

## **Venous Thrombosis Update**

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**Victoria, BC**

Victoria Heart Institute Foundation



Cardiovascular Research

# CCPN Has Been Providing Speakers and Workshops at ACC Lake Louise and ACC Rockies for 15 Years.



The screenshot shows the CCPN website homepage. At the top, there is a browser window with the address bar showing 'ccpn.ca/index.php'. The website header features the CCPN RCPC logo on the left, the text 'Canadian Cardiovascular Pharmacists Network' in the center, and a 'MEMBER LOGIN' button on the right. Below the header is a navigation menu with buttons for 'HOME', 'MEMBERS', 'CALENDAR OF EVENTS', 'PRACTICE TOOLS', 'PROJECTS', 'PAST EVENTS', and 'CONTACT US'. The main content area is divided into three sections. On the left, there is a 'CCPN INITIATIVES' section with links to 'CCPN SPAF Tool' (with sub-links for 'Download Electronic Version' and 'Download Reference List'), 'Antithrombotic Guidelines Pocket Reference (2008)' (with a 'View Document' link), and 'Acute Coronary Syndrome (ACS) Patient Education Toolkit' (with a photo of a man and the CCPN logo). The central section features a large image of healthcare professionals in a meeting, with the text 'promoting excellence in clinical practice and research'. Below this image is a paragraph describing the network as an independent group of Canadian pharmacists and another paragraph stating their mission to optimize health outcomes. On the right, there is an 'UPCOMING EVENTS' section with details for the '17th ANNUAL CONTEMPORARY THERAPEUTIC ISSUES IN CARDIOVASCULAR DISEASES EVENING RECEPTION, TORONTO, ON' (2-day event: April 25-26, 2014) on April 25, 2014.



## Canadian Cardiovascular Pharmacists Network

MEMBER LOGIN

HOME

MEMBERS

CALENDAR OF EVENTS

PRACTICE TOOLS

PROJECTS

PAST EVENTS

CONTACT US

### CCPN INITIATIVES

#### CCPN SPAF Tool

Download Electronic Version  
Download Reference List

#### Antithrombotic Guidelines Pocket Reference (2008)

View Document

#### Acute Coronary Syndrome (ACS) Patient Education Toolkit



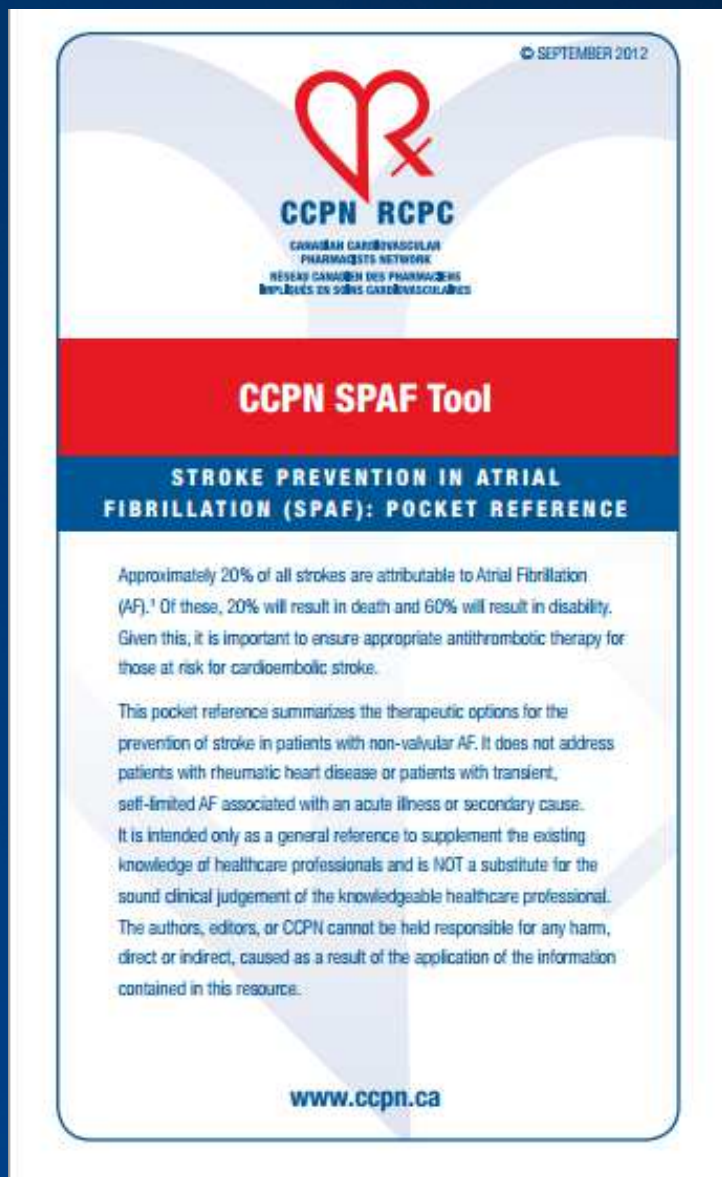
## promoting excellence in clinical practice and research

The Canadian Cardiovascular Pharmacist Network is an independent group of Canadian pharmacists involved in cardiovascular practice and research.

Our mission is to optimize the health outcomes of Canadians with or at risk of cardiovascular disease by promoting excellence in clinical practice and research. We also strive to enhance the knowledge and skills of pharmacists and their colleagues through the advancement of the pharmacotherapy of cardiovascular diseases.

### UPCOMING EVENTS

**17th ANNUAL CONTEMPORARY  
THERAPEUTIC ISSUES IN  
CARDIOVASCULAR DISEASES  
EVENING RECEPTION, TORONTO, ON  
(2-day event: April 25-26, 2014)  
April 25, 2014**



[ccpn.ca](http://ccpn.ca)

# CCPN SPAF Tool and Pocket Reference

Digital Version Available From Web Site

Popular With Students  
& Residents

## Acute Coronary Syndrome (ACS) Patient Education Toolkit



### ACS with Stent

Acute Coronary Syndrome (ACS) patients undergoing a revascularization strategy of Percutaneous Coronary Intervention (PCI) with Coronary Stent Implantation.

Enter >

### Medically Managed ACS

Acute Coronary Syndrome (ACS) patients not undergoing a revascularization strategy.

Enter >

### Elective PCI

Patients with Coronary Artery Disease (CAD) undergoing an Elective Percutaneous Coronary Intervention (PCI) with Coronary Stent Implantation.

Enter >

#### ACS with Stent

#### Medically Managed ACS

#### Elective PCI

Disease Information

Medication Information

Lifestyle Information

#### Printing Tools

##### Medically Managed ACS

(print all)

Disease Information

Medication Information

Lifestyle Information

##### Wallet Card

Print Selected Items >

##### Medication schedule

(fill in and print)

Print Medication schedule >

### Medically Managed ACS - Disease Information



#### The healthy artery

Blood flows easily supplied with the body.



#### Artery damage

Plaque (a fatty m artery. This is call artery wall beco



#### Artery narrow

Plaque build-up

### ACS With Stent - Medication Information

Many of the medications you have been prescribed are a part of your life-long therapy for ACS and are important for the prevention of another ACS event.

#### Antiplatelet Medication

Antiplatelet medications are often prescribed with ASA (81 or 325mg once daily) in ACS. These medications:

- Work together to stop platelets from sticking together
- Protect you from blood clots that block coronary arteries
- Prevent heart attack, unstable angina, stroke or death

Common antiplatelet medications that are used together with ASA are:

- clopidogrel
- ticagrelor
- prasugrel

Possible side effects include:

- diarrhea or indigestion
- bruising or nosebleeds
- bleeding from gastrointestinal tract with may result in dark black stools

Even if you experience unwanted side effects, it is important you don't stop taking your antiplatelet medication without first speaking with your doctor or pharmacist.

