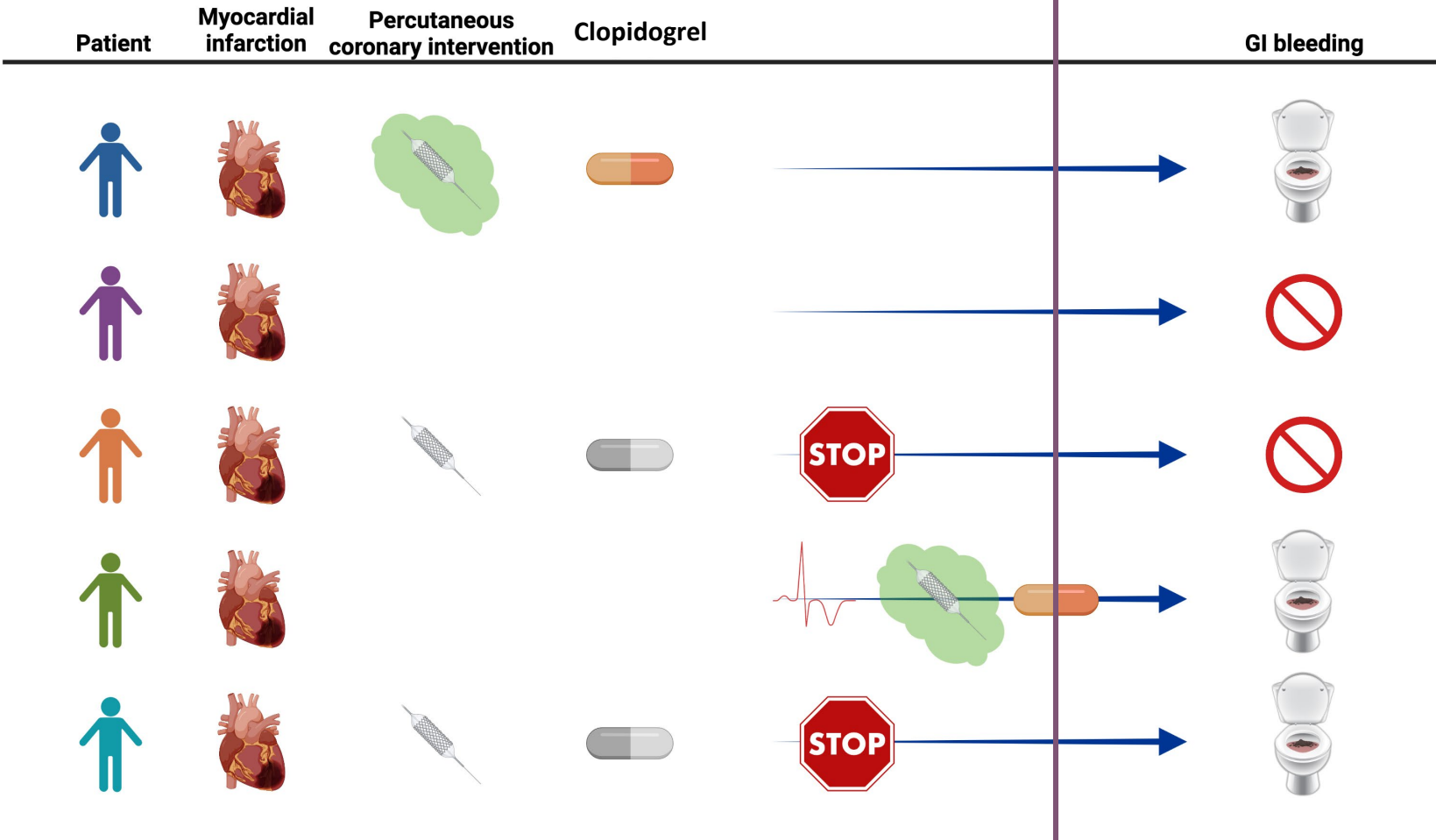
# Exposure assessment



	GI bleeding	No GI bleeding
Clopidogrel	3	0
No clopidogrel	0	2



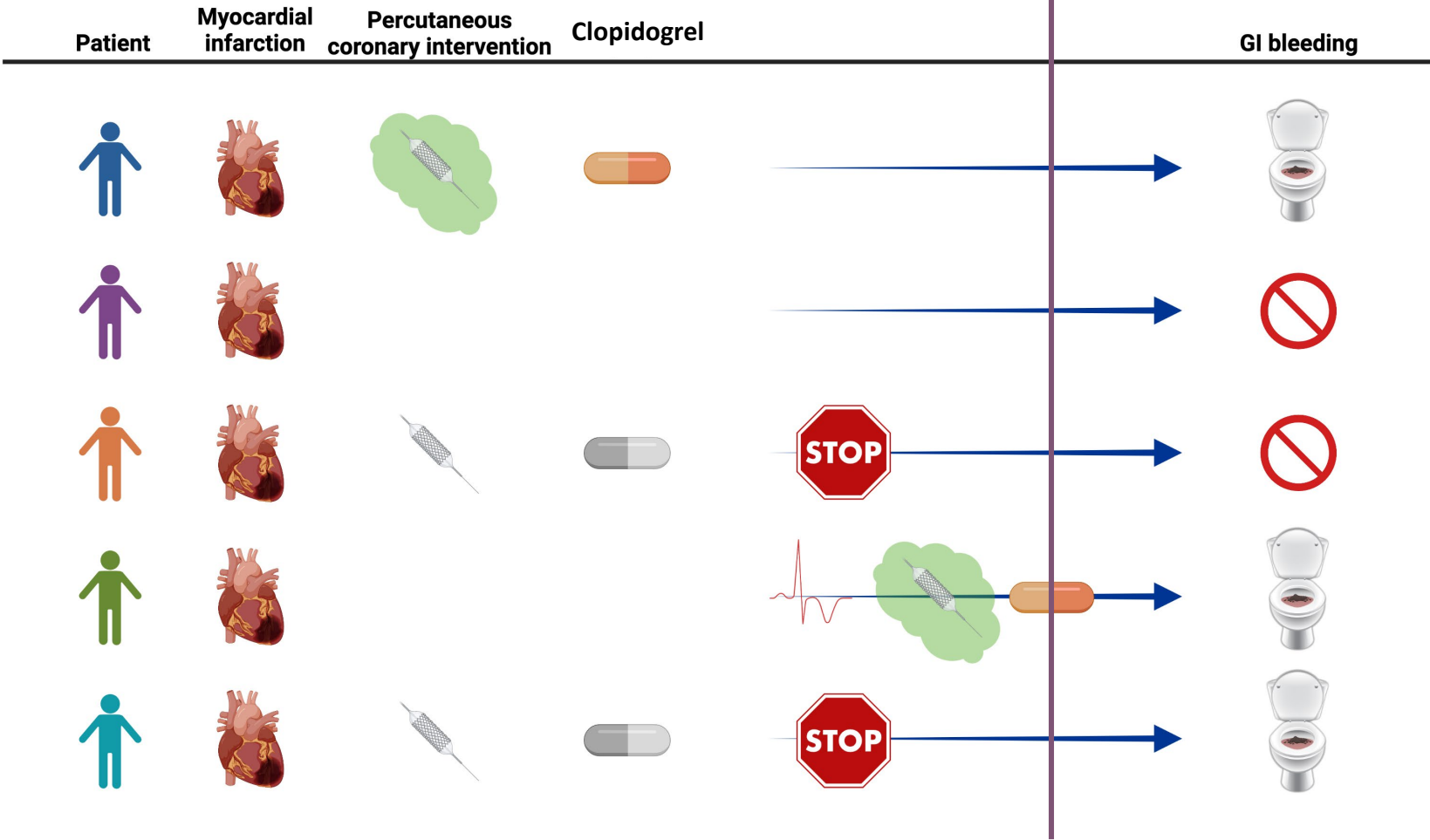
# Exposure assessment



	GI bleeding	No GI bleeding
Clopidogrel	2	0
No clopidogrel	1	2



# Exposure assessment



	GI bleeding	No GI bleeding
Clopidogrel	2	0
No clopidogrel	1	2

**RR = 3.0**



# Study team

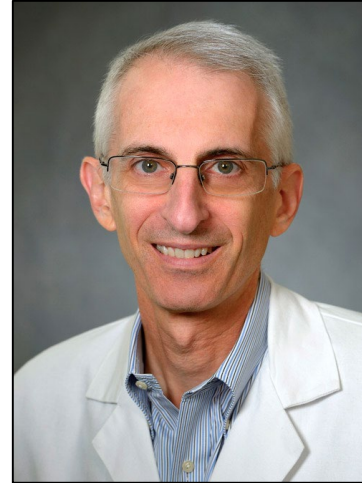
## University of Colorado



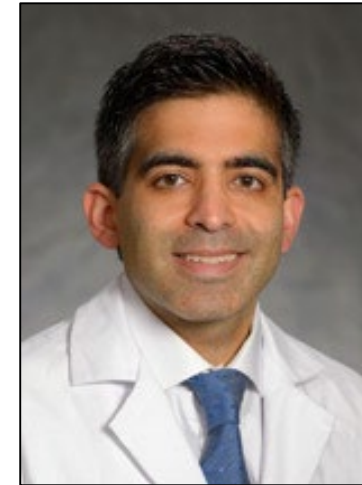
**Ravy K.  
Vajravelu**  
MD MSCE



**Frank I.  
Scott**  
MD MSCE



**James D.  
Lewis**  
MD MSCE



**Ronac  
Mamtani**  
MD MSCE



**Adam  
Waxman**  
MD MSCE

Hematology/Oncology





# Optum's de-identified Clinformatics® Data Mart Database

Medical claims data from large commercial and Medicare Advantage health plans in the United States



