# New Indications & Doses for Direct Oral Anticoagulants (DOACs)

A presentation for HealthTrust Members

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# DISCLOSURES

- The presenter has no financial relationships with any commercial interests pertinent to this presentation

- This program may contain the mention of drugs, brands or suppliers presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular drug, brand or supplier.

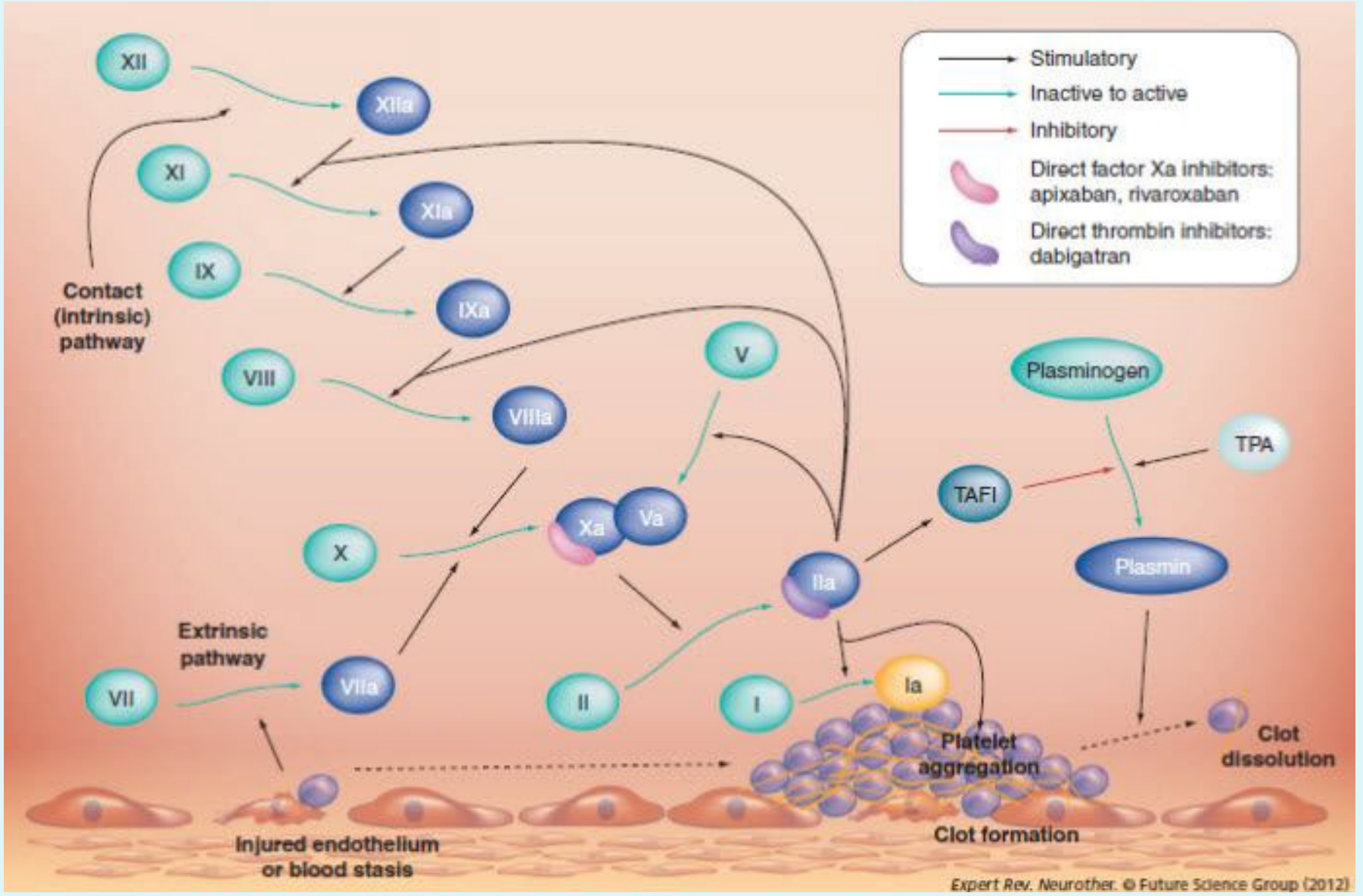
# Objectives for Pharmacists

- describe the new applications and indications for apixaban and rivaroxaban
- evaluate the evidence associated with each indication
- select a DOAC dose and schedule for a novel indication given a patient case

# Objectives for Pharmacy Technicians

- list the new doses available for apixaban and rivaroxaban
- determine key dosing differences for rivaroxaban and apixaban

# Inhibition of Factor Xa

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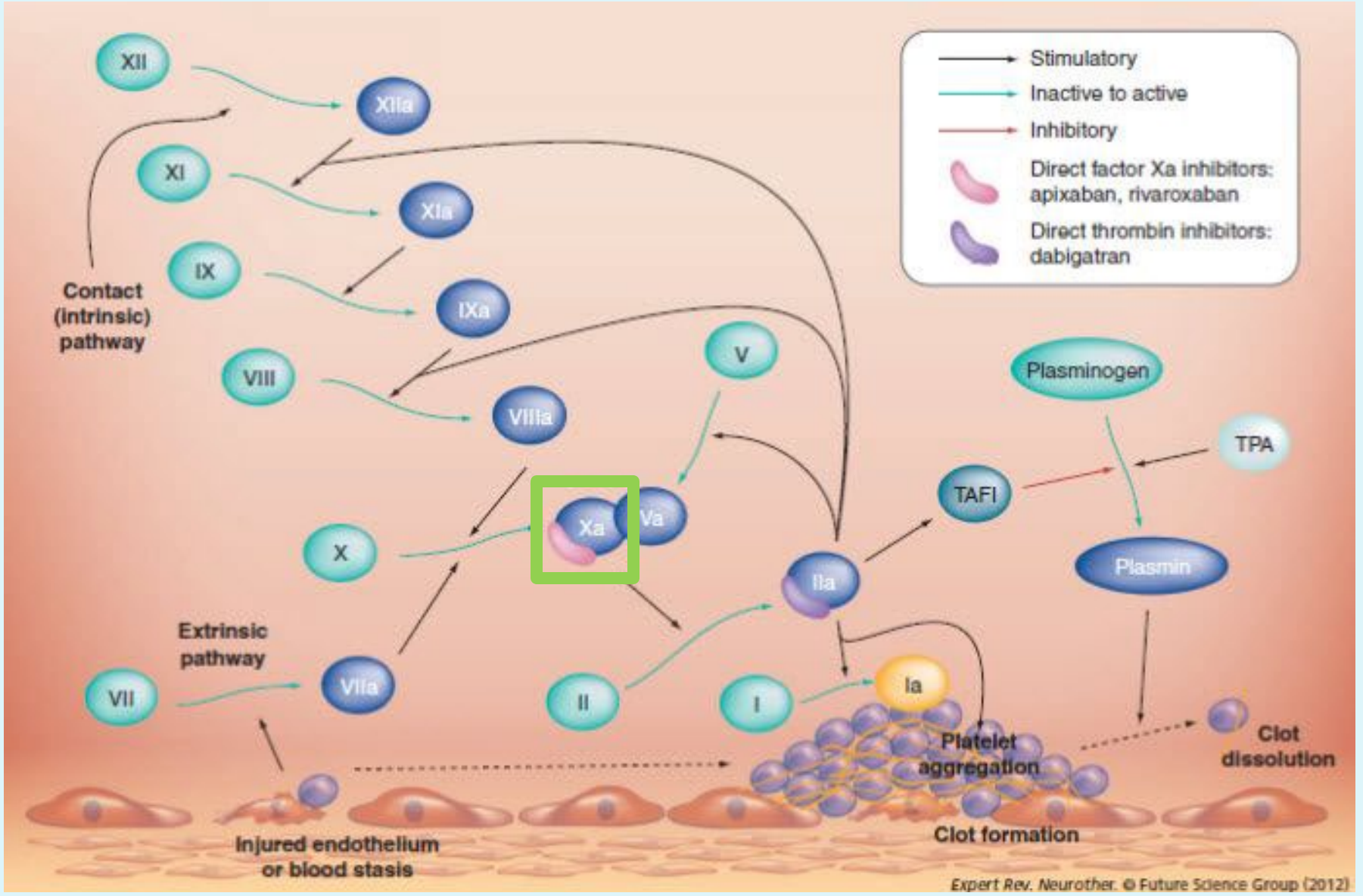


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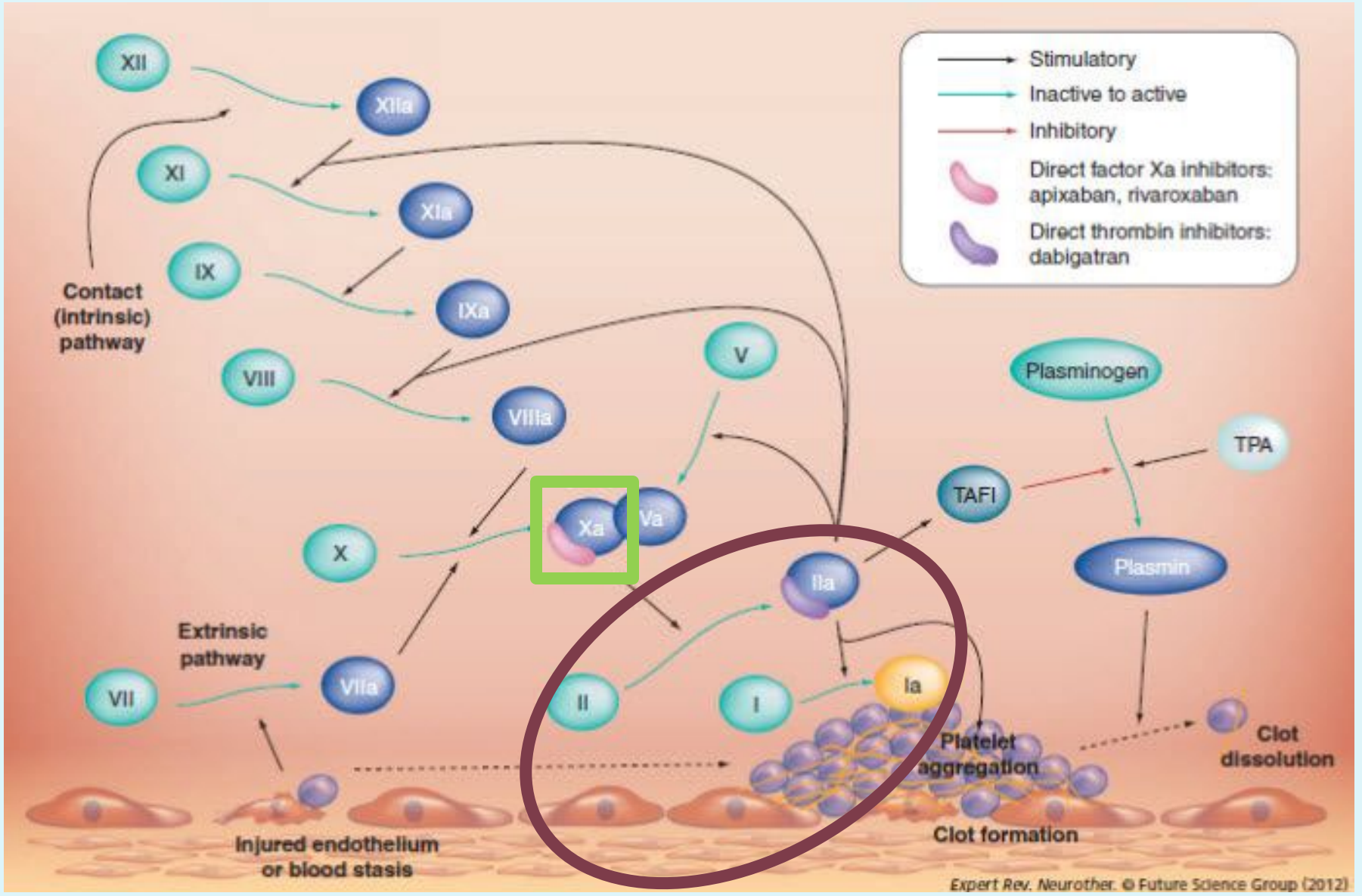


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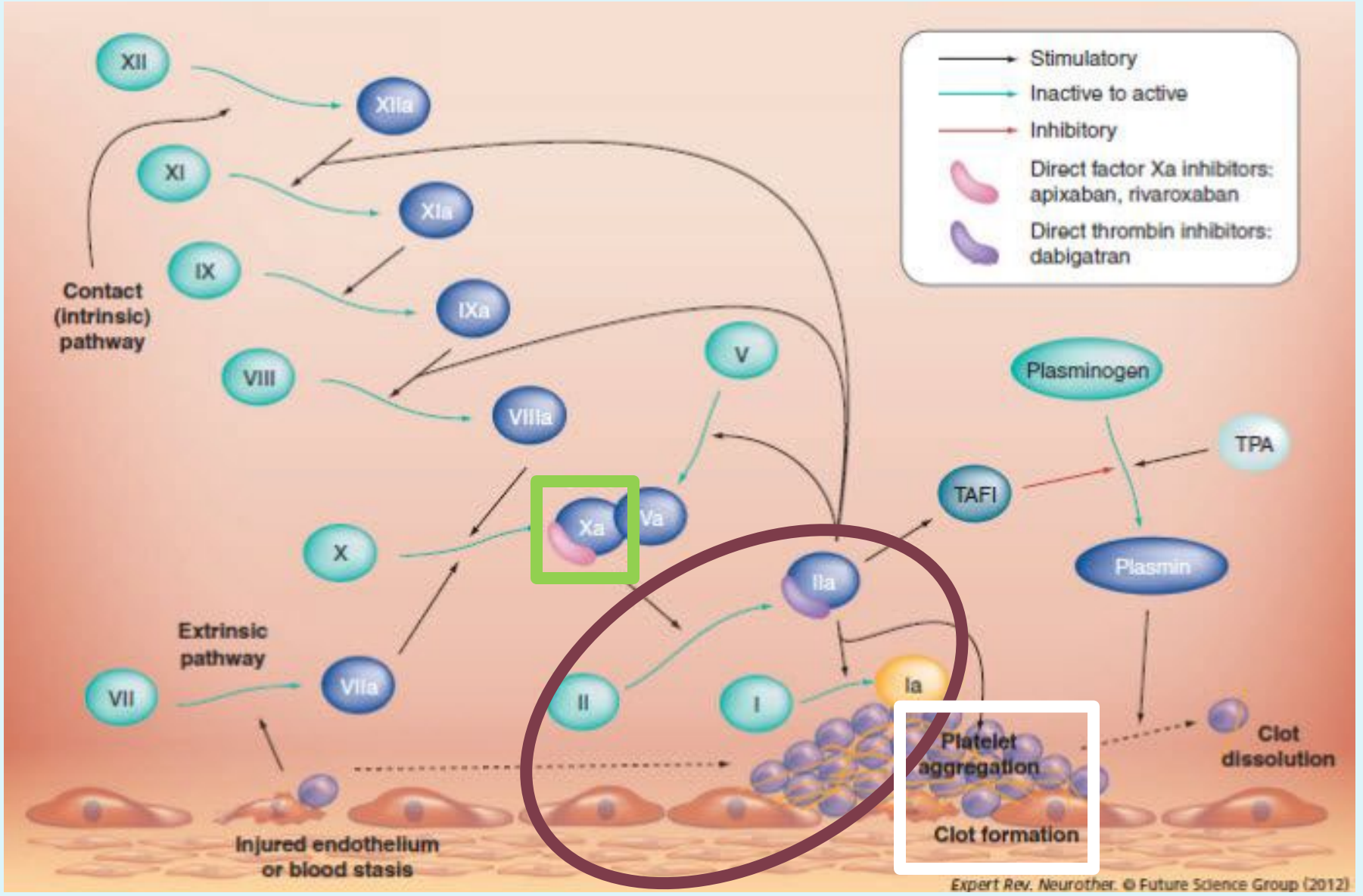


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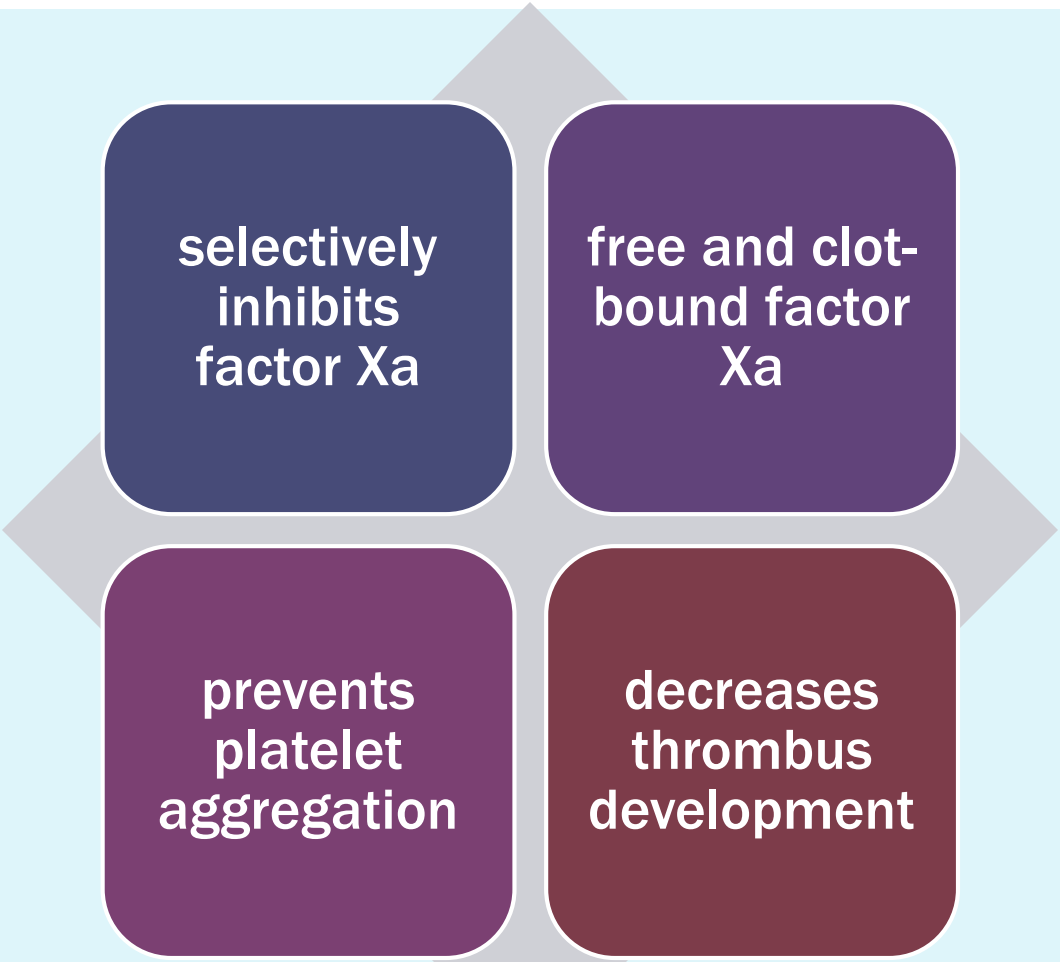
# Mechanism of Action




Sources: Eliquis® (apixaban) [package insert]. New York, NY: Pfizer Inc; 2016.
Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011

# Apixaban

# Available Doses

## 2.5 mg

- twice daily

Source: Eliquis® (apixaban) [package insert]. New York, NY: Pfizer Inc; 2016.

# Available Doses

## 2.5 mg

- twice daily

## 5 mg

- twice daily

Source: Eliquis® (apixaban) [package insert]. New York, NY: Pfizer Inc; 2016.

# Indication: Non-Valvular Atrial Fibrillation

## ARISTOTLE

apixaban vs. warfarin

results:

Sources: Eliquis® (apixaban) [package insert]. New York, NY: Pfizer Inc; 2016.
Granger CB, et al. N Engl J Med 2011; 365:981-992

# Indication: Non-Valvular Atrial Fibrillation

## ARISTOTLE

apixaban vs. warfarin

results:

apixaban was non-inferior in the prevention of stroke ($p<0.001$)

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## ARISTOTLE

apixaban vs. warfarin

results:

- apixaban was non-inferior in the prevention of stroke ($p<0.001$)
- apixaban had lower rates of major bleeding ($p<0.001$)
- apixaban had a lower rate of death from any cause ($p=0.047$)

Sources: Eliquis® (apixaban) [package insert]. New York, NY: Pfizer Inc; 2016.
Granger CB, et al. N Engl J Med 2011; 365:981-992

# Indication: The prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) following total knee replacement and hip surgery

## ADVANCE-2

apixaban vs. enoxaparin

results:

Sources: Eliquis® (apixaban) [package insert]. New York, NY: Pfizer Inc; 2016.