#### Medication Schedule

Patient Info

First Name:

HCP Info

Completed By:

Back

Medication	Take	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Notes
Antiplatelet Therapy <input type="text" value="Select One"/>	Take <input type="text" value=""/> time(s) a day.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Blood thinner; Report excessive bruising or bleeding to Doctor; Swallow whole
Additional Antiplatelet Therapy <input type="text" value="Select One"/>	Take <input type="text" value=""/> time(s) a day.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Duration: <input type="text" value="1"/> month Blood thinner; Report excessive bruising or bleeding to Doctor; Swallow whole
Angiotensin Converting Enzyme Inhibitor (ACE-I) - or - Angiotensin II Inhibitor <input type="text" value="Select One"/>	Take <input type="text" value=""/> time(s) a day.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	May cause dizziness or high potassium. Report dry cough or facial / neck swelling to your doctor.
Beta Blocker <input type="text" value="Select One"/>	Take <input type="text" value=""/> time(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	For heart & blood pressure. Do not stop without consulting your doctor



# Venous Thrombosis Update



**Something To Think About On The Trip Back Home**

# Typical Categories of VTE

## Unprovoked

- Active Cancer (Previously diagnosed)
- Occult Malignancy (15% @2 yrs post)
- Thrombophilia (More Likely < 40 yrs)
- Previously Undocumented DVT
- True Idiopathic

## Anatomical & Mechanical

- May Thurner Syndrome
- Iliac Artery Aneurysm
- Inferior Vena Caval Malformation
- Subclavian (Paget-Schroder)

## Provoked

- Post Surgeries & Injuries
- Pregnancy/Estrogens
- Long Distance Travel
- Pulmonary Vein Ablation
- Pacemaker/ICD (Subclavian)
- PICC Line

## Unusual

PE Following Wisdom Tooth Extraction

Subclavian Following Electrocution

PE Within 15 Minutes of Portacath Placement

DVT Calgary to Victoria Flight

# Deep Vein Clots Are Big

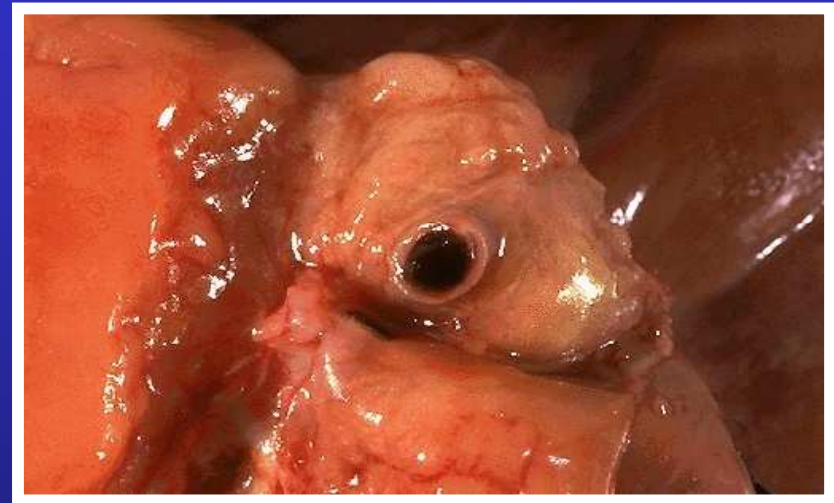
Measured In Centimeters



DVT Clots Can Be As Round As Your Finger And As Long As Your Leg

VS

Measured In Millimeters

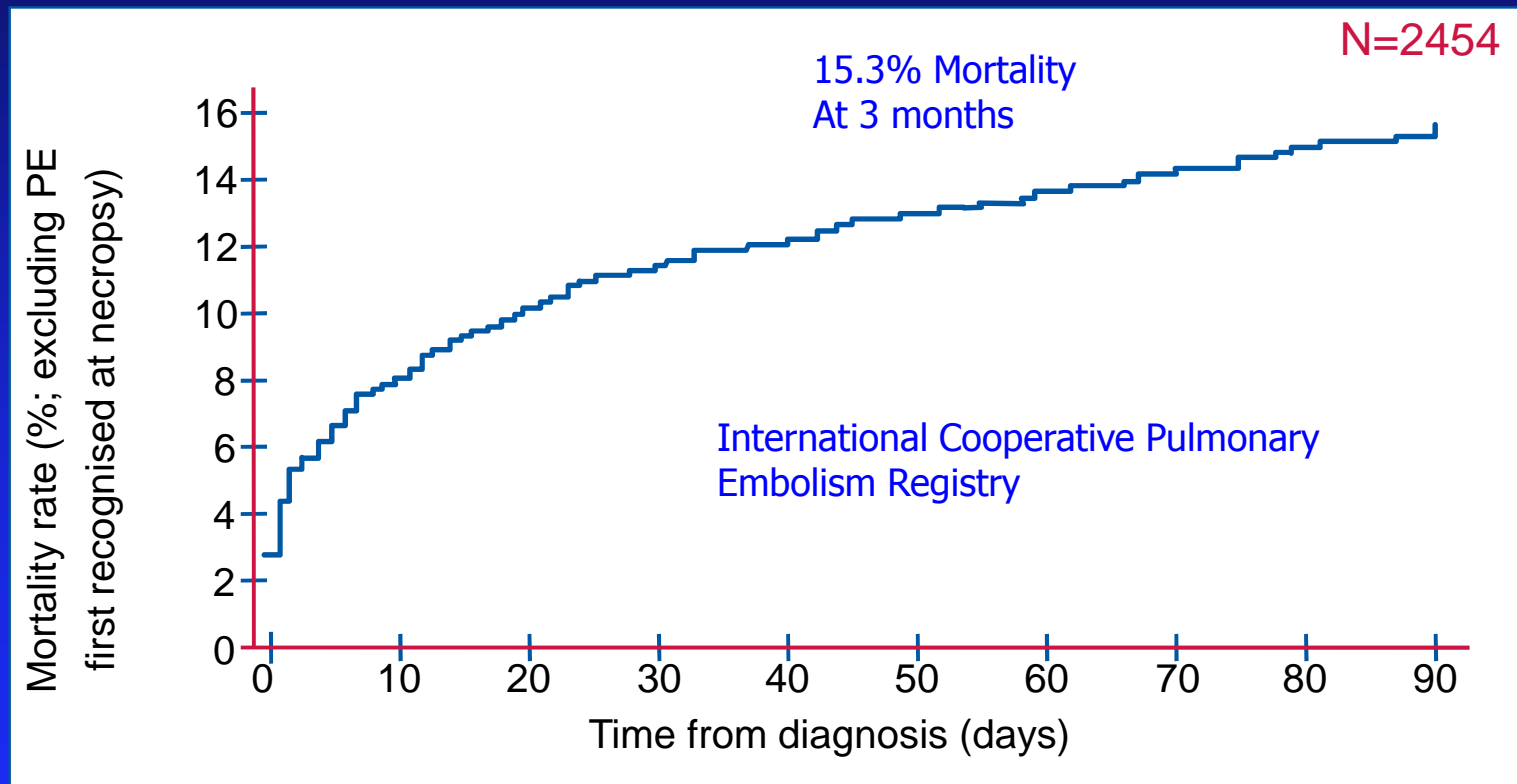


Coronary Clots Very Small



# Pulmonary Embolism: A Life-threatening Disease

## Cumulative mortality following acute PE





# Symptoms of DVT



**Symptomatic DVT**

- Leg pain (90%)
- Tenderness (85%)
- Ankle edema (76%)
- Calf swelling (42%)
- Dilated veins (33%)
- Dusky discoloration (30%)
- Warmth

**50% NO SYMPTOMS**

“DVT cannot be reliably diagnosed on the basis of history and physical exam, even in high-risk patients”

# Pharmacological Treatment of DVT/PE

# Therapy: Do We Need To Anticoagulate Patients With Acute VTE ?

- 19 Patients With PE Randomized To No Therapy
- 16 Patients Wit PE Randomized to Heparin 10,000 U SQ Q6H x 6 Doses Then Oral Anticoagulation x 2 Weeks