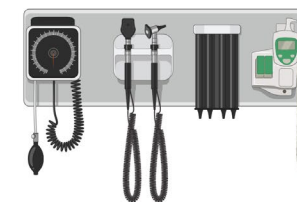
**OPTUM**

**77 million unique patients**

**from 2000 – 2016**



Hospitalizations



Outpatient care



Prescription medication dispensing



# Study design

## Cohort inclusion

### 1st diverticular hemorrhage during follow-up

Identified by ICD diagnosis code for  
diverticular hemorrhage during an  
inpatient encounter



# Study design

## Cohort inclusion

### 1st diverticular hemorrhage during follow-up

Identified by ICD diagnosis code for diverticular hemorrhage during an inpatient encounter

## Outcome

### 2nd episode of diverticular hemorrhage

- ICD diagnosis code for diverticular hemorrhage during a subsequent inpatient encounter
- At least **30 days** after the initial diverticular hemorrhage episode



# Exposures of interest

## Anticoagulants

- Warfarin
- Subcutaneous heparins  
*(heparin, enoxaparin, dalteparin)*
- Directly acting oral anticoagulants  
(DOACs)  
*(apixiban, dabigatran, rivaroxaban)*

## Antiplatelets

- Clopidogrel
- Prasugrel
- Ticagrelor

*(Time-varying exposures based on prescription date, refills, and days supplied)*



# Covariates

## Demographics

- Age
- Sex
- Race

## Prescriptions

- Aspirin
- NSAIDs
- SSRIs

## Diagnoses

- Risk factors for bleeding diathesis
- Risk factors for receiving anticoagulation or antiplatelets
- Risk factors for aspirin and NSAID use



# Results: Cohort characteristics

## 14,925 patients with initial diverticular hemorrhage

- Median age: 78 years (IQR 70 – 82)
- Sex: 51.9% female
- Race: 65.2% White and 16.0% Black

