Anticoagulation: Applying Innovation in Clinical Practice

Preceding the 59th ASH Annual Meeting & Exposition

Friday, December 8, 2017 – Atlanta, Georgia

Disclaimer

The following presentations may not be reproduced, distributed, displayed, or presented without the prior written permission of the presenter.

Introduction:
Global burden of thrombosis

Rt Hon Professor the Lord Kakkar
Thrombosis Research Institute and
University College London, UK

Disclosures for Ajay Kakkar

- Grants and personal fees from Bayer Healthcare;
- Personal fees from: Boehringer-Ingelheim Pharma, Daiichi Sankyo Europe, Sanofi SA, Janssen, Verseon Inc

Acknowledgement

This Symposium is provided by the Thrombosis Research Institute and UK HealthCare CECentral and supported by an unrestricted educational grant from Bayer Pharma AG.

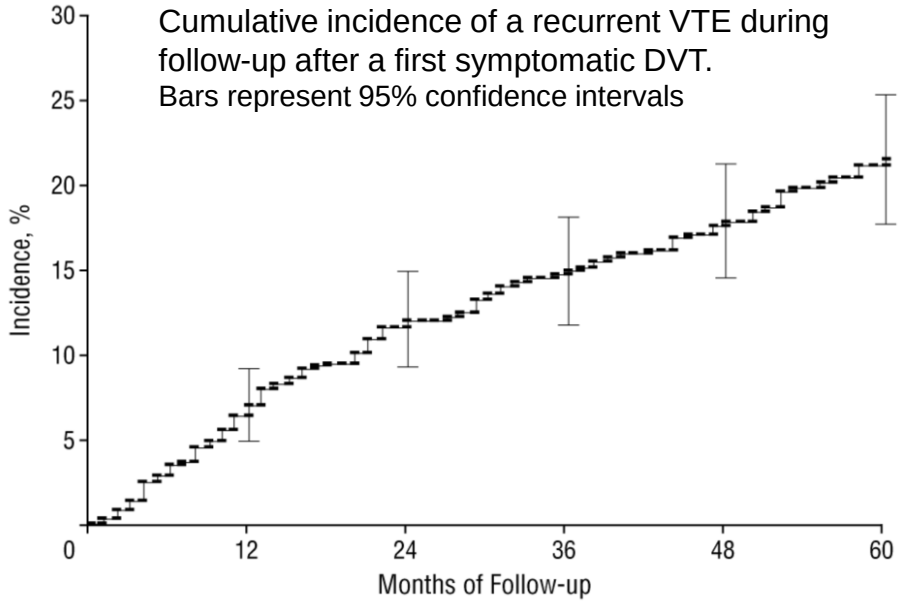
VTE Is a Serious, Potentially Life-Threatening Disease

- Third most common type of cardiovascular disease[1]
- Causes 12.4% of CV deaths[2]
- 30% of patients undergoing general surgery without thromboprophylaxis will develop VTE[3]
- Up to 15% of patients hospitalised for an acute medical illness develop VTE[4]
- Causes more deaths each year than breast cancer, prostate cancer, AIDS and transport accidents combined[5]

1. Goldhaber *at al*. J Am Coll Cardiol 1992;19:246–7. 2. Prandoni *et al*. *Blood* 2002;100:3484–8. 3. Kakkar. In: *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. 4. Tapson *et al*. *Chest*. 2007;132:936–45. 5. Cohen AT *et al*. *Thromb Haemost*. 2007;98:756–64.

Complications and Sequelae of Deep Vein Thrombosis (DVT)

- Pulmonary embolism (PE), which **contributes to 1 in 10 hospital deaths,** as well as:
  - Permanent damage to the lungs and other organs
  - Pulmonary hypertension (CTEPH)
    - 3–4% of patients who survive PE will develop this
  - Right heart ischaemia
- Post-thrombotic syndrome (PTS)
  - 20–50% of DVT patients go on to develop PTS
- Cumulative incidence of recurrent VTE
  - 7.0% after 1 year, up to 21.5% after 5 years

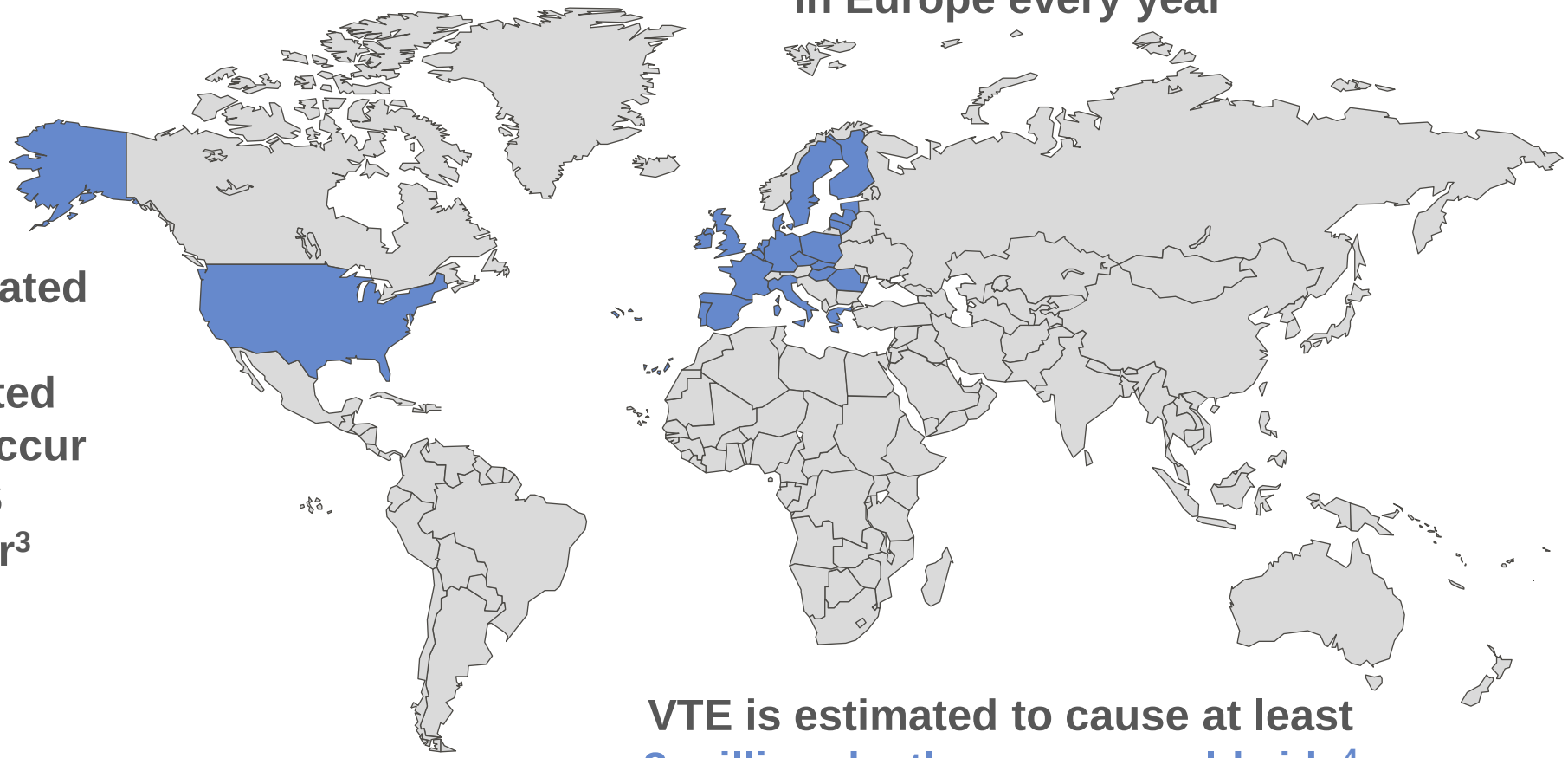


Cumulative incidence of a recurrent VTE during follow-up after a first symptomatic DVT. Bars represent 95% confidence intervals

1. The House of Commons Health Committee. 2005. 2. Pengo V et al. *N Engl J Med* 2004;350:2257–64. 3. Kahn et al. *Ann Intern Med* 2008;149:698–707. 4. Hansson et al. *Arch Intern Med* 2000;160:769–74.

VTE Is the Third Leading Cause of Cardiovascular Death[1]

VTE is estimated to cause >500,000 deaths in Europe every year[2]

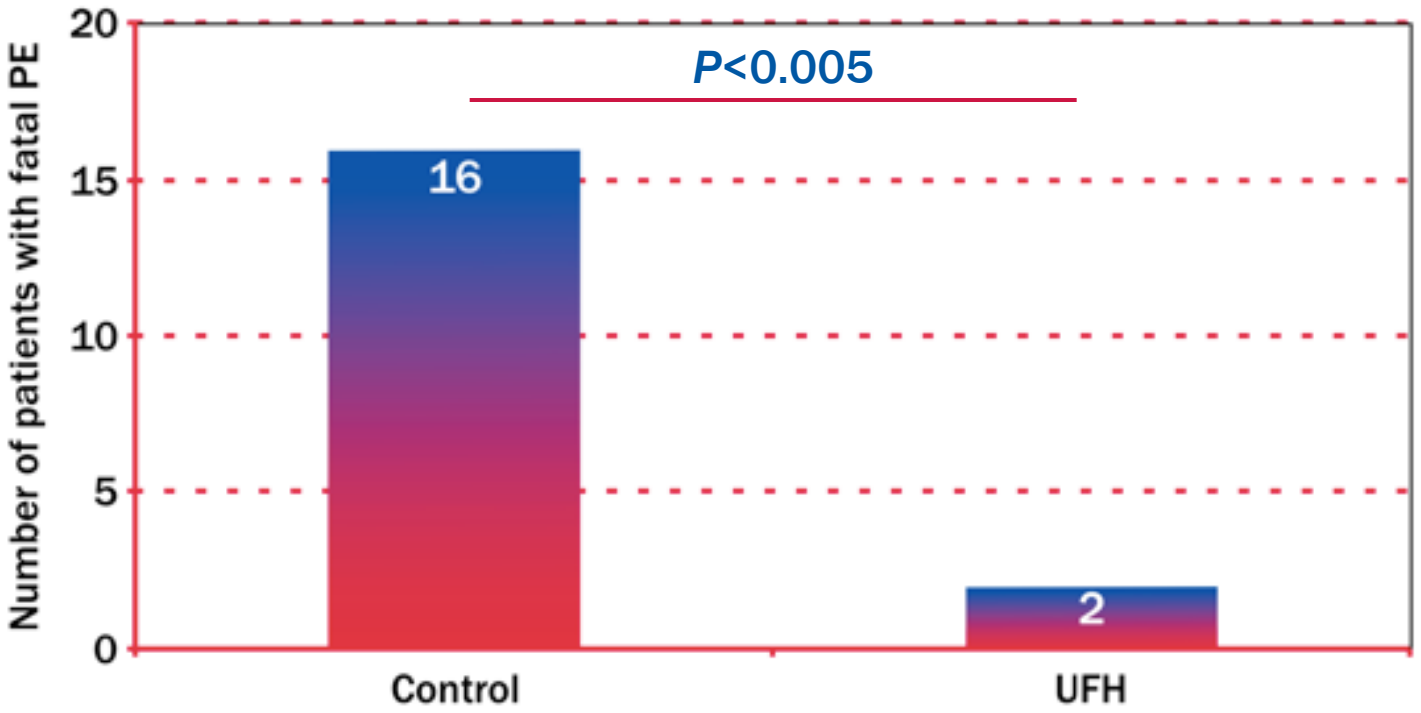


An estimated 200,000 VTE-related deaths occur in the US each year[3]

VTE is estimated to cause at least 3 million deaths a year worldwide[4]

1. Jha AK et al. *BMJ* 2013;22:809-815; 2. Cohen AT et al, *Thromb Haemost* 2007;98:756–764; 3. Heit JA et al, *Blood* 2005;106:Abstract 910; 4. ISTH Steering Committee for World Thrombosis Day J Thromb Haemost 2014;12:1580–90 .

Prophylaxis With UFH Reduces PE Mortality in Surgical Patients

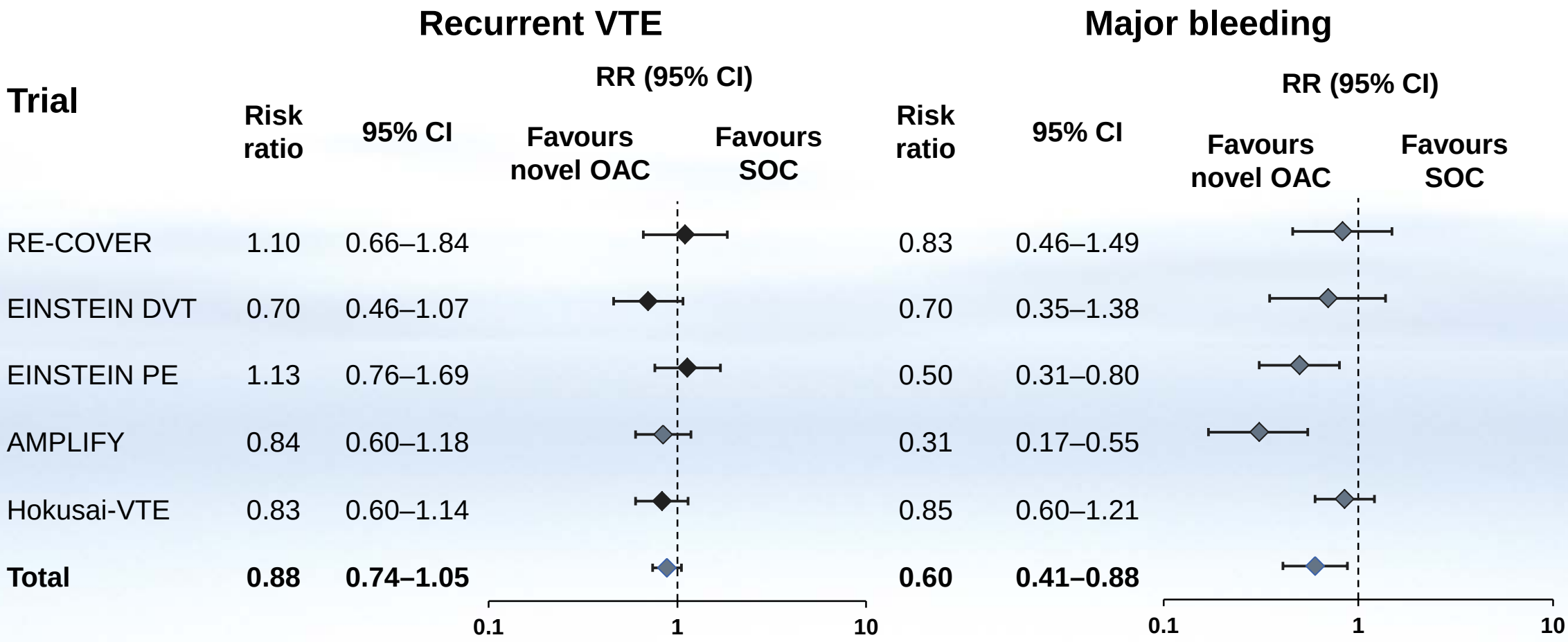


Low-dose UFH saves 7 lives for every 1000 operated patients

PE, pulmonary embolism; UFH, unfractionated heparin.

Kakkar VV et al. *Lancet* 1975;2:45–51.

Phase III Trials of NOACs for VTE Treatment



CI, confidence interval; NOAC, novel non-vitamin K antagonist anticoagulant; OAC, oral anticoagulant; RR, relative risk; SOC, standard of care; VTE, venous thromboembolism.

Van der Hulle T *et al. J Thromb Haemost* 2014;12:320–328.

The Global Burden of Stroke is Substantial and **Increasing**

- In the past **two decades, 1990–2010,** the global **number** of

- People who have a stroke each year:	↑ by **6.8 million**	**(68%)**
- Stroke survivors:	↑ by **15.1 million**	**(84%)**
- DALYs lost:	↑ by **16.2 million**	**(20%)**
- Deaths due to stroke:	↑ by **1.2 million**	**(25%)**

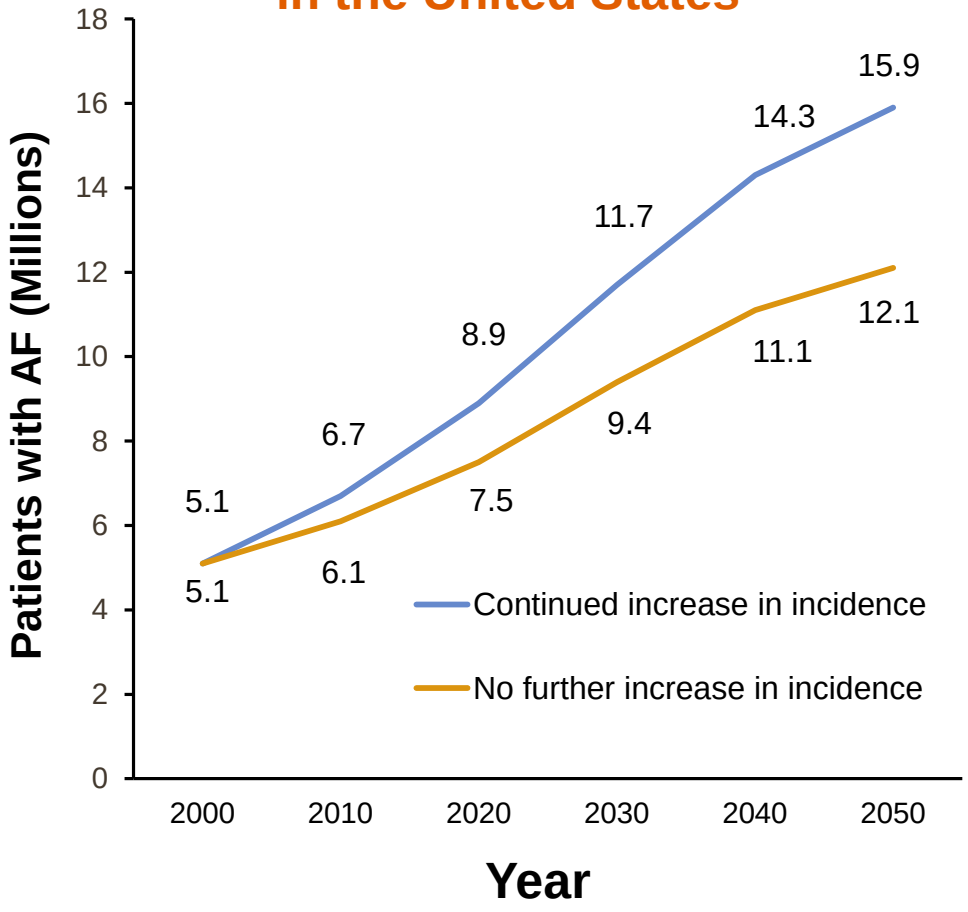
	1990	2010
	n	n
All ages		
Incidence	10 078 935	16 894 536
Prevalence	17 915 338	33 024 958
MIR	..	..
DALYs lost	86 010 384	102 232 304
Mortality	4 660 449	5 874 182

Feigin VL et al. *Lancet* 2014; 383:245–54.