	Deaths	Non-fatal recurrences
Untreated	5	5
Treated	0	0

Group	Mortality
No Therapy	26.3%
Heparin/ Oral Anticoag	0%
ARR= 26.3%	NNT 3.8



# New Antithrombotics In Treatment of VTE



## Clinical Trials of NOACs In DVT/PE

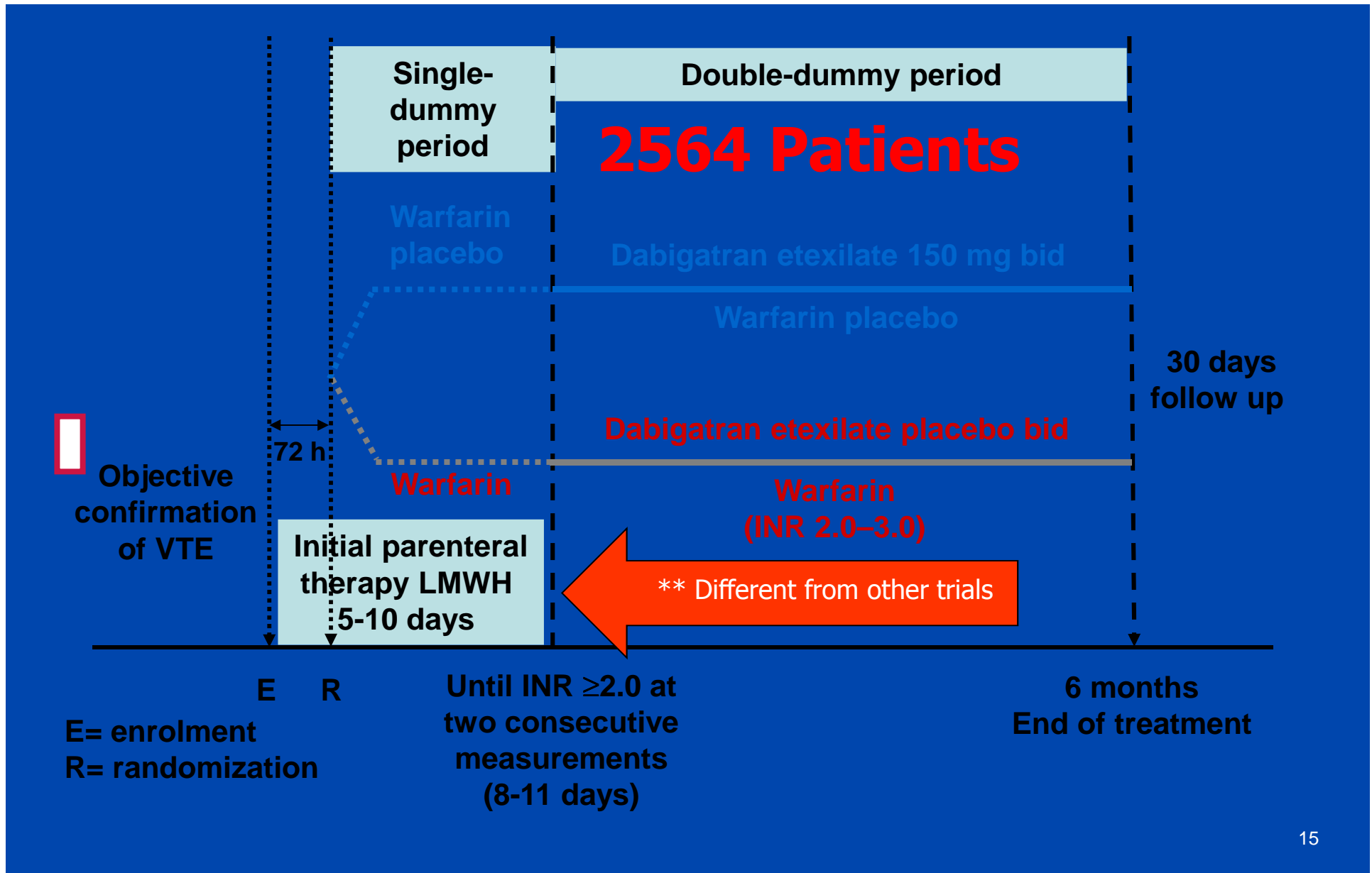
	Apixaban AMPLIFY	Dabigatran RECOVER I & II	Rivaroxaban EINSTEIN
Population	Unprovoked or History of Cancer	Any DVT/PE	Any DVT/PE
Design	Double Blind	Double Blind	Open Label
Sample Size	4816	2564	8281
Initial LMWH	Warfarin Group	Both Arms	Warfarin Group
Higher Initial Dose NOAC	Yes	No	Yes
CT Scan Baseline	No	Yes	No
Active Cancer	] Hx of Ca Inclusion Criteria	5%	5%
Unprovoked			49%
Previous VTE		26%	20%
Warfarin TTR		66%	61.7%