Lassen MR, et al. Lancet; 375(9717): 807-815

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apixaban vs. enoxaparin

results:

apixaban had lower rates of DVT, non fatal PE and all cause death ($p<0.0001$)

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- no difference in the rates of major bleeding (p=0.3014)

Sources: Eliquis® (apixaban) [package insert]. New York, NY: Pfizer Inc; 2016.
Lassen MR, et al. Lancet; 375(9717): 807-815

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apixaban vs. enoxaparin

results:

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- no difference in the rates of major bleeding ($p=0.3014$)
- no difference in rates of non-major bleeding ($p=0.09$)

Sources: Eliquis® (apixaban) [package insert]. New York, NY: Pfizer Inc; 2016.
Lassen MR, et al. Lancet; 375(9717): 807-815

# Indication: Treatment and Prophylaxis of DVT and PE

## AMPLIFY

apixaban vs. enoxaparin followed by warfarin

**results:**

Sources: Eliquis® (apixaban) [package insert]. New York, NY: Pfizer Inc; 2016.
Agnelli, G, et al. N Engl J Med 2013; 369:799-808

# Indication: Treatment and Prophylaxis of DVT and PE

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apixaban vs. enoxaparin followed by warfarin

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apixaban had lower rates of the primary outcome ($p<0.001$)

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- apixaban had lower rates of major bleeding ($p<0.001$)

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# Apixaban in Guidelines

2019 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation

CHEST Guideline for Antithrombotic Therapy in Venous Thromboembolism (VTE)

Antithrombotic Therapy and Prevention of Thrombosis, 9th edition

Sources: Falck-Yitter Y, et al. Chest; 141(2 Suppl): e278S-e325S

Kearon C, et al. Chest; 2016; 149:315-352

January CT, et al. 10.1016/j.jacc.2019.01.0011

# Rivaroxaban

# Available Doses Prior to 2018

## 10mg

- once daily with food

Source: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011

# Available Doses Prior to 2018

## 10mg

- once daily with food

## 15mg

- once or twice daily with food

Source: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011

# Available Doses Prior to 2018

## 10mg

- once daily with food

## 15mg

- once or twice daily with food

## 20mg

- once daily with food

Source: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011

# Indication: Non-Valvular Atrial Fibrillation

## ROCKET AF

rivaroxaban vs. warfarin

results:

Sources: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011
Patel MR, et al. N Engl J Med 2011; 365:883-891

# Indication: Non-Valvular Atrial Fibrillation

## ROCKET AF

rivaroxaban vs. warfarin

results:

rivaroxaban had lower rate of stroke or systemic embolism ($p<0.001$)

Sources: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011
Patel MR, et al. N Engl J Med 2011; 365:883-891

# Indication: Non-Valvular Atrial Fibrillation

## ROCKET AF

rivaroxaban vs. warfarin

results:

- rivaroxaban had lower rate of stroke or systemic embolism (p<0.001)
- no difference between the groups in rates of bleeding (p=0.44)



Sources: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011
Patel MR, et al. N Engl J Med 2011; 365:883-891

# Indication: Non-Valvular Atrial Fibrillation

## ROCKET AF

rivaroxaban vs. warfarin

results:

- rivaroxaban had lower rate of stroke or systemic embolism (p<0.001)
- no difference between the groups in rates of bleeding (p=0.44)
- rivaroxaban had a lower rate of intracranial hemorrhage (p=0.02)

Sources: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011
Patel MR, et al. N Engl J Med 2011; 365:883-891

# Indication: Treatment of DVT and/or PE

## EINSTEIN DVT/PE

rivaroxaban vs. enoxaparin

results:

Sources: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011
Prins MH, et al. Thrombis Journal 2013; 11:21

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Prins MH, et al. Thrombis Journal 2013; 11:21

# Indication: Treatment of DVT and/or PE

## EINSTEIN DVT/PE

rivaroxaban vs. enoxaparin

results:

- rivaroxaban had a lower rate of DVT and PE ($p<0.001$)
- rivaroxaban had a lower rate of major bleeding ($p=0.002$)

Sources: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011
Prins MH, et al. Thrombis Journal 2013; 11:21

# Indication: Prophylaxis of DVT Following Hip and Knee Replacements

## RECORD 3 Trial

rivaroxaban vs. enoxaparin

results:

Sources: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011
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# Indication: Prophylaxis of DVT Following Hip and Knee Replacements

## RECORD 3 Trial

rivaroxaban vs. enoxaparin

results:

rivaroxaban had lower rate of primary outcome ($p<0.001$)

Source: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011

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# Indication: Prophylaxis of DVT Following Hip and Knee Replacements

## RECORD 3 Trial

rivaroxaban vs. enoxaparin

results:

- rivaroxaban had lower rate of primary outcome ($p<0.001$)
- rivaroxaban had lower rate of VTE ($p=0.01$)

Source: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011

Lassen MR, et al. N Engl J Med 2008; 358:2776-2786

# Indication: Prophylaxis of DVT Following Hip and Knee Replacements

## RECORD 3 Trial

rivaroxaban vs. enoxaparin

results:

- rivaroxaban had lower rate of primary outcome (p<0.001)
- rivaroxaban had lower rate of VTE (p=0.01)
- rivaroxaban had lower rate of symptomatic VTE (p=0.005)

Sources: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011
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# Indication: Prophylaxis of DVT Following Hip and Knee Replacements

## RECORD 3 Trial

rivaroxaban vs. enoxaparin

results:

- rivaroxaban had lower rate of primary outcome (p<0.001)
- rivaroxaban had lower rate of VTE (p=0.01)
- rivaroxaban had lower rate of symptomatic VTE (p=0.005)
- similar rate of bleeding in both groups

Sources: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011

Lassen MR, et al. N Engl J Med 2008; 358:2776-2786

# Rivaroxaban in Guidelines

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Sources: Falck-Yitter Y, et al. Chest; 141(2 Suppl): e278S-e325S
Kearon C, et al. Chest; 2016; 149:315-352
January CT, et al. 10.1016/j.jacc.2019.01.0011

# Limitations of DOACs

## Patients:

| | | | |
|---|---|---|---|
| with cancer | with end stage kidney disease (ESKD) | receiving hemodialysis | with obesity |

# New Apixaban Evidence

# Apixaban to Prevent VTE in Patients with Cancer (AVERT Trial)

# AVERT: Background

patients with cancer are at an increased risk of developing VTE

at the time of this trial this population had not been studied

Source: Carrier M, et al. N Engl J Med 2019; 380:711-718

# AVERT: Methods

randomized, placebo controlled, double blinded trial

ambulatory patients with cancer and a Khorana score ≥ 2 out of 6

apixaban 2.5mg twice daily

Source: Carrier M, et al. N Engl J Med 2019; 380:711-718

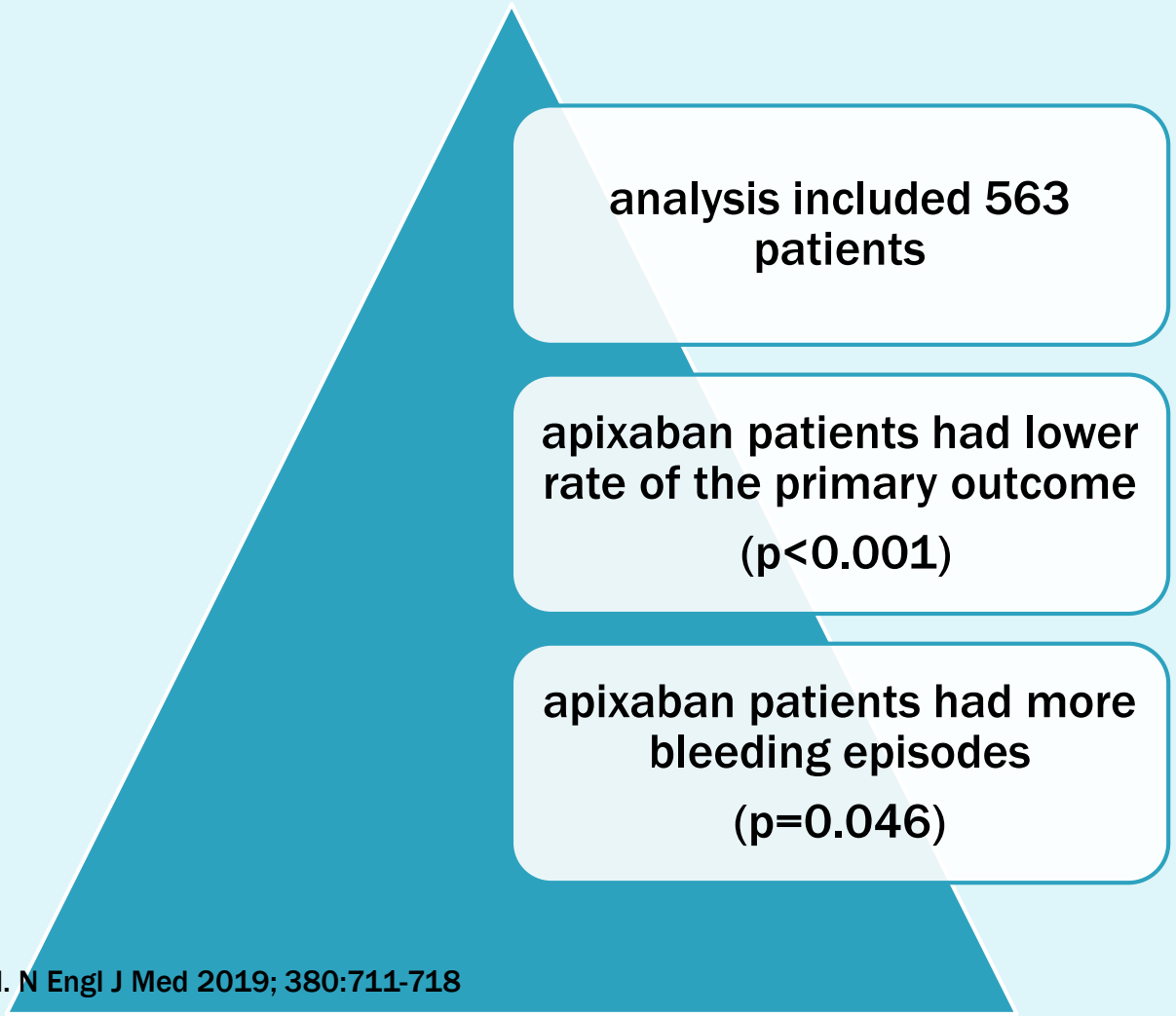
# AVERT: Methods

primary outcome: objectively documented VTE

secondary outcome: major bleeding episode

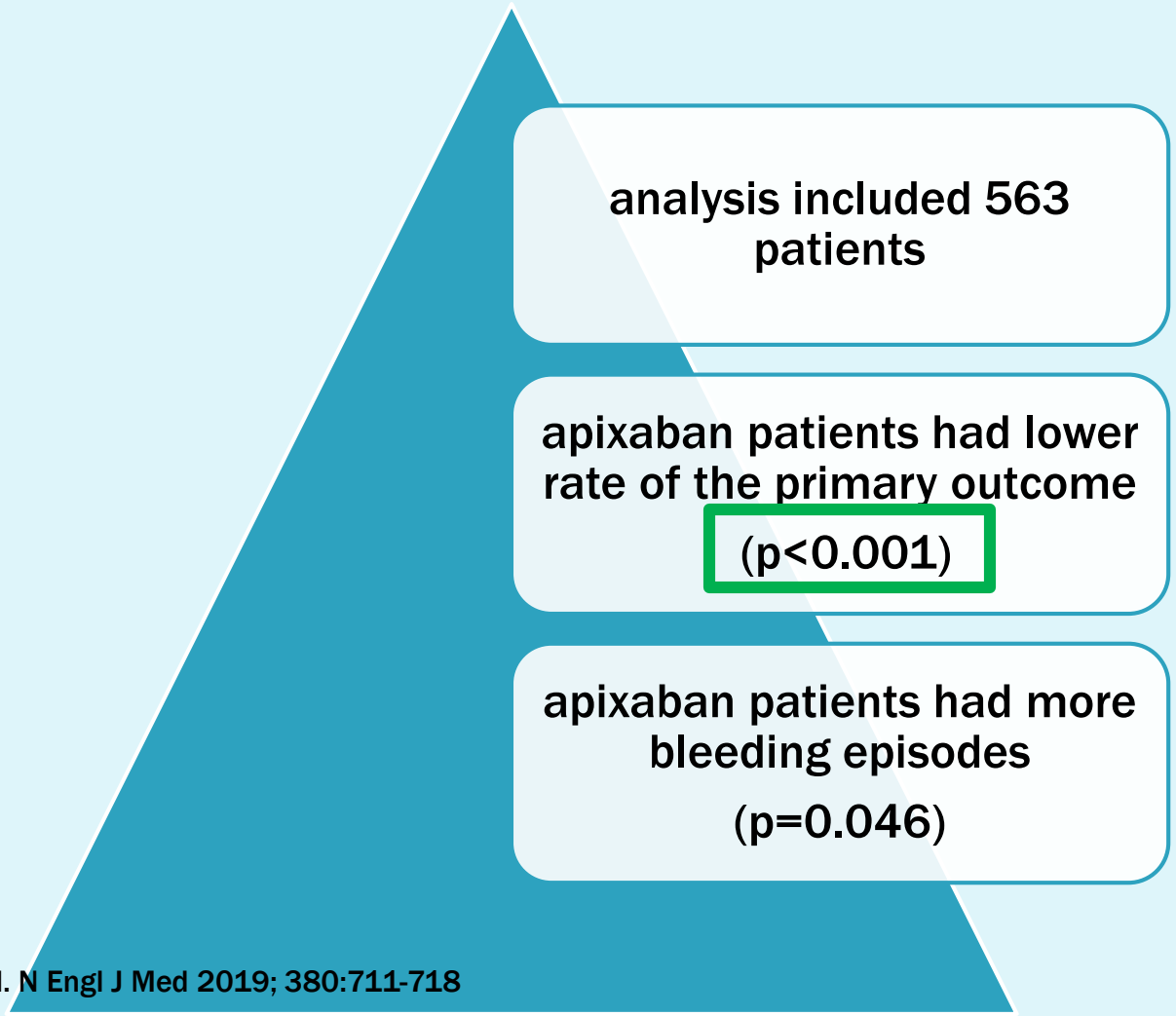
Source: Carrier M, et al. N Engl J Med 2019; 380:711-718

# AVERT: Results




Source: Carrier M, et al. N Engl J Med 2019; 380:711-718

# AVERT: Results




Source: Carrier M, et al. N Engl J Med 2019; 380:711-718

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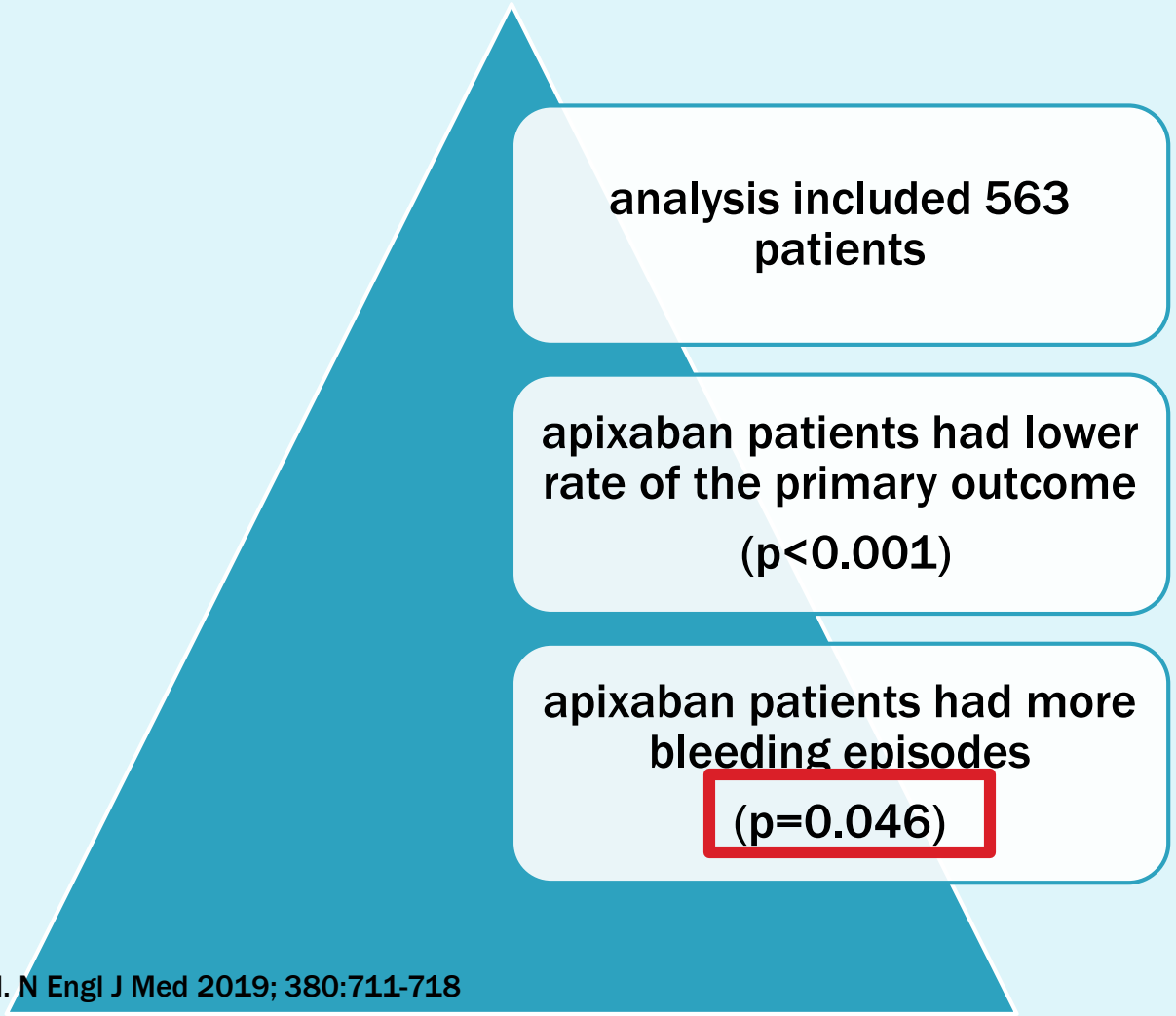
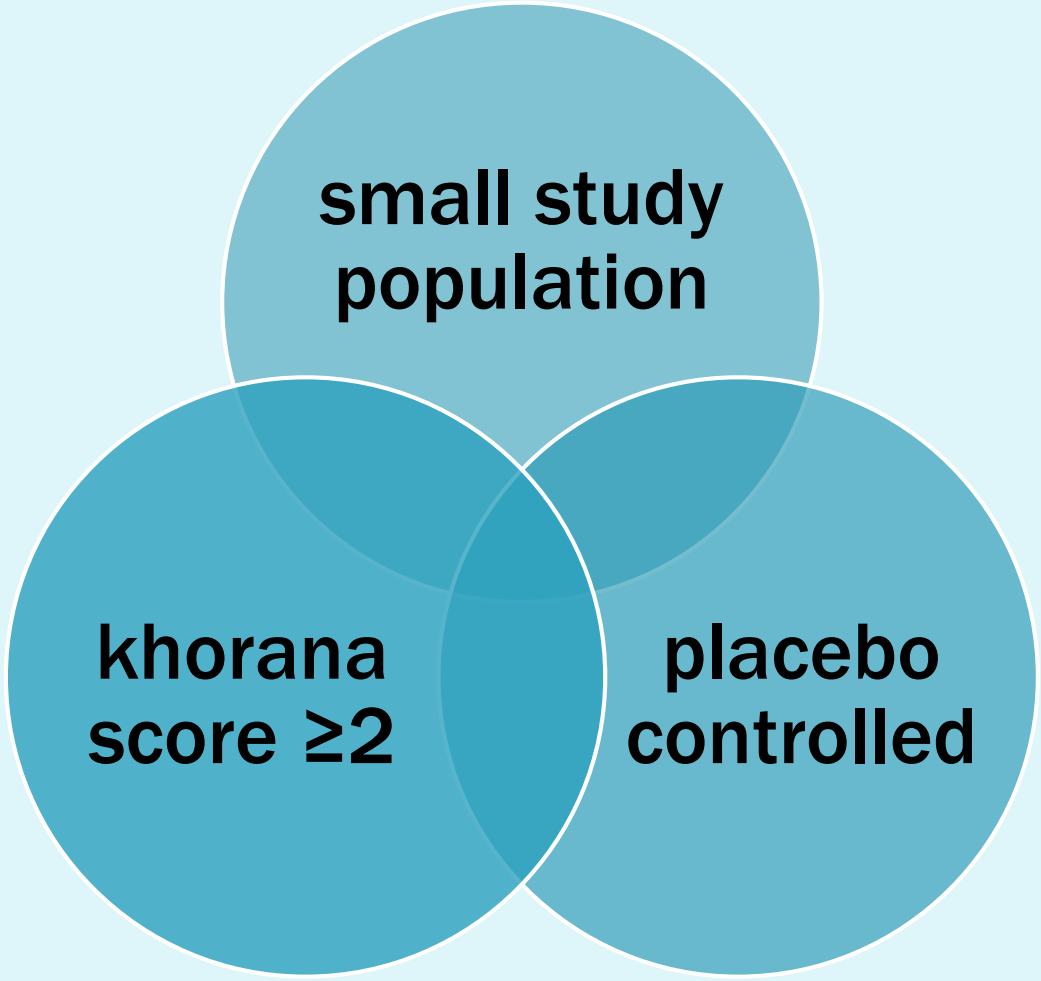


