

*Canadian Society of Internal Medicine*  
*Nov 2, 2017*

# Aspirin as Venous Thromboprophylaxis

Bill Geerts, MD, FRCPC

Thromboembolism Consultant, Sunnybrook HSC  
Professor of Medicine, University of Toronto

# Disclosures (past 2 years)

<b>Investments</b>	None
<b>Research grants</b>	None
<b>Program support</b>	Bayer Healthcare, Sanofi
<b>Advisory boards, consultancies</b>	Bayer Healthcare, Covidien, Jansen, Pfizer, Sanofi
<b>Honoraria for education</b>	Bayer Healthcare, Leo Pharma, Sanofi
<b>Humor in my presentations</b>	I wish there was more!

# Objectives

**To review recent evidence for the use of aspirin to prevent VTE:**

- **Aspirin as a thromboprophylaxis agent**
- **Evidence for aspirin as primary venous thromboprophylaxis**
- **Recommendations**
- **Aspirin to prevent recurrent VTE**

# Objectives

**The main studies I will review are:**

- **POISE-2**
- **EPCAT-1, EPCAT-2**
- **PEPPER**
- **WARFASA, ASPIRE, EINSTEIN CHOICE**

# Aspirin

---

- **1897:** ASA discovered by Felix Hoffmann, a chemist with Friedrich Bayer & Co. (*their 1<sup>st</sup> major product*)
- **1899:** marketed under the trade name “aspirin” for pain, fever, inflammation
- **1962:** aspirin shown to inhibit platelets
- **1994:** Antiplatelet Trialists’ Collaboration
- **2000:** PEP Trial
- **2013, 2017:** EPCAT trials

# Aspirin as Thromboprophylaxis

## *Rationale*

---

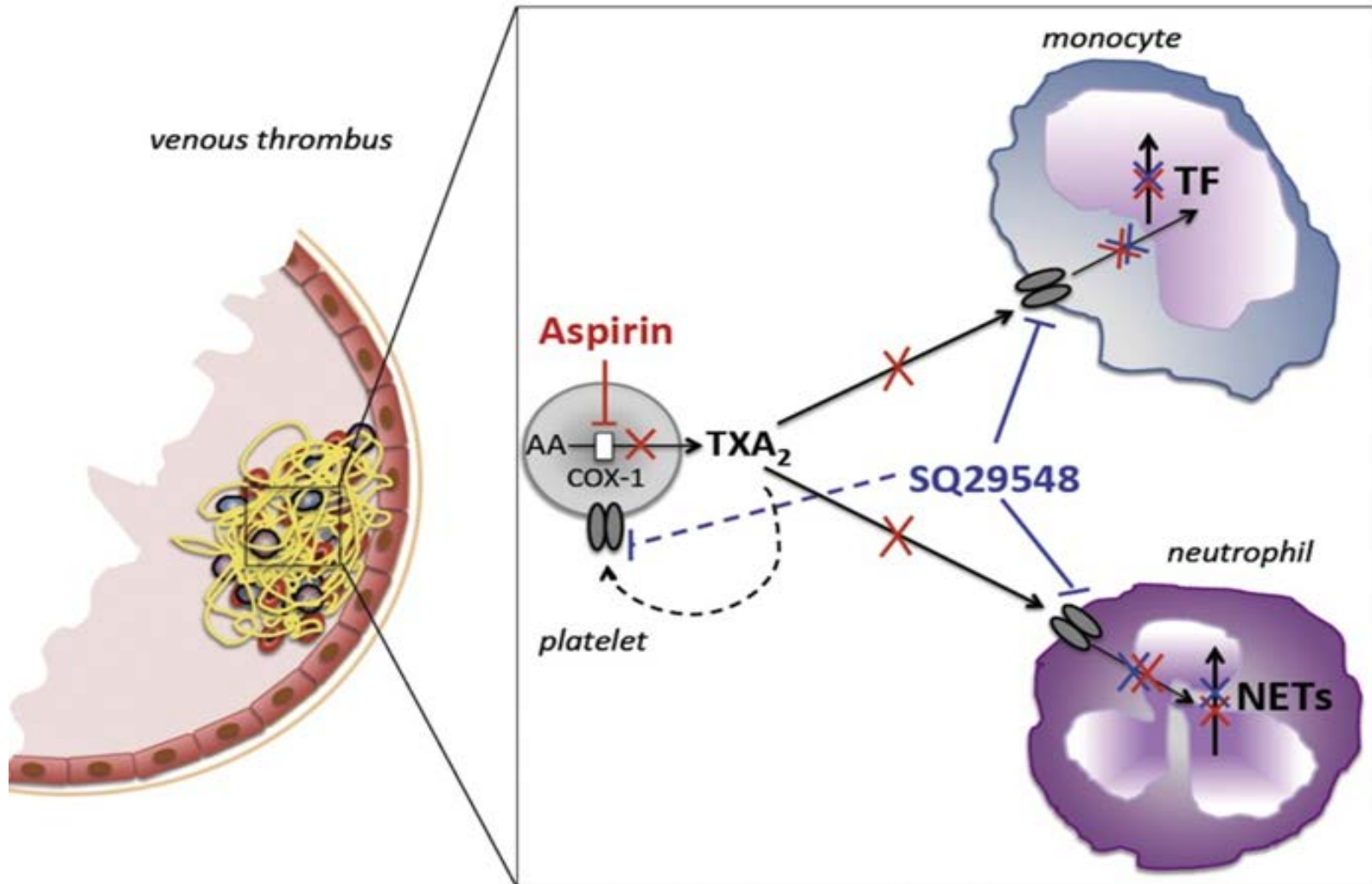
- Platelet activation has a major role in both arterial and venous thrombosis
- Aspirin reduces arterial thromboembolic events in coronary and cerebrovascular disease and is standard of care [*Antithrombotic Trialists' Collaboration – Lancet 2009;373:1849, Eikelboom – Chest 2012;141(2 Suppl):e89S, Tanguay – Can J Cardiol 2013;29:1334*]
- Some older studies and meta-analyses show that ASA can reduce venous TE [*APTC – BMJ 1994;308:235, PEP – Lancet 2000;355:1295*]