The Burden of AF is Substantial and Expected to Grow

- AF affects **1–1.5%** of the population in the developed world[1]
- Its prevalence is expected to **triple by 2050**[1]
- AF is a key risk factor for ischaemic stroke and mortality[2]
  - **5-fold** increased risk of stroke
  - **2-fold** increased risk of death

Projected prevalence of AF in the United States[3]



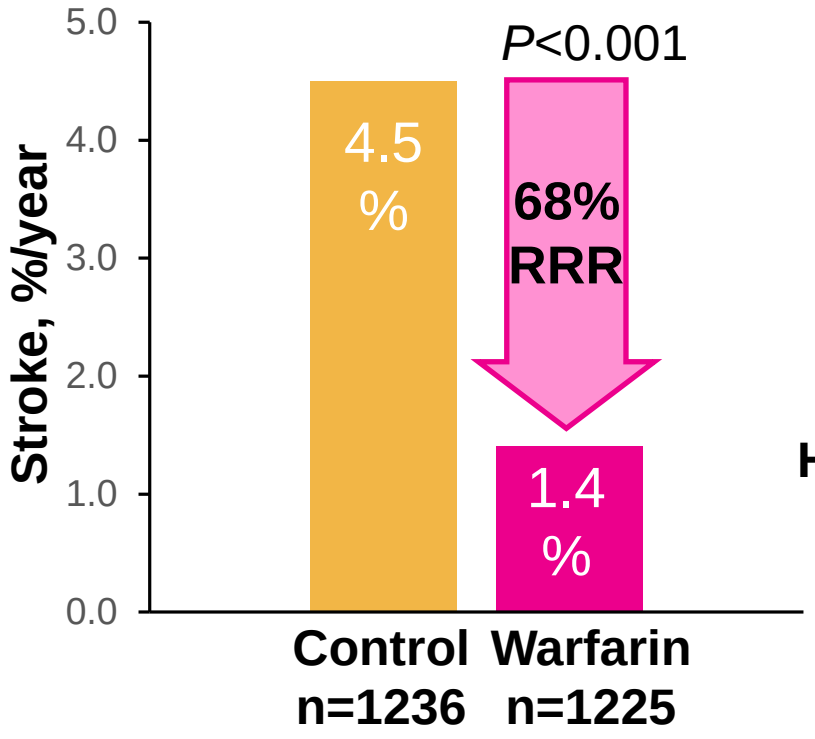
AF = atrial fibrillation

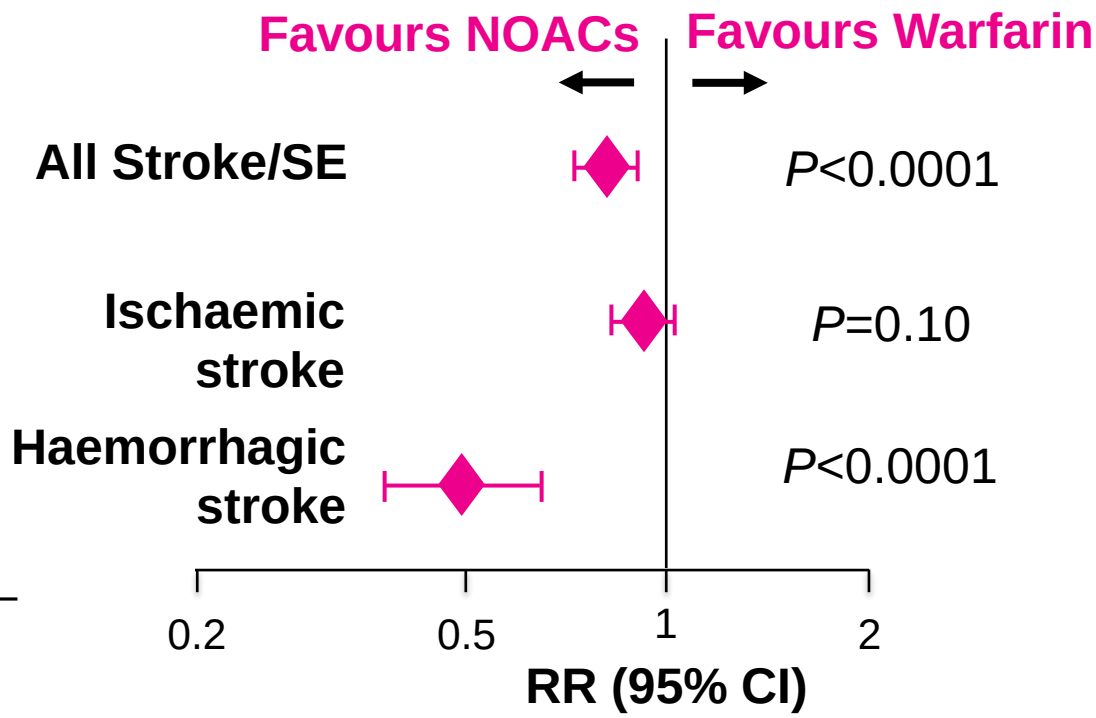
1. Savelieva I et al. *Clin Cardiol* 2008;31:55–6; 2. Wolf P et al. *Arch Intern Med* 1987;147:1561–4; 3. Miyasaka Y et al. *Circulation* 2006;114:119–25.

Anticoagulant Use Reduces Stroke Risk in Patients With AF

Warfarin significantly decreases the risk

NOACs demonstrate comparable reduction in

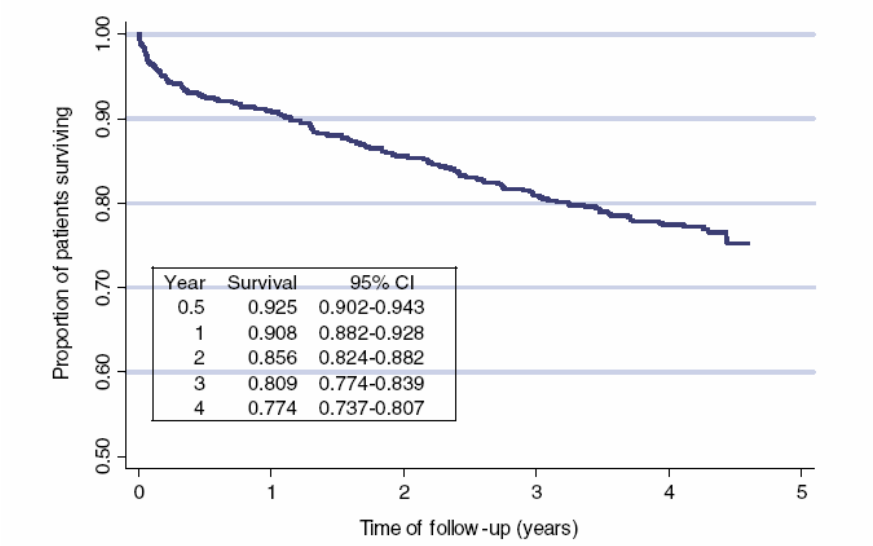




1. Atrial Fibrillation Investigators. *Arch Intern Med* 1994;154:1449–57; 2. Ruff CT et al. *Lancet* 2014;383:955–62.

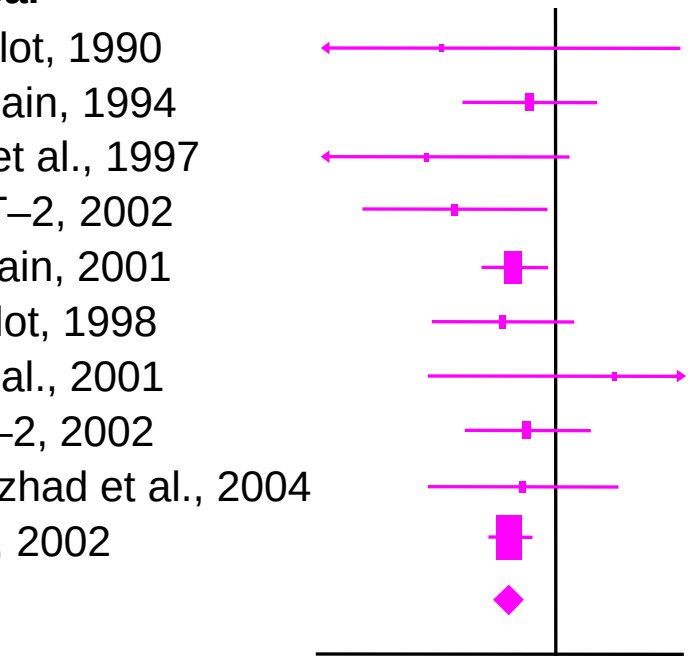
The Burden of Disease – Acute Coronary Syndrome

- **High recurrence** despite optimal application of evidence-based strategies
  - **Within 6 months** of the index event, **approximately 10%** of all ACS patients will suffer a recurrent ischaemic event, and **this increases to 20% after 3 years**[1]
  - **Overall survival 4 years after index event approximately 78%**
    - **73% of these deaths attributable to CV causes**[2]



1. Wallentin L, et al for the PLATO Investigators. *N Engl J Med*.2009;361:1045-57.
2. Taneja AK, *et al.* Eur Heart J 2004;25:2013–18.

Meta-Analysis of Anticoagulation: Efficacy – Recurrent MI

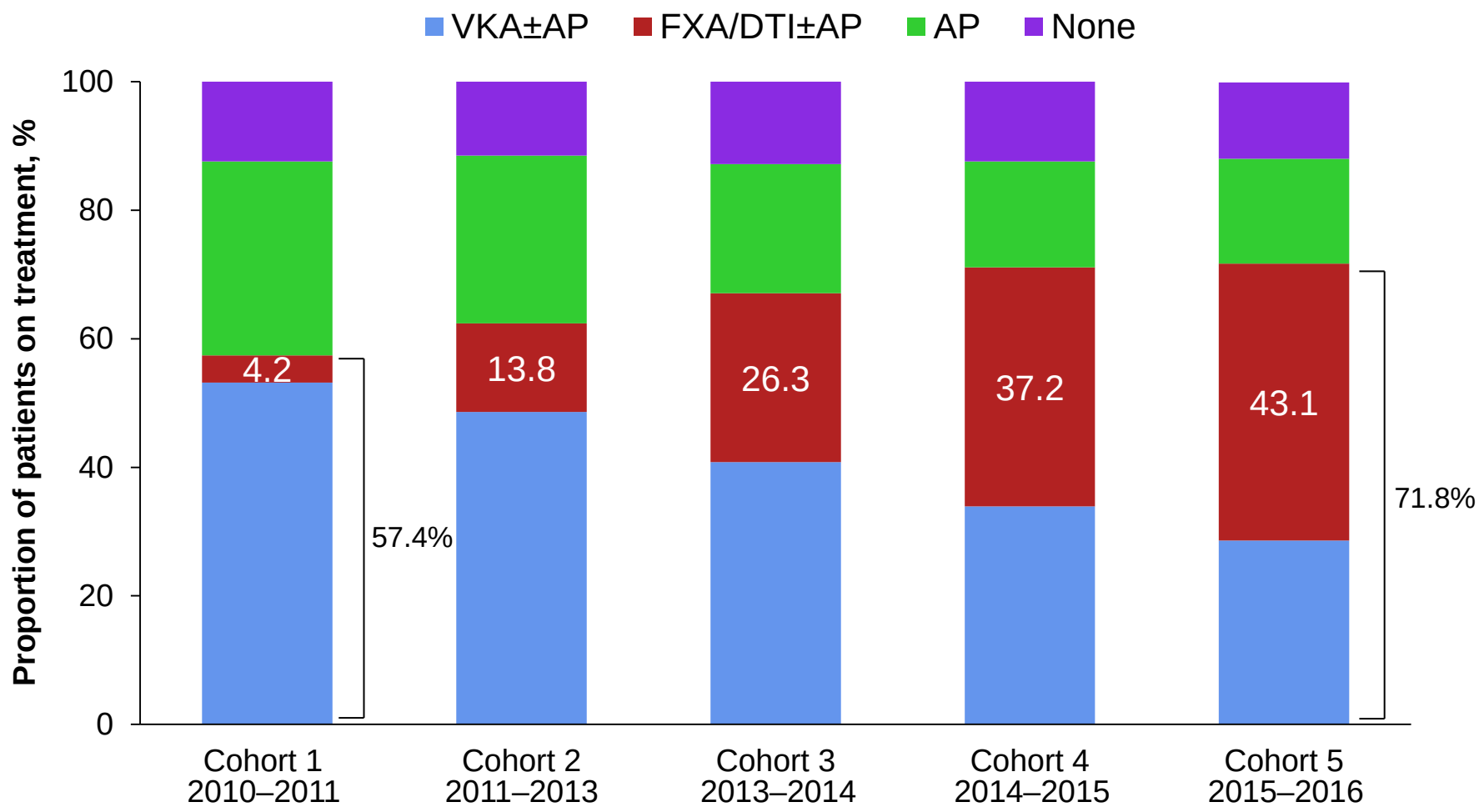


Study, year	Rate ratio (95% CI)	Weight (%)	Events/ patient-years: Warfarin	Events/ patient-years: ASA
ATACS pilot, 1990	0.22 (0.01 – 4.66)	0.5	0/9	1/7
ATACS main, 1994	0.69 (0.29 – 1.65)	5.7	6/24	9/25
Williams et al., 1997	0.19 (0.03 – 1.16)	1.3	1/6	5/5
APRICOT–2, 2002	0.28 (0.09 – 0.92)	3.1	3/34	11/35
OASIS main, 2001	0.58 (0.38 – 0.98)	23.9	30/373	52/375
OASIS pilot, 1998	0.51 (0.20 – 1.26)	5.2	5/25	10/25
Huynh et al., 2001	2.07 (0.20 – 21.85)	0.8	2/38	1/39
ASPECT–2, 2002	0.69 (0.31 – 1.53)	6.8	10/298	14/289
Zibaeenezhad et al., 2004	0.87 (0.20 – 2.28)	2.9	4/70	6/70
WARIS II, 2002	0.56 (0.42 – 0.75)	49.8	69/4,927	117/4669
Overall	0.56 (0.48 – 0.69)	100.0	130/5,834	228/5539

Prevent 19 MIs per 1000 patient-years

Rothberg MB et al. *Ann Int Med* 2005;143:241-50.

Evolution in Baseline Treatment for Patients Enrolled in Sequential Cohorts of GARFIELD-AF



Cohorts 1–5, N=51,270

Learning objectives

Upon completion of this educational activity, you will be able to:

1. Know the difference between data from the “real world” and randomised clinical trials
2. Comprehend the current status of anticoagulant therapy for:
   - Treatment of VTE
   - Thromboprophylaxis in: AF and coronary or peripheral arterial disease
3. Understand the gap between guideline-mandated therapy and treatment provided in the real world

Faculty

Lord Ajay Kakkar, MBBS, PhD, FRCS, FRCP, PC

- Professor of Surgery, University College London; Chairman, University College London Partners; Director, Thrombosis Research Institute London, United Kingdom

Jeffrey I. Weitz, MD, FRCP, FACP

- Professor of Medicine and Biochemistry and Biomedical Sciences at McMaster University; Executive Director, Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, Canada

Alexander G. Turpie, MB, FRCP, FACP, FACC, FRCPC

- Emeritus Professor of Medicine at McMaster University; internist on the staff of Hamilton Health Sciences, Hamilton, Ontario, Canada

Howard A. Liebman, MA, MD

- Chair in Medicine, Professor of Medicine and Pathology, Jane Anne Nohl Division of Hematology, USC Norris Cancer Hospital Los Angeles, California, USA

A. John Camm, QHP, MD, FRCP, FACC, FESC

- Professor of Clinical Cardiology, St. George's University of London; Honorary Consultant Cardiologist, St. George's Hospital, London, United Kingdom

Freek W.A. Verheugt, MD, FESC, FACC

- Emeritus Professor of Cardiology and was Chairman of the Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam, The Netherlands

Our Symposium Today

Anticoagulation: Applying Innovation in Clinical Practice

Chair: *A.K. Kakkar (UK)*

13.30 – 13.40	**Introduction – The global burden of thrombosis**	A.K. Kakkar (UK)
13.40 – 14.00	**VTE – Still a clinical challenge?**	J.I. Weitz (Canada)
14.00 – 14.20	**Therapeutic interventions for VTE – What is the standard of care?**	A.G.G. Turpie (Canada)
14.20 – 14.40	**Cancer-associated thrombosis – What is the true burden of disease?**	A.K. Kakkar (UK)
14.40 – 15.00	**Preventing and treating thrombosis in cancer patients**	Howard A. Liebman (USA**)**
15.00 – 15.20	**Anticoagulation and atrial fibrillation – Current perspectives**	A.J. Camm (UK)
15.20 – 15.40	**Is there a role for anticoagulation in patients with arterial disease?**	F.W.A. Verheugt (The Netherlands)
15.40 – 16.25	**Interactive discussions – Applying innovation in clinical practice**	J.I. Weitz (Canada), Howard A. Liebman (USA), F.W.A. Verheugt (The Netherlands)
16.25 – 16.30	**Closing remarks**	A.K. Kakkar (UK)

Venous Thromboembolism: Still a Clinical Challenge?

Jeffrey I. Weitz, MD, FRCP(C), FACP

Professor of Medicine and Biochemistry, McMaster University, Hamilton, Ontario, Canada; Canada Research Chair in Thrombosis, Heart & Stroke Foundation / J.F. Mustard Chair in Cardiovascular Research

Disclosures for Jeffrey Weitz

Research Support/P.I.	Canadian Institutes of Health Research, Heart and Stroke Foundation, Canadian Fund for Innovation
Employee	No relevant conflicts of interest to declare
Consultant	Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer, Portola, Ionis Pharmaceuticals, Janssen, Merck, Novartis
Major Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	No relevant conflicts of interest to declare
Scientific Advisory Board	Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer, Portola, Ionis Pharmaceuticals, Janssen, Servier

Educational Need / Practice Gap

- NOACs are increasingly used for VTE treatment
- Optimal duration of VTE treatment remains problematic
- Availability of usual and lower dose NOAC regimens enables patient-specific choices

Objectives

- **Understand clinical trial data supporting the use of NOACs for VTE**
  - **Initial**
  - **Long term and**
  - **Extended treatment**

Summary of ACCP 2016 Guidelines: Acute Treatment and Secondary Prevention

	ACCP recommendation	Grade of recommendation
Initial anticoagulation		
Acute DVT or haemodynamically stable PE and no cancer	NOAC preferred to LMWH / VKA	2B
	LMWH / VKA preferred to LMWH alone	2C
PE with hypotension	Thrombolytic therapy (systemic rather than catheter-directed unless bleeding risk is high)	2B (2C)
DVT or PE with cancer	LMWH suggested over NOAC or VKA	2C
Duration of anticoagulant therapy		
Proximal DVT or PE	3 months recommended over shorter duration	1B
First proximal DVT or PE provoked by surgery or other transient risk factor	3 months	1B (2B if low / moderate bleeding risk)
Unprovoked DVT or PE	Extended therapy if bleeding risk is low / moderate	2B
	3 months if bleeding risk is high	1B
DVT or PE associated with active cancer	Extended therapy recommended over 3 months' therapy	1B (2B if high bleeding risk)

ACCP = American College of Chest Physicians; DVT = deep vein thrombosis; LMWH = low molecular weight heparin; NOAC = non-vitamin K antagonist oral anticoagulant; PE = pulmonary embolism; VKA = vitamin K antagonist.

Kearon C et al. *Chest* 2016;149:315–52.