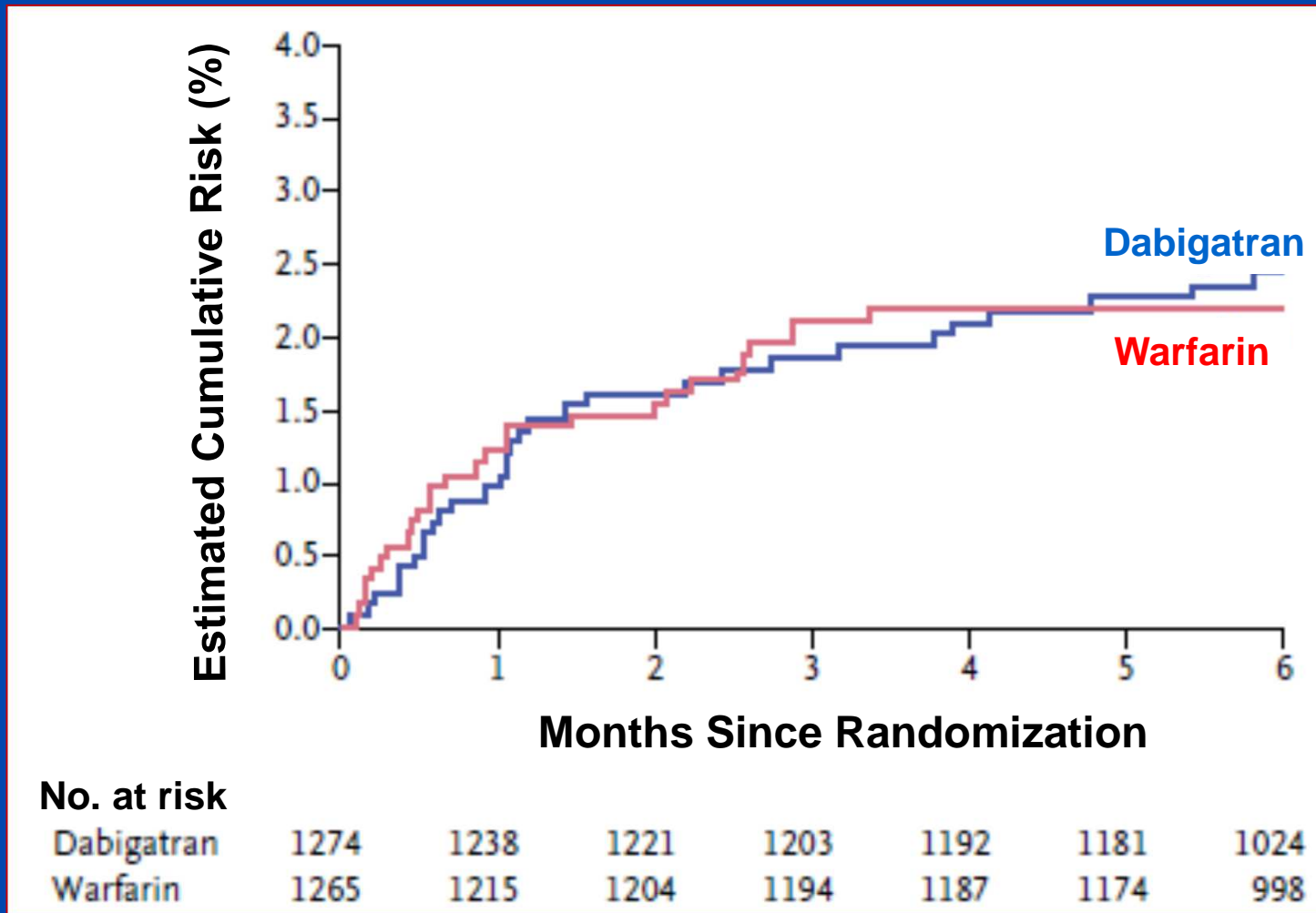
# **NOACS IN VTE**

## **Dabigatran**

# RE-COVER™ Trial Design

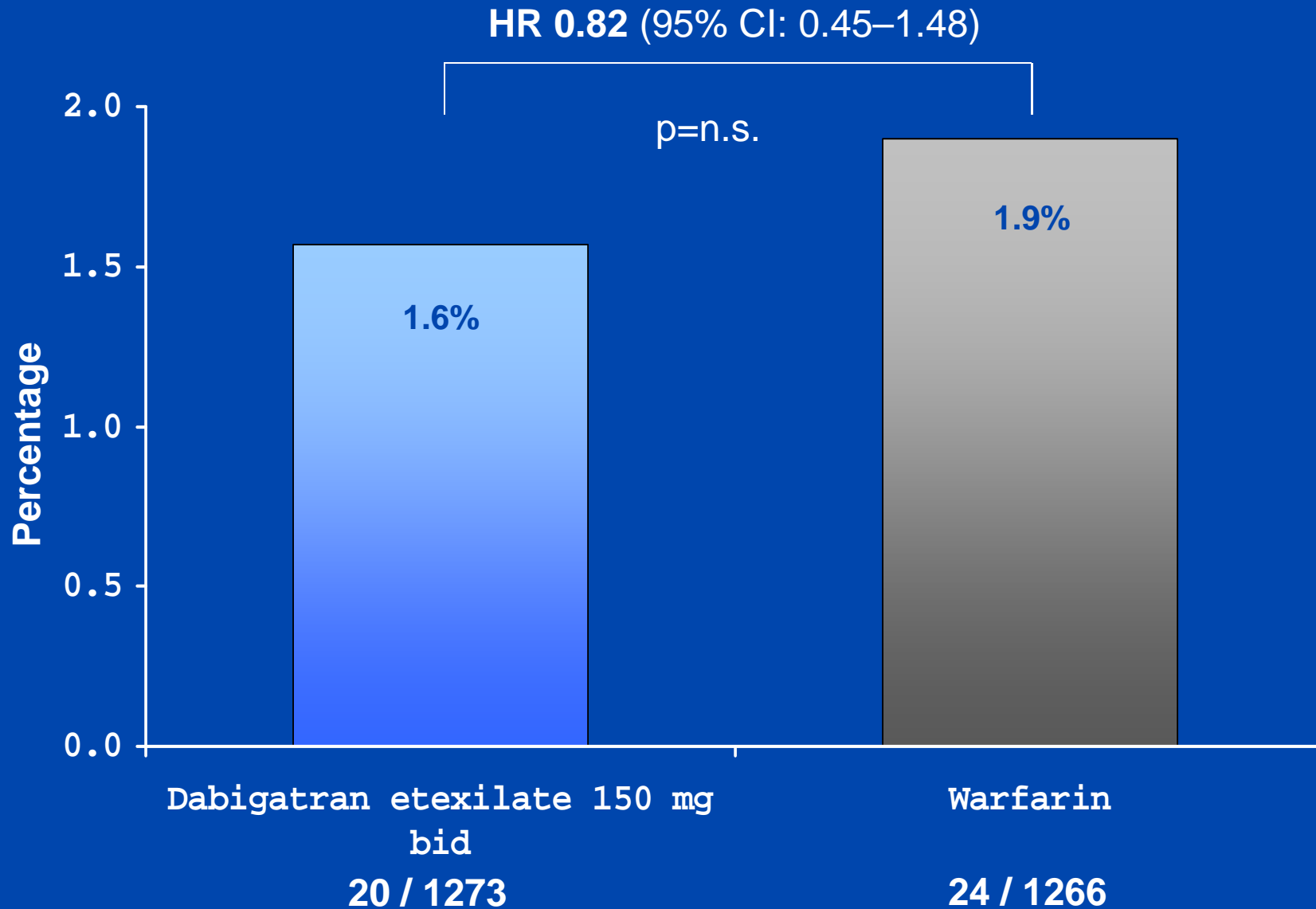


# Cumulative risk of recurrent VTE and related death



**Dabigatran was non-inferior to warfarin for prevention of recurrent or fatal VTE (P<0.001 for both hazard ratio and risk difference criteria).**

# Comparable on major bleeds



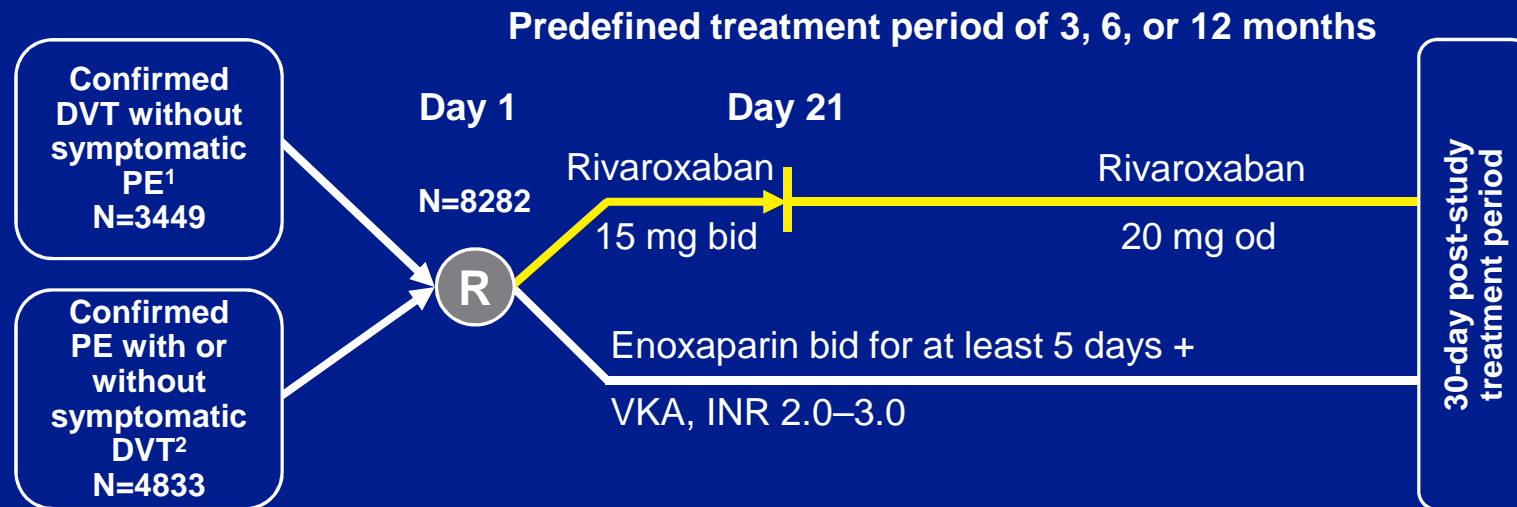
# **NOACS IN VTE**

## **Rivaroxaban**



# EINSTEIN DVT and EINSTEIN PE studies

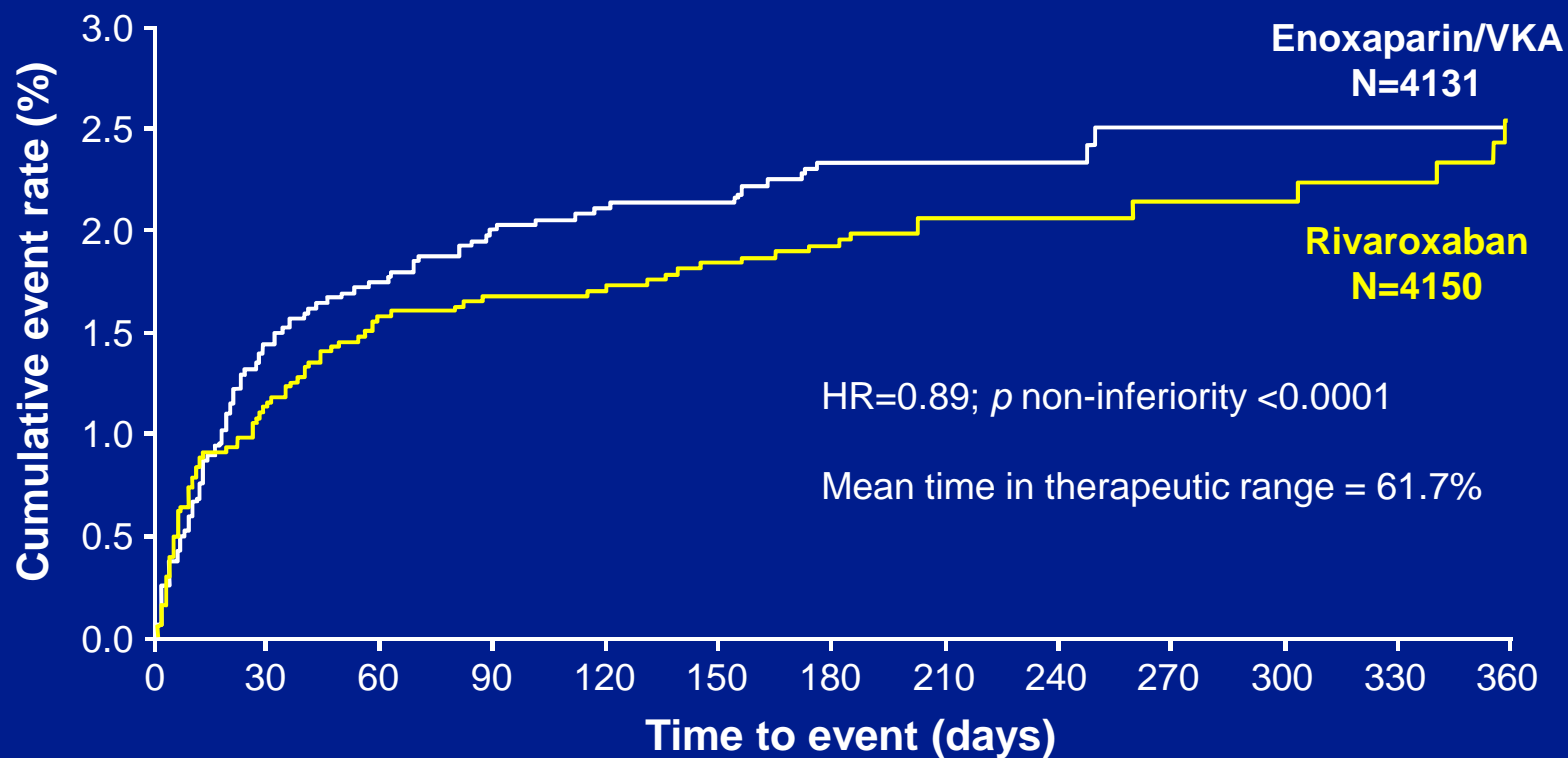
Randomized, open-label, event-driven, non-inferiority studies of identical design with *a priori* specified combined analyses