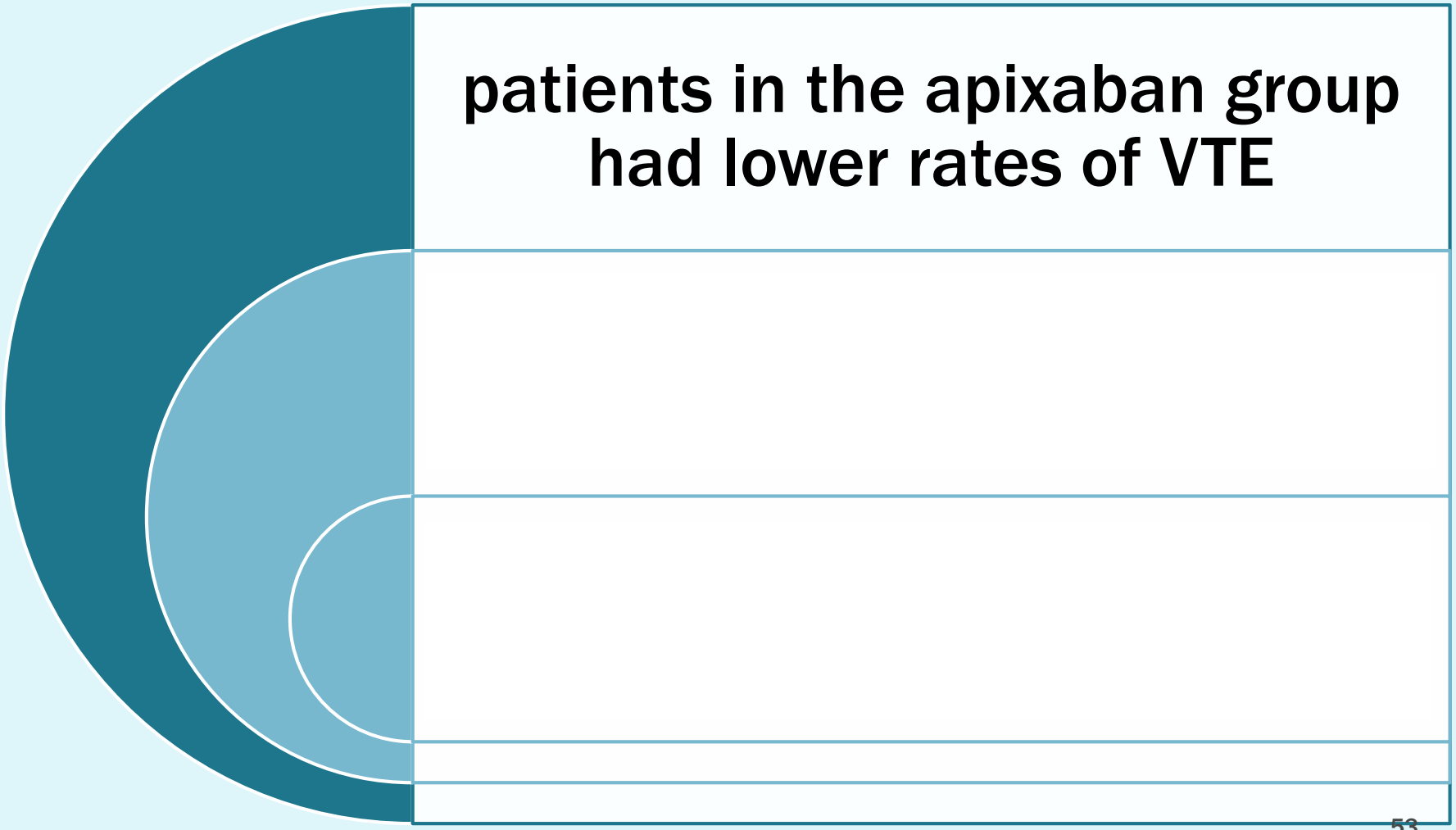

Source: Carrier M, et al. N Engl J Med 2019; 380:711-718

# AVERT: Limitations




Source: Carrier M, et al. N Engl J Med 2019; 380:711-718

# AVERT: Conclusions

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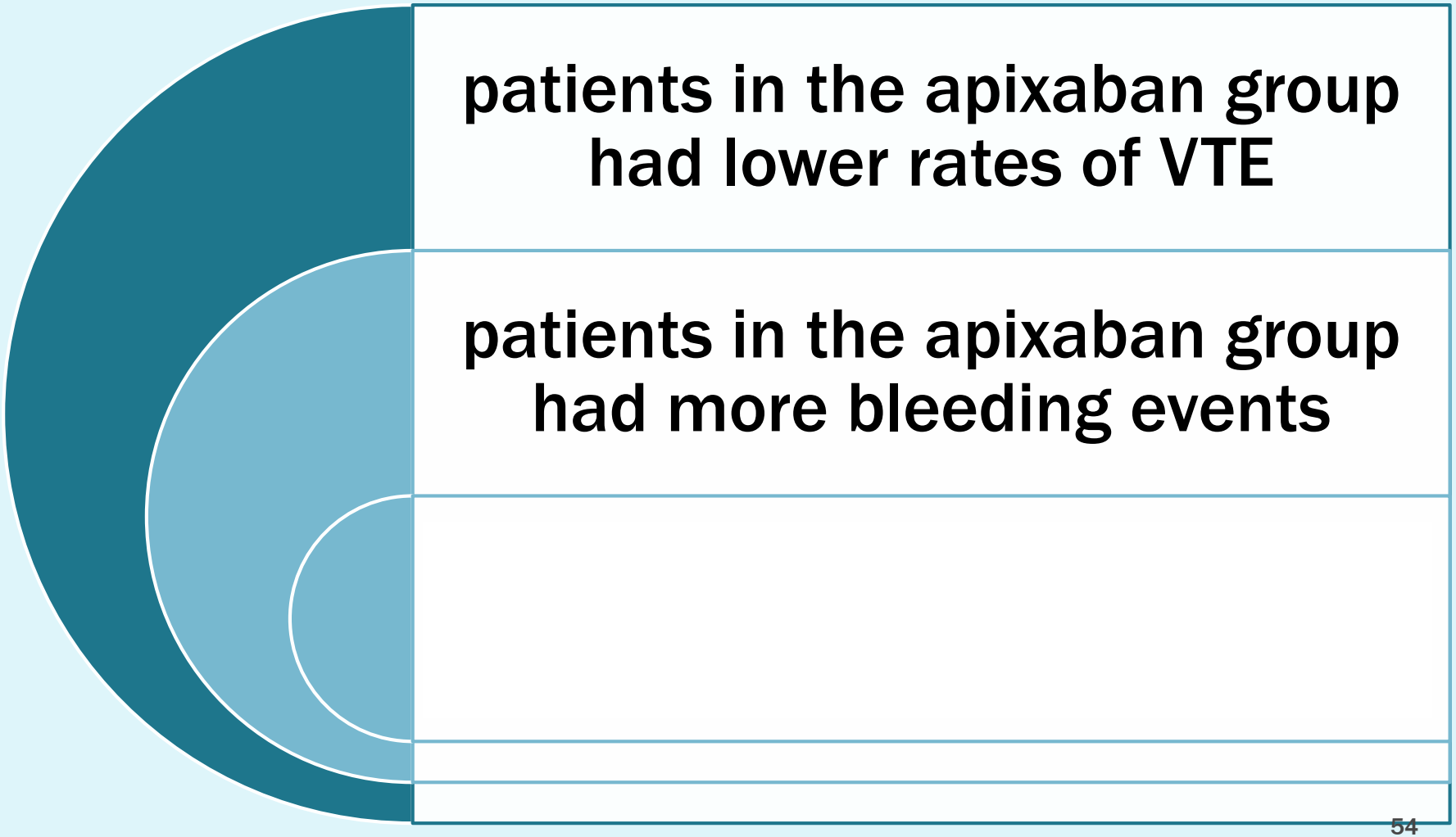


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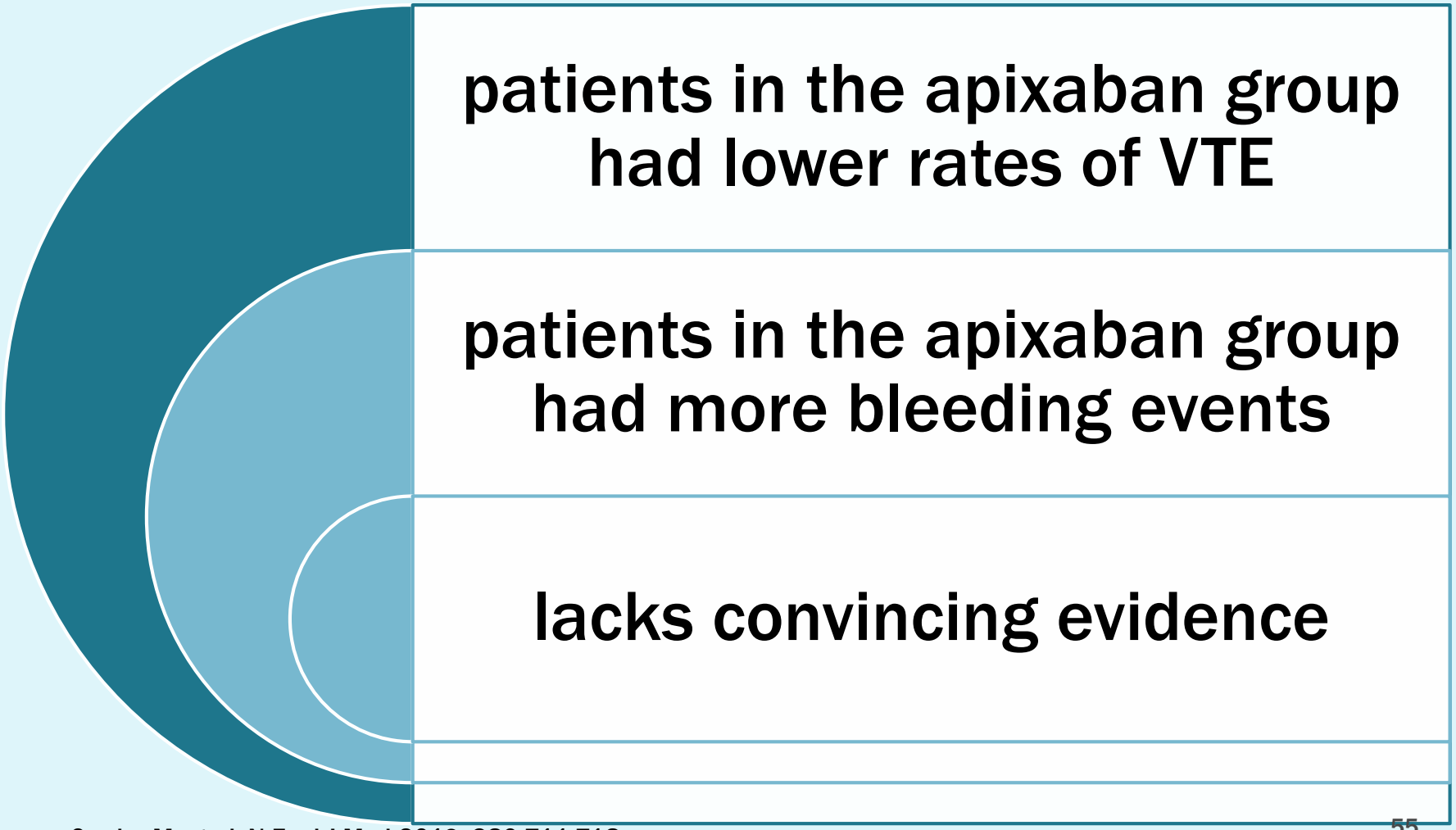