# *How* does aspirin prevent VTE?

---

- **Platelet activation has a major role in thrombosis** [*Davi – NEJM 2007;357:2482; Heestermans – Blood 2016;127:2630*]
- **Aspirin irreversibly inhibits platelet cyclooxygenase → suppresses TXA<sub>2</sub> production → reduces platelet activation and aggregation** [*Patrono – JACC 2015;66:74; Tarantino – Pharmacol Res 2016;107:415*]
- **Aspirin may inhibit thrombin generation and thrombosis** [*Herbert – Blood 1992;80:2281; van Bruhl – J Exp Med 2012;209:819; Tarantino – Pharmacol Res 2016;107:415*]

# Aspirin and Venous Thrombosis





# *Advantages* of Aspirin as Thromboprophylaxis

---

- 1. Demonstrated antithrombotic effect**
- 2. Few side effects**
- 3. Easy to use (including post-discharge)**
- 4. Low cost (<10 ¢/tablet)**

# *Adverse Effects* of Aspirin

---

1. Bleeding (low absolute rates):
  - **GI bleeding** ↑ 60-70% - dose-related + risk greatest early - case fatality rates 5-10% - PPIs ↓ GIB ≥50%<sup>1</sup>
  - **Major bleeding** ↑ 60-70%<sup>1</sup>
  - **Bleeding requiring transfusion** ↑ 21% in hip fracture<sup>2</sup>
  - **Hemorrhagic stroke** – rare (0.03%/yr)<sup>3</sup>
2. Allergy

1. Thorat – *Eur J Epidem* 2015;30:5  
2. PEP Trial – *Lancet* 2000;355:1295  
3. ATTC - *Lancet* 2009;373:1849

# POISE-2 Trial

- Aspirin vs placebo in 10,100 noncardiac surgery patients from 135 centers in 23 countries
- Aspirin 200 mg 2-4 hr preop → 100 mg daily x 30 d
- No routine screening for asymptomatic DVT

Outcomes at 30 days	Placebo (n=5,012)	Aspirin (n=4,998)	HR
Death			
VTE			
Severe PE			
Major bleeding			

# POISE-2 Trial

- Aspirin vs placebo in 10,100 noncardiac surgery patients from 135 centers in 23 countries
- Aspirin 200 mg 2-4 hr preop → 100 mg daily x 30 d
- No routine screening for asymptomatic DVT

Outcomes at 30 days	Placebo (n=5,012)	Aspirin (n=4,998)	HR
Death	60 (1.2%)	65 (1.3%)	1.05 [0.74-1.49]
VTE	60 (1.2%)	53 (1.1%)	0.89 [0.61-1.28]
Severe PE	13 (0.3%)	9 (0.2%)	0.69 [0.30-1.62]
Major bleeding	256 (5.1%)	312 (6.3%)	1.22 [1.04-1.44]

- Aspirin did not reduce VTE (or any vascular events) but increased bleeding

# VTE in *Major Orthopedic Surgery (MOS)*

---

- MOS is “**high risk**” for VTE
- Thromboprophylaxis is **standard of care**
- **Sympt. VTE without prophylaxis unknown**
- **Sympt. VTE with prophylaxis: 0.5-2.5%**
- **Clinical practice has changed past 20 yrs**
- Perception by some of **↑ bleeding, wound complications with LMWH, DOACs**
- **Most VTE present after discharge**

# Aspirin in Major Orthopedic Surgery

---

- **Aspirin 600 mg BID reduced DVT in THA**  
*[Harris – NEJM 1977;297:1246]*
- **Antiplatelet Trialists showed a 23% reduction in VTE in 1,761 major orthopedic patients** *[APTC – BMJ 1994;308:235]*
- **Several studies show that ASA + IPC as effective as warfarin or LMWH**
- **Both AAOS and ACCP consider aspirin an acceptable option in THA/TKA** *[AAOS – 2011; Falck-Ytter – Chest 2012;141:e278S]*

# Aspirin as Thromboprophylaxis

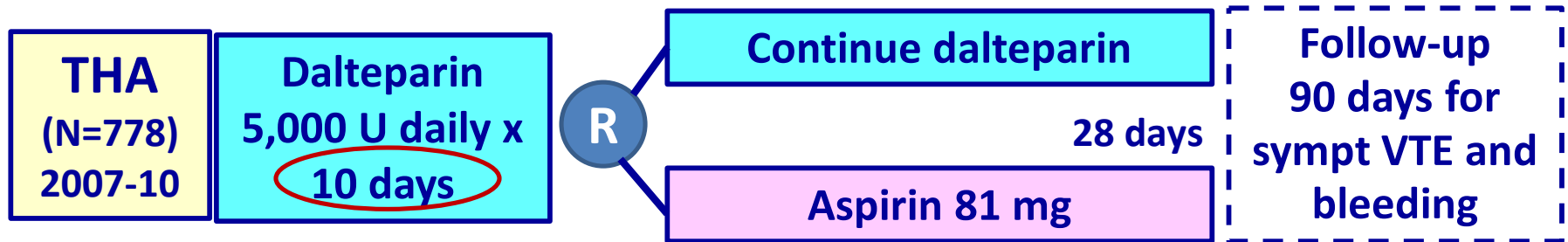
---

## Limitations of Evidence:

- **Few, small, old RCTs**
  - **Most serious methodological limitations**
  - **Aspirin doses 200-3,000 mg/day**
  - **Variable, sometimes contradictory results**
  - **Many trials negative**
  - **Aspirin often part of multimodal therapy**
- ∴ Evidence supporting aspirin alone is weak**