Current Recommendations for the Management of Unprovoked VTE

		ACCP recommendation	Grade of recommendation
2016 CHEST guidelines[1]	Unprovoked DVT or PE	Extended therapy if bleeding risk is low / moderate	2B
		3 months if bleeding risk is high	1B

In patients with DVT of the leg or PE and no cancer, as long-term anticoagulant therapy (first 3 months) we suggest dabigatran, rivaroxaban, apixaban or edoxaban over VKA therapy (all Grade 2B)[1]

		Class of recommendation	Level of evidence
2014 ESC PE guidelines[2]	Unprovoked PE: ≥3 months	I	A
	First episode of unprovoked PE and low bleeding risk: consider extended treatment (>3 months)	IIa	B
	Second episode of unprovoked PE: indefinite duration	I	B
	Risk-benefit of continuing anticoagulation should be reassessed at regular intervals	I	C

Rivaroxaban (20 mg OD), dabigatran (150 mg BID, or 110 mg BID for patients >80 years of age or those under concomitant verapamil treatment) or apixaban (2.5 mg BID) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary[2]

BID = twice daily; OD = once daily

1. Kearon C et al. *Chest* 2016;149:315–52; 2. Konstantinides SV et al. *Eur Heart J* 2014;35:3033–69.

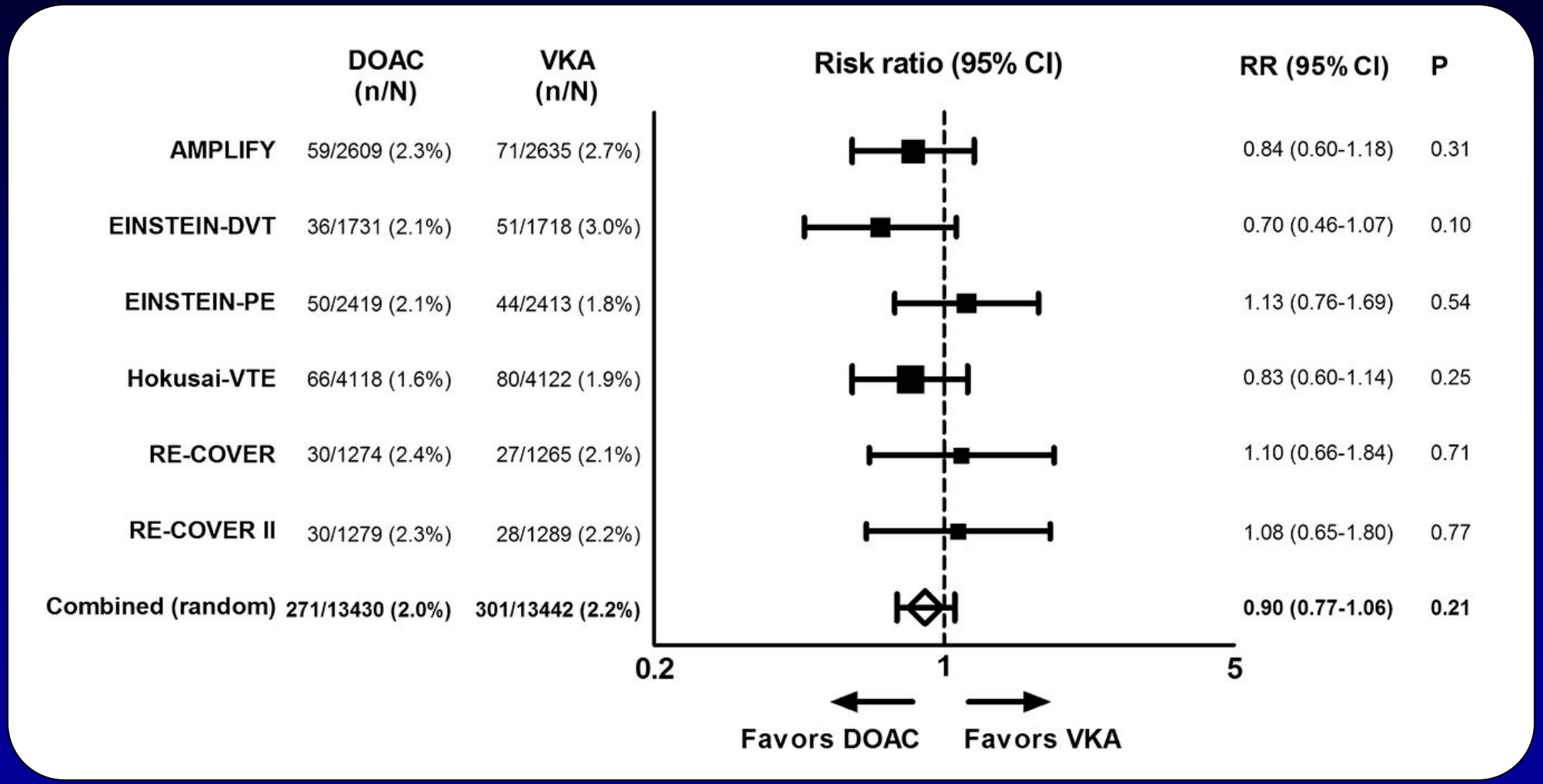
Phase III NOAC VTE Treatment Studies

Drug	Trial	Design	Treatments and dosage	Duration (months)	Patients (n)	Index event*	Primary efficacy event	Principal safety outcome
Rivaroxaban	EINSTEIN DVT[1] EINSTEIN PE[2]	Open-label	Riva (15 mg BID for 3 weeks, then 20 mg OD) *vs* enoxaparin/VKA	3, 6 or 12	3449 4832	DVT PE	Recurrent VTE	Major/clinically relevant non-major bleeding
Apixaban	AMPLIFY[3]	Double-blind, double-dummy	Apix (10 mg BID for 7 days, then 5 mg BID) *vs* enoxaparin/ warfarin	6	5395	DVT/PE	Recurrent VTE or related death	Major bleeding
Dabigatran	RE-COVER[4] RE-COVER II[5]	Double-blind, double-dummy	Parenteral/dabigatran (150 mg BID)* *vs* parenteral/ warfarin	6	2539 2589	DVT/PE DVT/PE	Recurrent VTE or related death	Major bleeding
Edoxaban	Hokusai-VTE[6]	Double-blind, double-dummy	Parenteral/edoxaban (60 mg OD or 30 mg OD*) *vs* parenteral/warfarin	3–12	8240	DVT/PE	Recurrent VTE	Major/clinically relevant non-major bleeding

*All index DVT/PE events were acute, symptomatic and objectively confirmed

1. The EINSTEIN Investigators. *N Engl J Med* 2010; 363:2499–2510; 2. The EINSTEIN–PE Investigators. *N Engl J Med* 2012; 366:1287–1297; 3. Agnelli G, et al. *N Engl J Med* 2013; 369:799–808; 4. Schulman S, et al. *N Engl J Med* 2009; 361:2342–2352; 5. Schulman S, et al. *Circulation* 2014; 129:764–772; 6. The Hokusai-VTE investigators. *N Engl J Med* 2013; 369:1406–1415

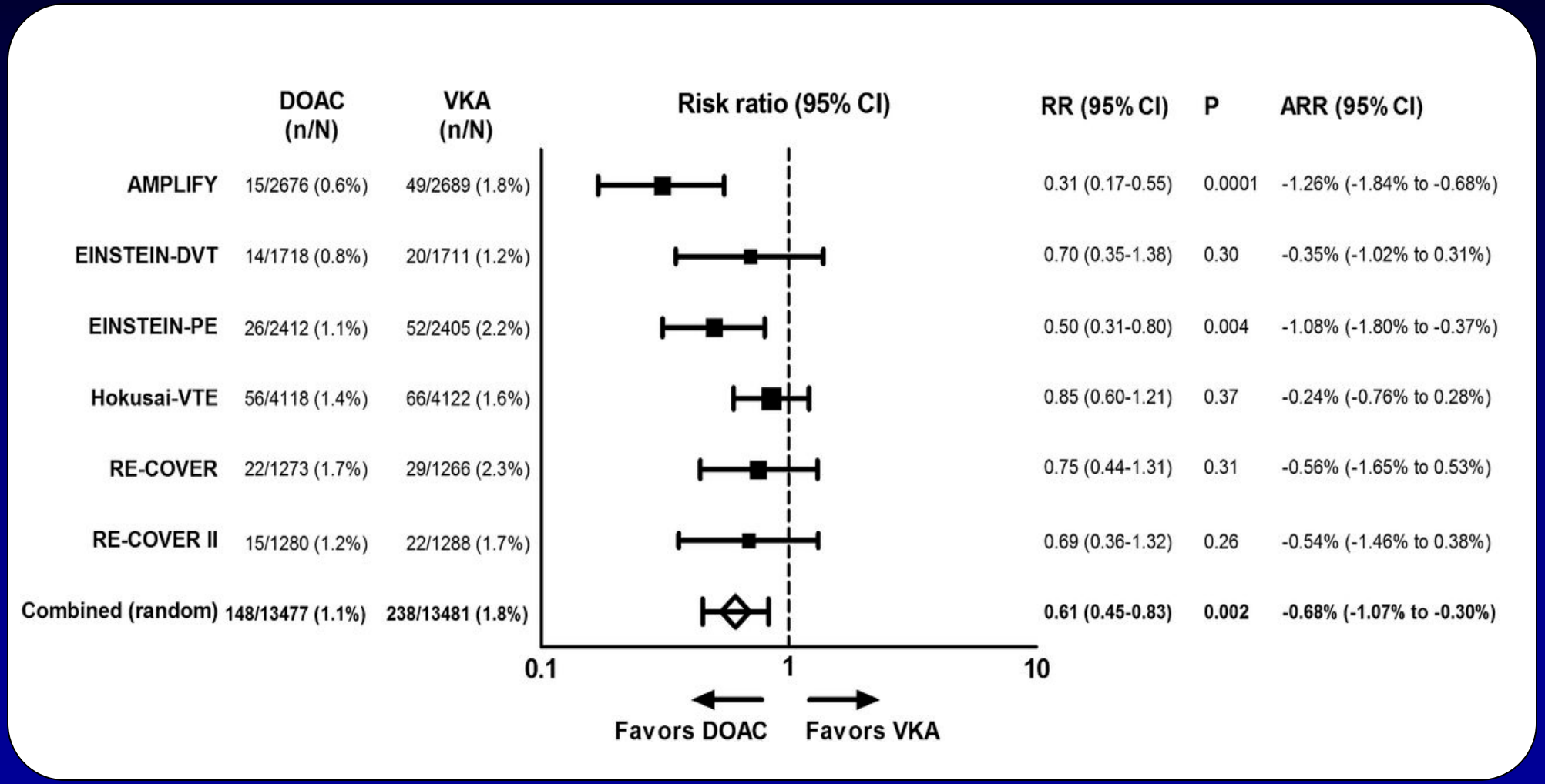
NOACs versus VKAs: Recurrent VTE



CI = confidence interval; DOAC = direct oral anticoagulant; RR = relative risk.

van Es N, et al. *Blood* 2014; 124:1968–1975.

NOACs versus VKAs: Major bleeding

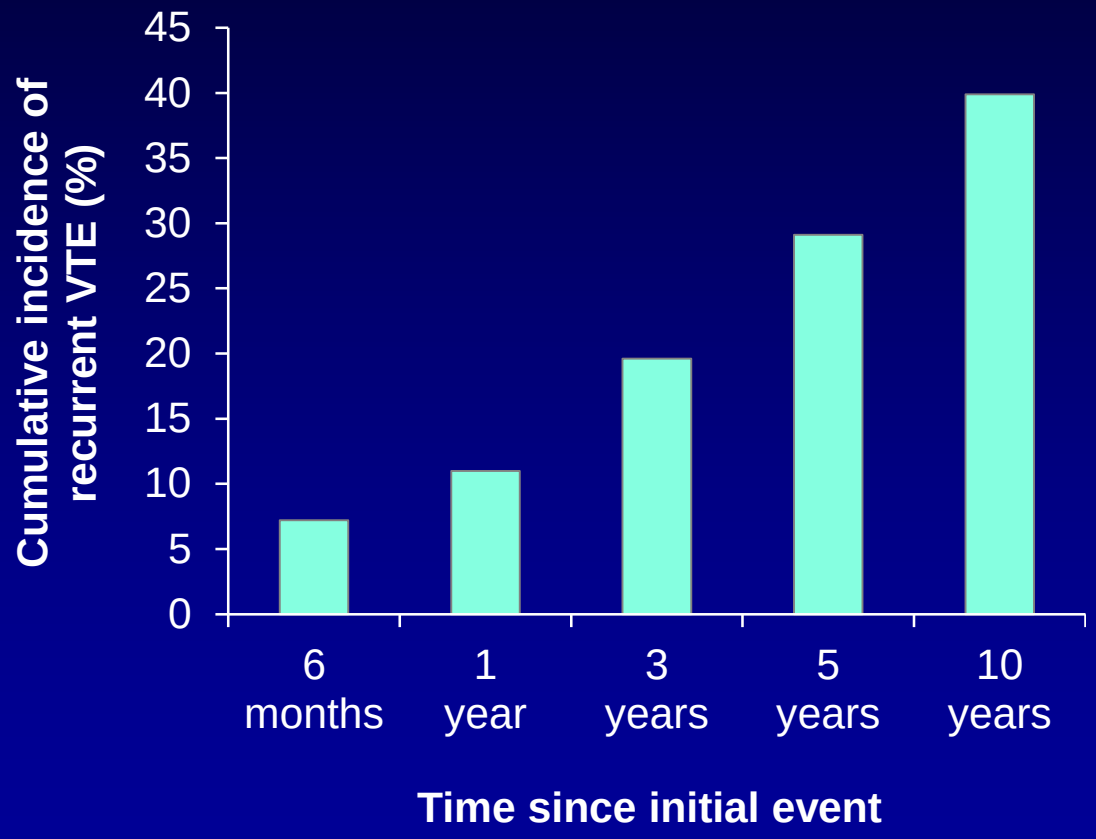


ARR = absolute risk reduction.

van Es N, et al. *Blood* 2014; 124:1968–1975.

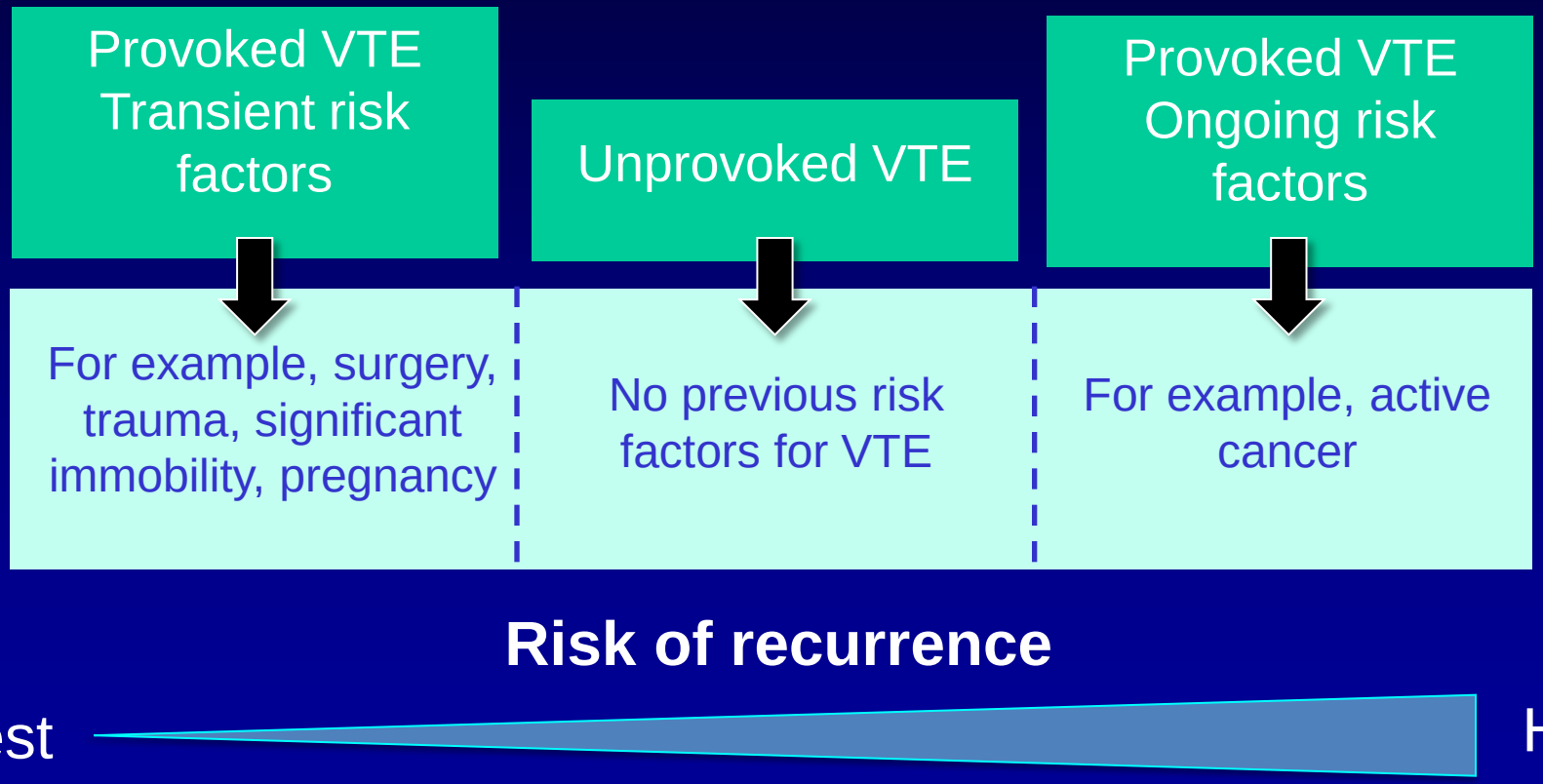
High Risk of Recurrent VTE After Discontinuing Anticoagulation

- Anticoagulation effectively resolves VTE, but stopping treatment increases cumulative VTE recurrence risk[1]
- The cumulative incidence of recurrent VTE is approximately 10% in the first year if anticoagulation is stopped[1]



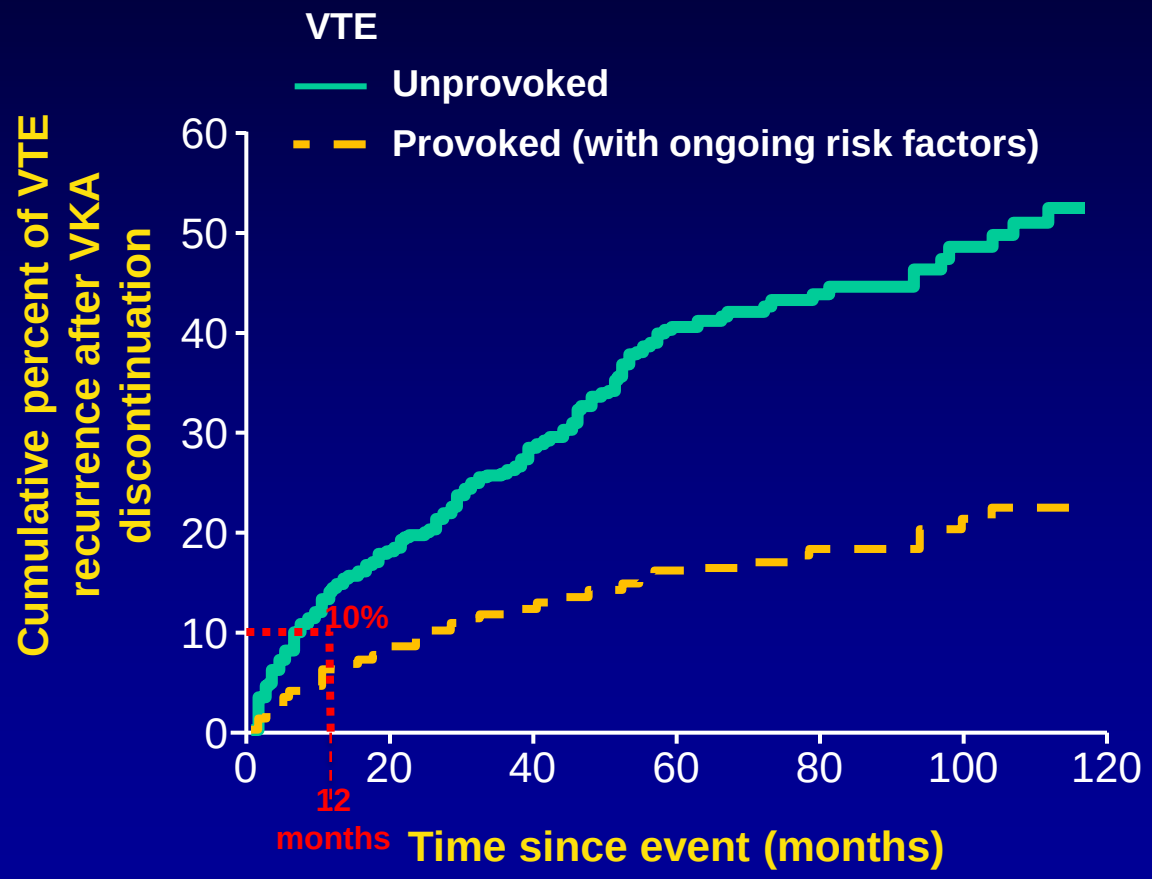
1. Prandoni P, et al. *Haematologica* 2007; 92:199–205.