Source: Carrier M, et al. N Engl J Med 2019; 380:711-718

# Apixaban for the Treatment of VTE in Patients with Active Cancer

# (ADAM VTE Trial)

# ADAM VTE: Background

low molecular weight heparin (LMWH) is the treatment of choice

apixaban has not been studied in patients with active cancer

Source: McBane RD, et al. Blood 2018; 132:421

# ADAM VTE: Methods

randomized, active control trial

patients with cancer associated VTE

apixaban 10 mg BID for 7 days followed by 5 mg BID for 6 months

dalteparin 200 IU/kg for 1 month followed by 150 IU/kg for 6 months

Source: McBane RD, et al. Blood 2018; 132:421

# ADAM VTE: Methods

primary outcome: major bleeding

Source: McBane RD, et al. Blood 2018; 132:421

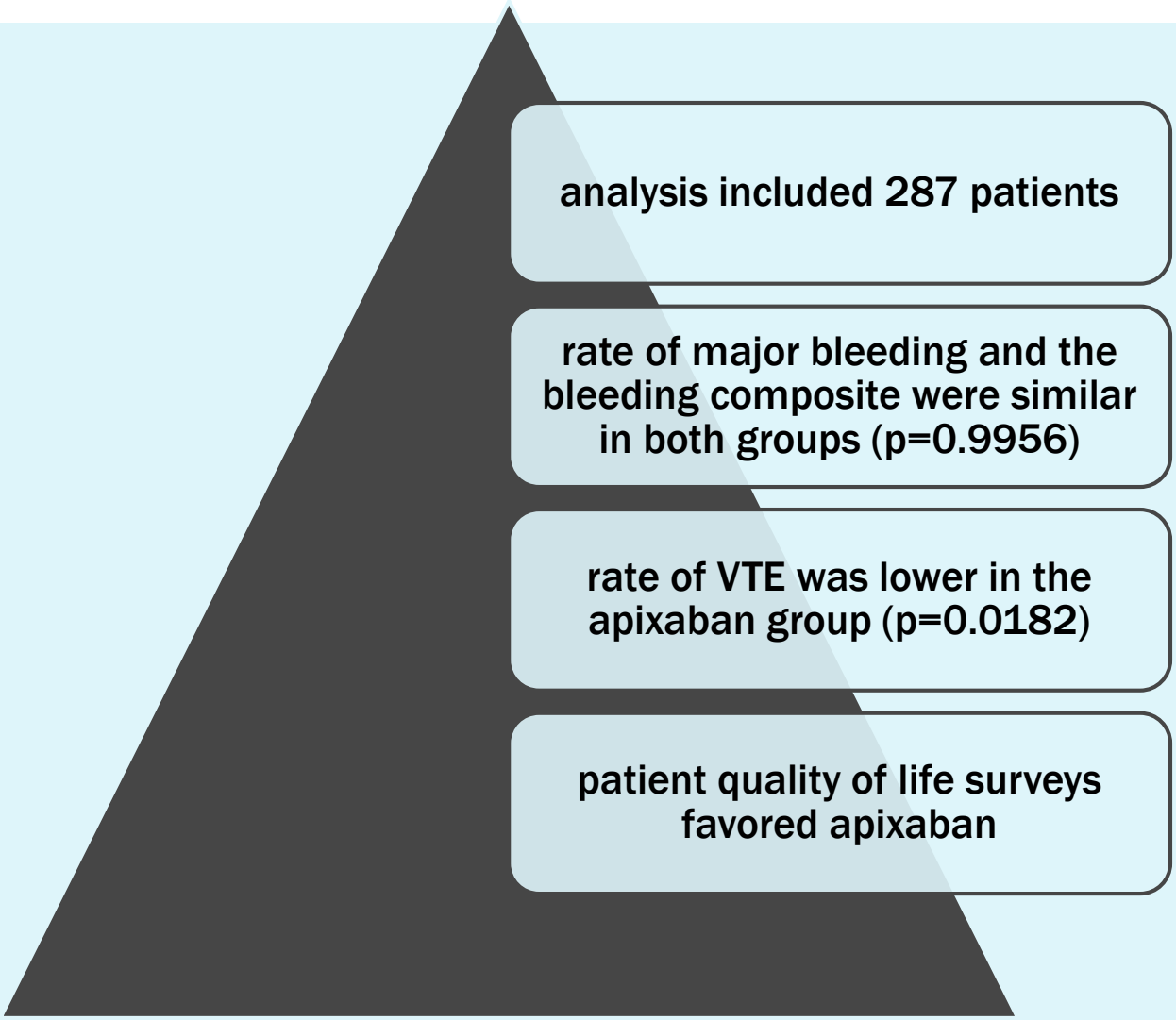
# ADAM VTE: Methods

primary outcome: major bleeding

secondary outcome: VTE recurrence and composite measure

Source: McBane RD, et al. Blood 2018; 132:421

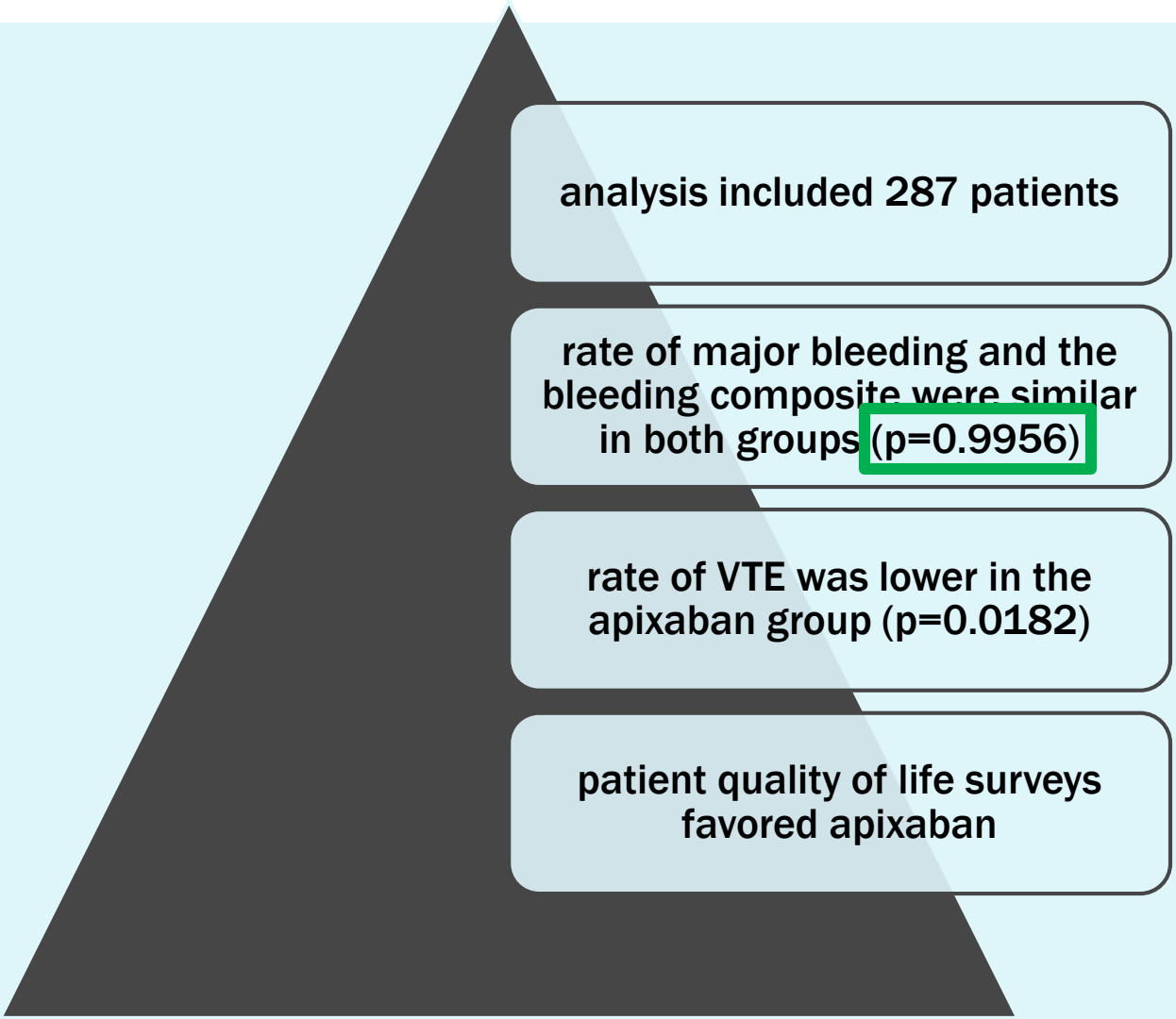
# ADAM VTE: Results






Source: McBane RD, et al. Blood 2018; 132:421

# ADAM VTE: Results



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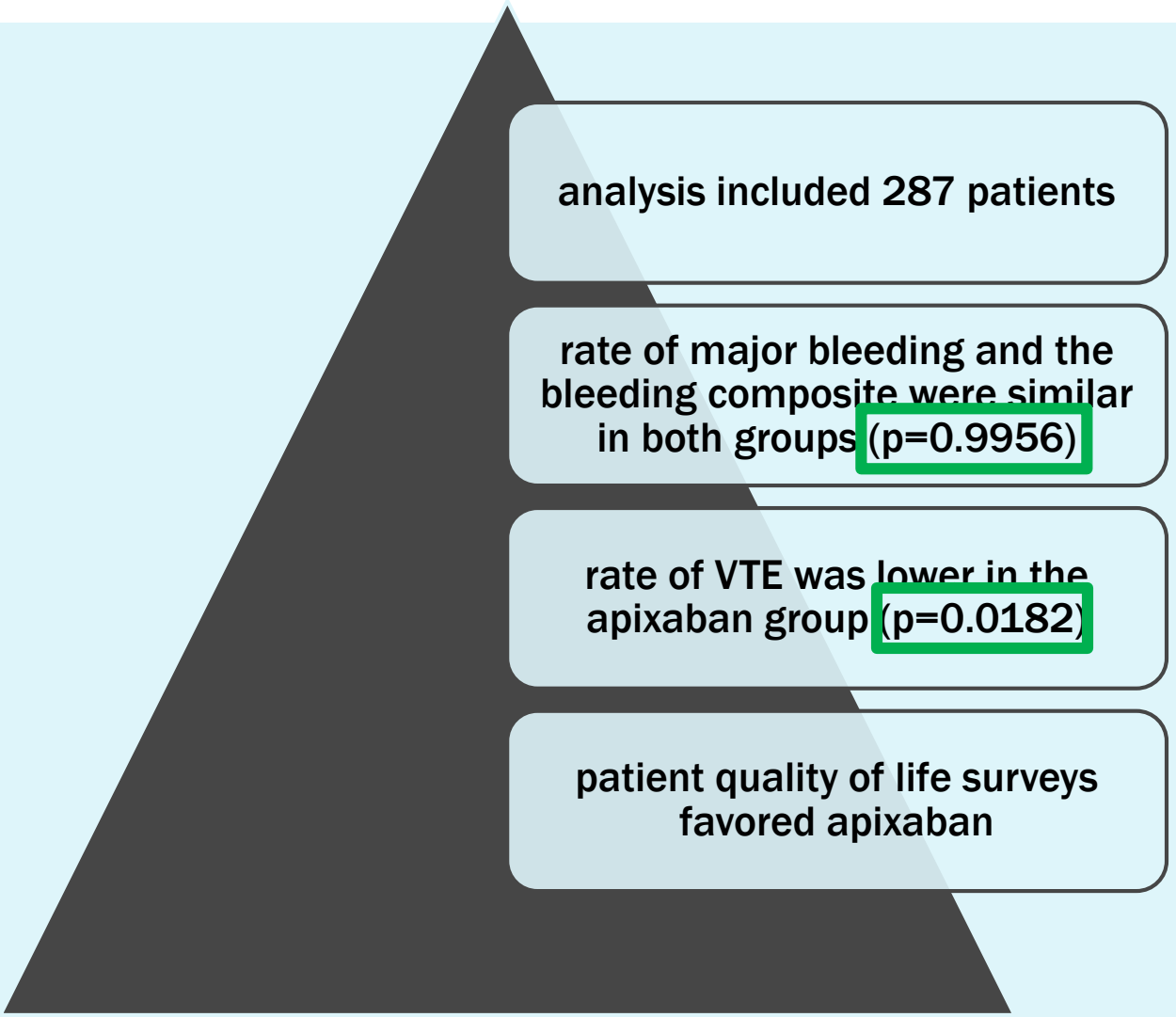
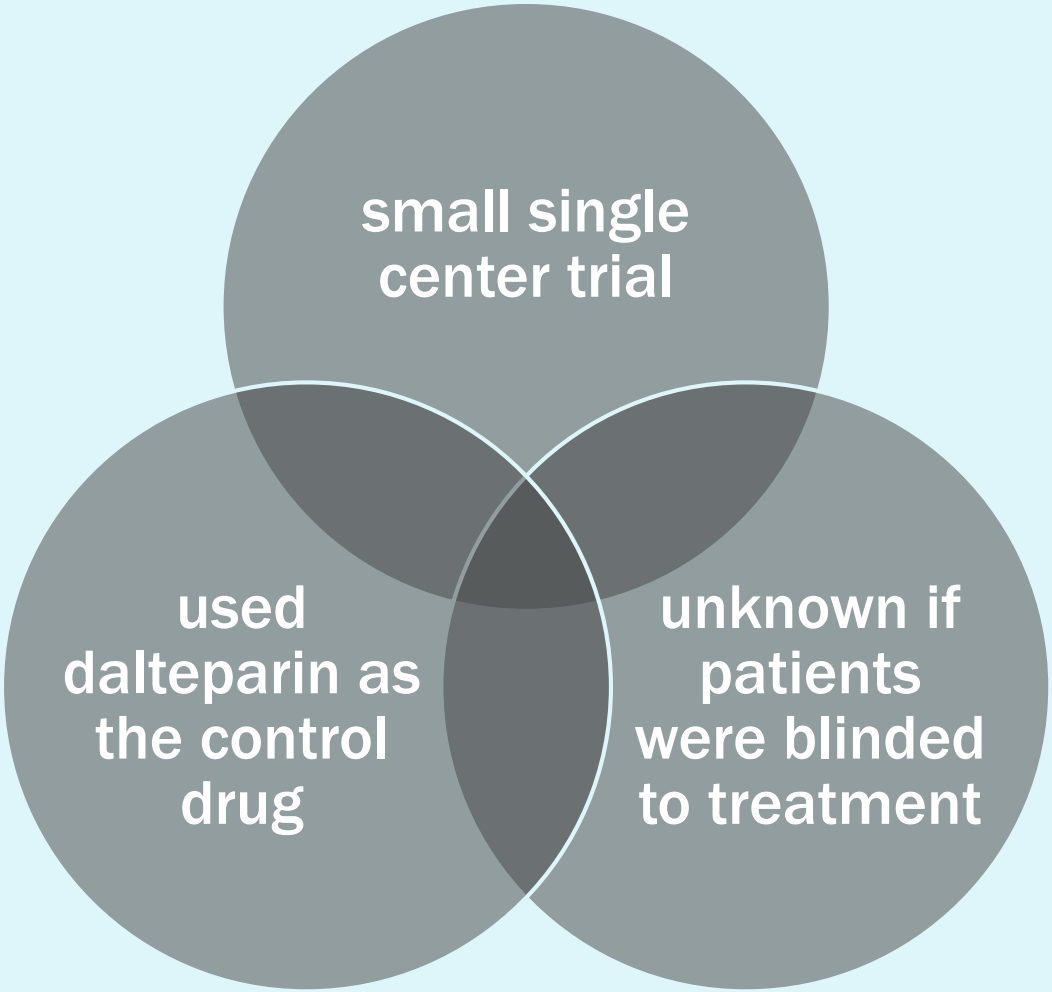





Source: McBane RD, et al. Blood 2018; 132:421

# ADAM VTE: Limitations

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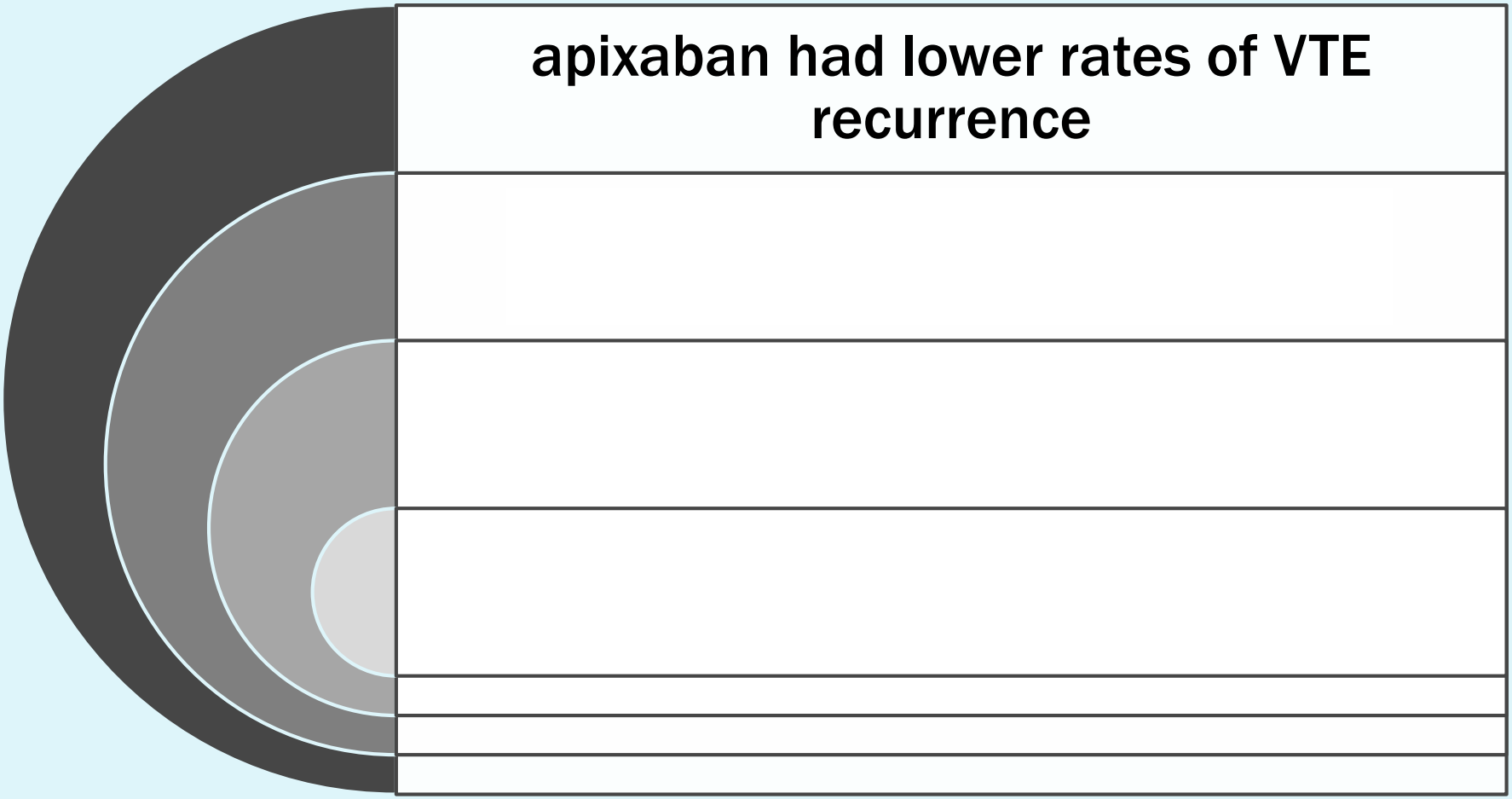


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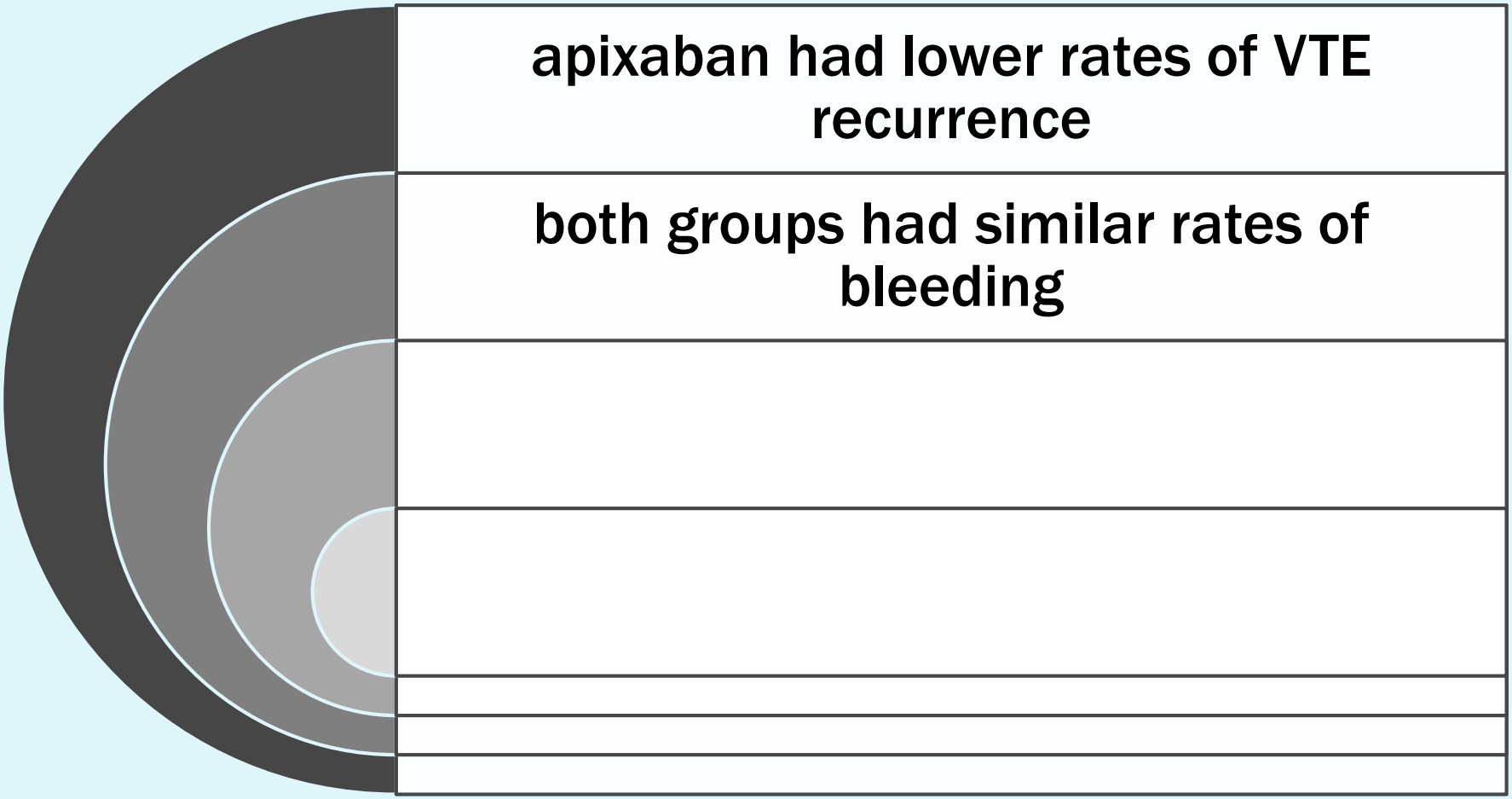
# ADAM VTE: Conclusions

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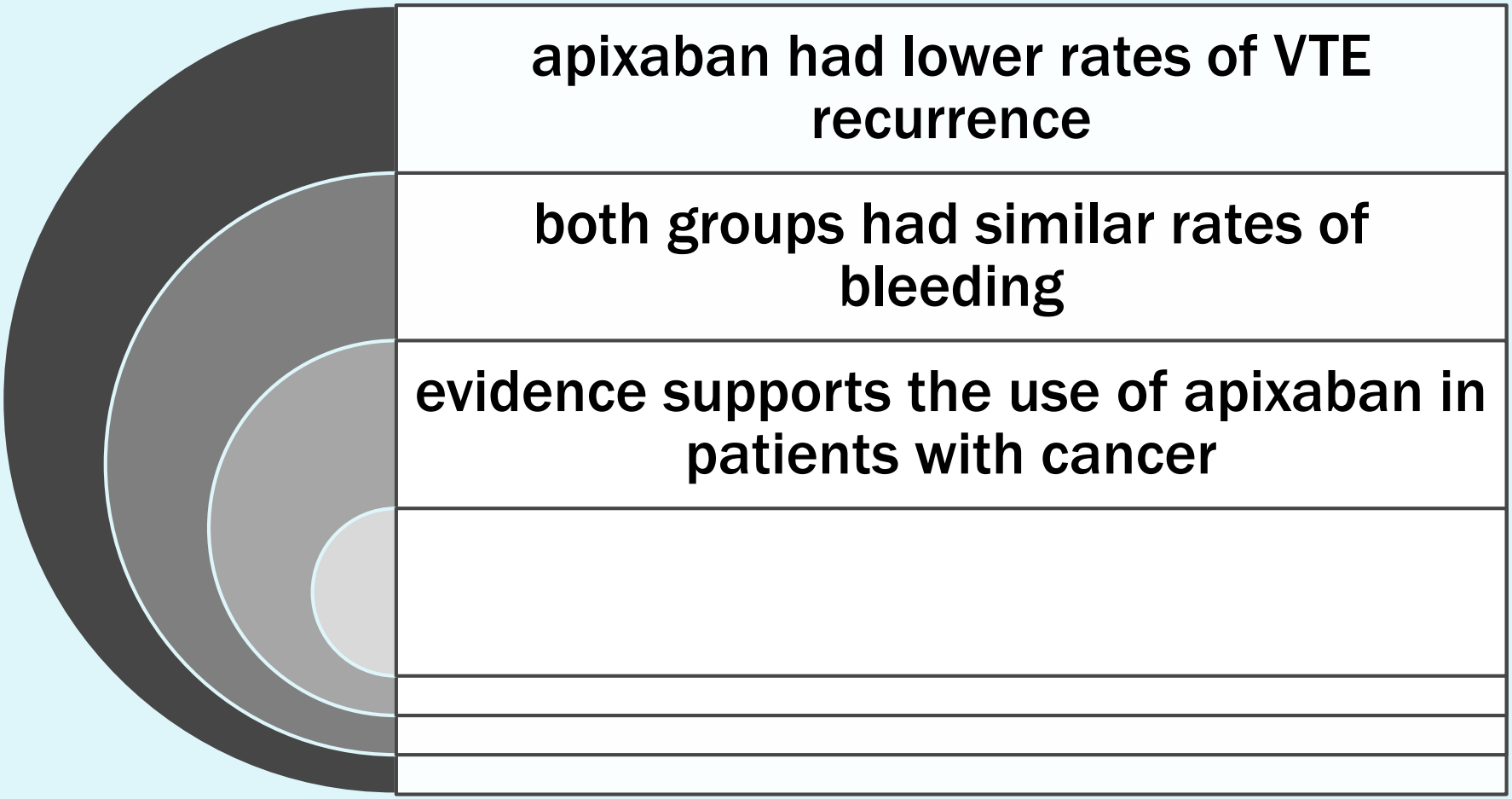
# ADAM VTE: Conclusions

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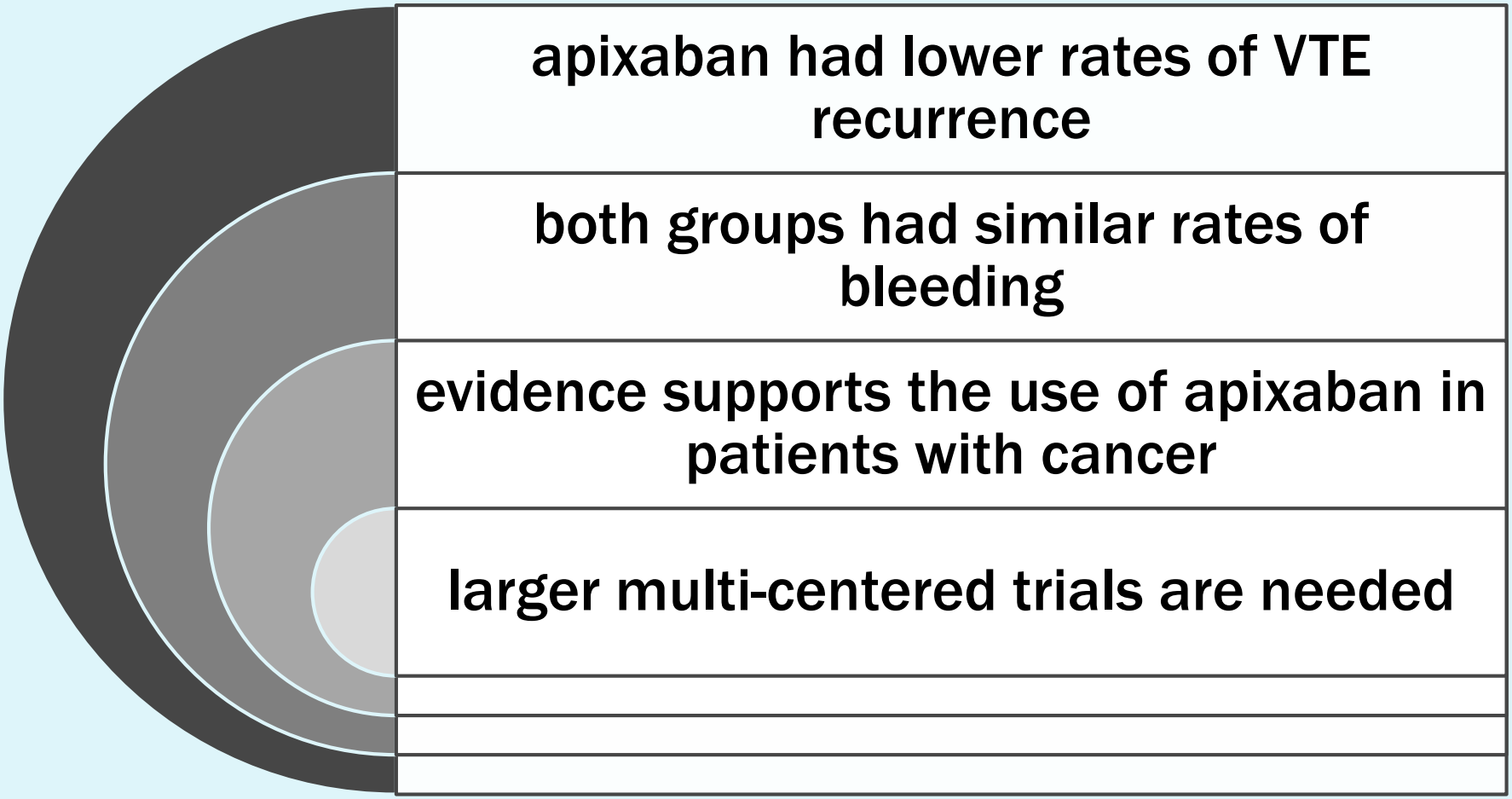
# ADAM VTE: Conclusions