# EPCAT I Study

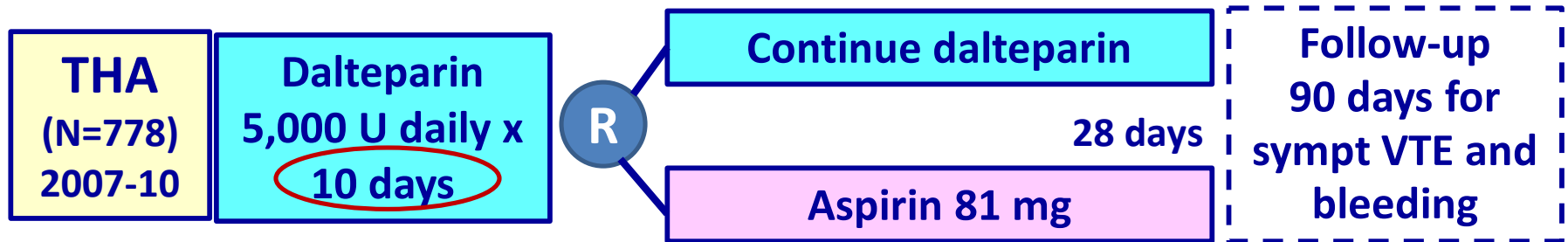
- Double-blind RCT in 12 Canadian centers





# EPCAT I Study

- Double-blind RCT in 12 Canadian centers



Outcomes Day 10-90	dalteparin (n=400)	aspirin (n=386)	<i>p</i>
Symptomatic VTE	5 (1.3%)	1 (0.3%)	0.22 <i>0.01 noninf</i>
Clinically impt bleeding	5 (1.3%)	2 (0.5%)	0.09
Net event rate	10 (2.5%)	3 (0.8%)	0.09

# EPCAT I Study: Limitations

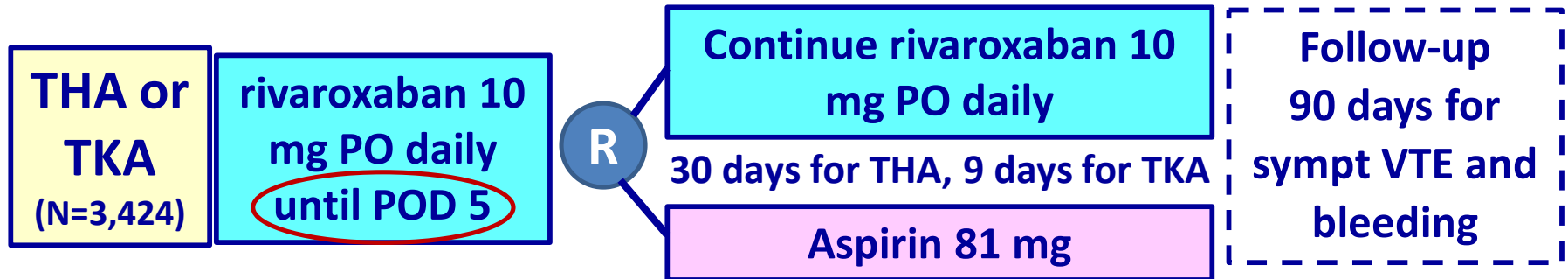
---

- 82% of THR patients excluded
- Premature study termination (after 36% of projected sample) due to slow recruitment (rivaroxaban approved)
- Lower adherence in LMWH group
- 5% of patients received long-term aspirin

*Anderson – Ann Intern Med 2013;158(11):800*  
*Granziera & Cohen – Ann Intern Med 2013;159(7):502*