Risk of Recurrence Depends on Type of VTE Event



Kearon C, et al. *J Thromb Haemost* 2016; 14:1480–1483.

High Risk of Recurrent VTE After Discontinuing Anticoagulation[1]



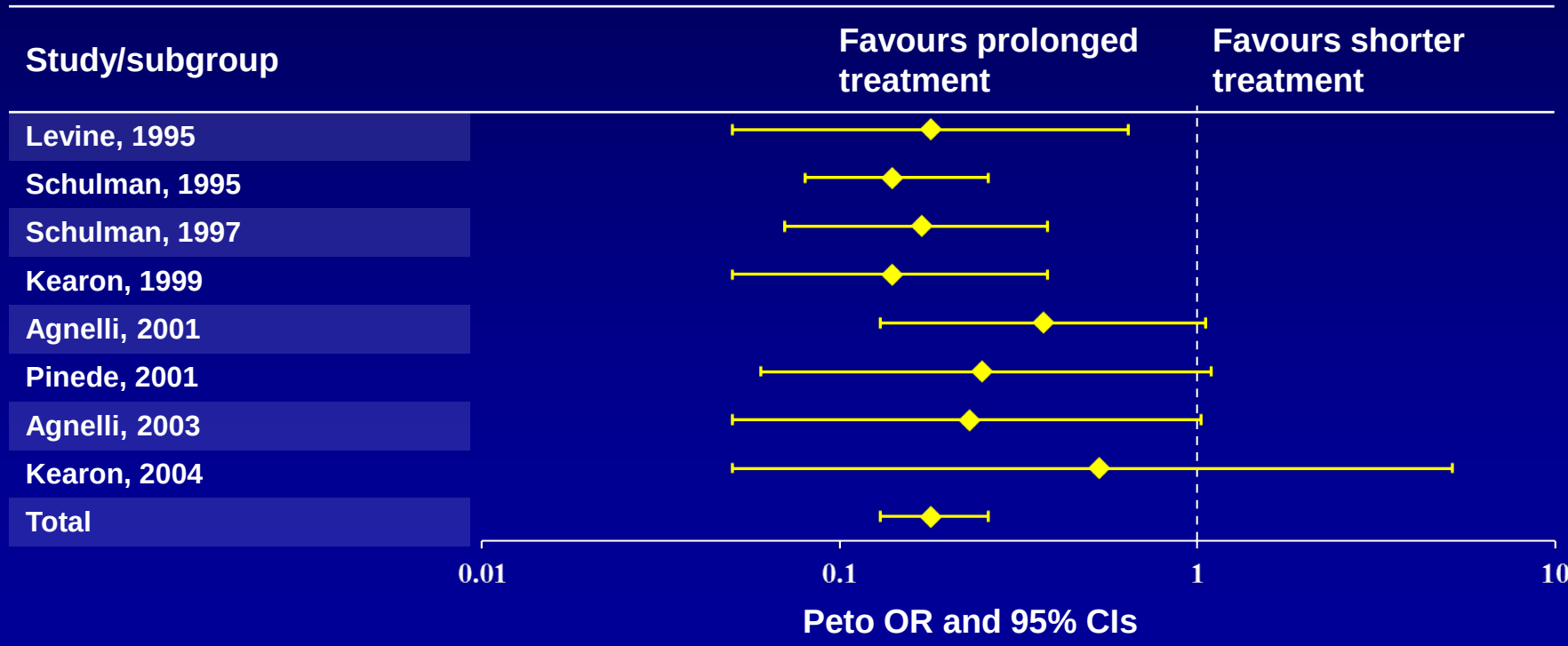
In patients with an unprovoked or provoked VTE (with ongoing risk factors), the risk of recurrence is about 10% in the first year if anticoagulant treatment is stopped[1]

1. Prandoni P, et al. *Haematologica*. 2007; 92:199–205.

VTE Recurrence with Continued Versus Shorter Duration VKA Treatment

Meta-analysis of eight studies of 2994 patients

Consistent reduction in VTE recurrence with prolonged versus shorter treatment (OR=0.18; 95% CI 0.13–0.26)



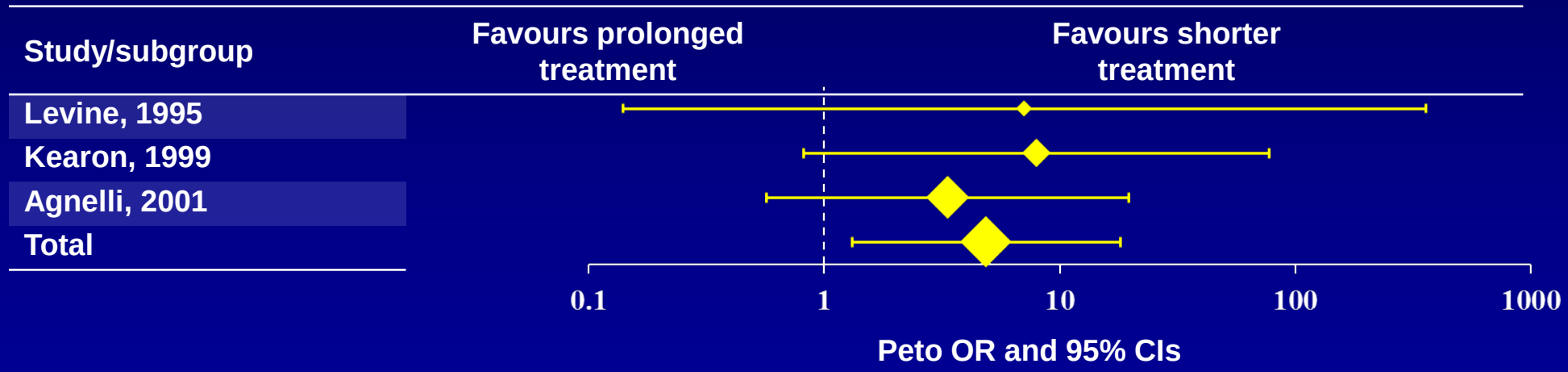
OR = odds ratio.

Hutten B & Prins M. *Cochrane Database Syst Rev* 2006; 1:CD001367.

Incidence of Major Bleeding with Continued Versus Shorter Duration VKA Treatment

Meta-analysis of four studies (N=808)*

Significant increase in major bleeding with prolonged versus shorter VKA treatment (OR=4.87; 95% CI 1.31–18.15)

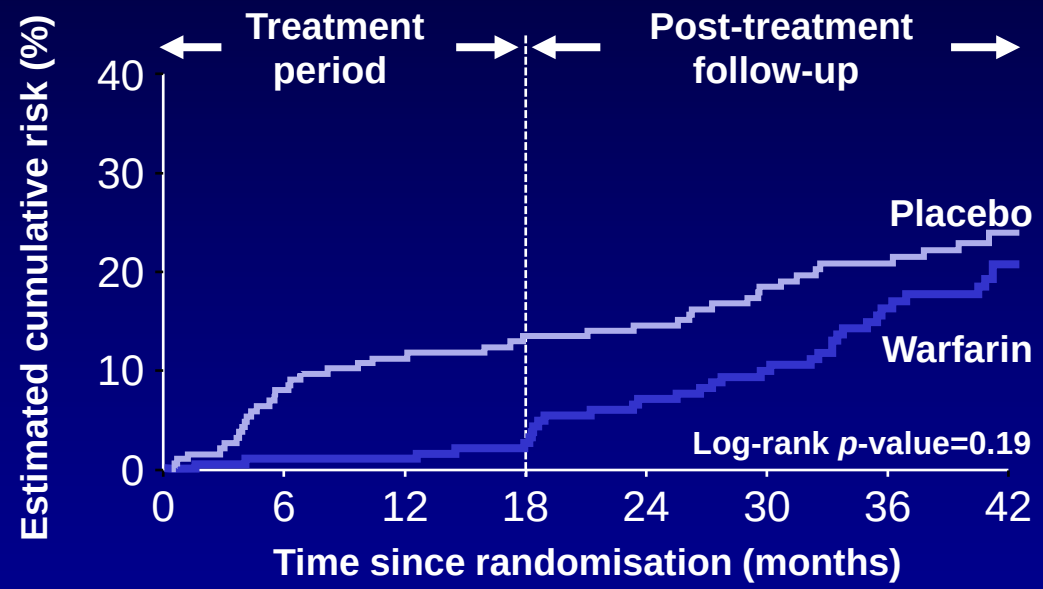


*Kearon, 2004 not presented (no major bleeding events)

Hutten B & Prins M. *Cochrane Database Syst Rev* 2006; 1:CD001367.

VTE Recurs Even After Extended Periods of Anticoagulation with VKA

- 371 patients with unprovoked PE
- Rx with extended warfarin versus placebo for 18 months
- Follow-up 24 months
- Entire study period: 42 months
- Composite outcome (recurrent VTE or major bleeding)
  - Unadjusted HR
    - 0.23 (95% CI 0.09–0.55) during treatment period
    - 0.74 (95% CI 0.47–1.17) for entire study period



No. at risk								
Placebo	187	170	162	158	155	140	117	104
Warfarin	184	182	180	174	168	150	120	110

HR = hazard ratio.

Couturaud F, et al. *JAMA* 2015; 314:31–40.

Clear Guidelines Exist for VTE Treatment Up to 3 Months. However, There Is a Lack of Clear Guidance for Extended Treatment Beyond This

3 months anticoagulation treatment recommended

- If unprovoked with low-to-moderate bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B)
- If provoked by surgery or a non-surgical transient risk factor, anticoagulate for 3 months (Grade 1B)

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

Prediction Rules

Model	HERDOO2	Vienna	DASH
Author	Rodger, et al.	Eichinger, et al.	Tosetto, et al.
Yr of publication	2008	2010	2012
Country	Four countries (unspecified)	Austria	Austria, Canada, Italy, Switzerland, UK, USA
Study setting	Twelve tertiary care centres Patients enrolled between October 2001 and March 2006	Recruited from four thrombosis centres in Vienna between July 1992 and August 2008	Patient-level, meta-analysis of previously published studies
Study design	Multicentre prospective cohort study	Prospective cohort study	IPD from seven prospective studies
Clinical outcome	Recurrent VTE	Recurrent VTE	Recurrent VTE
Total sample size, n	646	929	1818
Events, n	91	176	239

HERDOO2, hyperpigmentation, oedema, redness/D-dimer, obese (BMI >30km/m^2), old (aged >65 years)/two or more factors should indicate for patients to continue therapy

BMI = body mass index; IPD = Individual patient data.

Ensor J, et al. *Health Technol Assess* 2016; 20:i-xxxiii,1–190.

D-dimer is of Limited Value for Excluding Recurrent VTE

	Risk of Recurrence	
	Negative D-dimer	Positive D-dimer
Men	8% per year	16% per year
Women	5% per year	10% per year

Kearon C, et al. *Ann Intern Med* 2015; 162:27–34.

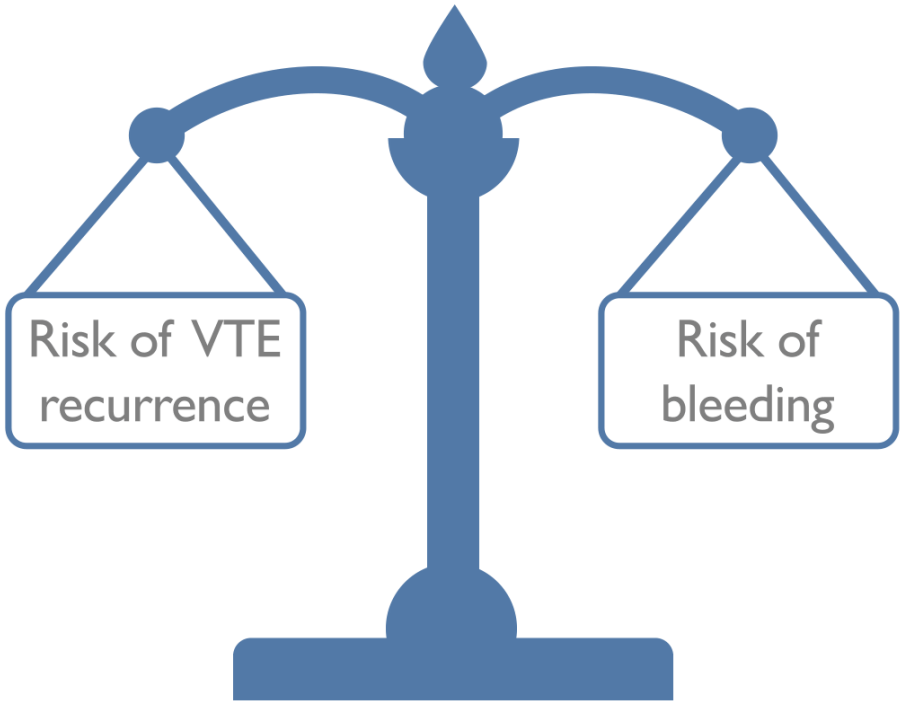
Duration of Anticoagulant Therapy for VTE

?

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

Need for Extended Anticoagulation

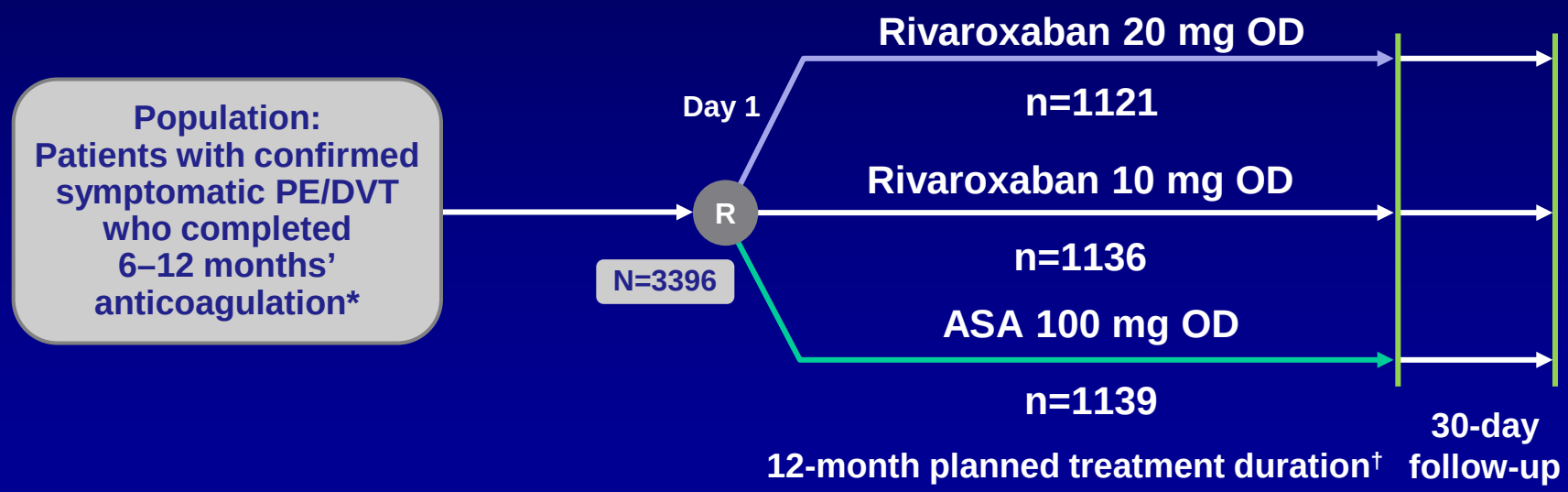
Depends on Balance Between Risk of Recurrence off Treatment and Risk of Bleeding on Treatment



EINSTEIN CHOICE Evaluated Rivaroxaban Versus ASA for Extended Treatment of VTE

Objectives: Compare the efficacy and safety of OD rivaroxaban (20 or 10 mg) with aspirin (100 mg) in VTE patients who completed 6–12 months of treatment and with equipoise regarding the need for extended anticoagulation

Multicentre, randomised, double-blind, active-comparator, event-driven, superiority study



*Completed 6–12 months anticoagulation at randomisation with no interruption of anticoagulation >1 week.

† Patients randomised after the requisite number of primary efficacy outcomes was reached were treated for ≥6 months.

ASA = Acetylsalicylic acid.

Weitz JI, et al. *Thromb Hemost* 2015; 114:645–650; Weitz JI, et al. *N Engl J Med* 2017; 376:1211–1222.

Rationale for Study Arms

Rivaroxaban 20 mg OD	Rivaroxaban 10 mg OD	ASA 100 mg OD
In EINSTEIN EXT, rivaroxaban 20 mg OD reduced the risk of recurrent VTE by 82% compared with placebo, with similar risk of major bleeding[1]	Rivaroxaban 10 mg OD offered effective thromboprophylaxis after elective hip or knee arthroplasty[2,3]	ASA 100 mg OD has been shown to reduce the risk of recurrent VTE by more than 30% compared with placebo, without increasing the risk of major bleeding[4,5]

1. The EINSTEIN Investigators. *N Engl J Med* 2010; 363:2499–2510;
2. Eriksson BI, et al. *J Bone Joint Surg [Br]* 2009; 91-B:636–644; 3. Cohen AT, et al. *N Engl J Med* 2013; 368:513–523;
4. Becattini C, et al. *N Engl J Med* 2012; 366:1959–1967; 5. Simes J, et al. *Circulation* 2014; 130:1062–1071.

EINSTEIN CHOICE
Study Outcomes

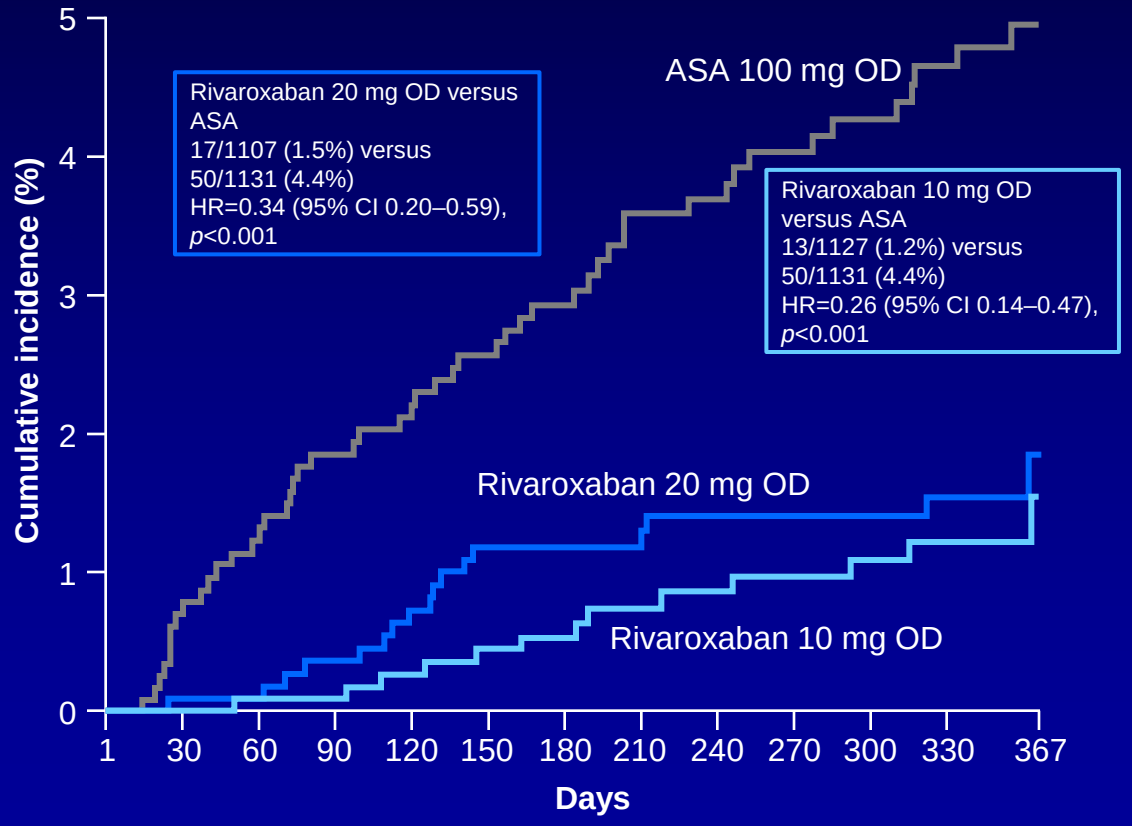
- **Primary efficacy outcome**
  - Fatal or non-fatal symptomatic recurrent VTE
- **Other efficacy outcomes**
  - Primary efficacy outcome or myocardial infarction, ischaemic stroke or systemic embolism
  - Primary efficacy outcome or symptomatic venous thrombosis in other locations
  - Primary efficacy outcome and all-cause mortality
- **Principal safety outcome**
  - Major bleeding (ISTH)
- **Other safety outcomes**
  - Non-major bleeding associated with study drug interruption for >14 days
  - Clinically relevant non-major bleeding (ISTH)

ISTH = International Society on Thrombosis and Haemostasis.