Source: McBane RD, et al. Blood 2018; 132:421

# Outcomes Associated with Apixaban Use in Patients with End-Stage Kidney Disease and Atrial Fibrillation in the United States

# Background

historically excluded from DOAC clinical trials

apixaban has labeling that supports its use in this population

this study is to determine the outcomes for apixaban in patients with ESKD and a. fib



Source: Siontis KC, et al. Circulation 2018; 138:1519-1529

# Methods

retrospective cohort study

Medicare beneficiaries from October 2010 to December 2015

Source: Siontis KC, et al. Circulation 2018; 138:1519-1529

# Methods

retrospective cohort study

Medicare beneficiaries from October 2010 to December 2015

patients taking apixaban were matched to warfarin

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# Methods

retrospective cohort study

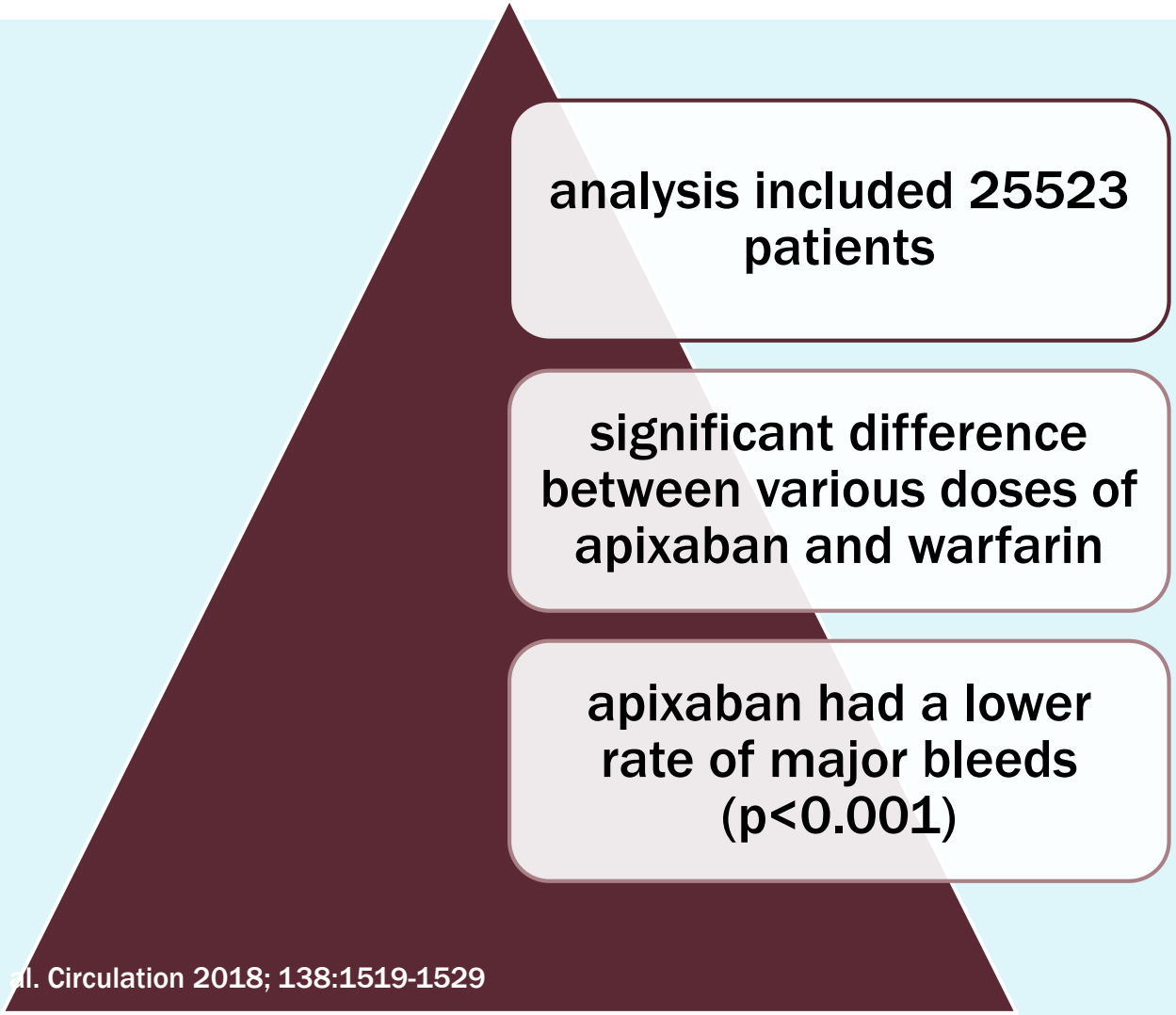
Medicare beneficiaries from October 2010 to December 2015

patients taking apixaban were matched to warfarin

differences between the groups were assessed for a variety of data points

Source: Siontis KC, et al. Circulation 2018; 138:1519-1529

# Results

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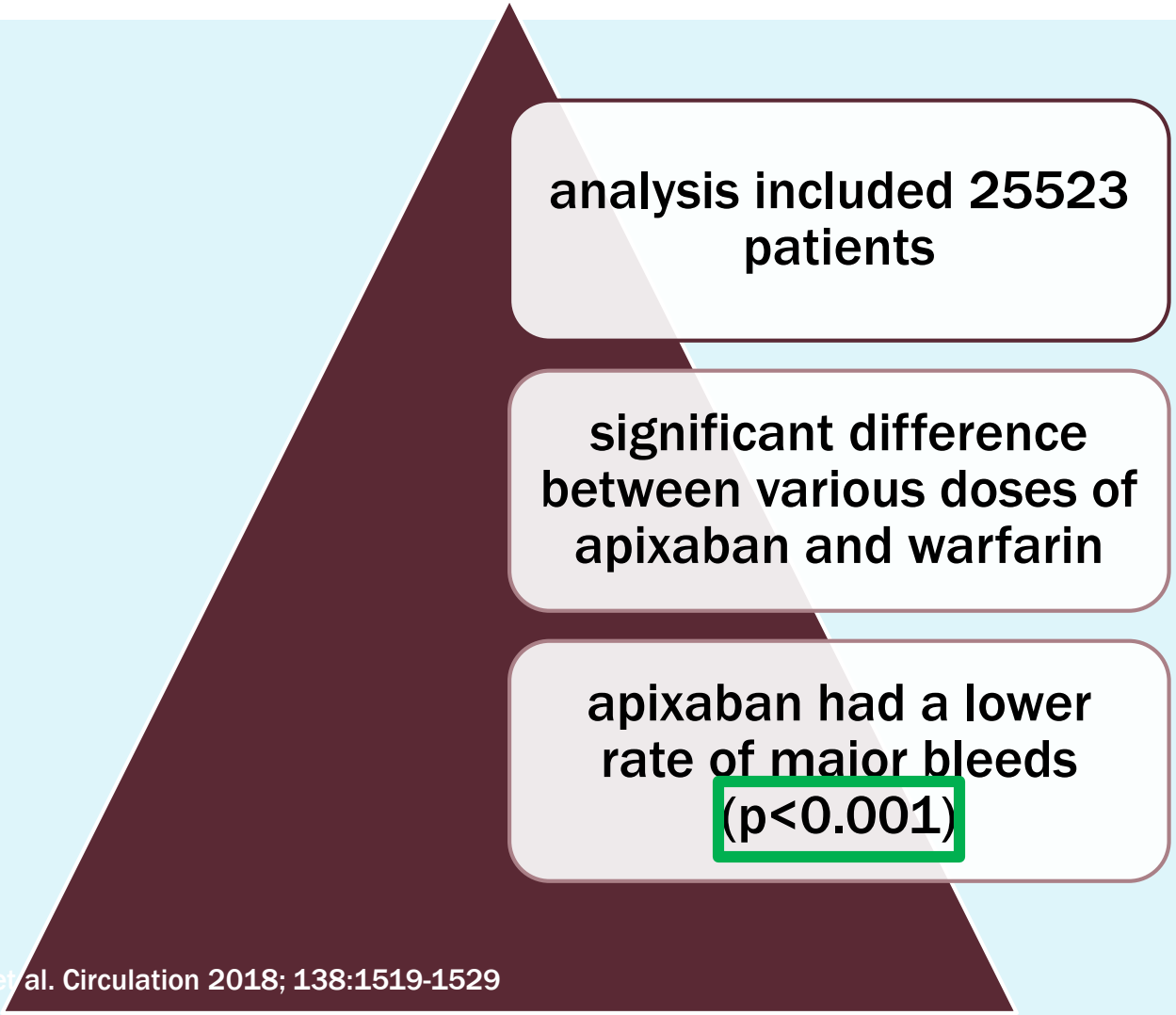
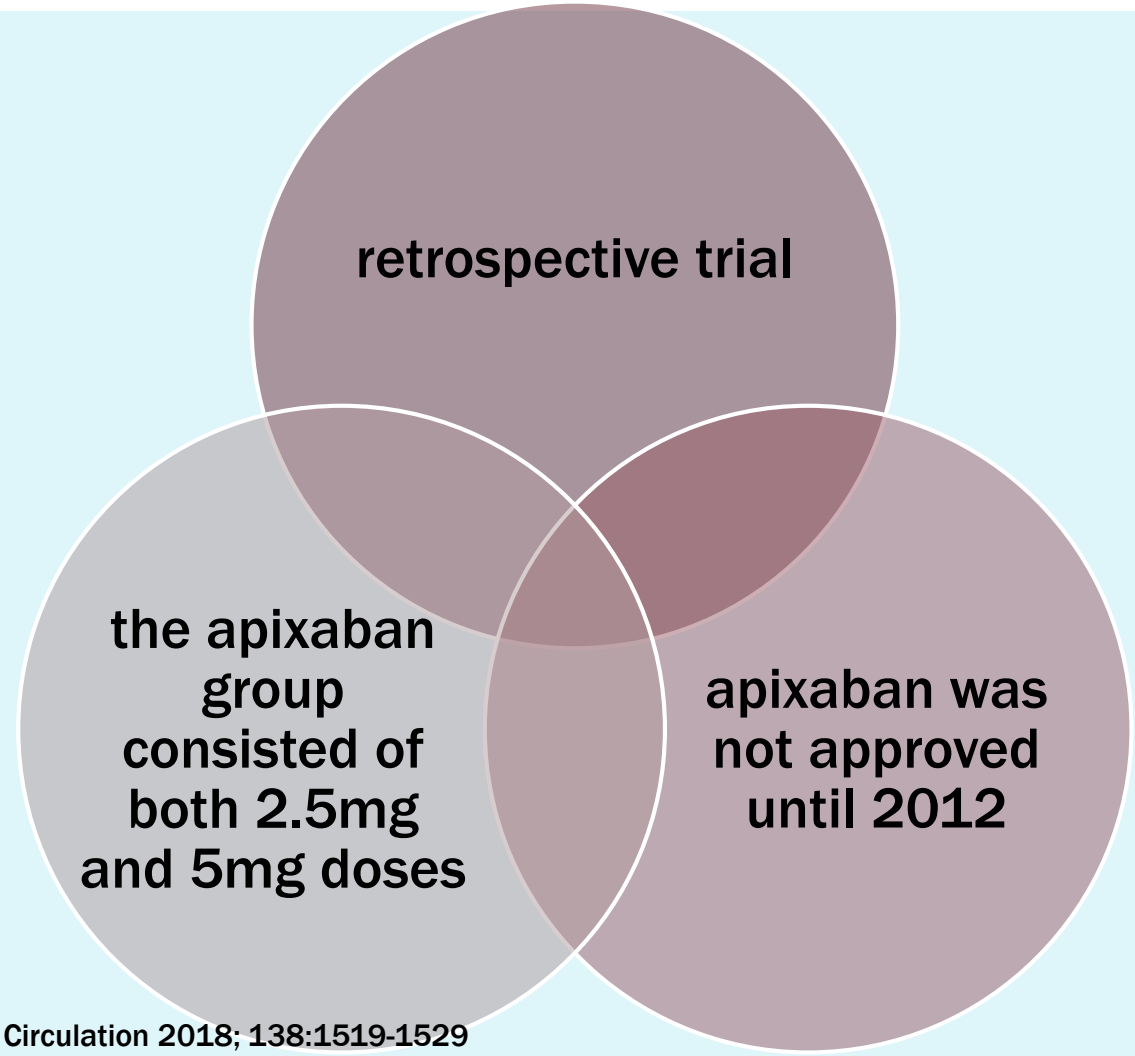


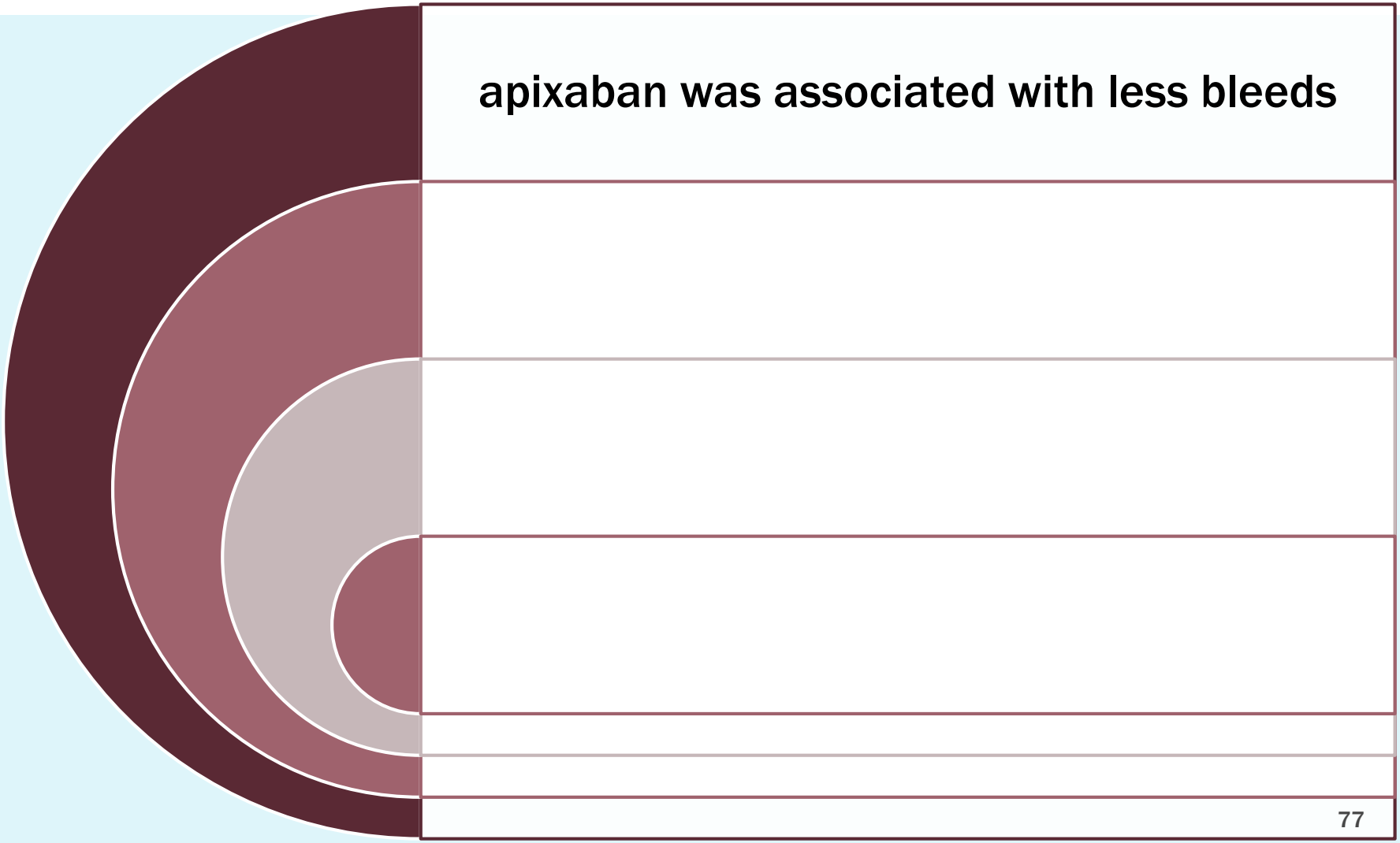

Source: Siontis KC, et al. Circulation 2018; 138:1519-1529

# Limitations




Source: Siontis KC, et al. Circulation 2018; 138:1519-1529

# Conclusions



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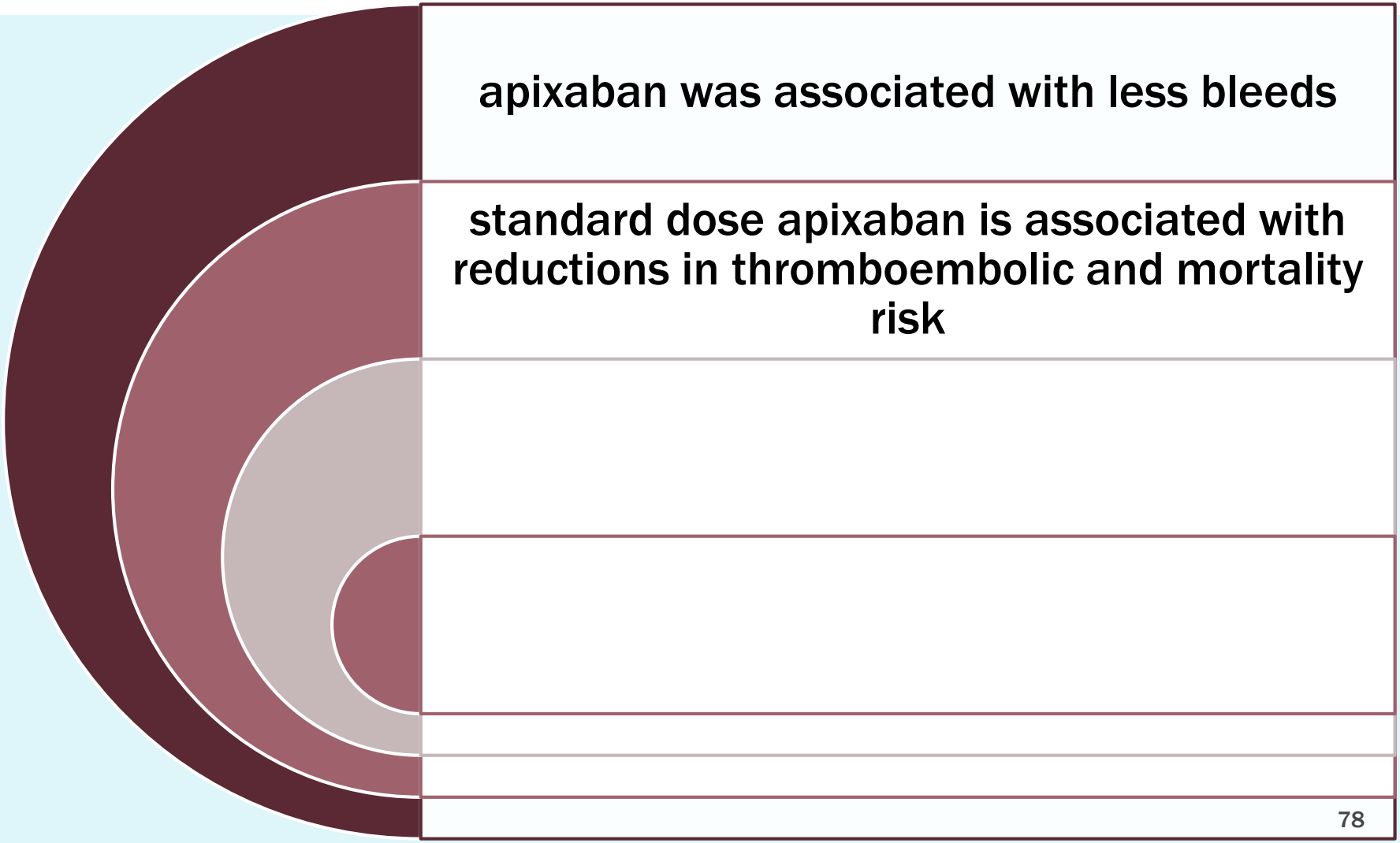