- ◆ **Primary efficacy outcome:** first recurrent VTE
- ◆ **Principal safety outcome:** first major or non-major clinically relevant bleeding

1. The EINSTEIN Investigators. *N Engl J Med* 2010;363:2499–510;  
2. The EINSTEIN-PE Investigators. *N Engl J Med* 2012;366:1287–97

# EINSTEIN DVT and EINSTEIN PE pooled analysis: primary efficacy outcome



## Number of patients at risk

Rivaroxaban	4150	4018	3969	3924	3604	3579	3283	1237	1163	1148	1102	1034	938
Enoxaparin/VKA	4131	3932	3876	3826	3523	3504	3236	1215	1149	1109	1071	1019	939

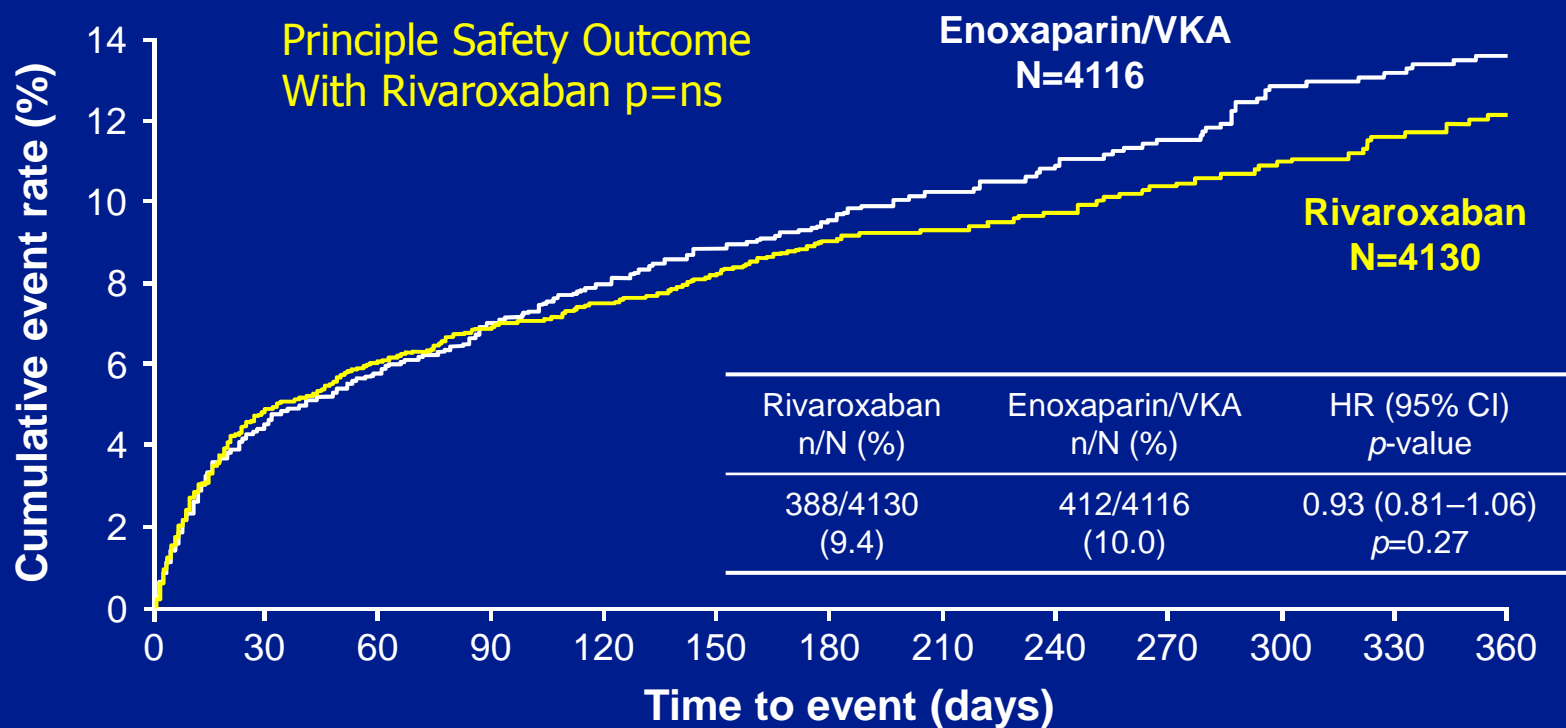
ITT population

# EINSTEIN DVT and EINSTEIN PE pooled analysis: principal safety outcome

## First major or clinically relevant non-major bleeding

Trend Towards Lower

Principle Safety Outcome  
With Rivaroxaban  $p=ns$



### Number of patients at risk

Rivaroxaban	4130	3768	3671	3406	3270	3210	1928	1051	1009	936	878	853	453
Enoxaparin/VKA	4116	3738	3618	3330	3186	3125	1711	1025	981	907	857	823	369

Safety population

# **NOACS IN VTE**

## **Apixaban**

# AMPLIFY: Efficacy and Safety of Apixaban for the Treatment of DVT or PE

N=4,816 (estimated)

### Patient Population

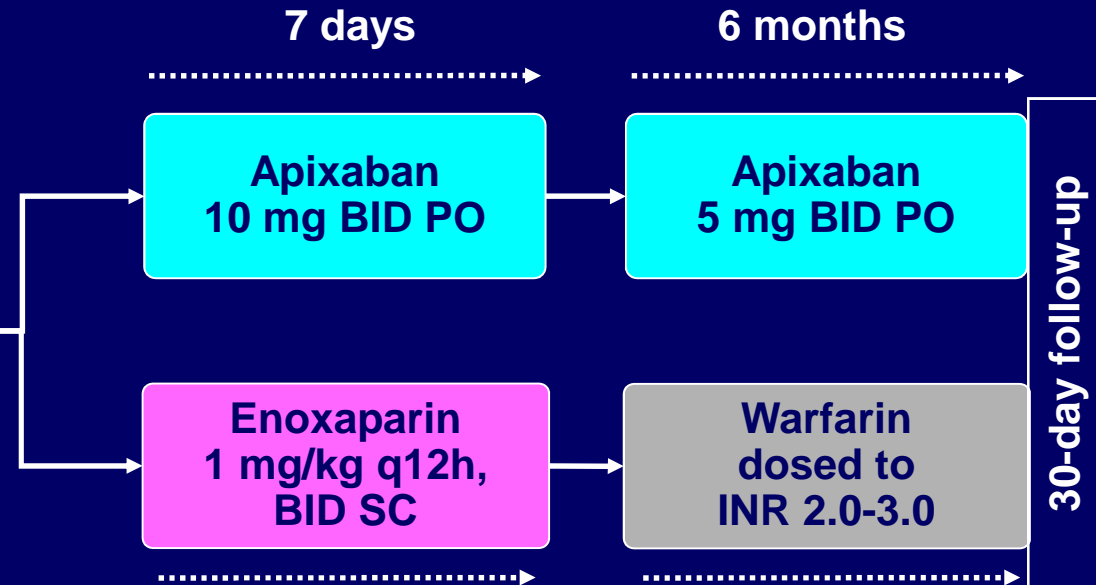
- Men and women ≥18 years with clinical diagnosis of DVT or PE
- Unprovoked or Hx of Cancer

### Primary Outcome

- VTE recurrence or death

### Secondary Outcome

- Bleeding



Until INR ≥2.0

6 months

481 centers

AMPLIFY=Apixaban after the initial Management of PuLmonary embolism and deep vein thrombosis with First-line therapY.