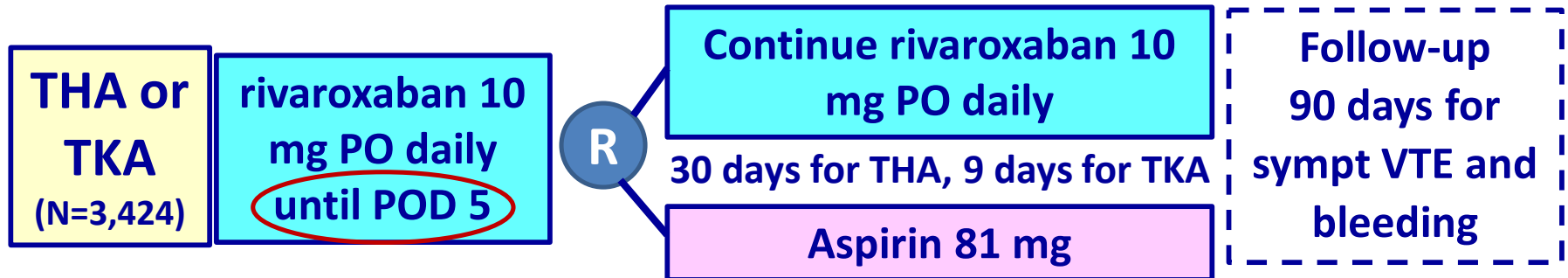
# EPCAT II Study

- Double-blind RCT in 15 Canadian centers



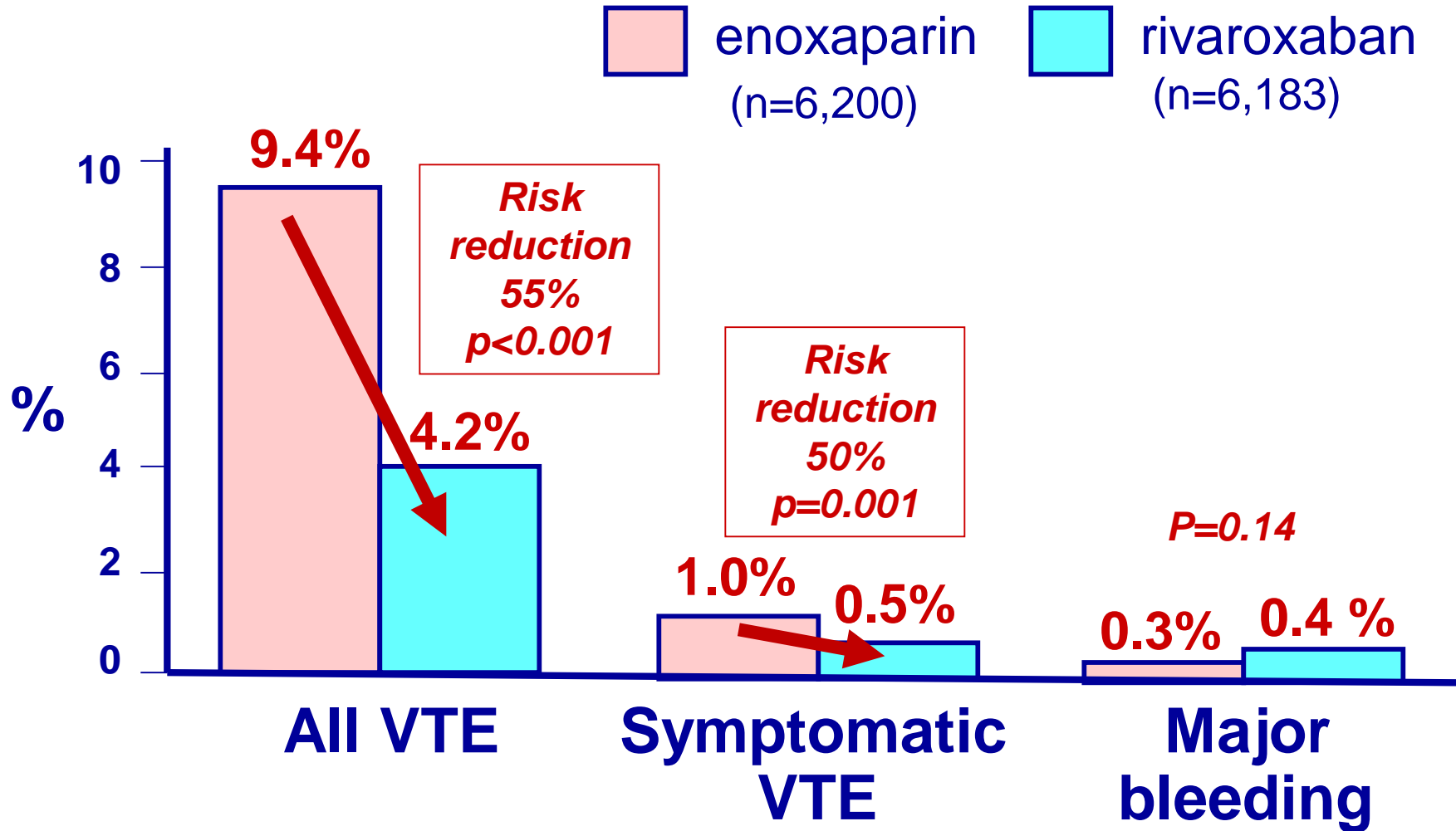
# EPCAT II Study

- Double-blind RCT in 15 Canadian centers



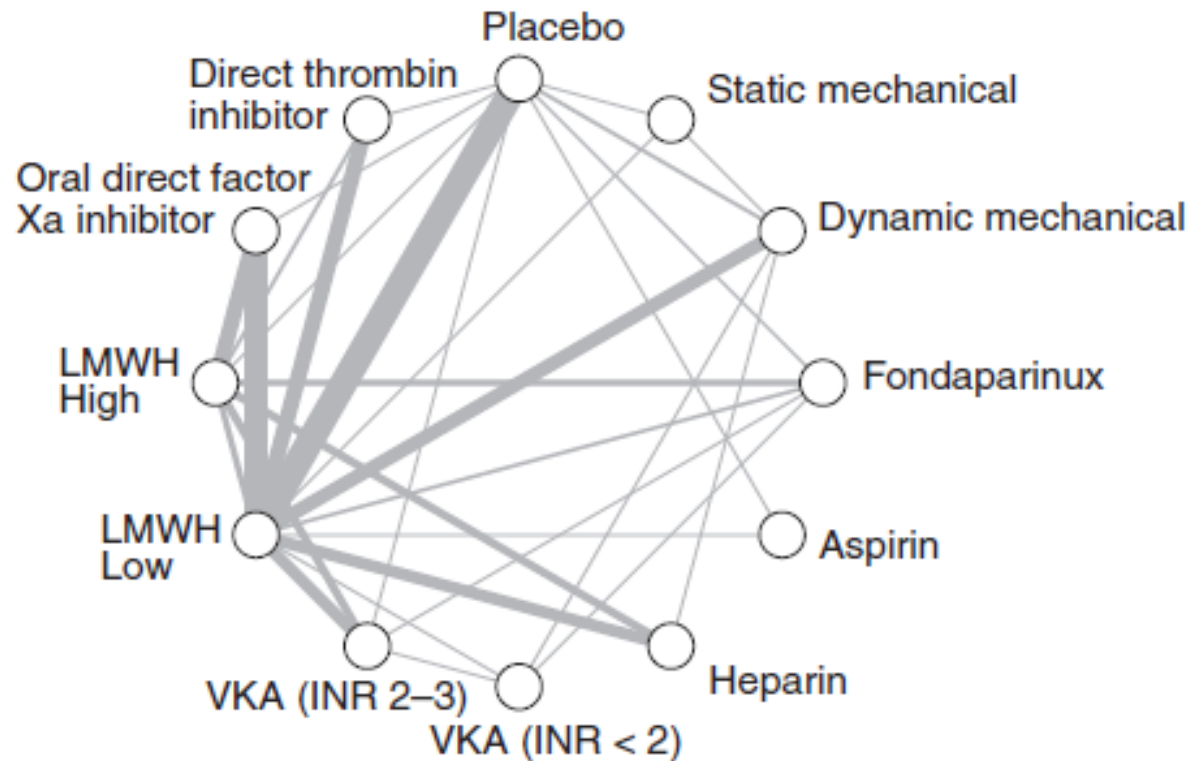
	Rivaroxaban (n=1,714)	Aspirin (n=1,719)	<i>p</i>
Symptomatic VTE	12 (0.7%)	11 (0.6%)	0.84 <0.0001 <i>noninf</i>
Clinically impt bleeding	17 (1.0%)	22 (1.3%)	0.43
Major bleeding	5 (0.3%)	8 (0.5%)	0.42