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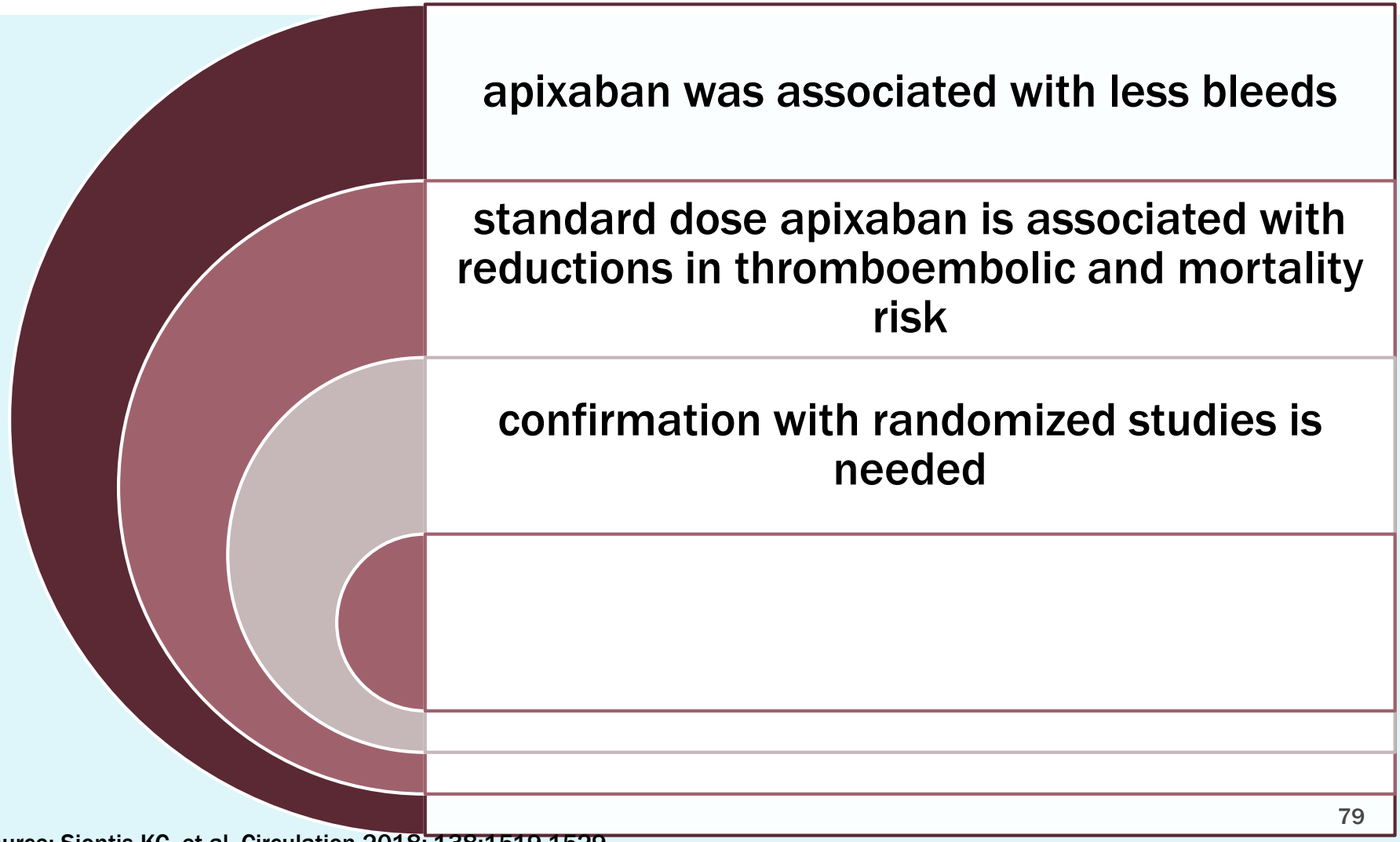




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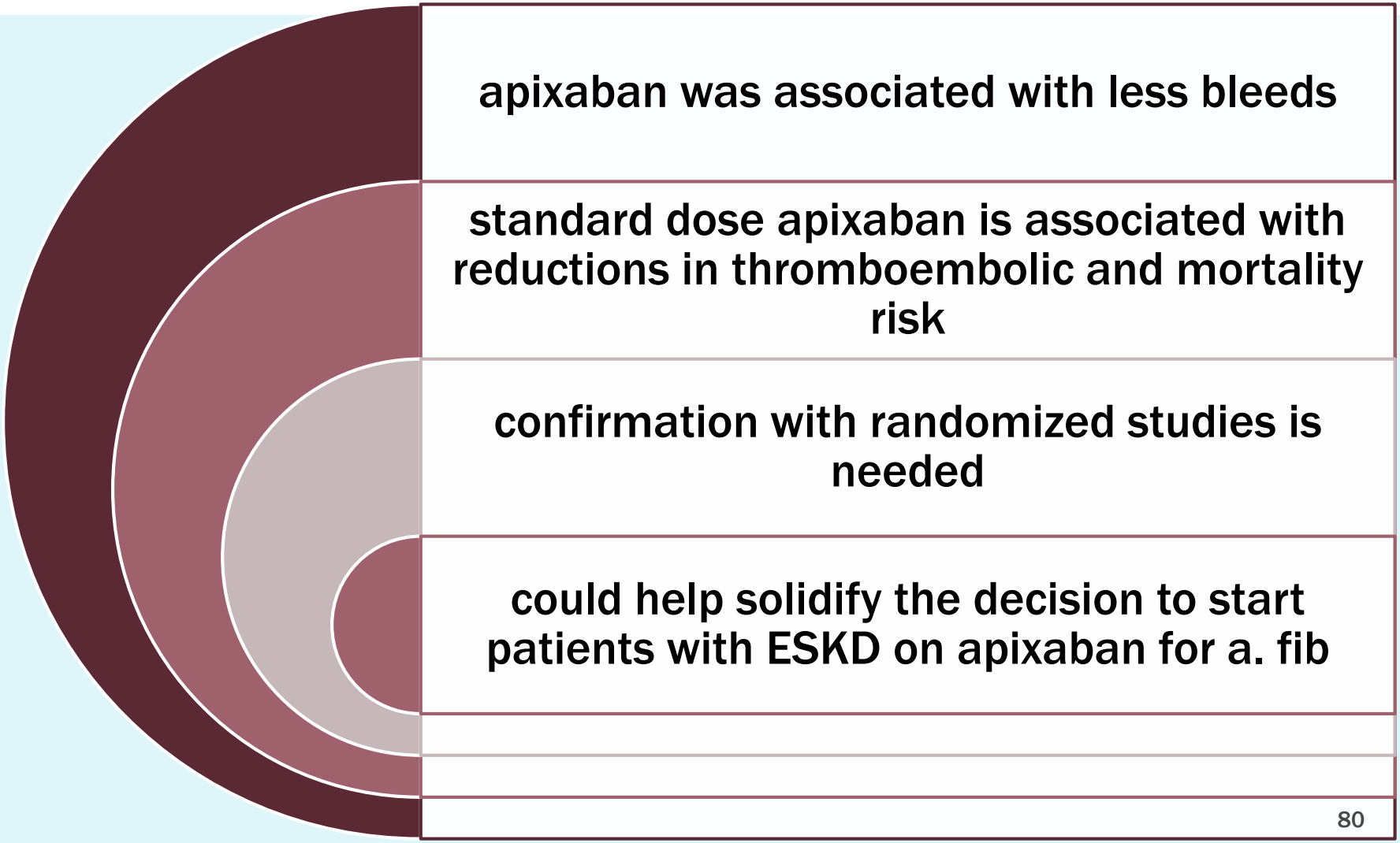




Source: Siontis KC, et al. Circulation 2018; 138:1519-1529

# Changes to Indications/Guidelines

**no changes have been made to indications or guidelines**

# Changes to Indications/Guidelines

no changes have been made to indications or guidelines

changes in practices may be seen

# Applications

## provides data to support use in difficult situations

- patients with cancer who cannot or will not use LMWH or warfarin
- patients on hemodialysis who have been unstable on warfarin or are non-compliant with the necessary follow up

# Pharmacist Assessment Question 1

What evidence currently supports the use of apixaban in patients with ESKD?

A. The ARISTOTLE, ADVANCE-2 and AMPLIFY trials
B. The ADAM-VTE Trial
C. The Outcomes Associated with Apixaban Use in Patients with ESKD and A. Fib trial and pharmacokinetic data from the manufacturer
D. No evidence currently supports the use of apixaban in ESKD patients

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# New Rivaroxaban Indications and Doses

# Rivaroxaban or Aspirin for Extended Treatment of VTE (EINSTEIN CHOICE Trial)

# EINSTEIN CHOICE: Background

patients who have experienced VTE may require extended treatment

currently no guidance for the use of anticoagulation or aspirin

Source: Weitz JI, et al. N Engl J Med 2017; 376:1211-1222

# EINSTEIN CHOICE: Methods

randomized, double blind, phase 3 trial

included patients who were being treated for VTE prophylaxis

Source: Weitz JI, et al. N Engl J Med 2017; 376:1211-1222

# EINSTEIN CHOICE: Methods

randomized, double blind, phase 3 trial

included patients who were being treated for VTE prophylaxis

10 mg or 20 mg rivaroxaban daily vs. 100 mg aspirin daily

median duration of treatment was 351 days



Source: Weitz JI, et al. N Engl J Med 2017; 376:1211-1222

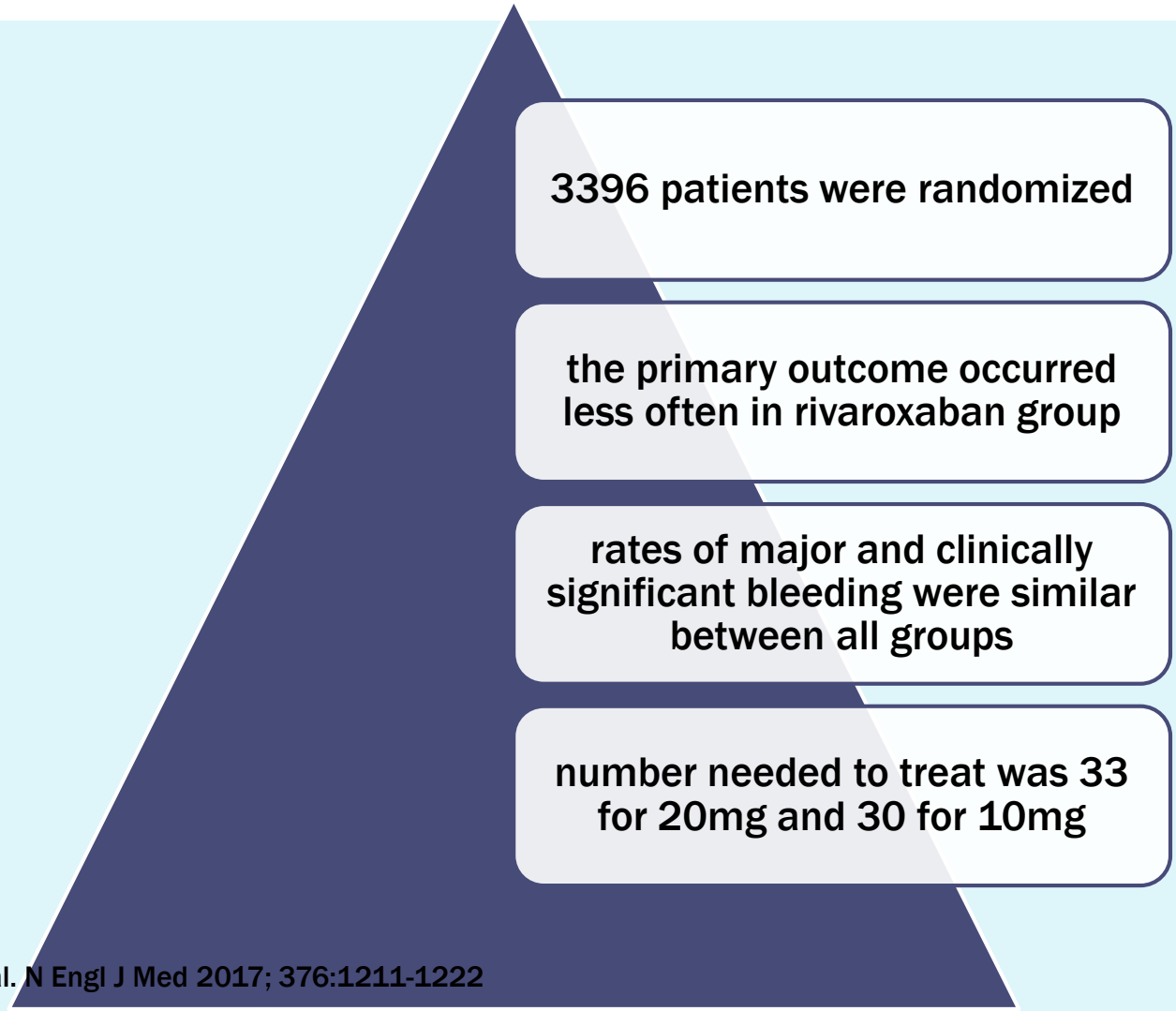
# EINSTEIN CHOICE: Methods

primary efficacy outcome: symptomatic, recurrent, fatal or nonfatal VTE

primary safety outcome: major bleeding

Source: Weitz JI, et al. N Engl J Med 2017; 376:1211-1222

# EINSTEIN CHOICE: Results




Source: Weitz JI, et al. N Engl J Med 2017; 376:1211-1222

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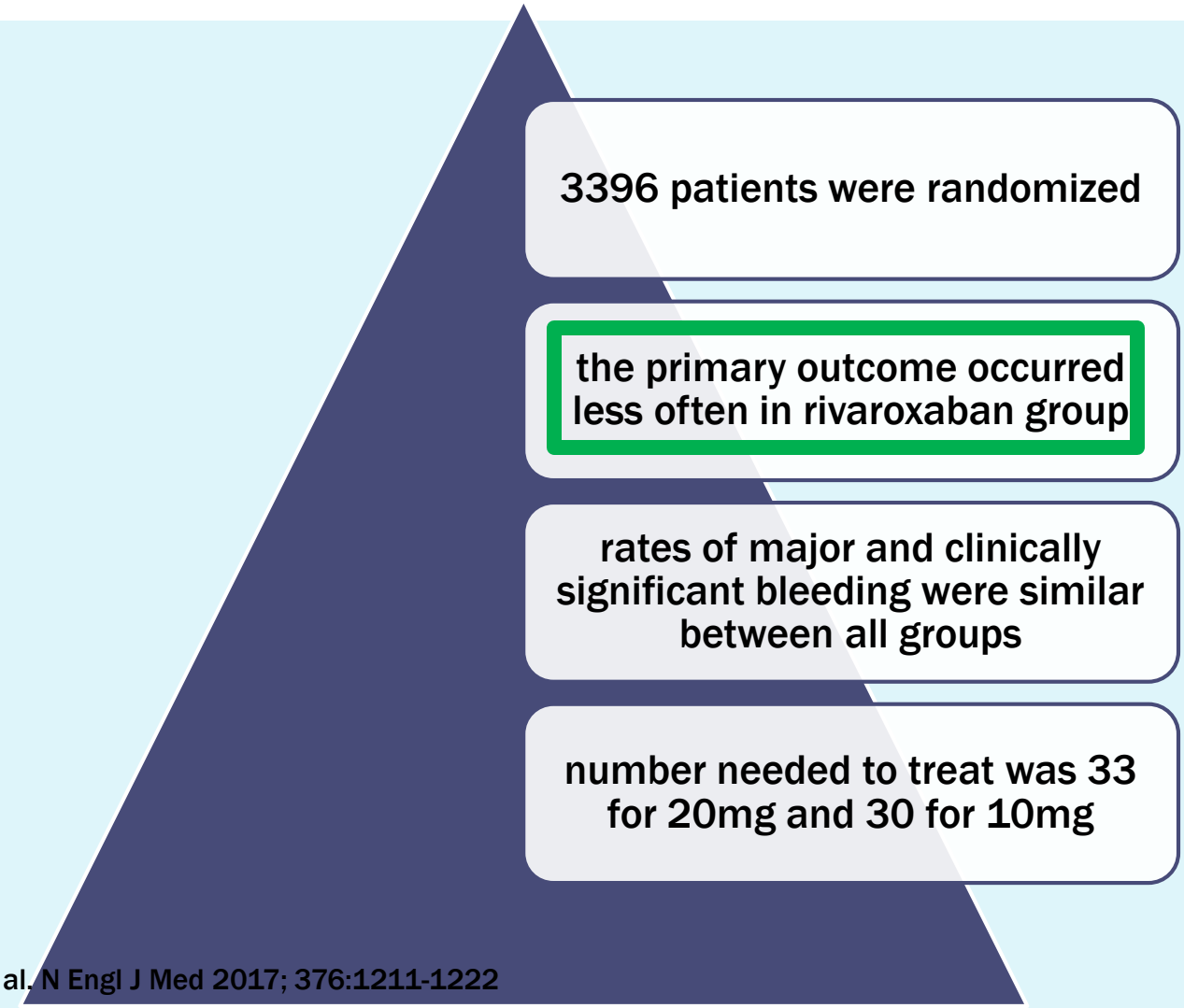