<http://www.clinicaltrials.gov>. Identifier: NCT00643201.



# Oral Apixaban for the Treatment of Acute Venous Thromboembolism

AMPLIFY randomized 5,395 patients to apixaban or conventional therapy with enoxaparin bridging to warfarin for 6 months.

	<b>Apixaban (n = 2,691)</b>	<b>Conventional Therapy (n = 2,704)</b>	<b>RR (95% CI)</b>
<b>Recurrent VTE or Death Related to VTE</b>	2.3%	2.7%	0.84 (0.60-1.18)
<b>Major Bleeding</b>	0.6%	1.8%	0.31 (0.17-0.55)

**Conclusion:** Apixaban was noninferior to enoxaparin/vitamin K antagonist for the primary efficacy endpoint but resulted in substantially less bleeding.

Agnelli G, et al. *N Engl J Med.*  
2013;Epub ahead of print.

**NOACS IN VTE**  
**Extended Treatment**  
**Following Initial**  
**Therapy**

# Recurrent VTE – Long Term Perspective

## Olmstead County Minnesota Registry

### Rate Of Recurrent VTE Following Initial DVT/PE



DVT=deep vein thrombosis; VTE=venous thromboembolism  
Heit JA, et al. *Arch Intern Med* 2000;160:761-768.

# Extended Treatment Apixaban



# **Apixaban for Extended Treatment of Venous Thromboembolism (VTE)**

## The AMPLIFY-EXTENSION Study

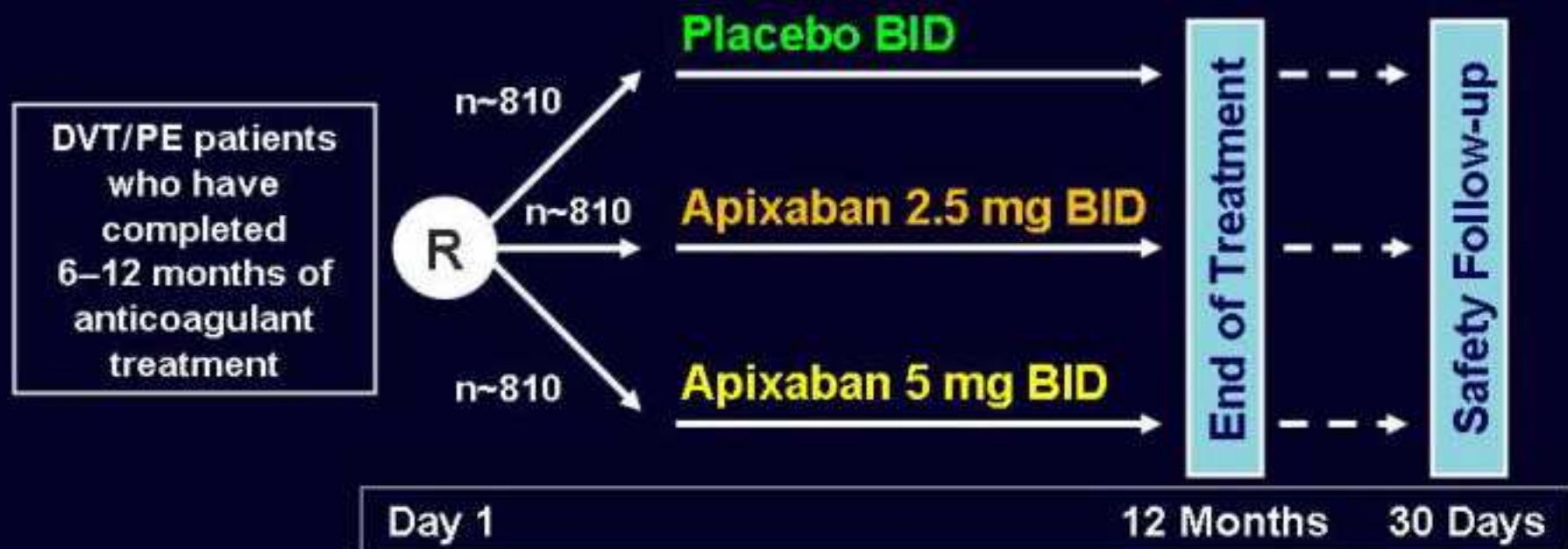
Giancarlo Agnelli, Harry R. Buller, Alexander Cohen, Madelyn Curto, Alexander Gallus, Margot Johnson, Anthony Porcari, Gary E. Raskob, and Jeffrey I. Weitz  
for the AMPLIFY-EXT Investigators

*Sponsored by Bristol-Myers Squibb and Pfizer*

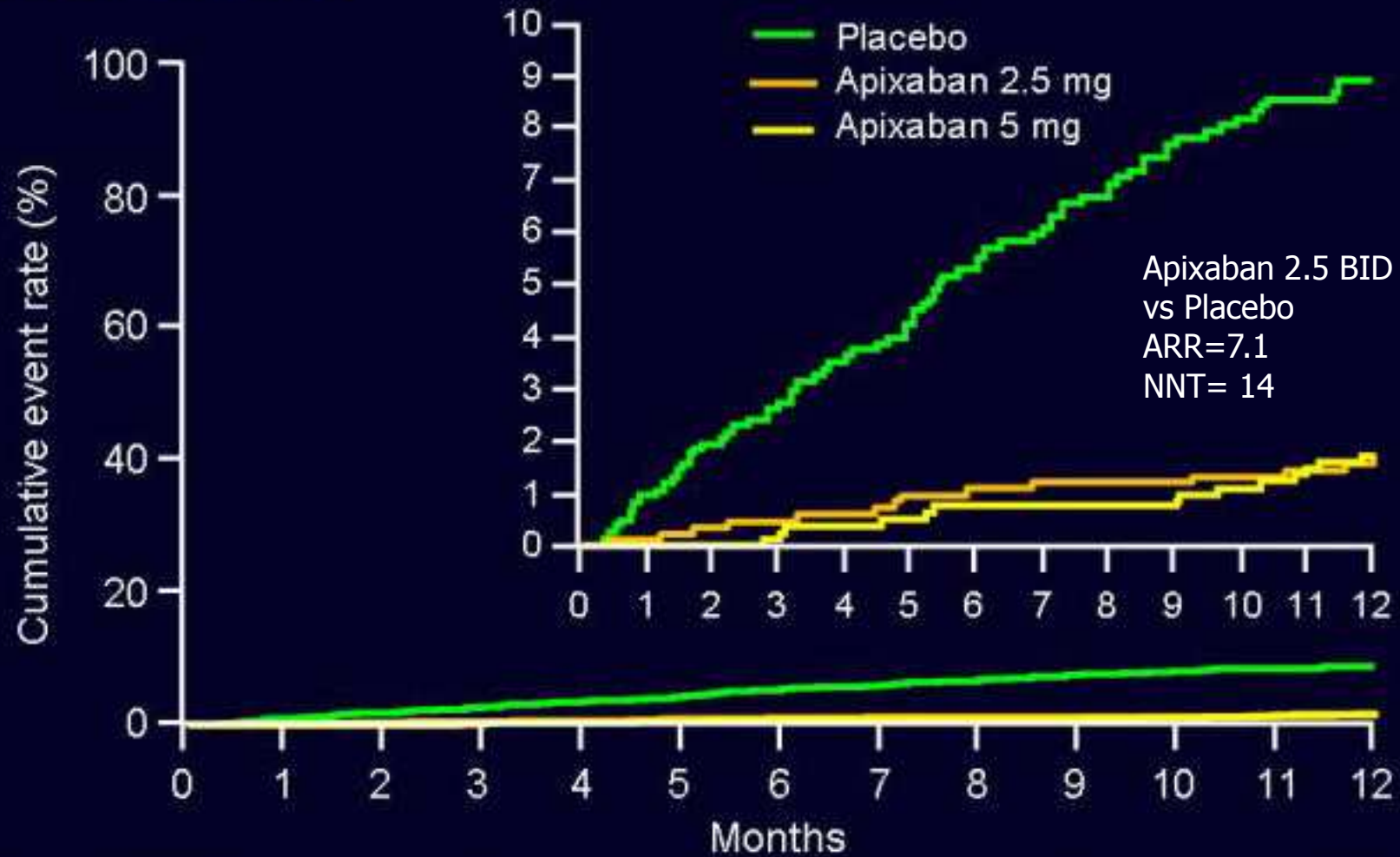


# AMPLIFY-EXT Aim and Study Design

- **Aim:** To compare the efficacy and safety of two doses of apixaban with placebo for the extended treatment of VTE
- **Design:** Randomized, double blind, placebo-controlled, superiority study, 1 year duration