# Oral Rivaroxaban after *THR/TKR*



# Network Meta-Analysis of Thromboprophylaxis Options

- Systematic review of 94 RCTs, 1990-June 2016
- 11 prophylaxis options compared to LWMH

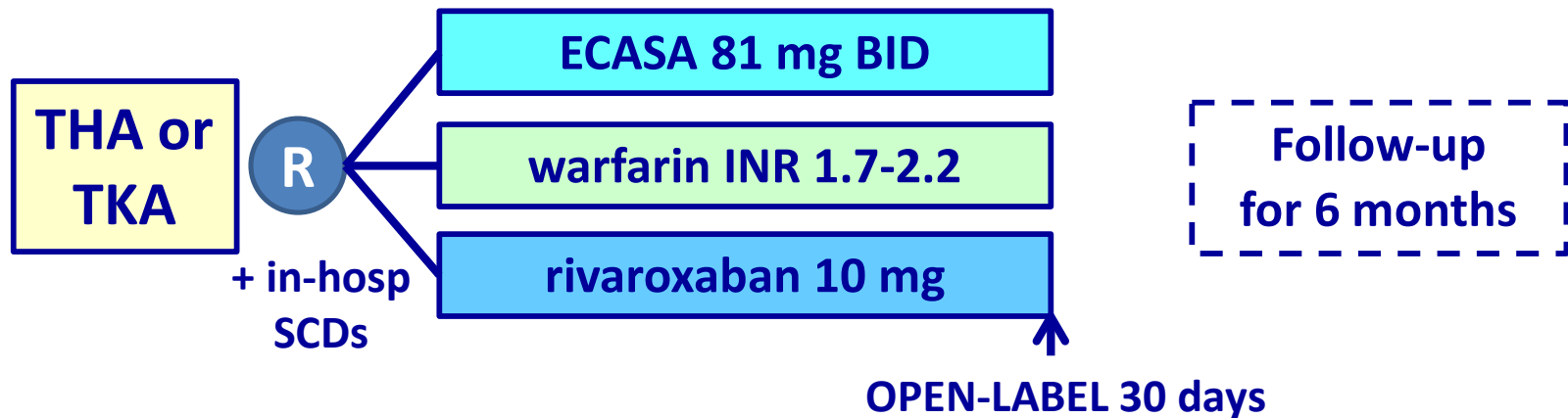


# Network Meta-Analysis of Thromboprophylaxis Options

94 RCTs	Odds ratio vs LMWH		
	All DVT	Sympt DVT	Major bleed
Fondaparinux	0.5 [0.3-0.9]	3.1 [0.9-15]	2.3 [1.2-4.5]
Direct FXa inhibitor	0.5 [0.4-0.6]	0.3 [0.1-0.5]	1.2 [0.8-1.9]
Dir thrombin inhibitor	0.8 [0.6-1.1]	0.7 [0.4-1.4]	1.5 [0.9-2.2]
LMWH BID	0.7 [0.6-0.9]	0.5 [0.2-0.9]	1.6 [1.1-2.4]
LMWH once daily	Reference	Reference	Reference
VKA INR 2-3	1.6 [1.1-2.1]	1.4 [0.7-2.9]	0.9 [0.6-1.4]
VKA INR <2	9.5 [2.2-52]	0 [0-∞]	2.7 [0.1-100]
Heparin	1.3 [0.9-2.0]	3.1 [0.9-12]	1.9 [1.1-3.4]
Aspirin	0.8 [0.3-1.9]	2.0 [0.6-7.4]	1.1 [0.5-2.4]
IPC	1.2 [0.8-1.8]	1.1 [0.1-12]	0.2 [0.0-0.6]
Placebo	2.9 [2.2-3.8]	2.6 [1.2-5.6]	1.1 [0.5-2.2]

# Comparative Effectiveness of Thromboprophylaxis in TJA (PEPPER)

- Compare the 3 most common prophylaxis options
- RCT in 24 American centers; N=25,000; 2016-2021



## Outcomes at 6 mos:

- Efficacy: VTE leading to readmission + death
- Safety: bleeding (major, clin-impt, wound-related)
- Joint function, patient well-being

[Clinicaltrials.gov:NCT02810704](https://clinicaltrials.gov/NCT02810704)



# Aspirin as Thromboprophylaxis

## *Conclusions*

---

1. Aspirin is somewhat effective in preventing VTE but less effective than anticoagulants
2. In **major orthopedic surgery**, aspirin alone is less effective than alternatives
3. ∴ **Aspirin alone** should not be used
4. Aspirin likely to be noninferior to LMWH or DOACs if combined with SCDs
5. In **major orthopedic surgery**, after initial prophylaxis with a DOAC or LMWH, aspirin appears to be noninferior to DOAC or LMWH

# *Thromboprophylaxis* options in Major Orthopedic Surgery

---

## 1. DOACs

- rivaroxaban 10 mg PO QD
- apixaban 2.5 mg PO BID

## 2. LMWH\*

- dalteparin 5,000 U QD
- enoxaparin 40 mg QD or 30 mg BID
- tinzaparin 4,500 U QD