Incidence rate: 10.9 per 100,000 person-years



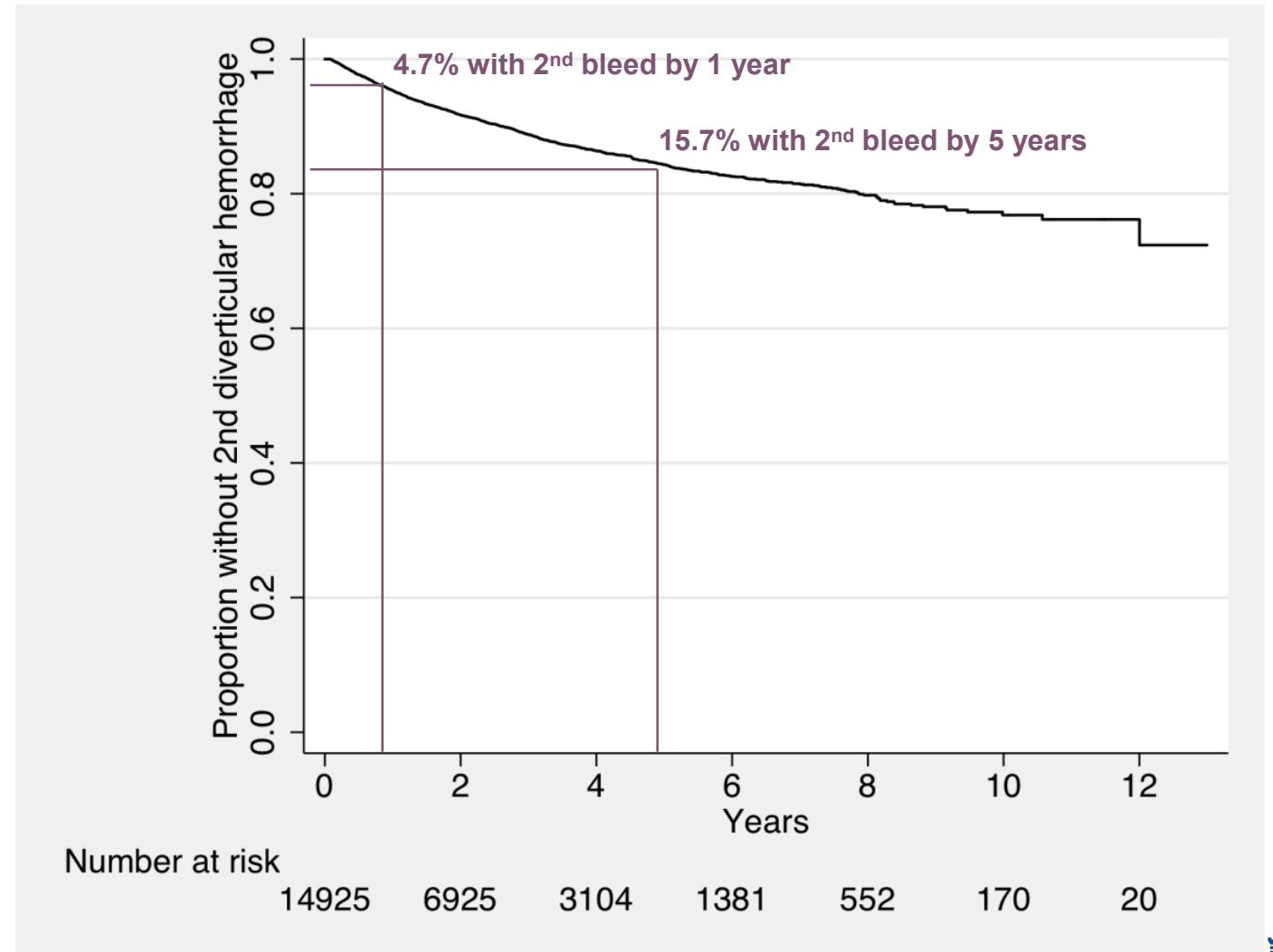
# 2<sup>nd</sup> diverticular hemorrhage

**1,368 patients**

**Incidence rate:**

**3,626 per 100,000 person years**

*(>300 times the incidence rate of initial  
diverticular hemorrhage)*



# Risk factors for 2<sup>nd</sup> diverticular hemorrhage

	aHR	95% CI	
Antiplatelets	1.47	1.15 - 1.88	*
Anticoagulants			
DOACs	0.68	0.33 - 1.41	
Warfarin	0.95	0.74 - 1.22	
Heparins	1.28	0.78 - 2.08	





# Takeaways

- Rate of recurrent diverticular hemorrhage is:
  - **5% after 1 year**
  - 16% after 5 years.
- **Antiplatelets**, but not anticoagulants, are associated with recurrent diverticular hemorrhage



# How to prevent recurrent diverticular hemorrhage

Recommend that prescribers consider **discontinuation of antiplatelets if patients don't have strong indications.**

## Candidates for discontinuation:

- Bare metal coronary stent implanted >1 month ago
- Drug-eluting coronary stent implanted >6 months ago
- Secondary stroke prevention: Assess other antiplatelet options.
- Peripheral artery disease: Assess other antiplatelet options.



# Conclusions

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# Takeaways

1. **Should we treat uncomplicated diverticulitis with antibiotics?**
2. Should we order colonoscopies to evaluate for colorectal cancer after diverticulitis?
3. Can we prevent recurrent diverticular bleeding?



# Takeaways

## 1. **Should we treat uncomplicated diverticulitis with antibiotics?**

No, if diverticulitis is truly uncomplicated and patient is likely to follow-up.

## 2. Should we order colonoscopies to evaluate for colorectal cancer after diverticulitis?

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# Takeaways

1. Should we treat uncomplicated diverticulitis with antibiotics?

No, if diverticulitis is truly uncomplicated and patient is likely to follow-up.

2. Should we order colonoscopies to evaluate for colorectal cancer after diverticulitis?

Yes, but there is room for clinical judgment based on colorectal cancer screening history.

3. **Can we prevent recurrent diverticular bleeding?**

Yes, through team medicine by discontinuing unnecessary antiplatelet prescriptions.



# Thank you!

Ravy.Vajravelu@pitt.edu