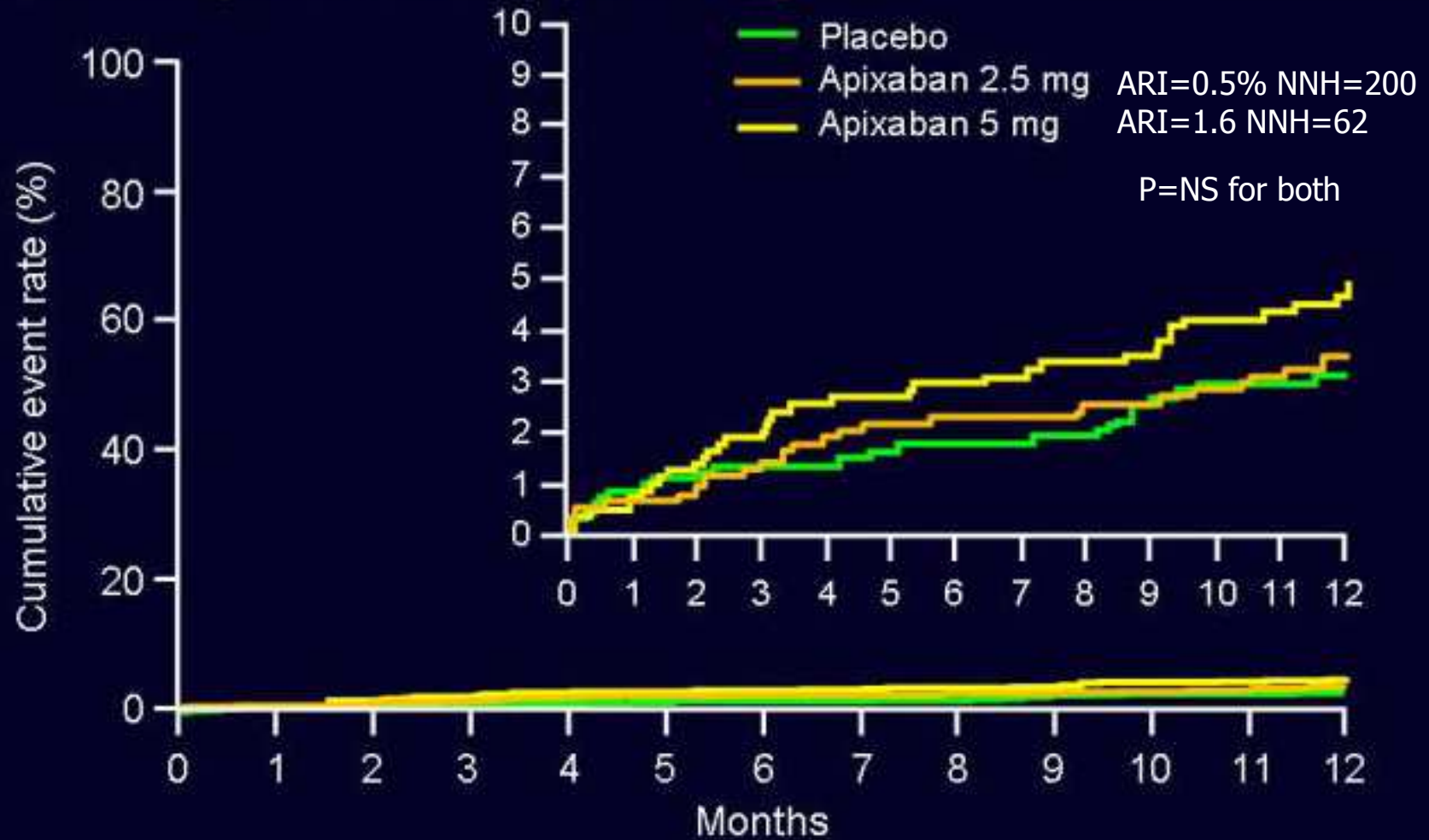
# Kaplan–Meier: Non-fatal and fatal VTE



No. at risk	Baseline	Month 3	Month 6	Month 9	Month 12
Apixaban 2.5 mg	840	836	825	818	533
Apixaban 5 mg	813	807	799	791	513
Placebo	826	796	768	743	471

# Kaplan–Meier:

## Major or Clinically relevant non major bleeding



No. at risk	Baseline	Month 3	Month 6	Month 9	Month 12
Apixaban 2.5 mg	840	786	759	737	354
Apixaban 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298



# Case Study



**39 year old male with right proximal DVT 71 Kg**

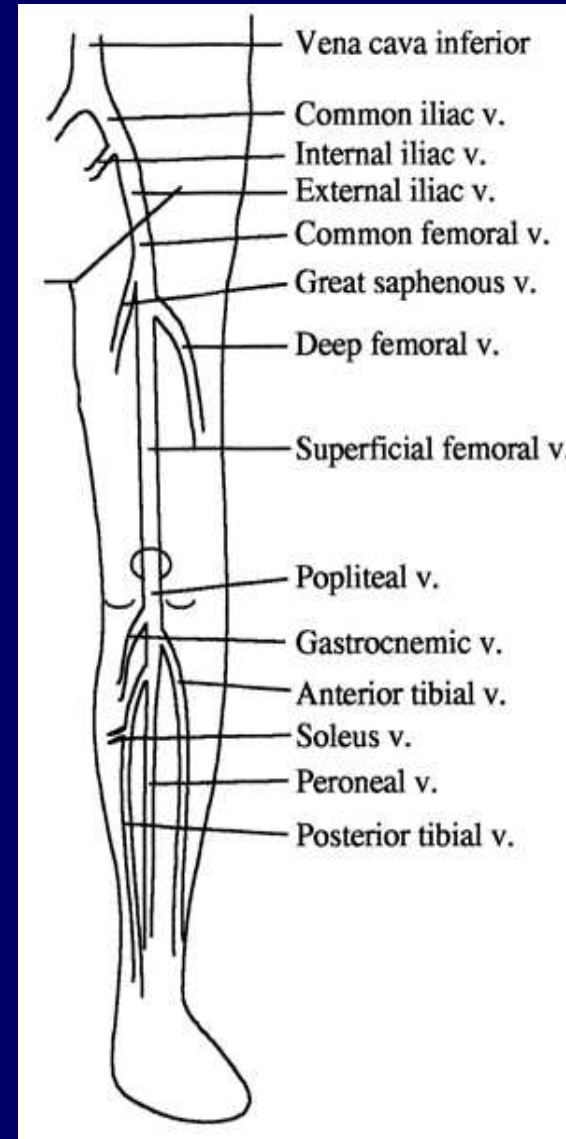
**No chronic medications using tylenol #3 prn for knee pain**