\*higher dose if wt >100 kg

3. ASA - ?after early use DOAC or LMWH

# Thromboprophylaxis for TJA

---

**Rivaroxaban\* 10 mg daily x 15-30 days**

**Rivaroxaban\* 10 mg  
daily x 5-10 days**

**Aspirin 81 mg  
daily x 10-25 days**

**Total  
prophylaxis  
15-30 days**



**\*or apixaban 2.5 mg BID**

# Aspirin as Thromboprophylaxis:

## *Excellent References*

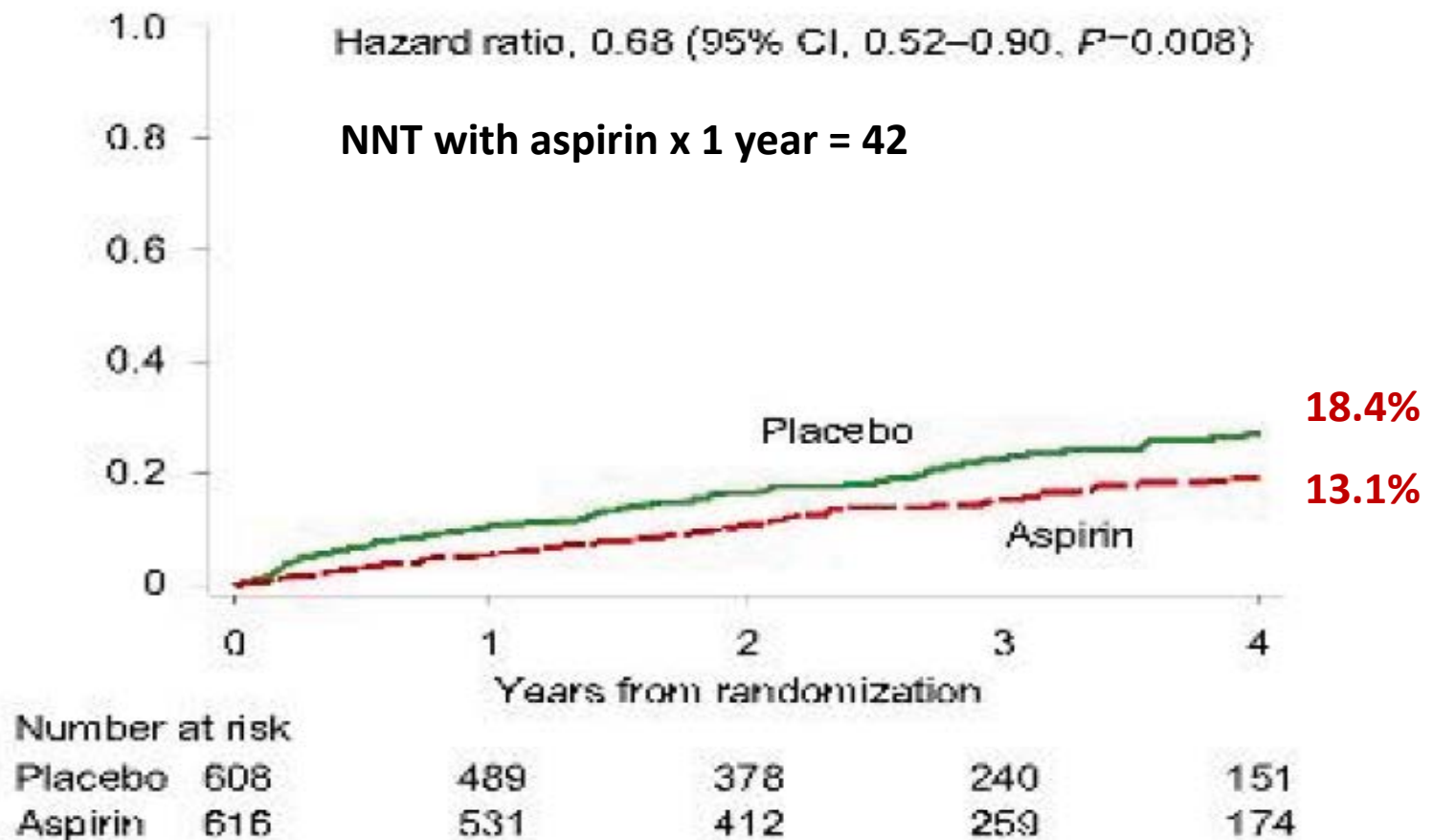
---

- **Karthikeyan** – Does acetyl salicylic acid (ASA) have a role in the prevention of venous thromboembolism? Br J Haematol 2009;146:142.
- **Kapoor A** – Comparative effectiveness of venous thromboembolism prophylaxis options for the patient undergoing total hip and knee replacement: a network meta-analysis. J Thromb Haemost 2017;15:284.
- **Cohen AT** – The use of aspirin for primary and secondary prevention in venous thromboembolism and other cardiovascular disorders. Thromb Res 2015;135:217.
- **Anderson D** – Extended venous thromboembolism prophylaxis comparing rivaroxaban to aspirin following total hip or knee arthroplasty (EPCAT II). ISTH 2017:OC 52.2.
- **Eikelboom JW** – Perioperative aspirin for prevention of venous thromboembolism: the PeriOperative ISchema Evaluation-2 trial and a pooled analysis of the randomized trials. Anesthesiology 2016;125:1121.