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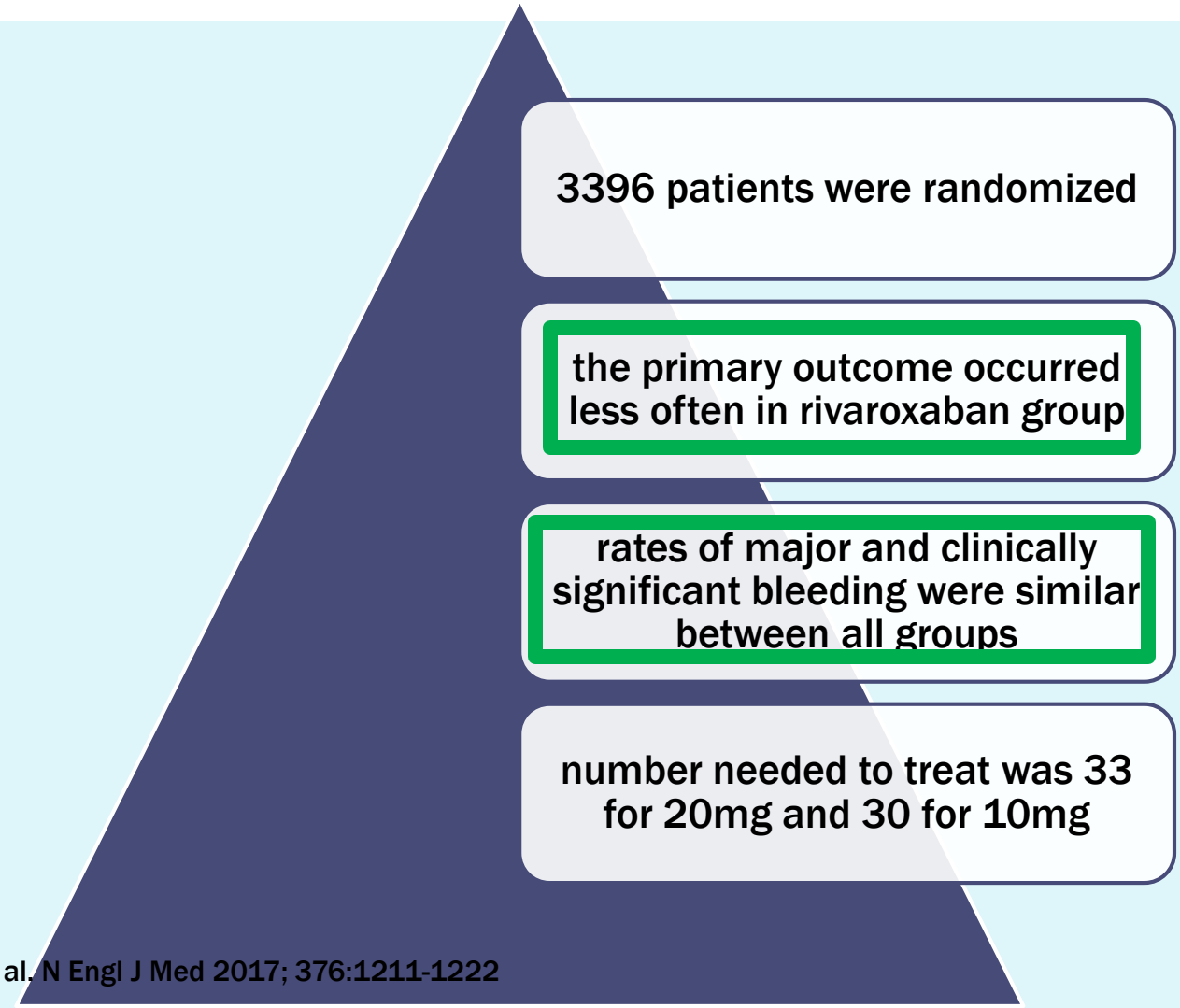
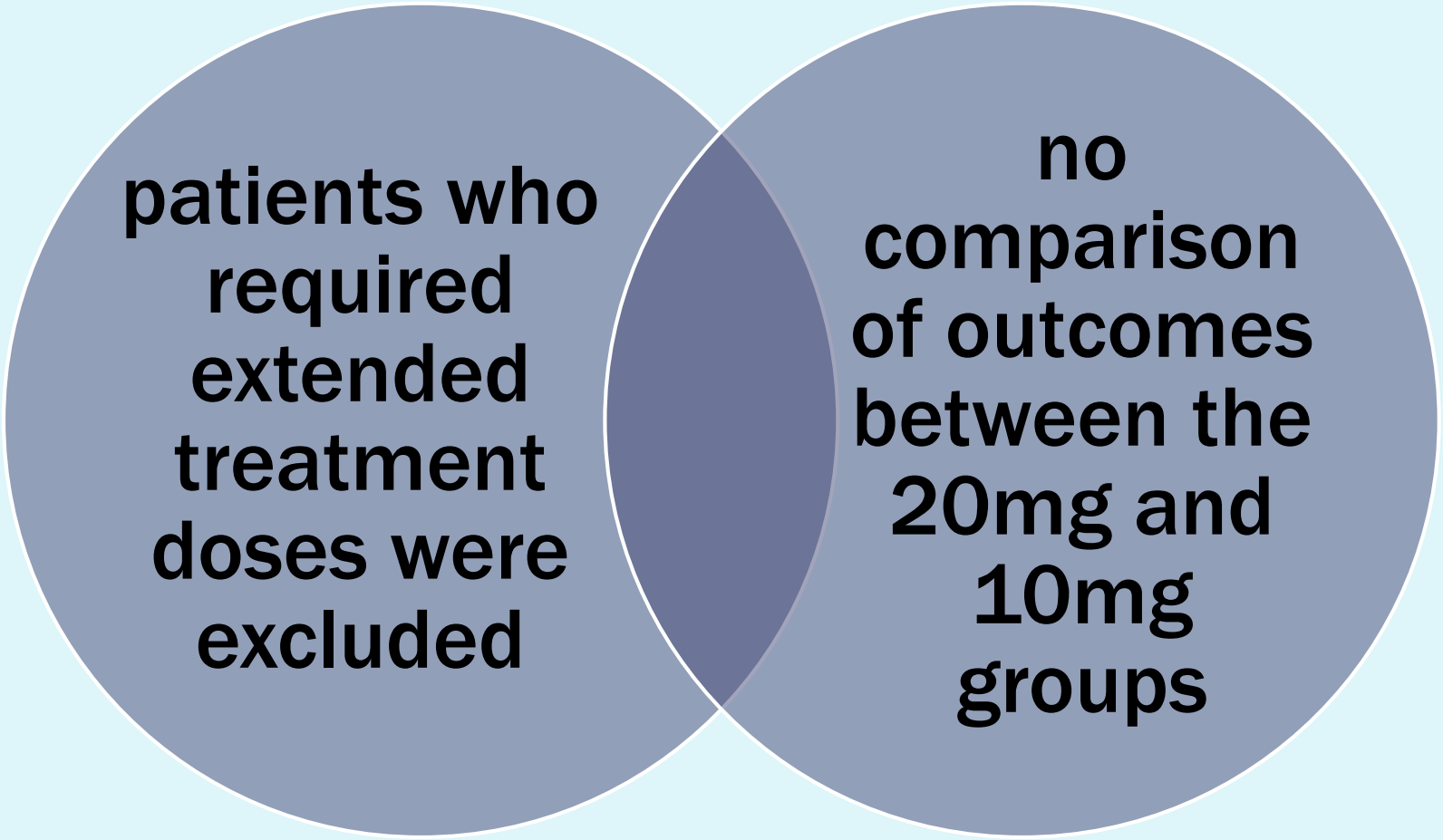


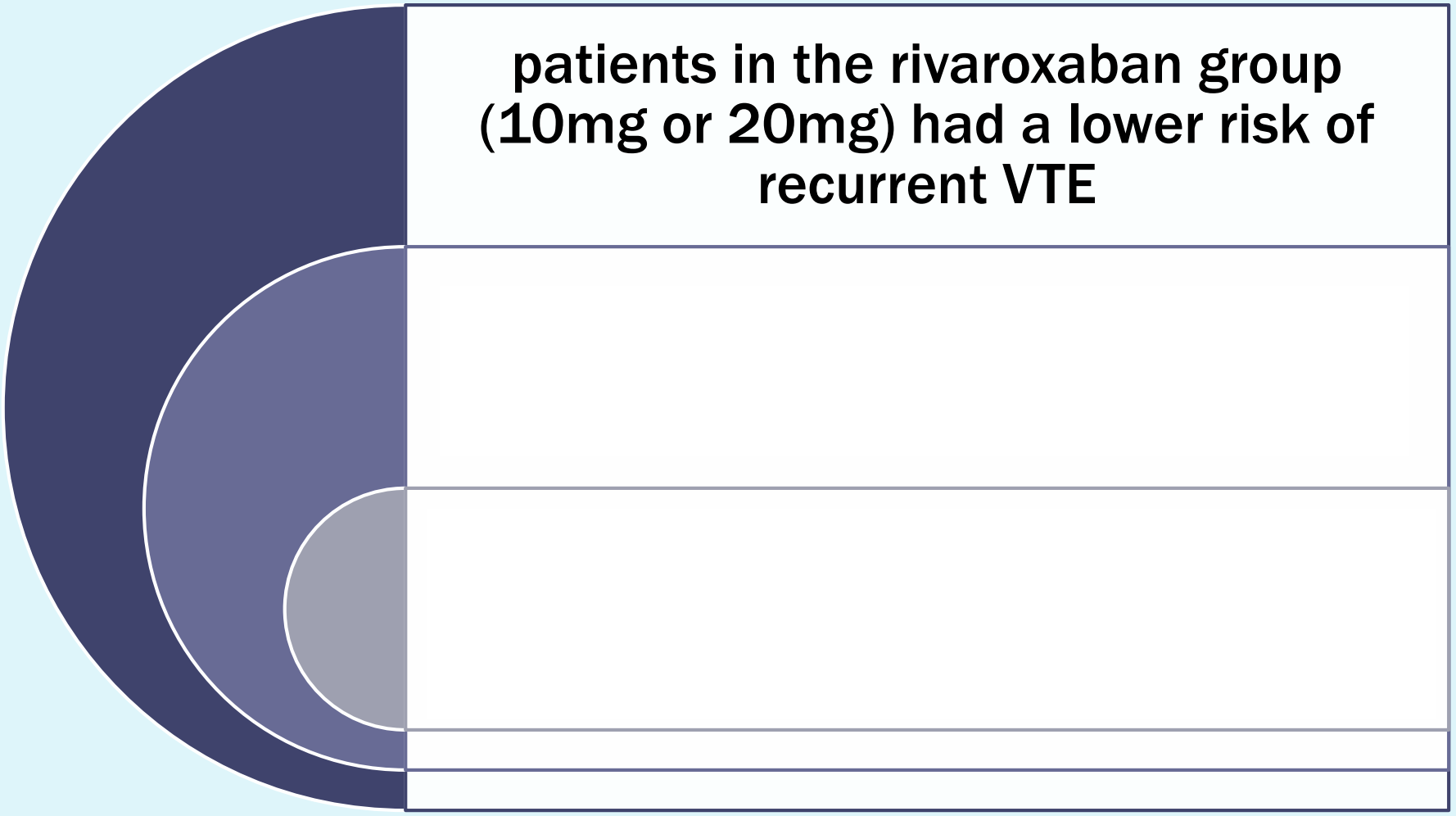

Source: Weitz JI, et al. N Engl J Med 2017; 376:1211-1222

# EINSTEIN CHOICE: Limitations




Source: Weitz JI, et al. N Engl J Med 2017; 376:1211-1222

# EINSTEIN CHOICE: Conclusions

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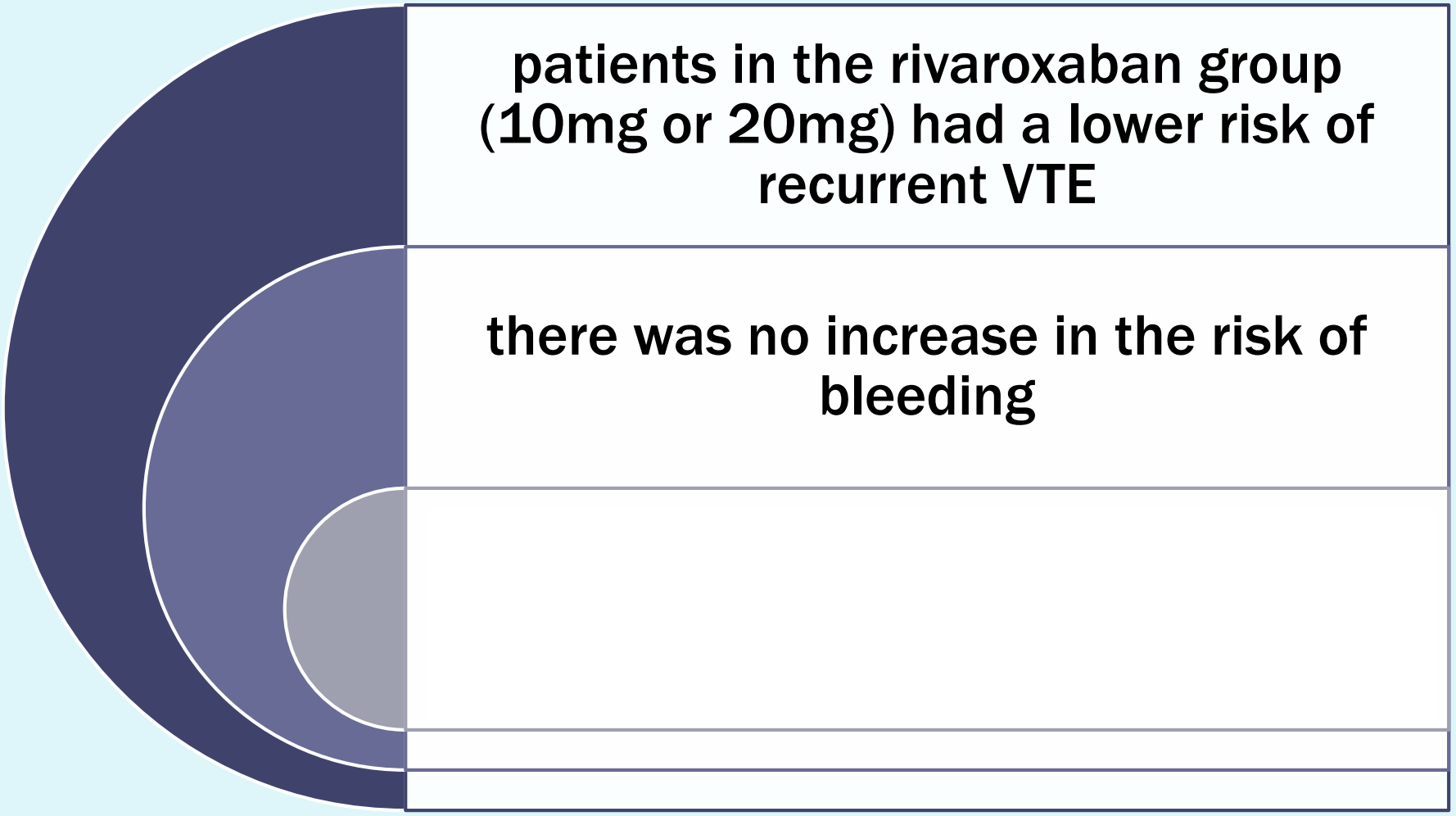


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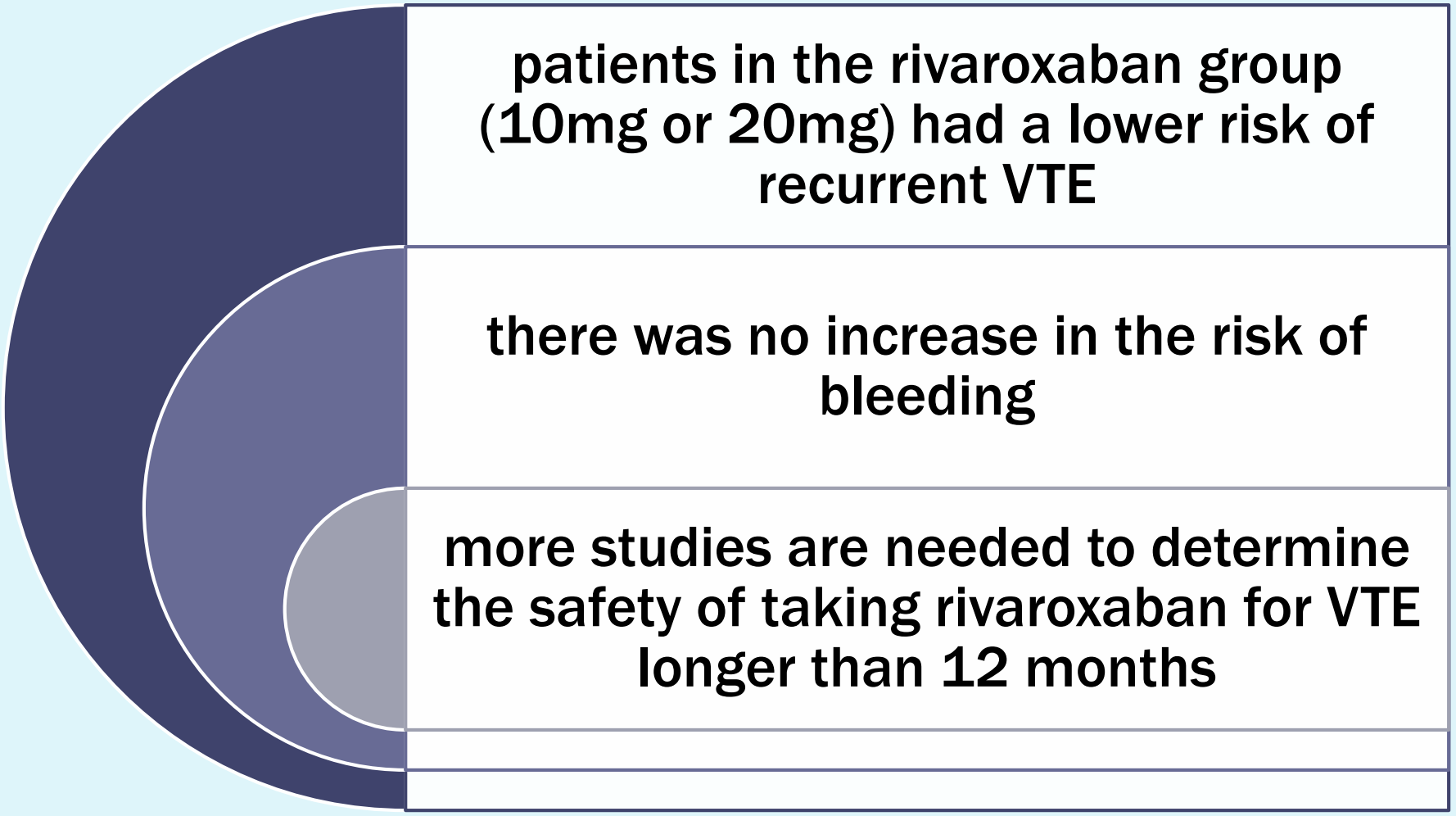


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# Rivaroxaban With or Without Aspirin in Stable Cardiovascular Disease (COMPASS Trial)

# COMPASS: Background

aspirin has traditionally been used for secondary prevention of cardiovascular outcomes in patients with cardiovascular disease

the use of a DOAC, specifically rivaroxaban, for secondary prevention in patients has not been studied previously