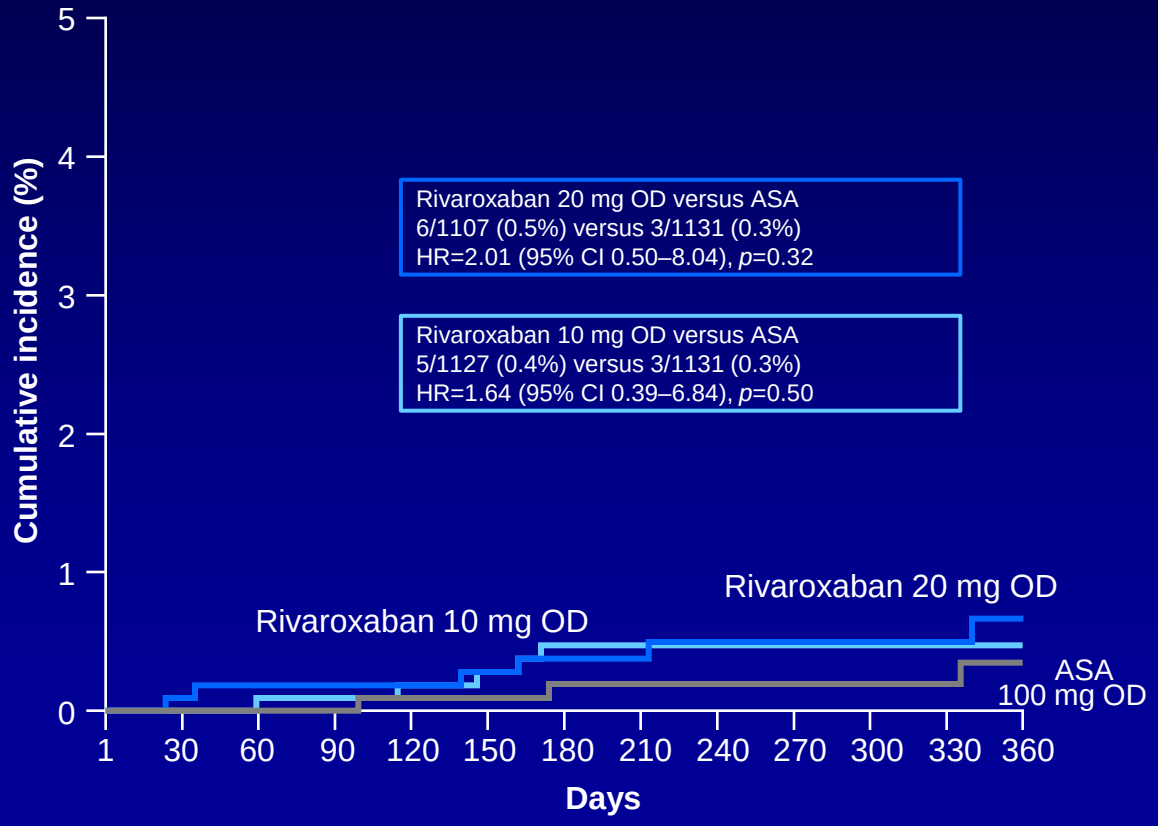
1. Weitz J, et al. *N Engl J Med* 2017; 376:1211–1222.

Both Rivaroxaban Doses Reduced Recurrent VTE Rates with Similar Risk of Bleeding versus ASA

Efficacy



Major bleeding



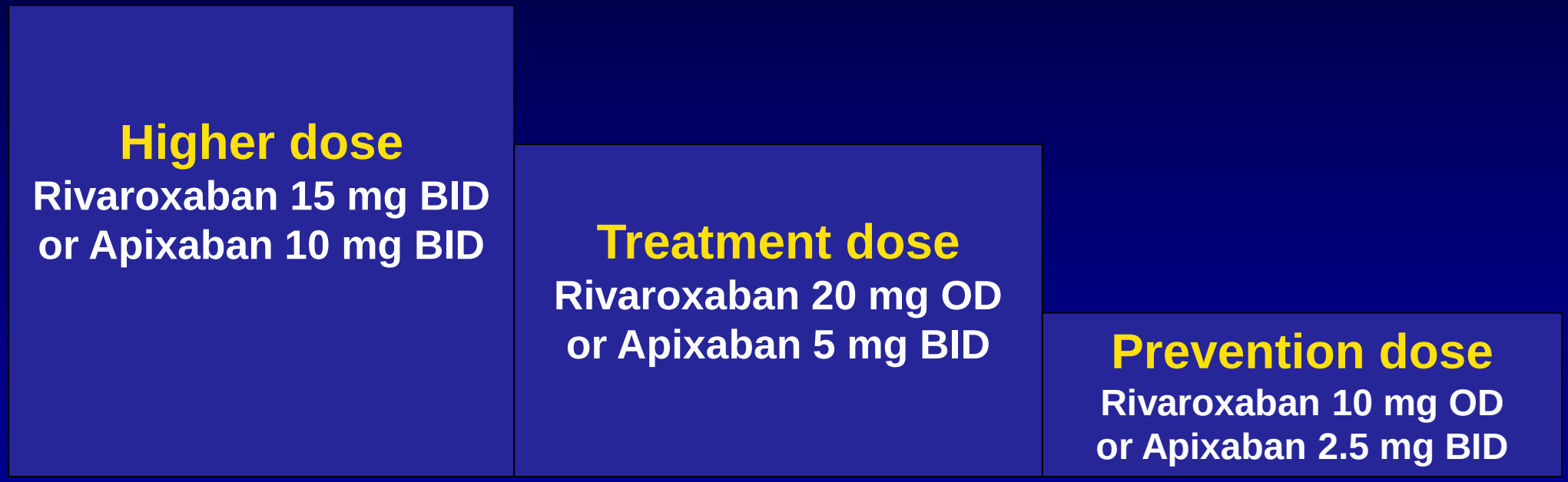
Weitz JI. *N Engl J Med* 2017; 376:1211–1222.

AMPLIFY EXTENSION Study

	Apixaban (2.5 mg BID)	Apixaban (5 mg BID)	Placebo
Recurrent VTE	1.7%	1.7%	8.8%
Major bleeding	0.2%	0.1%	0.5%
Non-major bleeding	3.0%	4.2%	2.3%

Agnelli G, et al. *N Engl J Med* 2012; 368:699–708.

Stepped Down Treatment of VTE



Conclusions

- VTE is often a chronic condition
- NOACs are at least as effective as VKAs, but produce less bleeding
- Availability of usual and lower dose NOAC regimens enable patient-specific choices

Therapeutic Intervention for Venous Thromboembolism – Is there a New Standard of Care?

Alexander G. G. Turpie
Emeritus Professor
Department of Medicine
McMaster University
Hamilton ON
Canada

Faculty Disclosure

- Consultant to: Bayer Pharma
- Speakers Bureau: Janssen
- Speakers Bureau: Portola

Educational Need/Practice Gap

- DOACs have been shown to be effective in the treatment of VTE
- To determine the uptake of DOACs in current VTE management strategies

Objectives

- To determine the uptake of DOACs in current VTE management strategies
- Upon completion of this educational activity, you will be able to:
  - Understand current management of VTE
  - Review outcomes of VTE treatment at 6 months from the Garfield VTE Registry

Are Phase III Clinical Trials the Final Word?

- "*At its best a trial shows what can be accomplished with a medicine under careful observation and certain restricted conditions. The same results will not invariably or necessarily be observed when the medicine passes into general use.*"

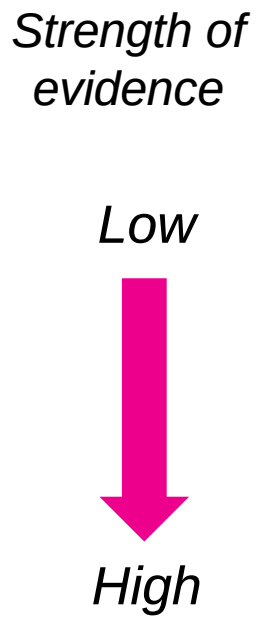
  Austin Bradford Hill – Father of the modern RCT

- *"Between measurements based on randomized controlled trials and benefit in the community there is a gulf which has been much under-estimated"*

  A. L. Cochrane – Cataloguer of RCTs

Real World Evidence

- Real-world evidence is a broad term for many different study designs, including, in order of strength of evidence:
  - Retrospective clinical studies (including case/case series studies)
  - Claims database analyses
  - Prospective registries
  - Phase IV non-interventional studies



Introduction

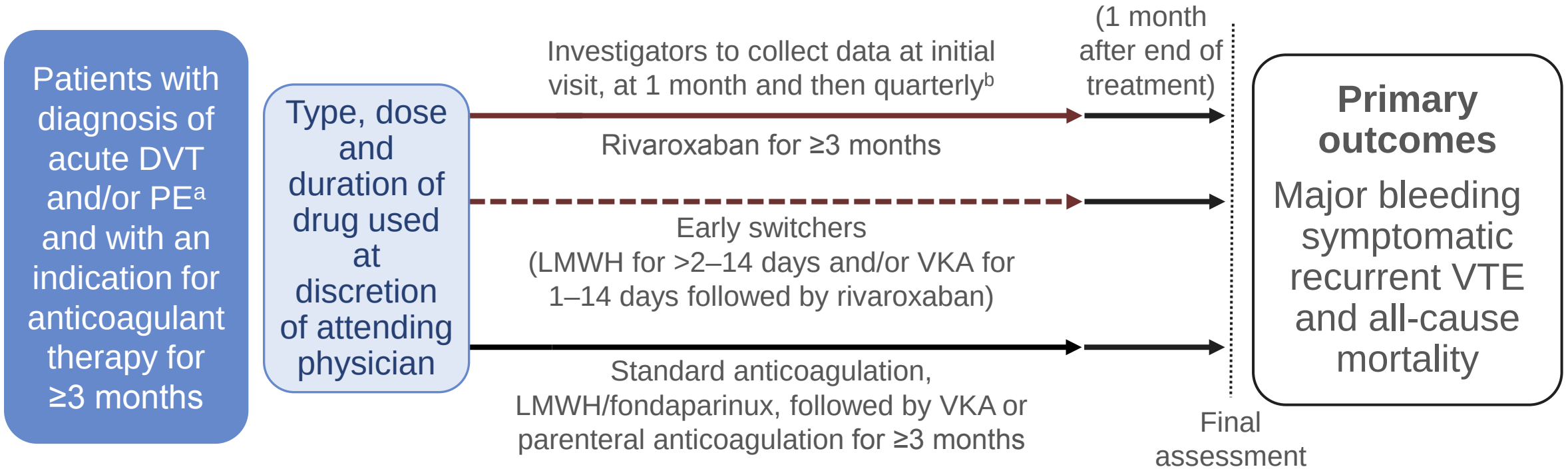
- XALIA and XALIA-LEA are multicentre, prospective, non-interventional studies of rivaroxaban versus standard anticoagulation for the treatment of VTE[1,2]
- XALIA was conducted, in part, to fulfil post-approval regulatory requirements[1]
- In contrast, there was no regulatory requirement for XALIA-LEA to be conducted; its main purposes were to:[2]
  - Increase the knowledge base of rivaroxaban in VTE in routine clinical practice
  - Collect data from regions not studied in XALIA
- Additionally, unlike in XALIA, patients with isolated PE were eligible to enrol in XALIA-LEA[2]

VTE = venous thromboembolism.

1. Ageno , et al. *Lancet Haematol* 2016; 3:e12–e21; 2. ClinicalTrials.gov NCT02210819.

XALIA and XALIA-LEA: Prospective, Non-interventional Studies

Objective: collect real-life data in patients with acute DVT treated with rivaroxaban or standard anticoagulation[1,2]



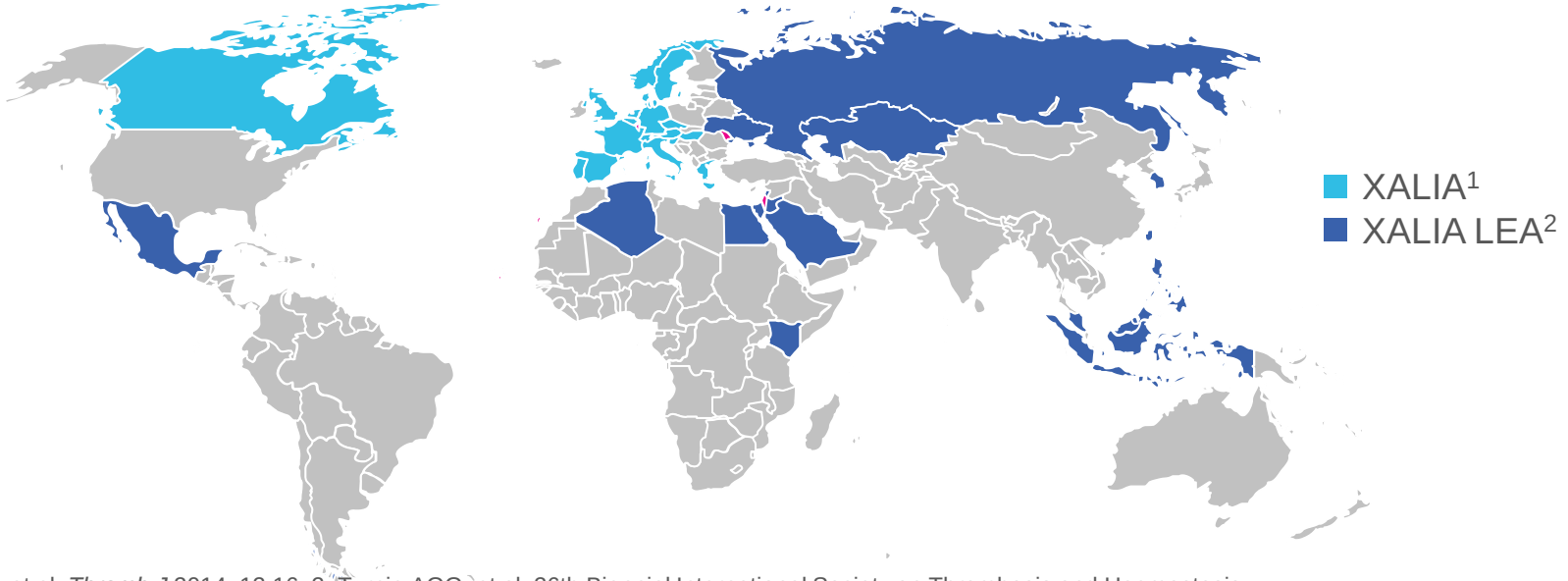
ClinicalTrials.gov NCT01619007, NCT02210819; [a]In XALIA, patients with DVT with concomitant PE permitted but isolated PE was excluded. In XALIA-LEA, patients with isolated PE were also permitted; [b]Data were collected at the initial visit and during routine follow-up visits or via mail, telephone, or email.

DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; VKA = vitamin K antagonist; VTE = venous thromboembolism.

1. Ageno W, et al. *Thromb J* 2014; 12:16; 2. Turpie AGG, et al. 26th Biennial International Society on Thrombosis and Haemostasis (ISTH) 2017, 8–13 July 2017, Berlin, Germany.

Participating Countries

- XALIA recruited 5142 patients from 19 European countries, Canada and Israel[1]
- XALIA LEA recruited 1987 patients from 16 countries across the Asia-Pacific region, Eastern Europe, the Middle East, Africa and Latin America [2]



1. Ageno W, et al. *Thromb J* 2014; 12:16; 2. Turpie AGG, et al. 26th Biennial International Society on Thrombosis and Haemostasis (ISTH) 2017, 8–13 July 2017, Berlin, Germany.

XALIA: Baseline Demographics and Clinical Characteristics

	Rivaroxaban (n=2619)	Standard anticoagulation (n=2149)	Early switchers (n=386)
Age, years, median (IQR)	59.0 (45.0–71.0)	66.0 (47.0–73.0)	61.0 (47.5–73.0)
Male sex, n (%)	1428 (55)	1116 (52)	211 (57)
Index diagnosis, n (%)			
DVT without PE	2399 (92)	1894 (88)	291 (79)
DVT with PE	220 (8)	255 (12)	77 (21)
First available CrCl, n (%)[a]			
≥80 ml/min	1125 (43)	797 (37)	169 (46)
≥50–<80 ml/min	419 (16)	398 (19)	71 (19)
≥30–<50 ml/min	88 (3)	157 (7)	20 (5)
<30 ml/min	13 (1)	61 (3)	4 (1)
Previous VTE, n (%)	630 (24)	481 (22)	79 (22)
Previous major bleeding, n (%)	37 (1)	64 (3)	17 (5)
Active cancer, n (%)	146 (6)	411 (19)	30 (8)
Thrombophilia, n (%)	157 (6)	112 (5)	25 (7)

[a]First available measurement of CrCl (not all patients had CrCl at baseline); time in therapeutic range for VKA-treated patients: 56.2%.

Ageno W, et al. *Lancet Haematol* 2016; 3:e12–21.

XALIA: Treatment-Emergent Clinical Outcomes

Crude outcome, n (%)	Rivaroxaban (n=2619)	Standard anticoagulation (n=2149)	Hazard ratio[a] (95% CI)	
Major bleeding	19 (0.7)	48 (2.3)	**0.41 (0.24–0.70)**	
Recurrent VTE	37 (1.4)	55 (2.6)	**0.67 (0.44–1.03)**	
All-cause mortality	12 (0.5)	88 (4.1)	**0.26 (0.14–0.49)**	
Propensity score-adjusted outcome, n (%)	**Rivaroxaban (n=2505)**	**Standard anticoagulation (n=2010)**	**Hazard ratio (95% CI)**	**p-value**
Major bleeding	19 (0.8)	43 (2.1)	**0.77 (0.40–1.50)**	0.44
Recurrent VTE	36 (1.4)	47 (2.3)	**0.91 (0.54–1.54)**	0.72
All-cause mortality	11 (0.4)	69 (3.4)	**0.51 (0.24–1.07)**	0.07

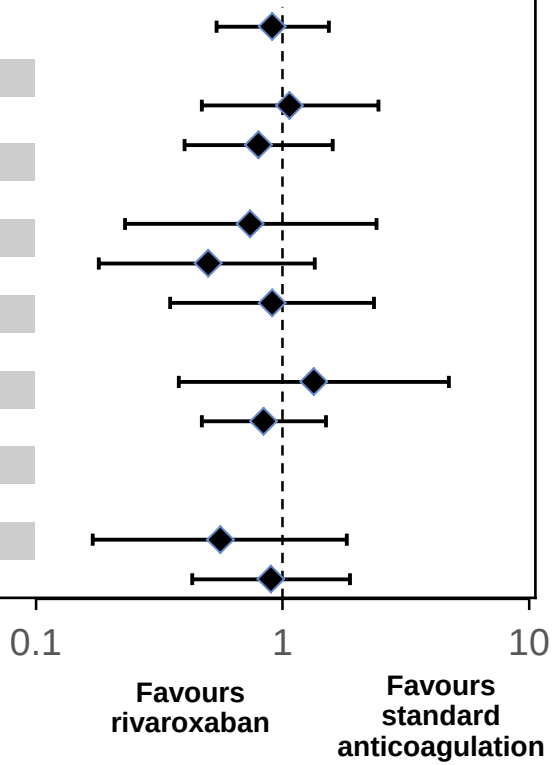
[a]Adjusted for cancer at baseline.
CI = confidence interval; VTE = venous thromboembolism.
Ageno W, *et al. Lancet Haematol* 2016; 3:e12–21.