# **Aspirin for extended VTE treatment**

# Aspirin to Prevent Recurrent VTE

## Recurrent venous thromboembolism

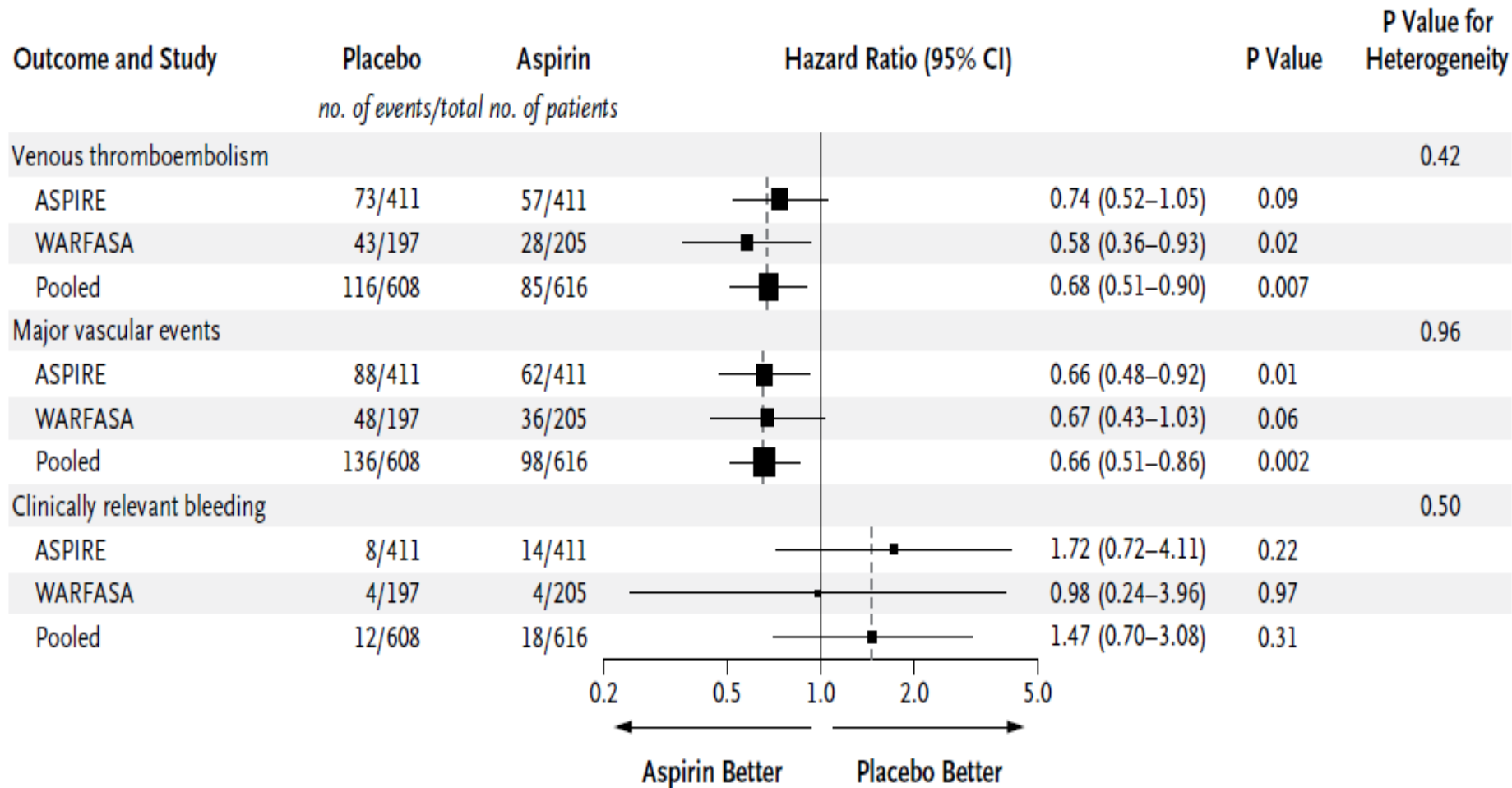


WARFASA N=402

ASPIRE N=822

*Simes – Circulation 2014;130:1062*

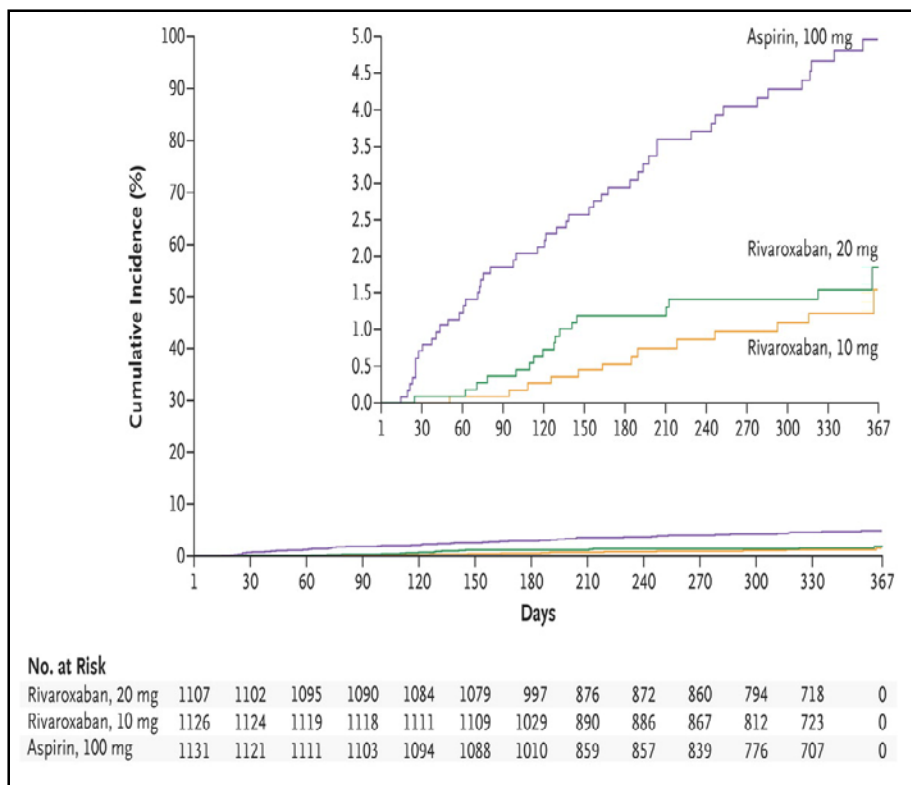
# Aspirin to Prevent Recurrent VTE



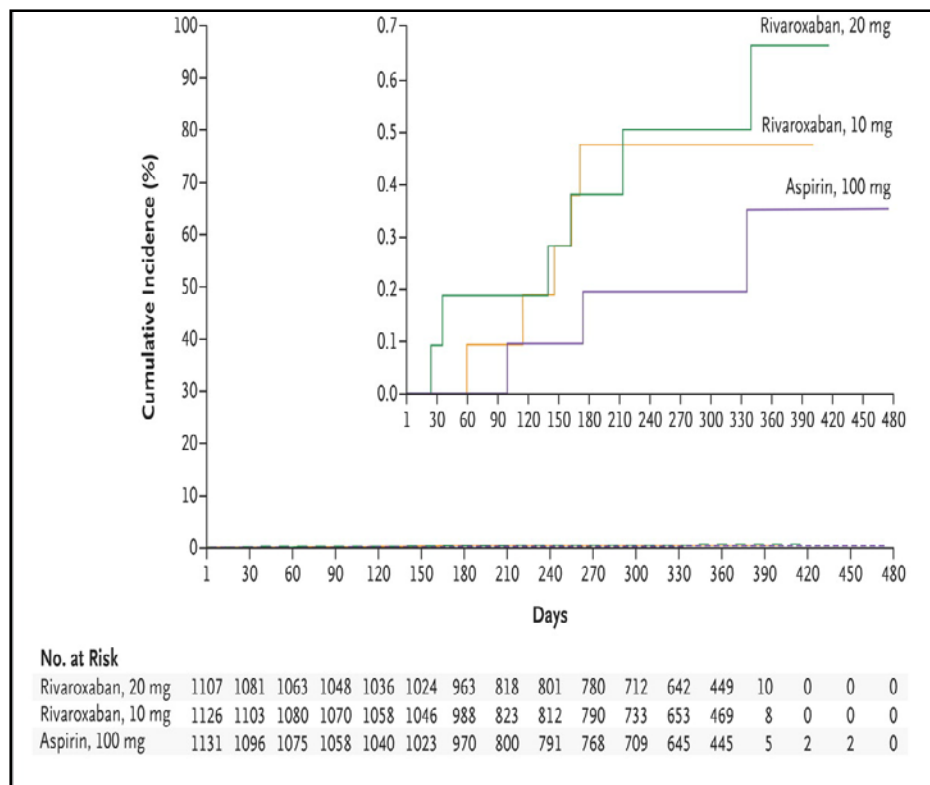
**Brighton – NEJM 2012;367:1979**

# Rivaroxaban for Extended VTE Treatment (*EINSTEIN CHOICE*)

## Symptomatic Recurrent VTE



## Major Bleeding



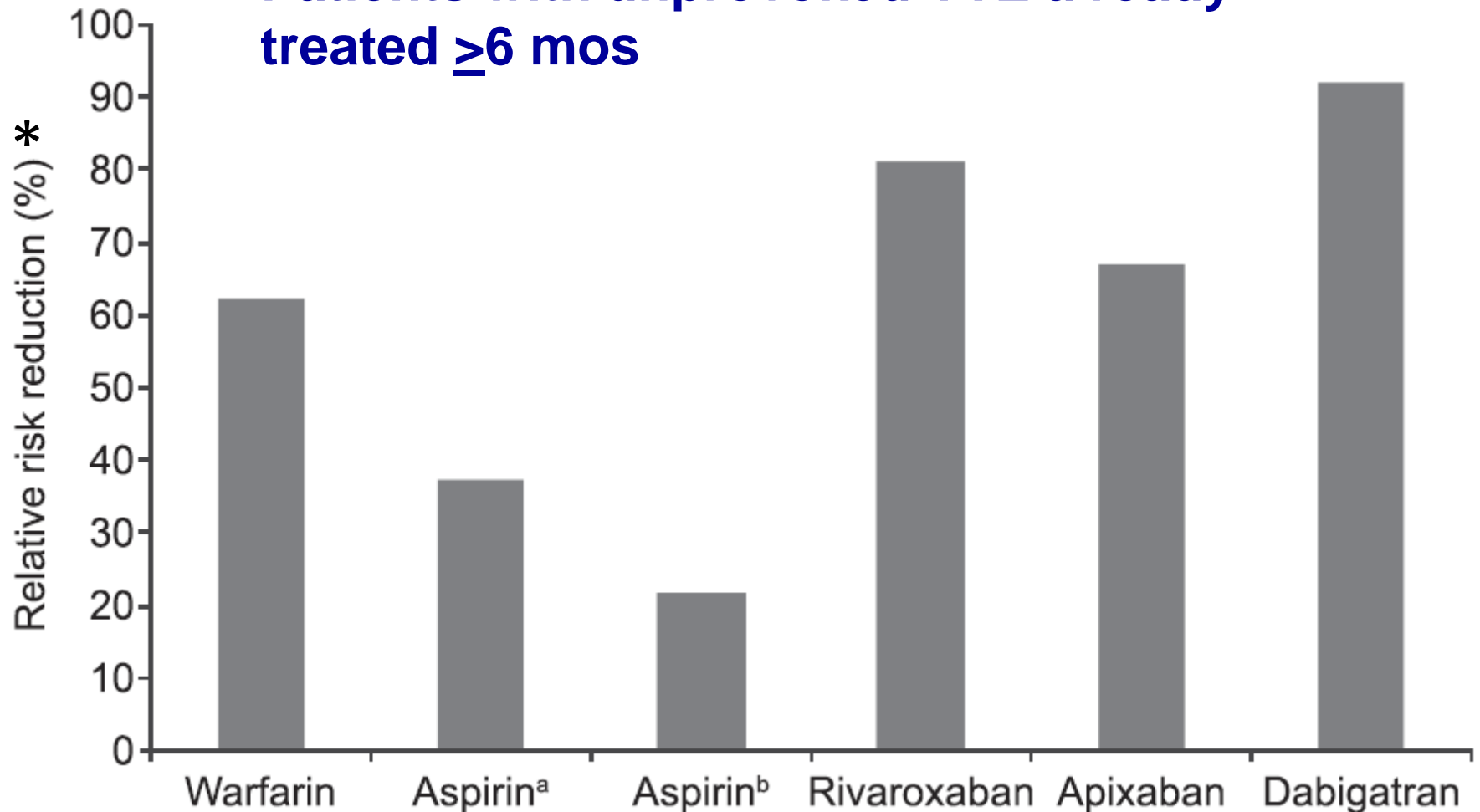
**MB + CRNMB: ASA 2.0%**  
**riva 10 2.4%**  
**riva 20 3.3%**

**Weitz – NEJM 2017;376(13):1211**



# Secondary Prevention of VTE

- Patients with unprovoked VTE already treated  $\geq 6$  mos



\*vs placebo

*Cohen – Thromb Res 2015:135:217*

# Aspirin as Thromboprophylaxis

## *Conclusions*

---

- 1. Aspirin is less effective than anticoagulants in preventing primary or secondary venous thrombosis**
- 2. In major orthopedic surgery, aspirin alone should not be used**
- 3. Aspirin likely to be noninferior to LMWH or DOACs if combined with SCDs**
- 4. In major orthopedic surgery, after initial prophylaxis with a DOAC or LMWH, aspirin appears to be noninferior to DOAC or LMWH**