Source: Eikelboom JW, et al. N Engl J Med 2017; 377:1319-1330

# COMPASS: Methods

patients were included if they had documented stable atherosclerotic disease

randomized 1:1:1

rivaroxaban 2.5mg plus aspirin
rivaroxaban 5mg
aspirin 100mg



Source: Eikelboom JW, et al. N Engl J Med 2017; 377:1319-1330

# COMPASS: Methods

primary outcome: composite of cardiovascular death, stroke or MI

Source: Eikelboom JW, et al. N Engl J Med 2017; 377:1319-1330

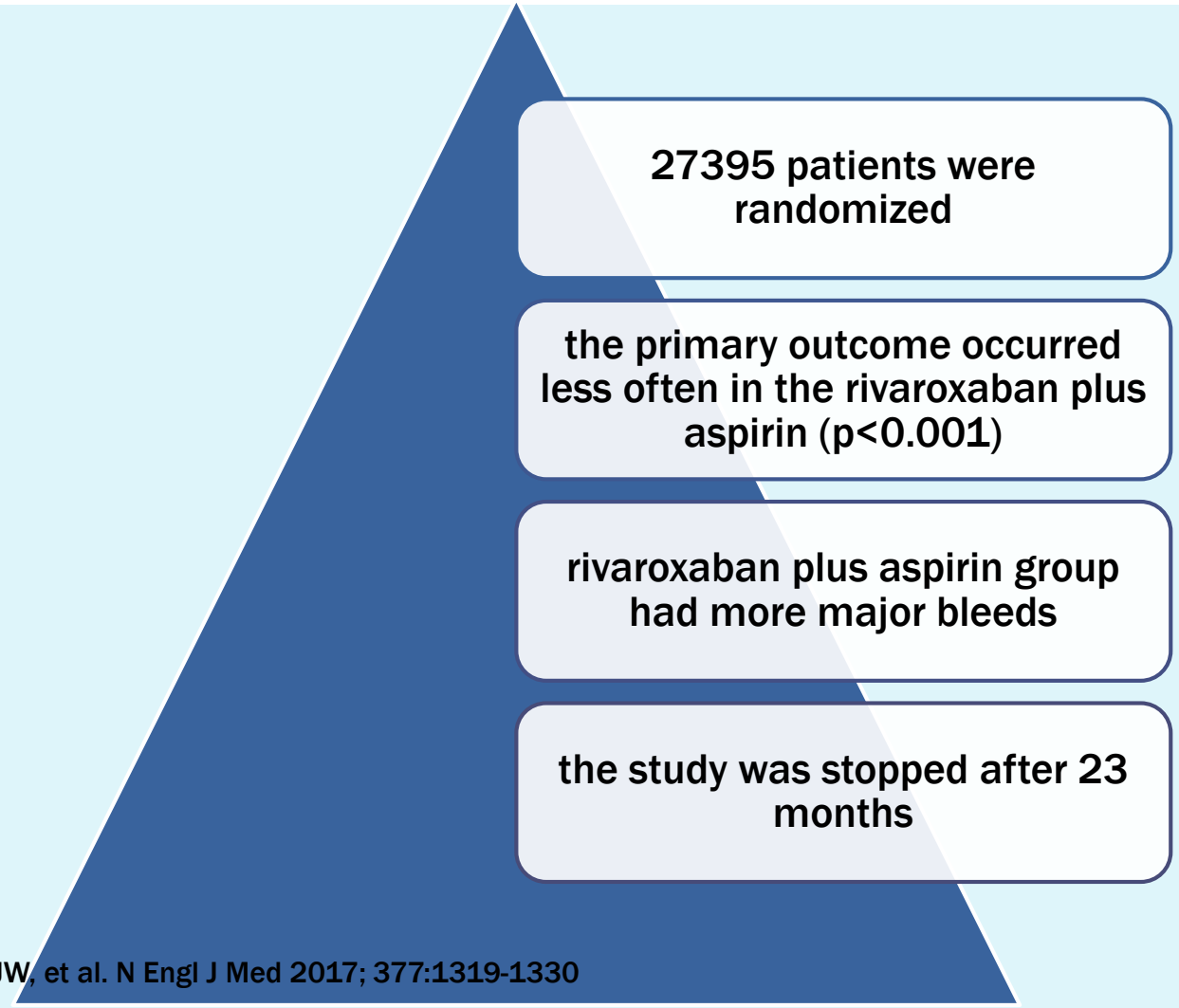
# COMPASS: Methods

primary outcome: composite of cardiovascular death, stroke or MI

safety outcome: major bleeding events

Source: Eikelboom JW, et al. N Engl J Med 2017; 377:1319-1330

# COMPASS: Results




Source: Eikelboom JW, et al. N Engl J Med 2017; 377:1319-1330

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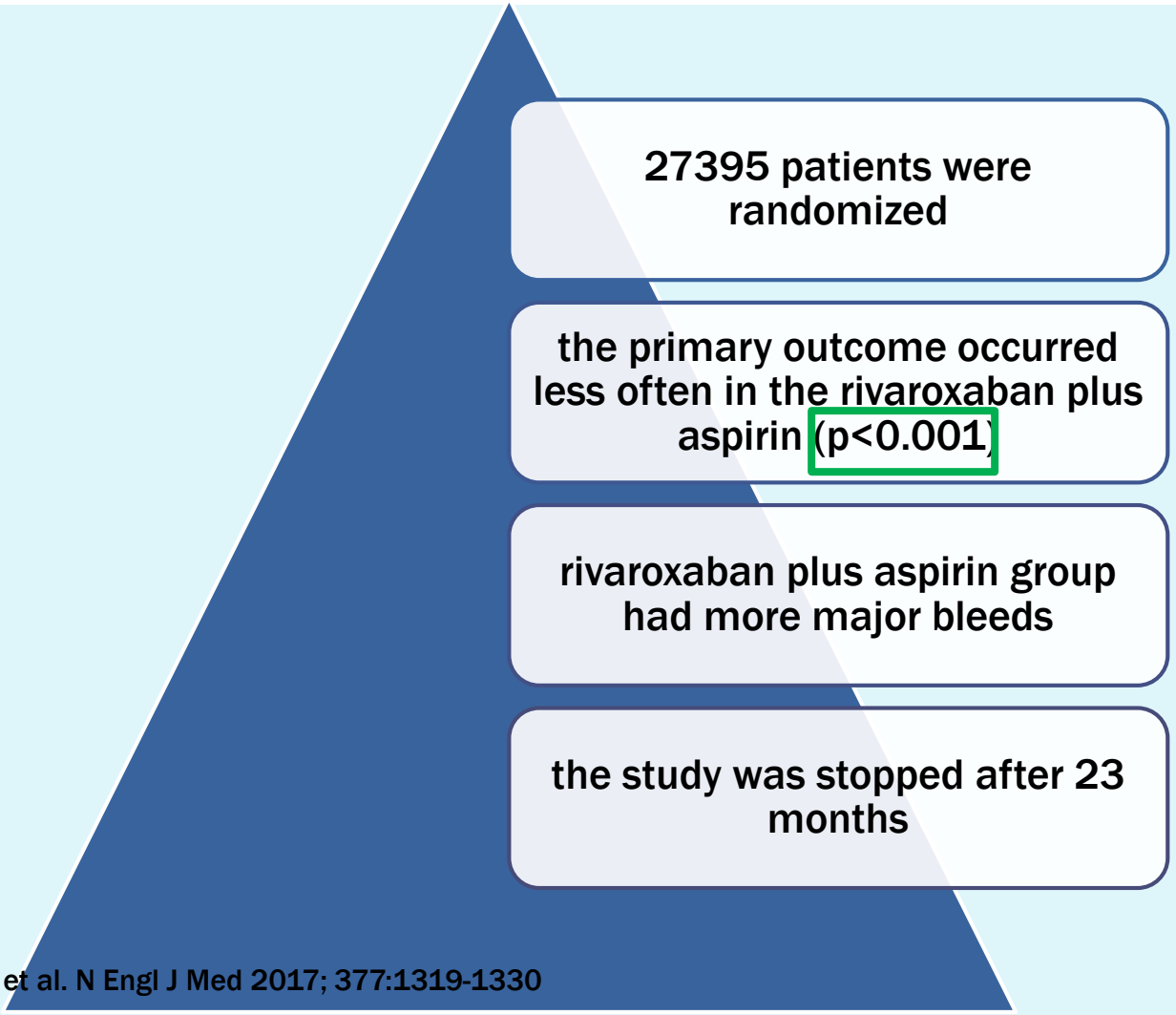
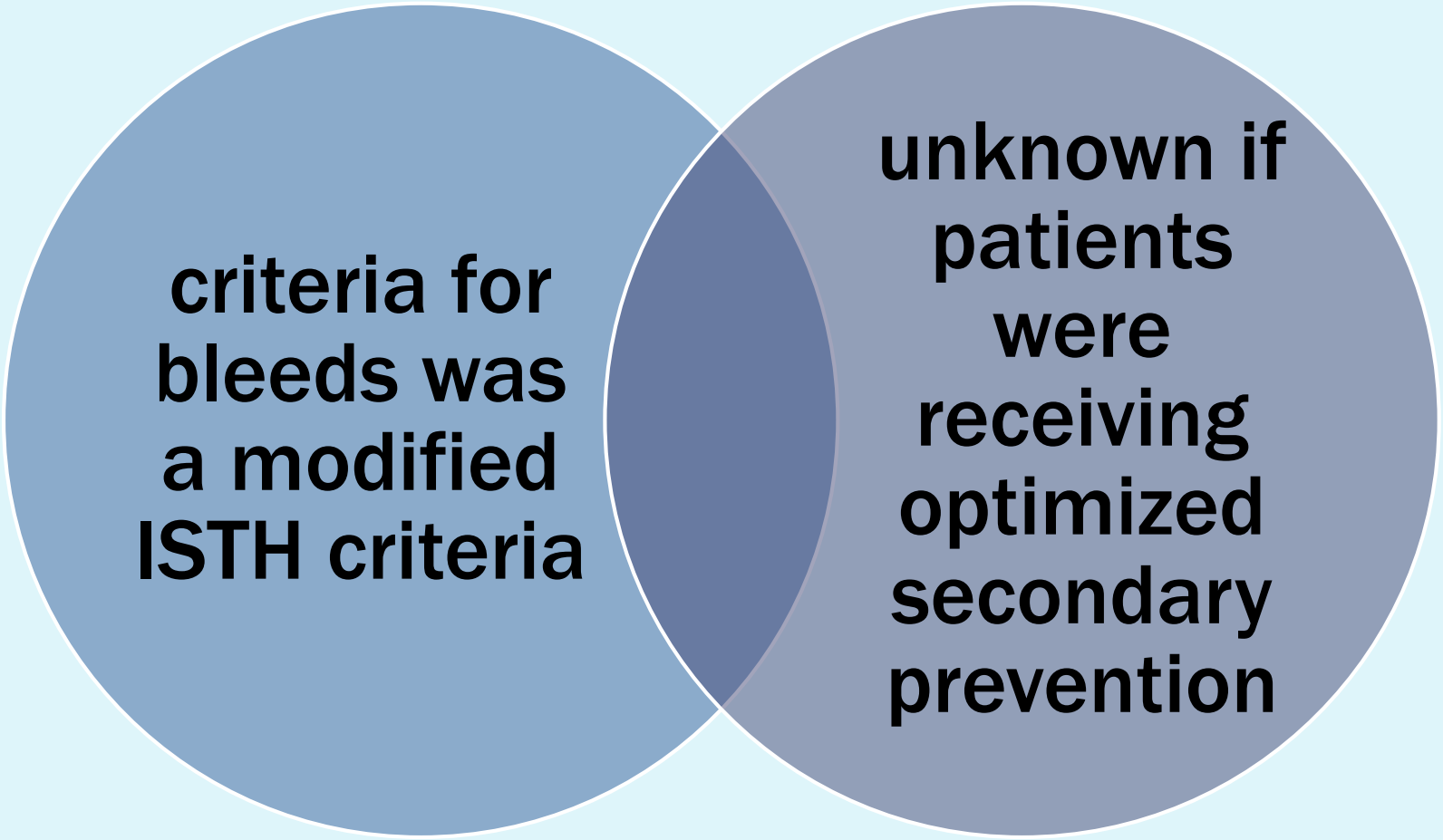



Source: Eikelboom JW, et al. N Engl J Med 2017; 377:1319-1330

# COMPASS: Limitations

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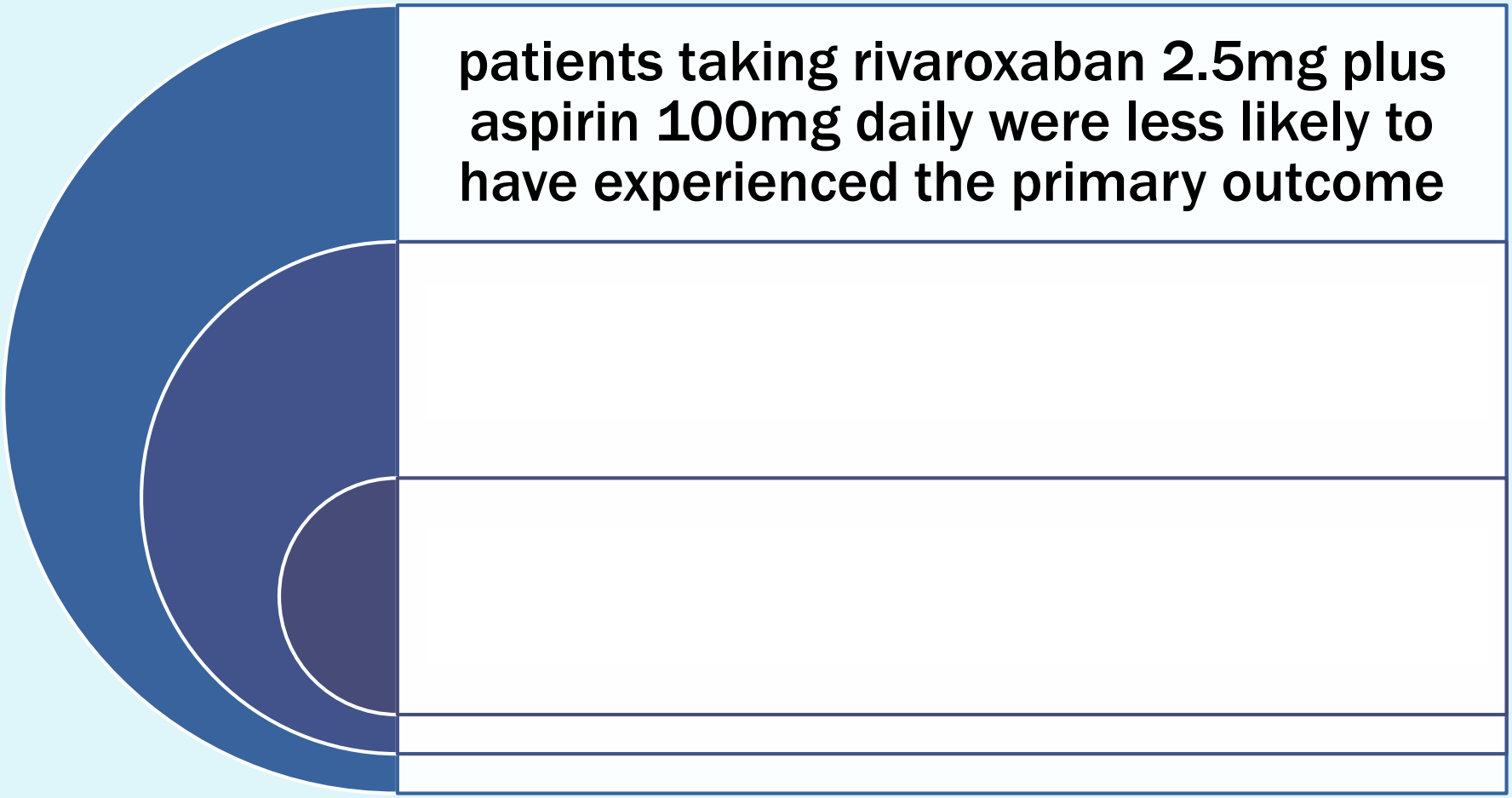


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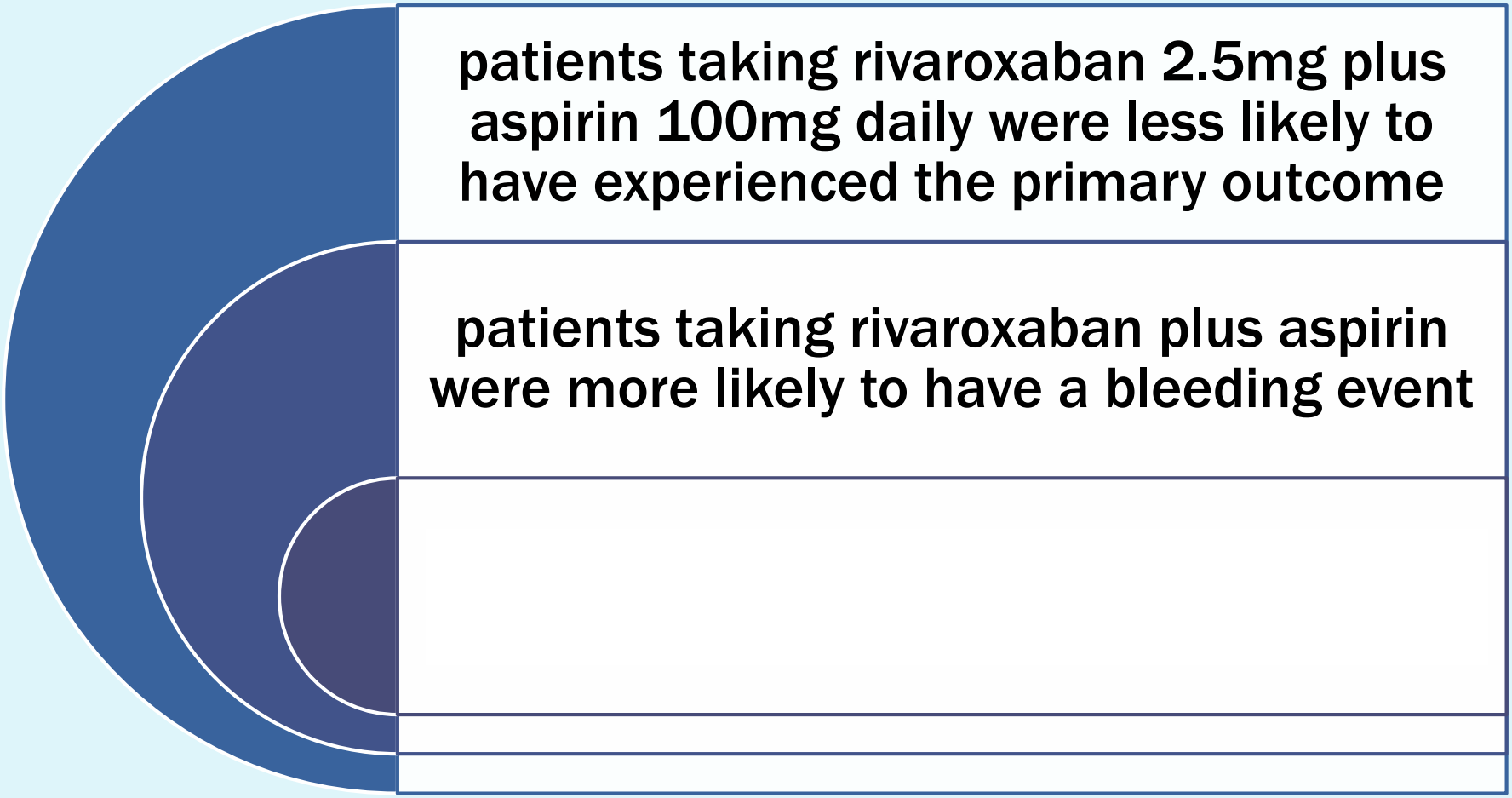


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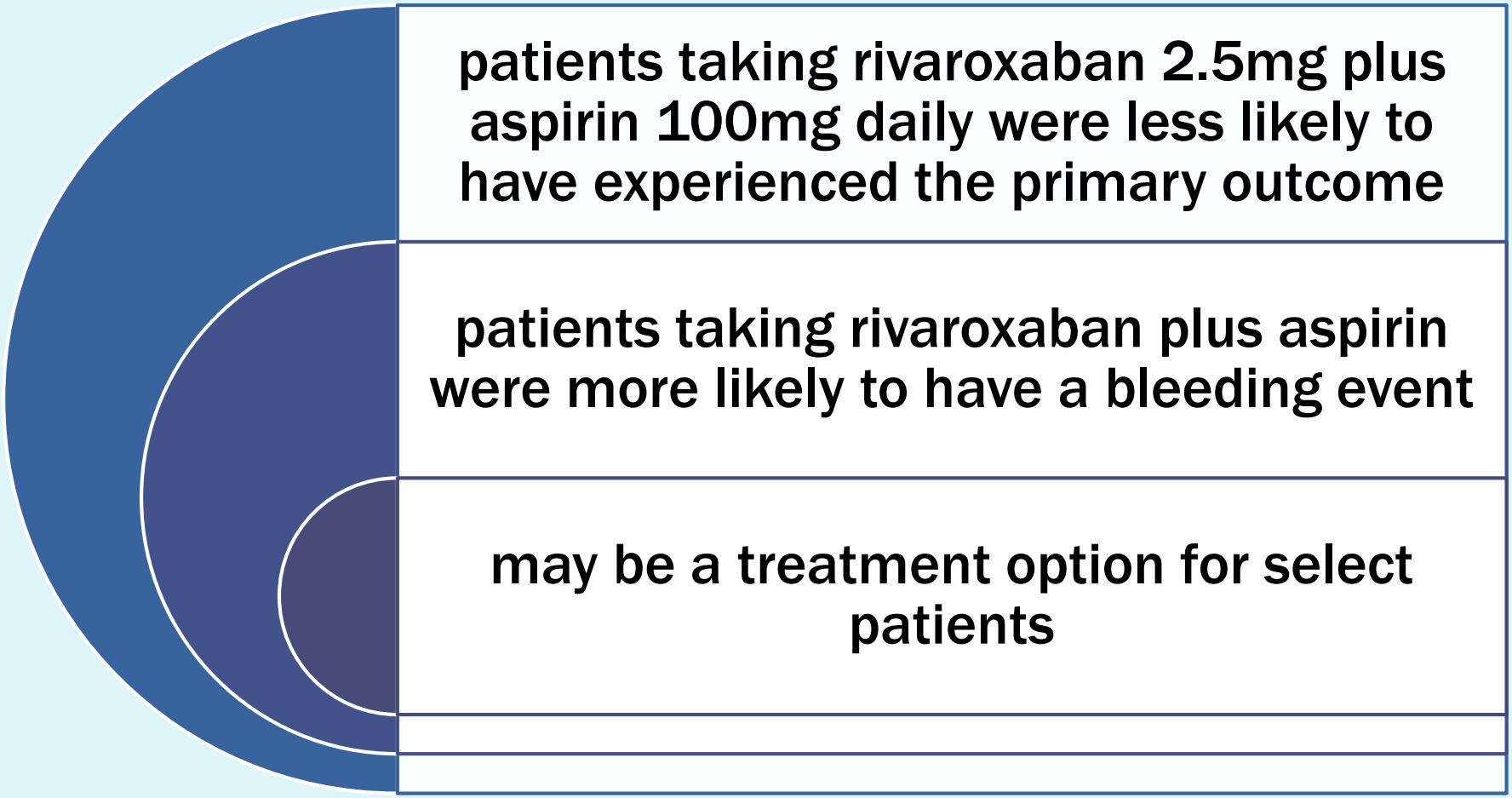


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# Changes to Indications

**reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE**

- 10mg daily with or without food

Source: Xarelto® (rivaroxaban) [package insert]. Titusville, NJ. Janssen Pharmaceutical Companies; 2011

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**reduction of risk of major cardiovascular events (CV death, MI and stroke) in patients with chronic CAD and PAD**

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# Changes to Guidelines

no change have been made to the associated guidelines at this time

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changes in practice may be seen

# Applications

- the new indications may be applied to specific patients
- rivaroxaban for the use of extended VTE prophylaxis could be beneficial for specific patient populations
- the populations to which rivaroxaban 2.5mg can be applied are less clear

# Patient Case

JD is a 74-year-old female patient who presents to your clinic for follow up about recent hospitalization for a TIA. She has a PMH of CAD, HLD and T2DM. Her medication for secondary prevention has been optimized and has been taking aspirin 81mg daily for several years. Do you suggest additional medication?

A. There is nothing else that can be started, so you do not recommend any additional medication at this time.
B. You suggest adding rivaroxaban 2.5 mg BID to her current regimen, after discussing risks and benefits
C. You suggest starting rivaroxaban 20mg once daily
D. You suggest starting warfarin therapy to prevent any further cardiovascular events

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# Technician Assessment Question

What is the new dosage form of rivaroxaban that is now available?

A. 2.5mg tablet
B. There is no new dosage form
C. 15mg tablet
D. 1mg tablet

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# Summary

# Apixaban

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- for VTE prevention and treatment in patients with active cancer
- for the prevention of stroke in patients on HD and who have atrial fibrillation

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- for the prevention of stroke in patients on HD and who have atrial fibrillation

**no new indications have been approved by the FDA**

**no updates have been made to the relevant guidelines to include the evidence for apixaban**

# Rivaroxaban

new evidence supports the use of rivaroxaban for extended DVT/PE prophylaxis

# Rivaroxaban

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- secondary prevention of cardiovascular events in patients with CAD and PAD

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# Thank you!

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