**eGFR 120 ml/min**

**Had ACL reconstruction right knee 3 weeks ago**



**Proximal DVT Involving:**  
**Superficial Femoral Vein**  
**Common Femoral Vein**  
**Distal Common Iliac**



# Which Option Do You Choose?

**A) Write Prescription, discharge patient to care of GP**

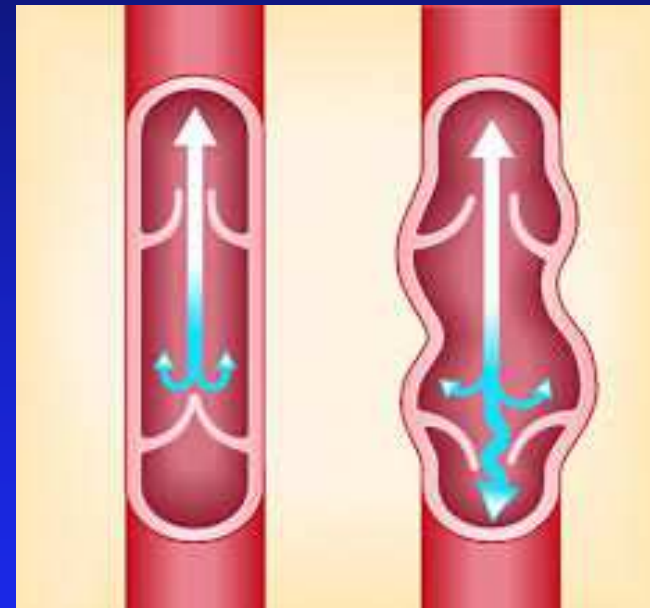
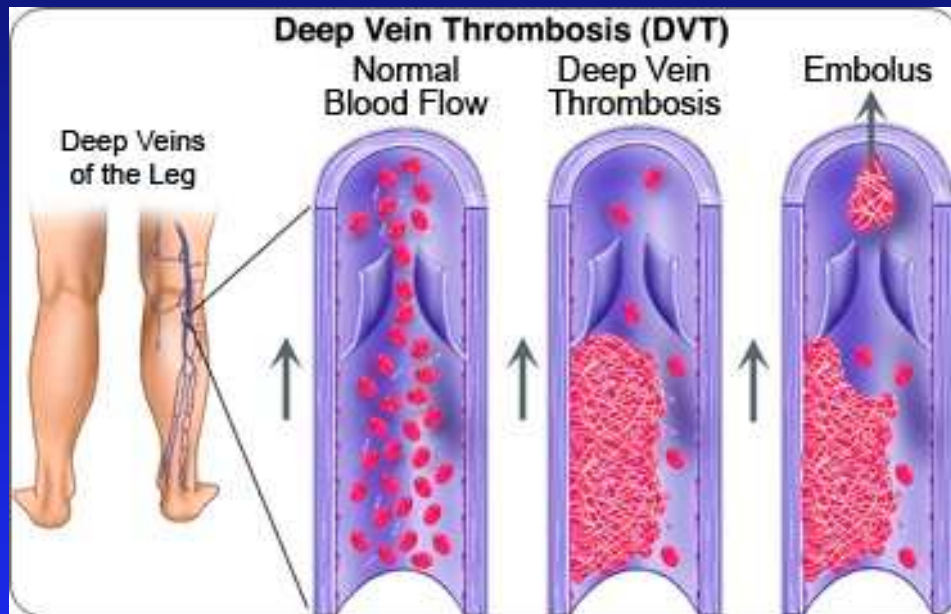
**Rivaroxaban 15 mg/day BID for 3 weeks,  
then 20 mg/day x 3 months**

**B) Outpatient Anticoagulation Clinic**

**LMWH minimum 5 days, Warfarin INR 2-3 x 3 Months**

**C) Admit to acute care, as patient has extensive clot**

## Venous Thrombosis Leads To Valve Loss, Reflux & Venous Hypertension



**Anticoagulation Therapy Seldom Results In Complete Thrombus Resolution**

# ***Post Thrombotic Syndrome Nasty and Painful***



40 to 60 %  
Develop PTS

4 to 6%  
Develop  
Severe PTS  
With  
Ulceration

<sup>1</sup> Kahn *et al.* *Ann Int Med.* 2008;149:698-707

# Clot Removal May Prevent PTS

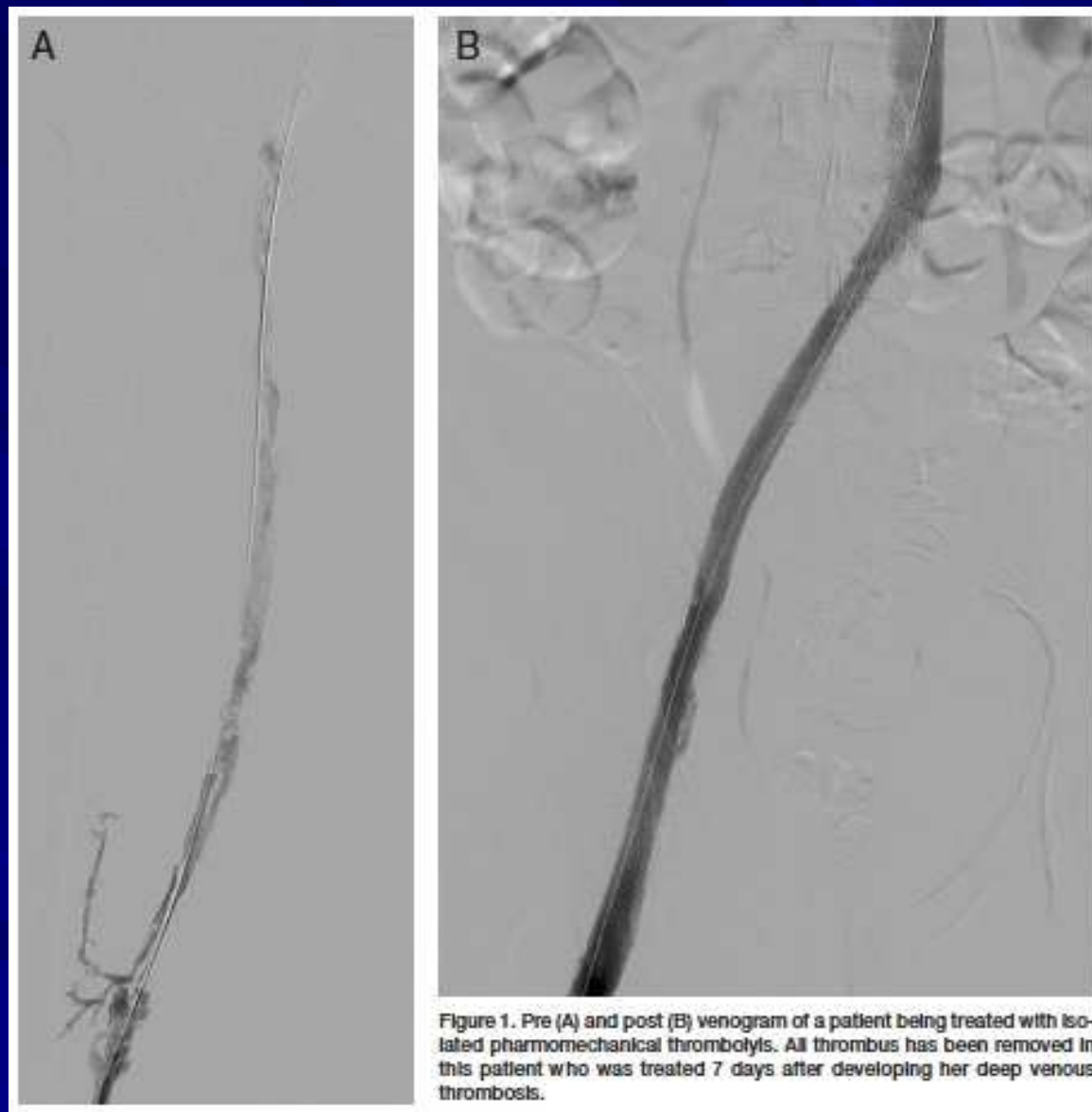
<u>Author/Year</u>	<u>Intervention</u>	<u>PTS Rates</u>	<u>RRR</u>
Elliott 1979	Systemic SK	92% vs 35%	<b>62%</b>
Arnesen 1982	Systemic SK	67% vs 24%	<b>64%</b>
Plate 1984	Modern Surg Thrombectomy	93% vs 58%	<b>38%</b>
Turpie 1990	Systemic TPA	56% vs 25%	<b>55%</b>
AbuRahma 2001	CDT - UK/TPA	70% vs 22%	<b>69%</b>



# Trellis Pharmacomechanical Thrombolysis



## Venogram Pre and Post Pharmacomechanical Thrombolysis





# Anticoagulants Alone Have Very Limited Efficacy

## Post-Anticoagulation

6 Weeks After Treatment



**Leg Swollen: Symptoms Unresolved  
AND**

... 47% of Patients Develop  
Post Thrombotic Symptom

## Post-Trellis

8 Weeks After Treatment



**Clot Removed: Symptoms Resolved**

... Trellis Isolated Thrombolysis  
Plus PTA and Stent Placement