XALIA Subgroups

- Elderly
- Body weight
- Cancer
- Renal insufficiency

XALIA: Recurrent VTE in Patient Subgroups

	Rivaroxaban		Standard anticoagulation		HR (95% CI)
	n/N	(%)	n/N	(%)	
All patients	**36/2505**	**(1.4)**	**47/2010**	**(2.3)**	
Age					
<60 years	17/1286	(1.3)	16/785	(2.0)	
≥60 years	19/1219	(1.6)	31/1225	(2.5)	
Weight					
≤70 kg	8/522	(1.5)	13/495	(2.6)	
>70–<90 kg	8/843	(0.9)	18/663	(2.7)	
≥90 kg	11/599	(1.8)	12/482	(2.5)	
Active cancer at baseline					
Yes	5/144	(3.5)	14/338	(4.1)	
No	31/2361	(1.3)	33/1672	(2.0)	
First available CrCl					
<50 ml/min[a]	1/98	(1.0)	3/194	(1.5)	
≥50–<80 ml/min	6/410	(1.5)	11/366	(3.0)	
≥80 ml/min	20/1047	(1.9)	21/757	(2.8)	

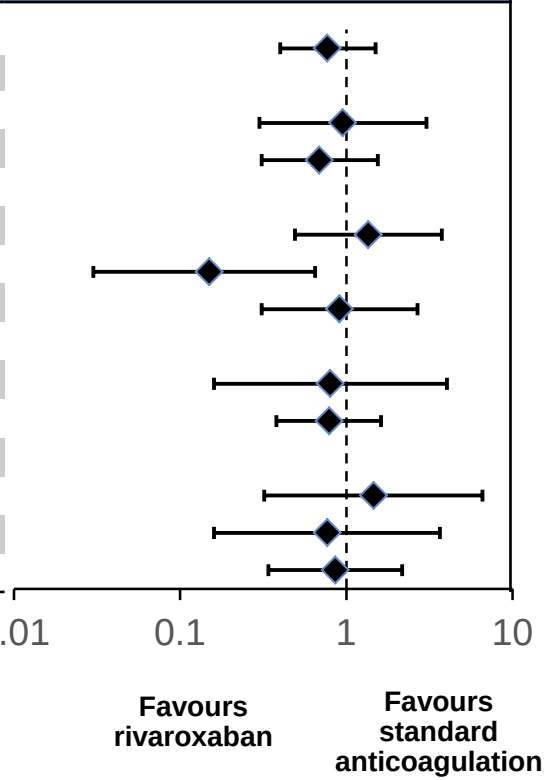


Note: some demographic parameters have data missing.
Propensity score-adjusted population.

[a]HR not calculated because of too few events.
CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio; VTE = venous thromboembolism.
Ageno W, et al. *Lancet Haematol* 2016; 3:e12–21.

XALIA: Major Bleeding in Patient Subgroups

	Rivaroxaban		Standard anticoagulation		HR (95% CI)
	n/N	(%)	n/N	(%)	
All patients	**19/2505**	**(0.8)**	**43/2010**	**(2.1)**	
Age					
<60 years	8/1286	(0.6)	11/785	(1.4)	
≥60 years	11/1219	(0.9)	32/1225	(2.6)	
Weight					
≤70 kg	7/522	(1.3)	14/495	(2.8)	
>70–<90 kg	3/843	(0.4)	14/663	(2.1)	
≥90 kg	6/599	(1.0)	12/482	(2.5)	
Active cancer at baseline					
Yes	2/144	(1.4)	13/338	(3.8)	
No	17/2361	(0.7)	30/1672	(1.8)	
First available CrCl					
<50 ml/min	3/98	(3.1)	9/194	(4.6)	
≥50–<80 ml/min	3/410	(0.7)	10/366	(2.7)	
≥80 ml/min	12/1047	(1.1)	16/757	(2.1)	



Note: some demographic parameters have data missing.
Propensity score-adjusted population.

CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio.

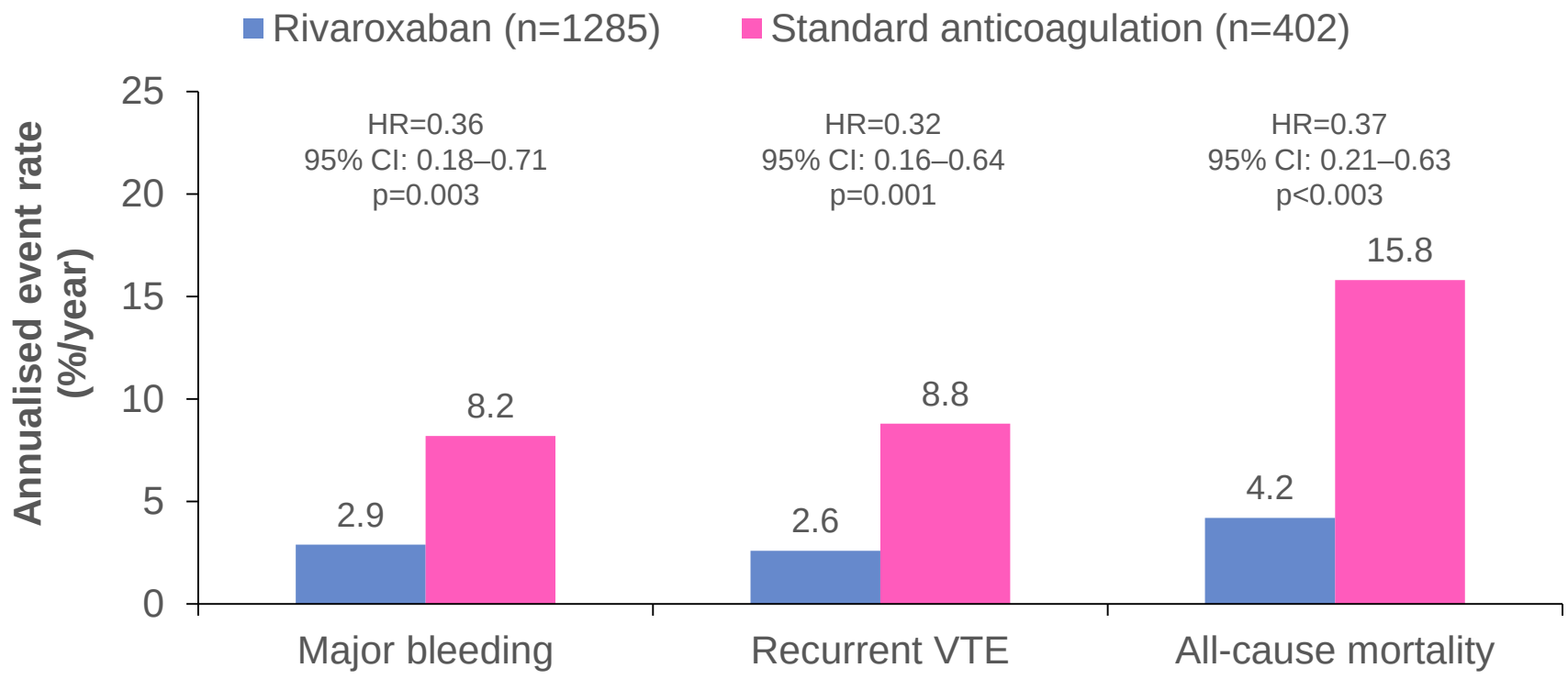
Ageno W, et al. *Lancet Haematol* 2016; 3:e12–21.

XALIA LEA: Baseline Demographics and Clinical Characteristics

	Rivaroxaban (n=1285)	Standard anticoagulation (n=402)	Early switchers (n=285)
Age, years, mean (SD)	59.6 (17.10)	58.0 (17.95)	59.0 (18.2)
Male sex, n (%)	623 (48.5)	180 (44.8)	133 (46.7)
Weight, kg, mean (SD)	71.6 (16.9)	73.5 (17.6)	72.4 (17.2)
Index diagnosis, n (%)			
DVT alone	882 (68.6)	238 (59.2)	163 (57.2)
PE ± DVT	403 (31.4)	164 (40.8)	122 (42.8)
First available CrCl, n (%)			
≥80 ml/min	449 (34.9)	131 (32.6)	123 (43.2)
≥50–<80 ml/min	275 (21.4)	90 (22.4)	57 (20.0)
≥30–<50 ml/min	103 (8.0)	41 (10.2)	35 (12.3)
<30 ml/min	22 (1.7)	19 (4.7)	8 (2.8)
Previous VTE, n (%)	150 (11.7)	55 (13.7)	26 (9.1)
Previous major bleeding, n (%)	28 (2.2)	9 (2.2)	9 (3.2)
Active cancer, n (%)	216 (16.8)	69 (17.2)	43 (15.1)
Thrombophilia, n (%)	49 (3.8)	12 (3.0)	6 (2.1)

Turpie AGG, et al. 26th Biennial International Society on Thrombosis and Haemostasis (ISTH) 2017, 8–13 July 2017, Berlin, Germany.

XALIA-LEA Primary Outcomes (Adjusted for Covariates)



Covariates were selected using a stepwise selection procedure with a threshold of p=0.10

CI = confidence interval; HR = hazard ratio; VTE = venous thromboembolism.

Turpie AGG, et al. 26th Biennial International Society on Thrombosis and Haemostasis (ISTH) 2017, 8–13 July 2017, Berlin, Germany.

Comparative Effectiveness of Rivaroxaban and Apixaban in Patients with Venous Thromboembolism – A Danish Nationwide Study

- Cross linkage of Danish nationwide registries
- 6181 patients with VTE identified during the study period: Jan 1 2015 – Dec 31 2016
- Rivaroxaban 5046 : Apixaban 1135
- Recurrent VTE and Bleeding
- Average treatment effects as standardised differences in absolute risk between rivaroxaban and apixaban at 90 and 180 days

Sindet-Pedersen K, et al. ESC 2017 Congress Presentation

Comparative Effectiveness of Rivaroxaban and Apixaban in Patients with Venous Thromboembolism – A Danish Nationwide Study

Standardised absolute risks (95% CI)
based on outcome-specific cox regression models at 180 days (6 months)

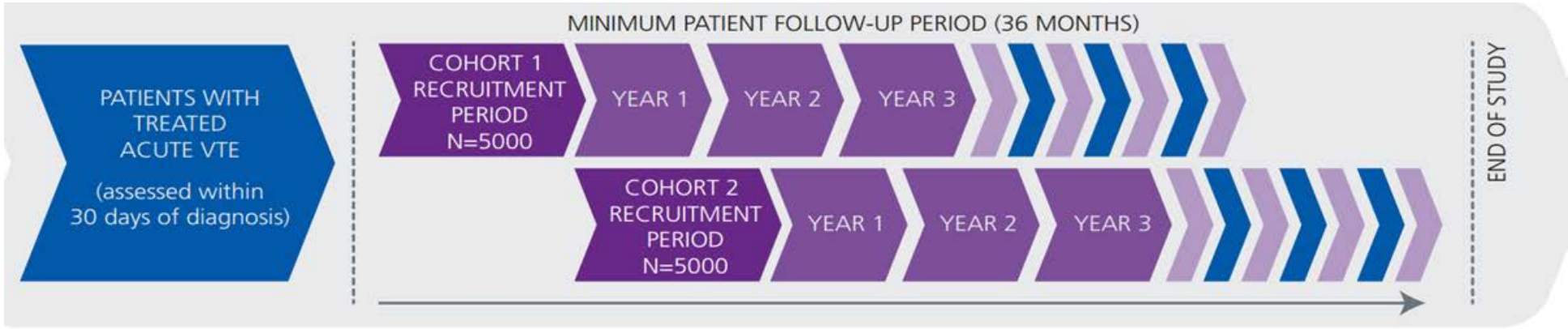
	Rivaroxaban (n=5046)	Apixaban (n=1135)
Recurrent VTE	2.36% (1.76% to 2.75%)	2.52% (1.66% to 3.59%)
Bleeding	1.90% (1.53% to 2.30%)	1.87% (1.20% to 2.62%)

There is no significant difference in the risk of recurrent VTE or bleeding

Sindet-Pedersen C *et al*, *ESC 2017 Congress Presentation*

GARFIELD-VTE: A Prospective Global Disease Registry

- **Objective: collect real-world data over a 3-year follow-up period in patients with a confirmed diagnosis of VTE from sites representative of national VTE care settings**

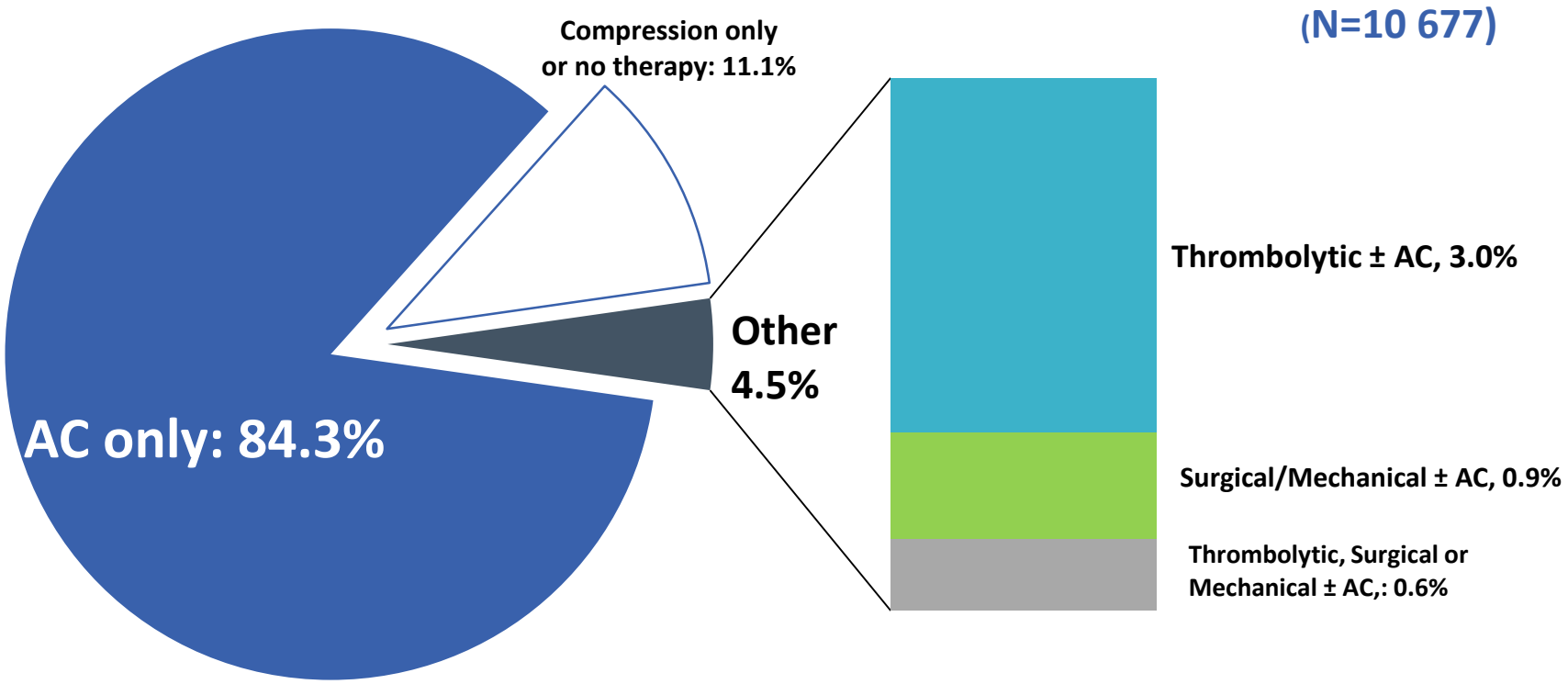


N.B. Striped area indicates possible follow-up for up to 2 years after the initial 36-month follow-up period
ClinicalTrials.gov identifier: NCT02155491

Weitz JI *et al*, *Thromb Haemost* 2016;116:1172–1179

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Treatment within 30 days of diagnosis



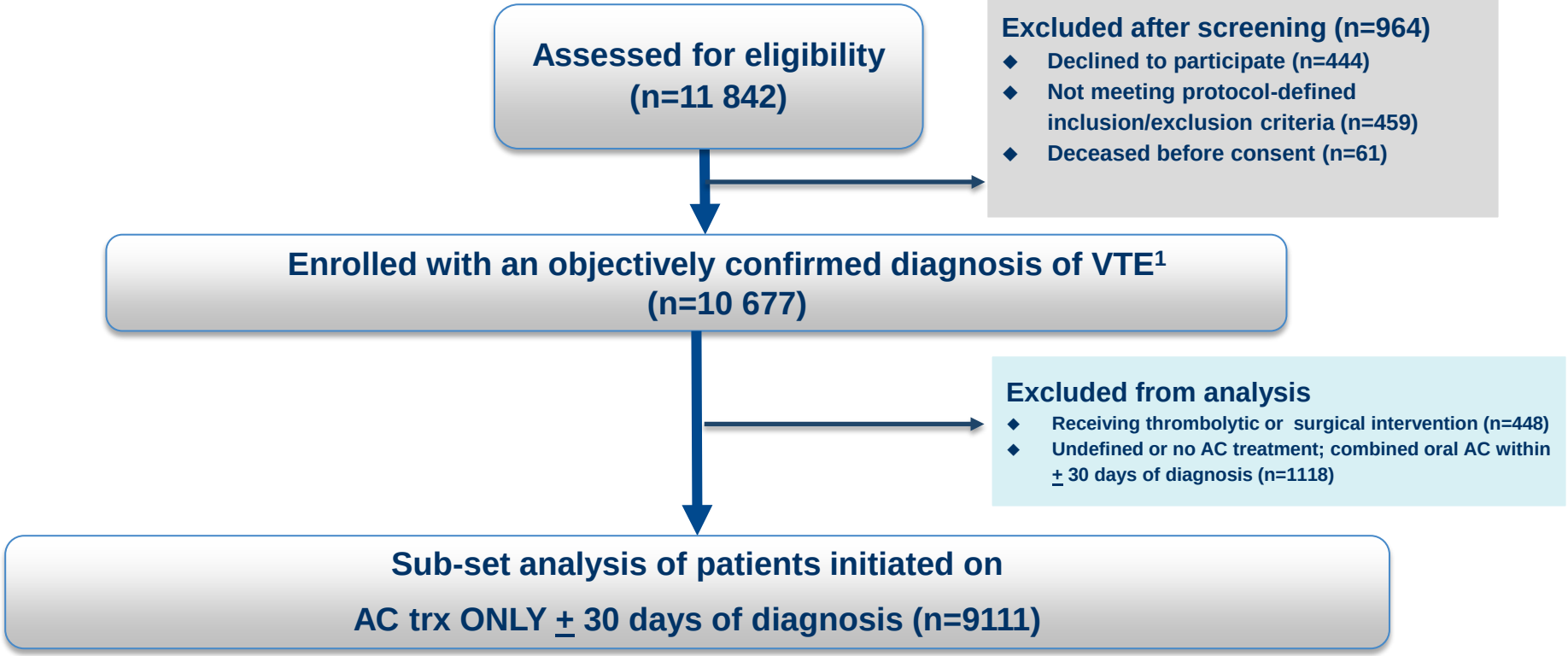
Thrombolytic: Systemic or catheter-directed
Surgical Mechanical: IVC filter, pulmonary embolectomy, thrombectomy
Compression: Bandages or stockings

Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Initial and longer term anticoagulation (AC) treatment patterns in patients prospectively enrolled in Garfield VTE from May 2014 to January 2017

Patient population

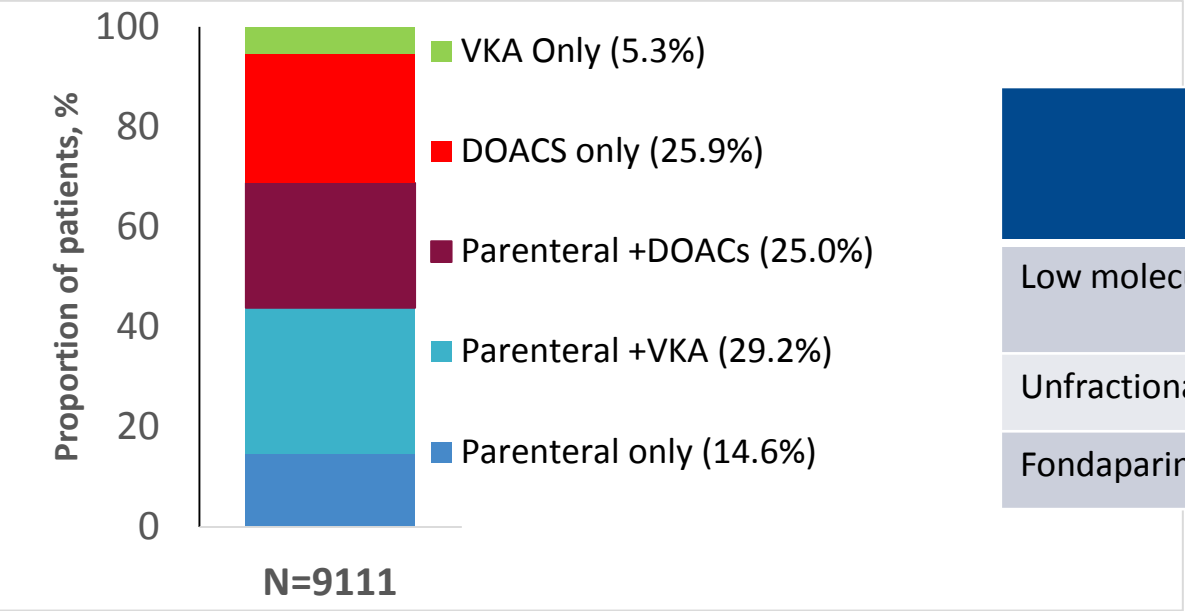


Date of analyses: 24th April 2017

[1] As defined by Bates et al. Chest 2012; 141(Suppl): e351S–e418S

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Treatment patterns of AC therapy within ± 30 days of diagnosis



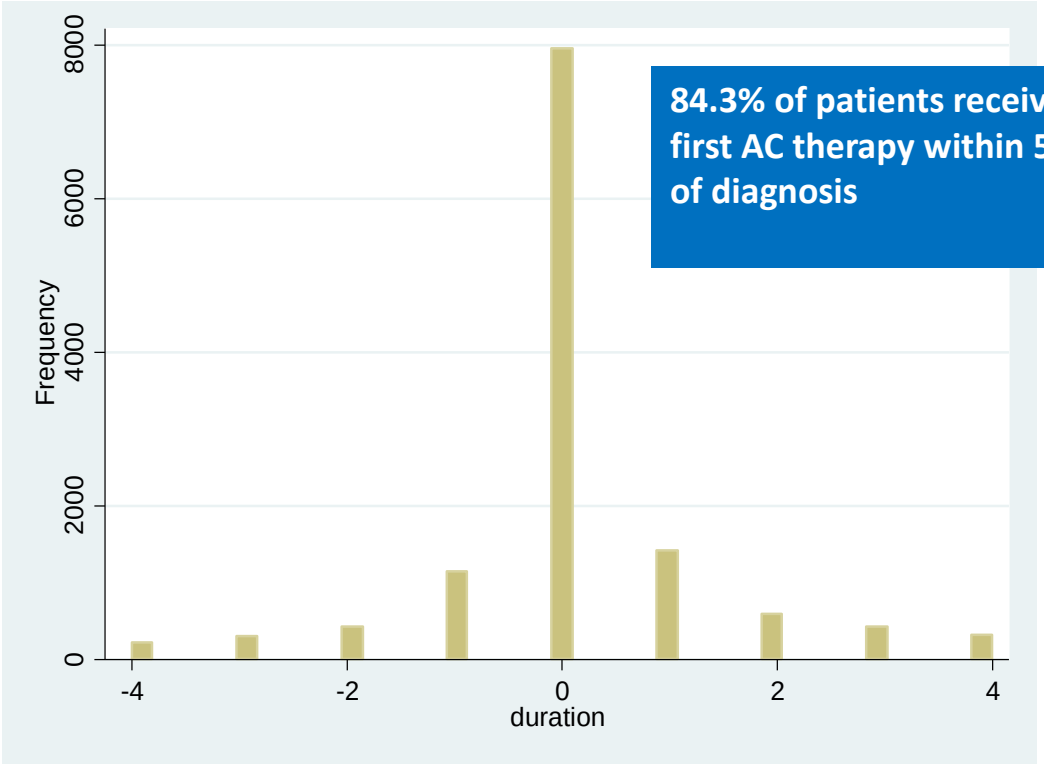
	% Patients on Parenteral AC (n=6272)
Low molecular weight heparin	83.8%
Unfractionated heparin	13.2%
Fondaparinux	3.0%

Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

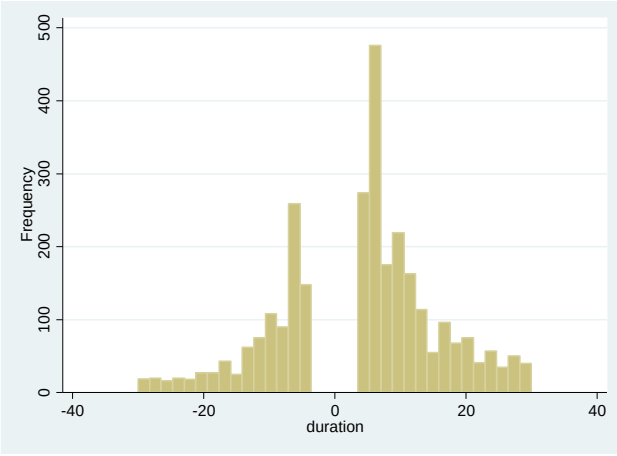
First AC treatment within 30 days of diagnosis

Within 4 days of diagnosis



84.3% of patients receive their first AC therapy within 5 days of diagnosis

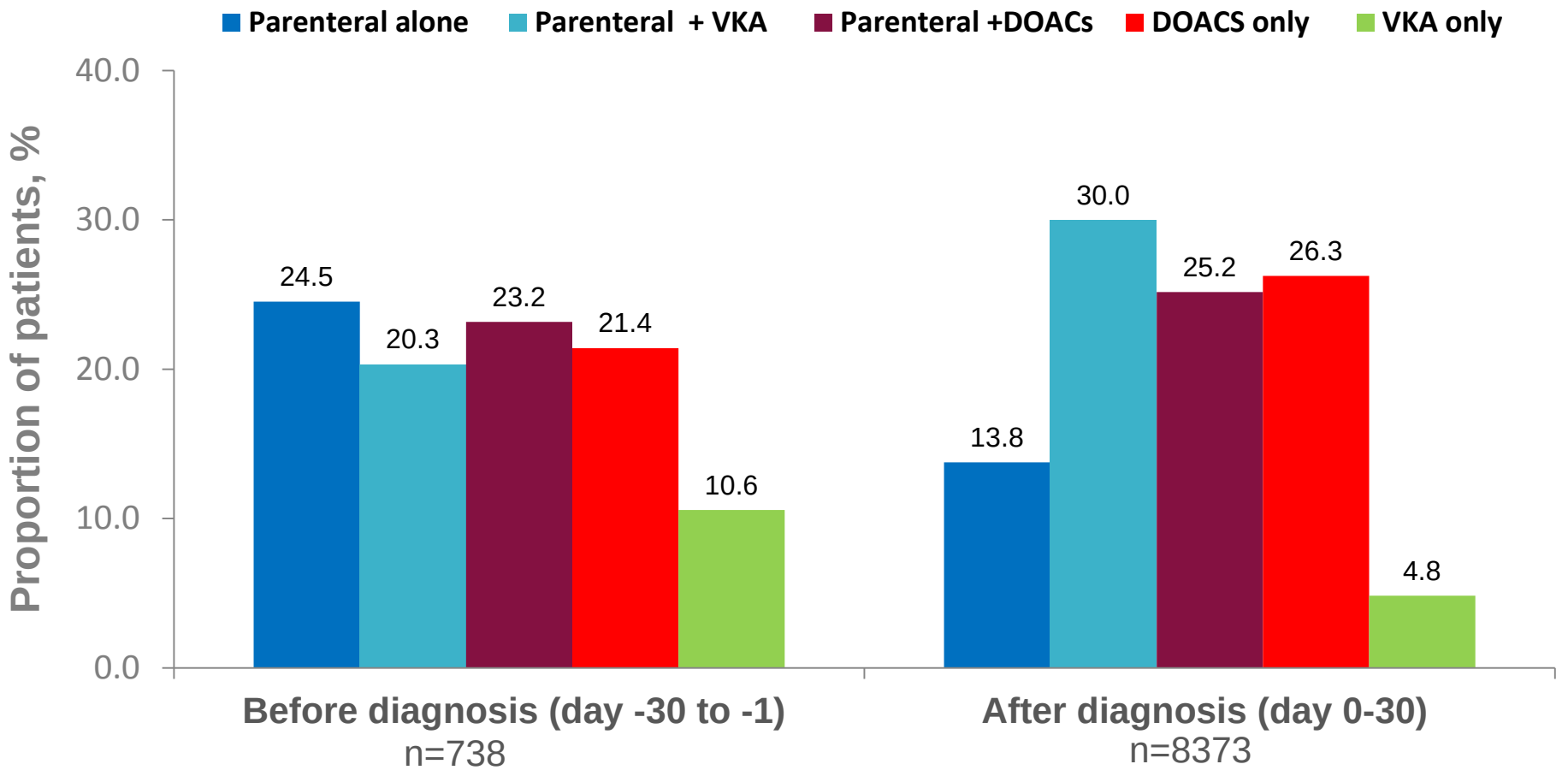
Beyond 4 days of diagnosis



Date of analyses: March 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

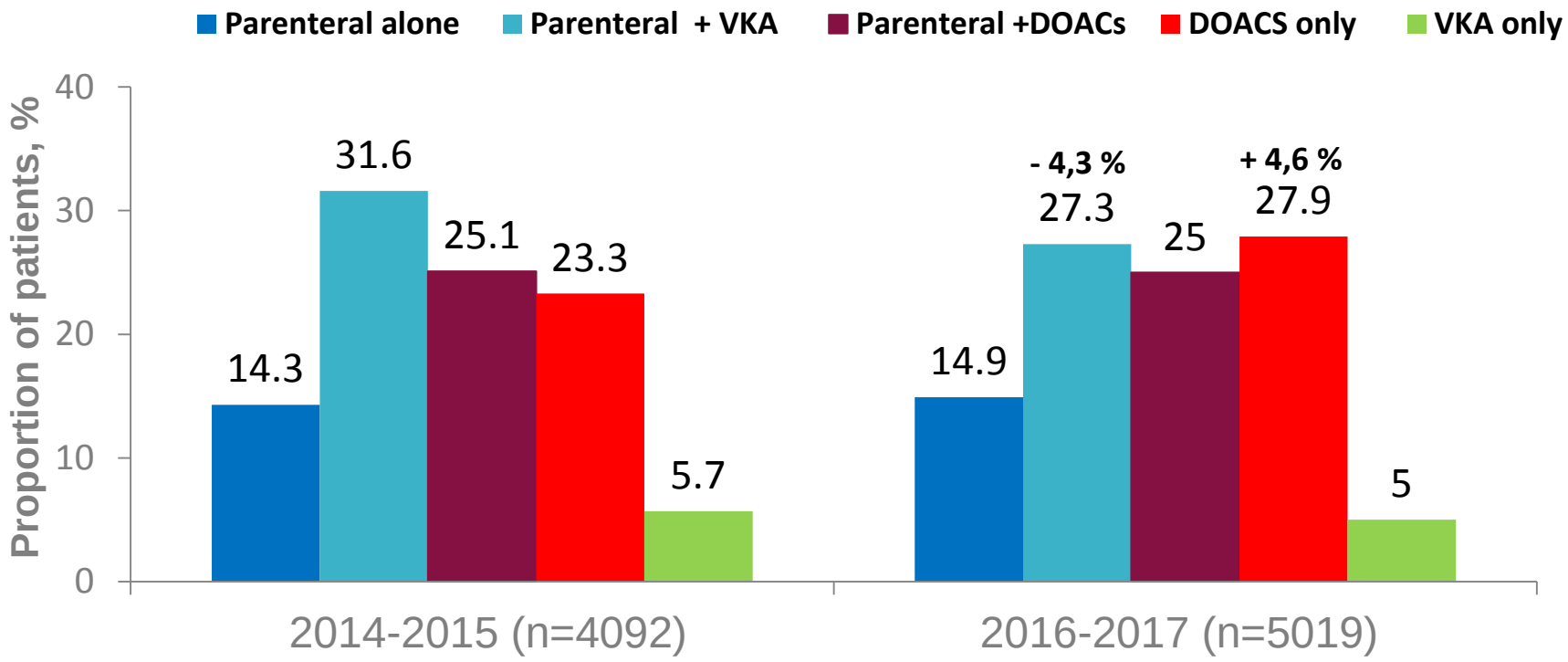
Initial AC treatment patterns before and after diagnosis



Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

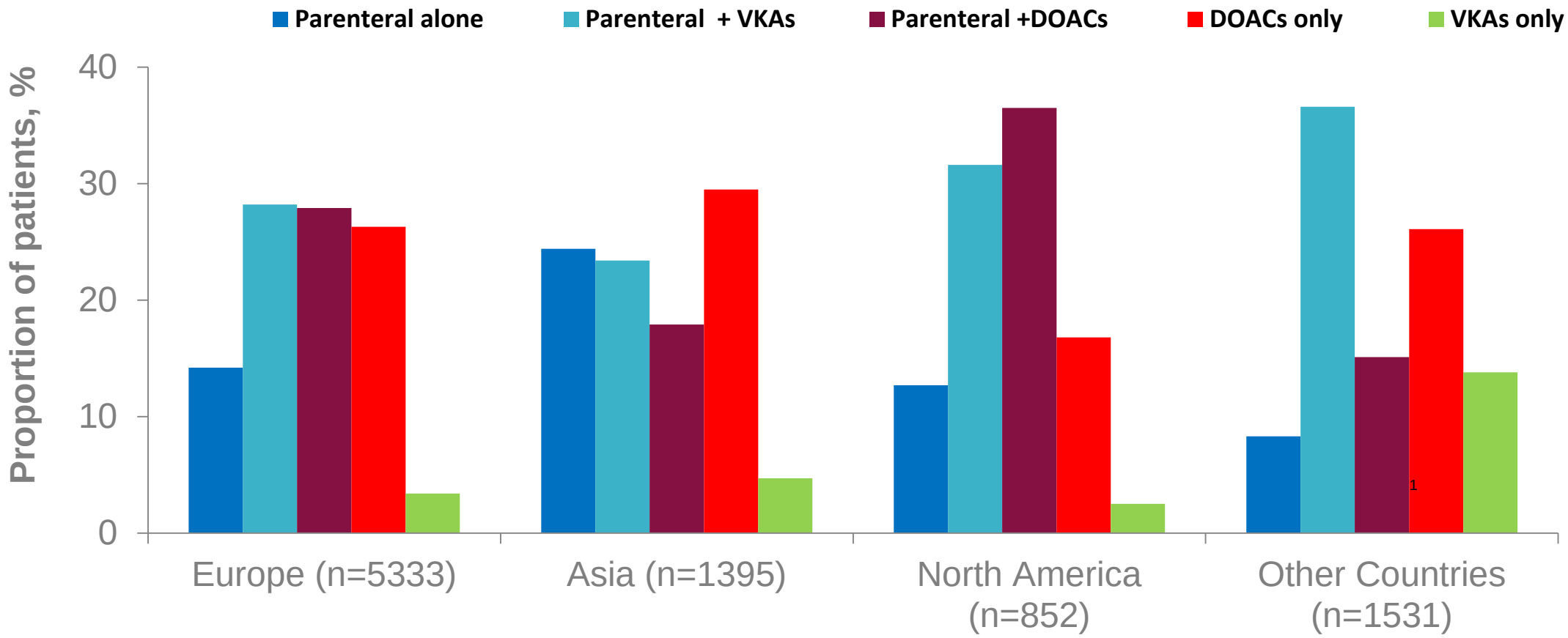
Initial AC treatment patterns by year of enrolment



Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

AC treatment patterns by geographic region

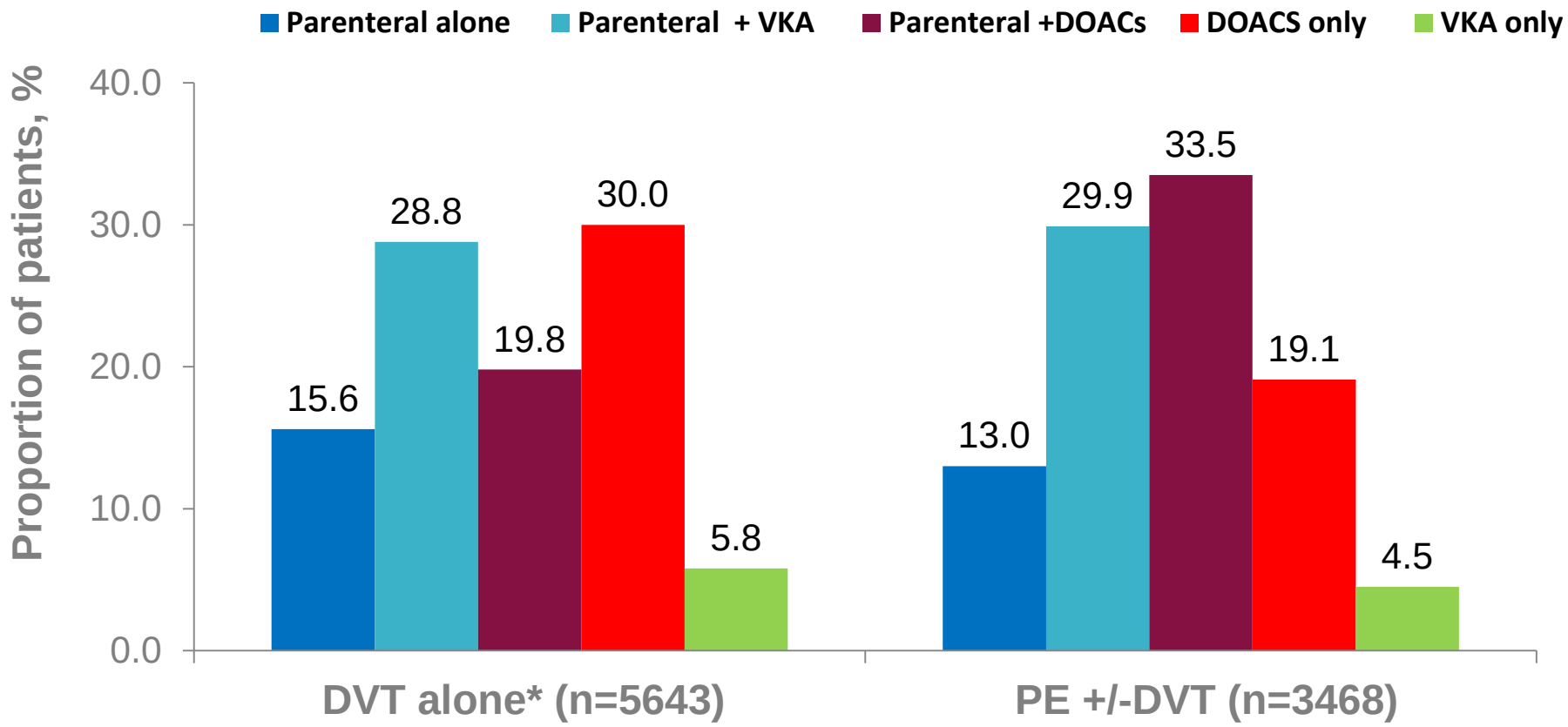


[1] Other is defined as: Argentina, Australia, Brazil, Egypt, Mexico, South Africa and United Arab Emirates

Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Initial AC treatment patterns by VTE site



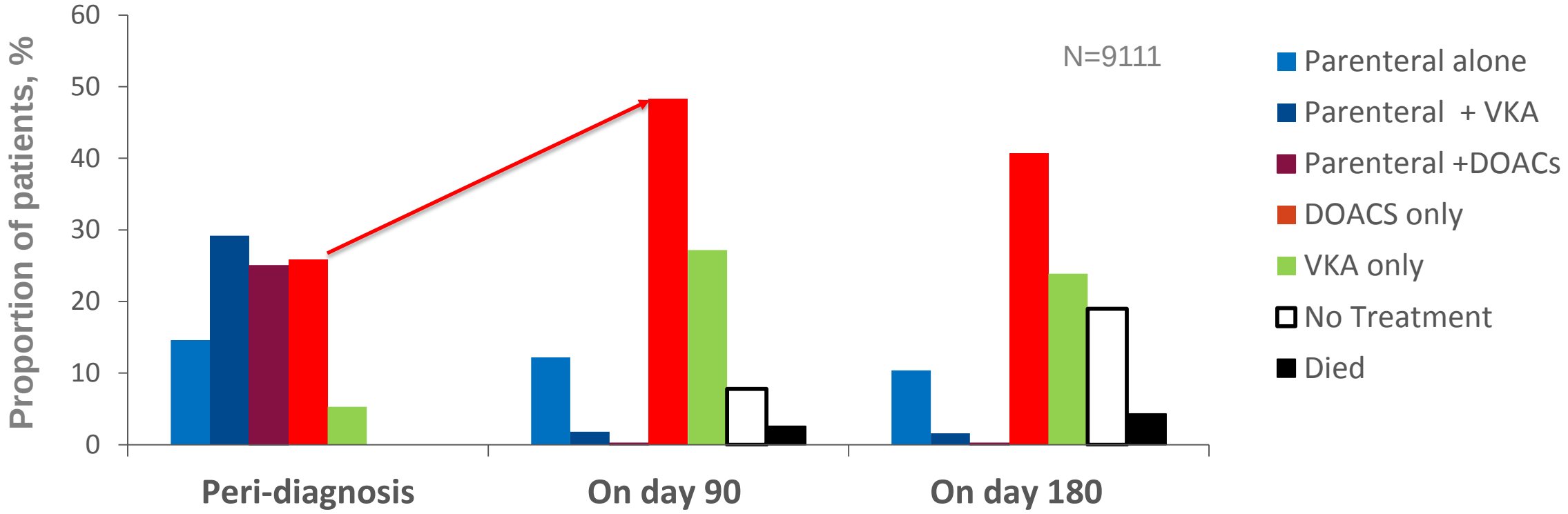
*DVT includes arm and leg thrombosis, vena cava and atypical sites

Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

From initial anticoagulation to secondary prevention and beyond

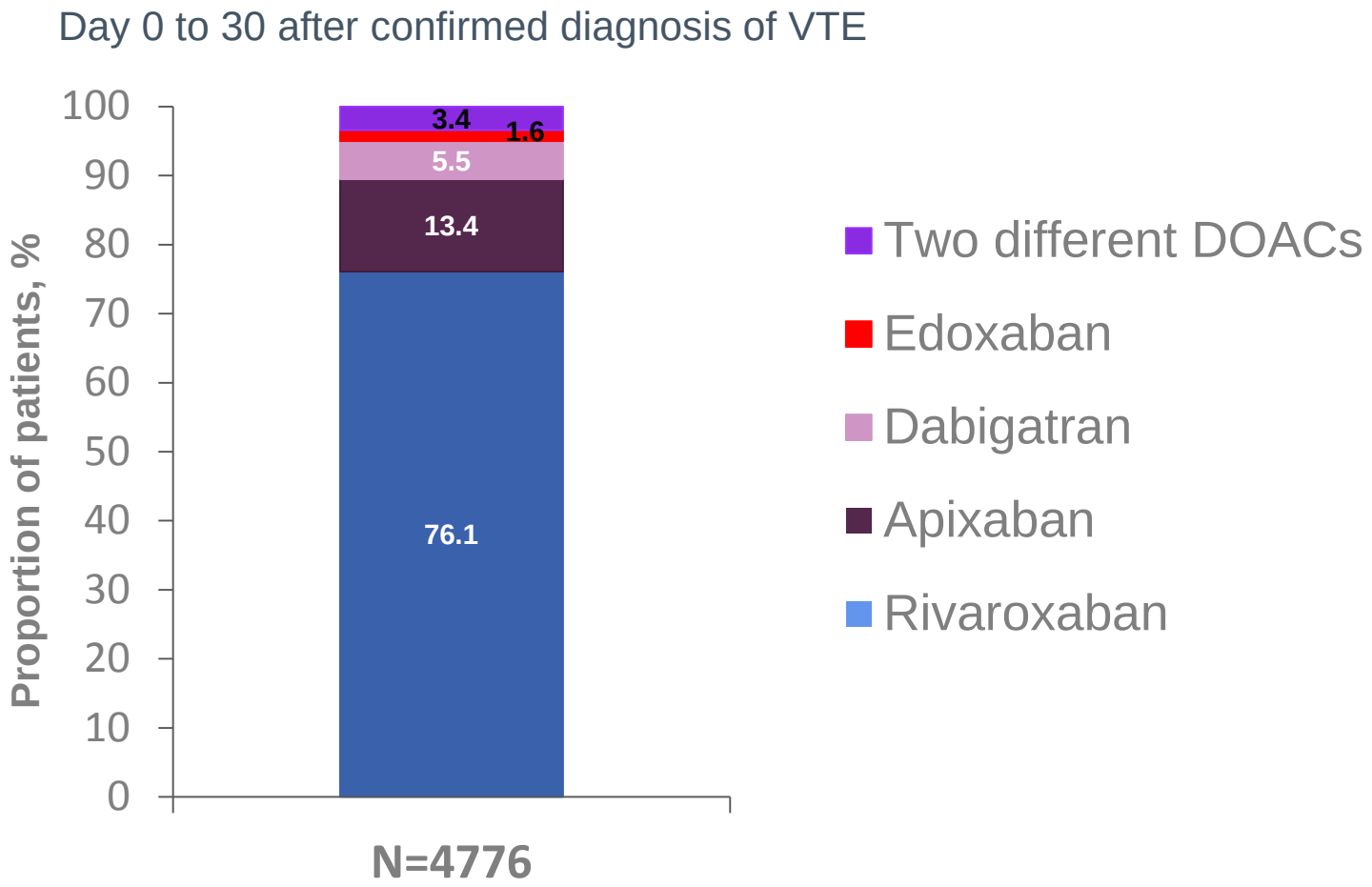
AC treatment within ± 30 days and on day 90 and day 180



Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

DOAC prescribing

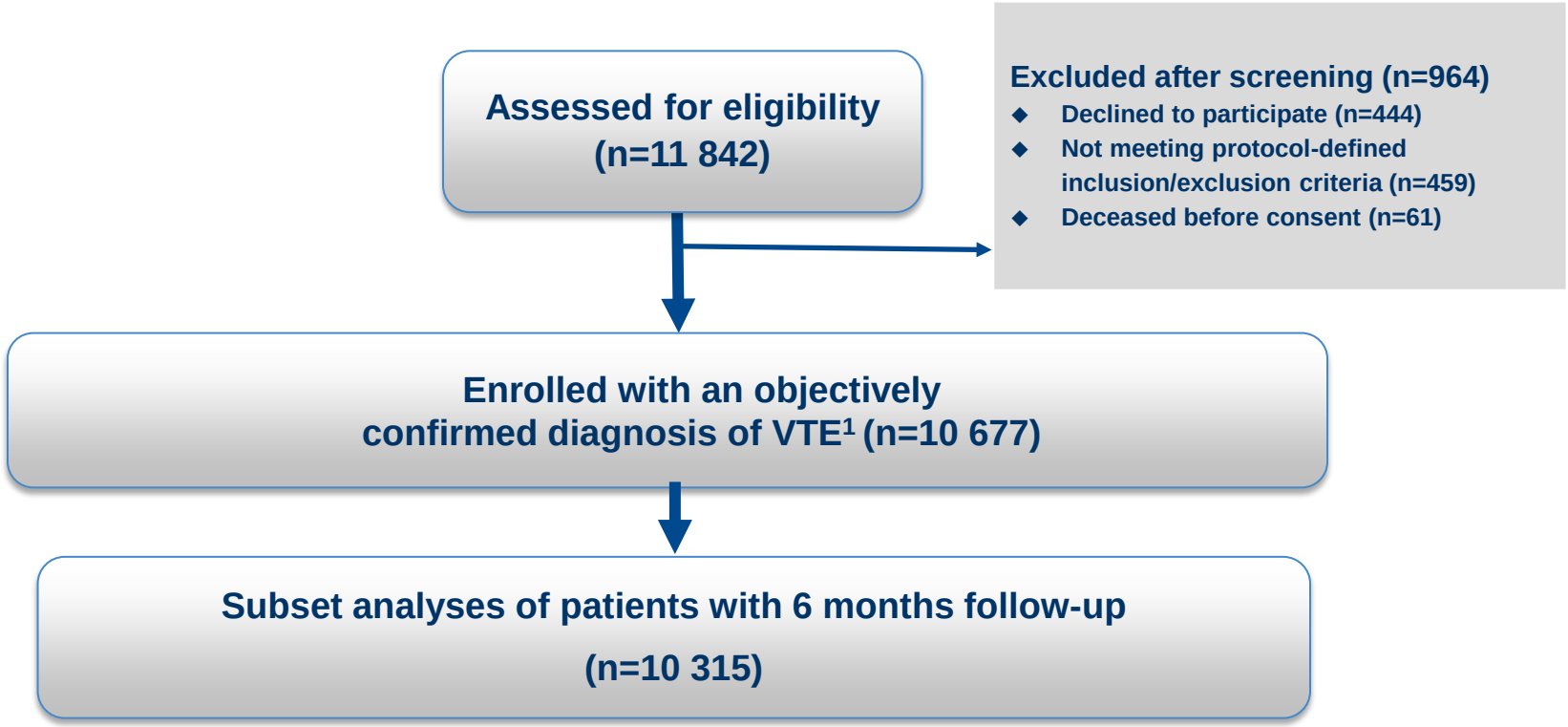


Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Outcomes over 6 months after an objectively confirmed diagnosis of VTE

Patient population



Date of analyses: 24th April 2017

[1] As defined by Bates et al. Chest 2012; 141(Suppl): e351S–e418S

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

0-6 month outcomes

	Events	Person-time	Event rate per 100 person-years (95% CI)
Primary endpoints			
All-cause mortality	460	4764.8	9.7 (8.8 to 10.6)
Recurrent VTE	169	4727.9	3.6 (3.1 to 4.2)
Major bleed	106	4725.6	2.2 (1.9 to 2.7)
Secondary endpoints			
Any bleed	622	4585.8	13.6 (12.5 to 14.7)
Myocardial infarction	42	4754.6	0.9 (0.7 to 1.2)
Stroke/TIA	38	4757.6	0.8 (0.6 to 1.1)

Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Outcomes in the first month and over the following 2 – 6 months after diagnosis of VTE

	Month 0-1		Months 2 - 6	
	Events	Rate per 100 person year (95% CI)	Events	Rate per 100 person year (95% CI)
Primary endpoints				
All-cause mortality	108	13.0 (10.7 to 15.6)	352	7.4 (6.7 to 8.2)
Major bleed	46	5.5 (4.2 to 7.4)	60	1.3 (1.0 to 1.7)
Recurrent VTE	35	4.2 (3.0 to 5.9)	134	2.9 (2.4 to 3.4)
Secondary endpoints				
Any bleed	239	29.0 (25.6 to 32.9)	383	8.4 (7.6 to 9.3)
Myocardial infarction	11	1.3 (0.7 to 2.4)	31	0.7 (0.5 to 0.9)
Stroke/TIA	9	1.1 (0.6 to 2.1)	29	0.6 (0.4 to 0.9)

Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Causes of death over 6 months after VTE

	n	%
Cancer-related	250	54.3
Cardiac	32	7.0
VTE-related events (including PE)	22	4.8
Bleed	15	3.3
Stroke	5	1.1
Other	82	17.8
Unknown	54	11.7
Total	460	100.0

Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Characteristics of bleeding

- 106 of 622 (17.0%) bleeds were reported by the investigator to be major bleed
- 90 of 622 (14.5%) patients required transfusion
- 15 of 622 (2.4%) bleeds were fatal

Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Conclusions from GARFIELD-VTE

- There is a shift from conventional parenteral + VKA treatment in the first 30 days towards DOACs in the following 5 months
- A higher percentage of parenteral + DOAC is prescribed in patients with PE/DVT than in patients with DVT only
- DOACs are becoming the new standard of care for long term anticoagulation
- Adverse outcomes at 6 months of follow-up of VTE treatment:
  - All-cause mortality (9.7 per 100 person-years)
  - VTE recurrence (3.6 per 100 person-years)
  - Major bleed (2.2 per 100 person-years)
- Myocardial infarction occurred at a rate of 0.9 per 100 person-years and stroke at a rate of 0.8 per 100 person-years
- New diagnoses of cancer occurred at rate of 4.1 per 100 person-years
- Fatal bleeding is a rare event

Date of analyses: 24th April 2017

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Cancer-Associated Thrombosis – What is the true burden of disease?

Rt Hon Professor the Lord Kakkar

Thrombosis Research Institute and

University College London UK

Disclosures

- Grants and personal fees from Bayer
- Personal fees from: Boehringer-Ingelheim Pharma, Daiichi Sankyo Europe, Sanofi SA, Janssen Pharma, Verseon Inc

Educational Need/Practice Gap

Venous thromboembolism (VTE) is a common complication and a major cause of morbidity and mortality in patients with cancer.

The pathophysiology of VTE in cancer is complex and multifactorial.

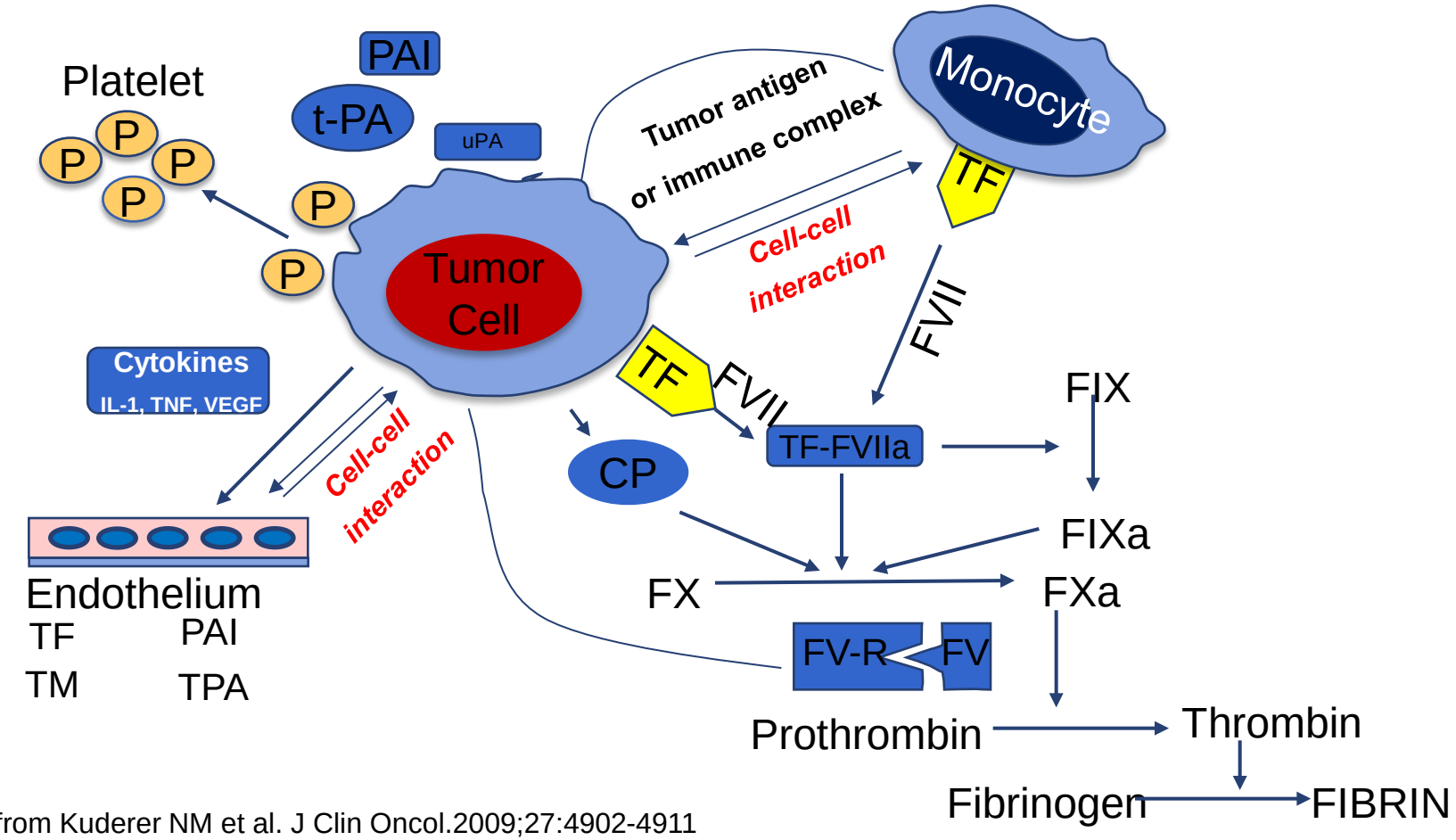
An appreciation of these factors is important so that patients at risk of cancer associated VTE receive appropriate thrombosis prevention and treatment.

My talk today

- Pathophysiology of cancer associated thrombosis
- Primary VTE
  - Surgical
  - Medical
- Recurrent VTE
- Mortality

Pathogenesis of Thrombosis in Cancer
Hypercoagulable state and cell-cell interactions

The most important factor contributing to the hypercoagulable state in patients with cancer derive from the tumor cells themselves



Adapted from Kuderer NM et al. J Clin Oncol.2009;27:4902-4911

VTE-Risk factors

Patient-related factors

- Older age
- Gender
- Race
  - Higher in African Americans
  - Lower in Asians
- Patient comorbidities
- History of VTE

Cancer-related factors

- Site of cancer
- Stage
- Initial period after diagnosis

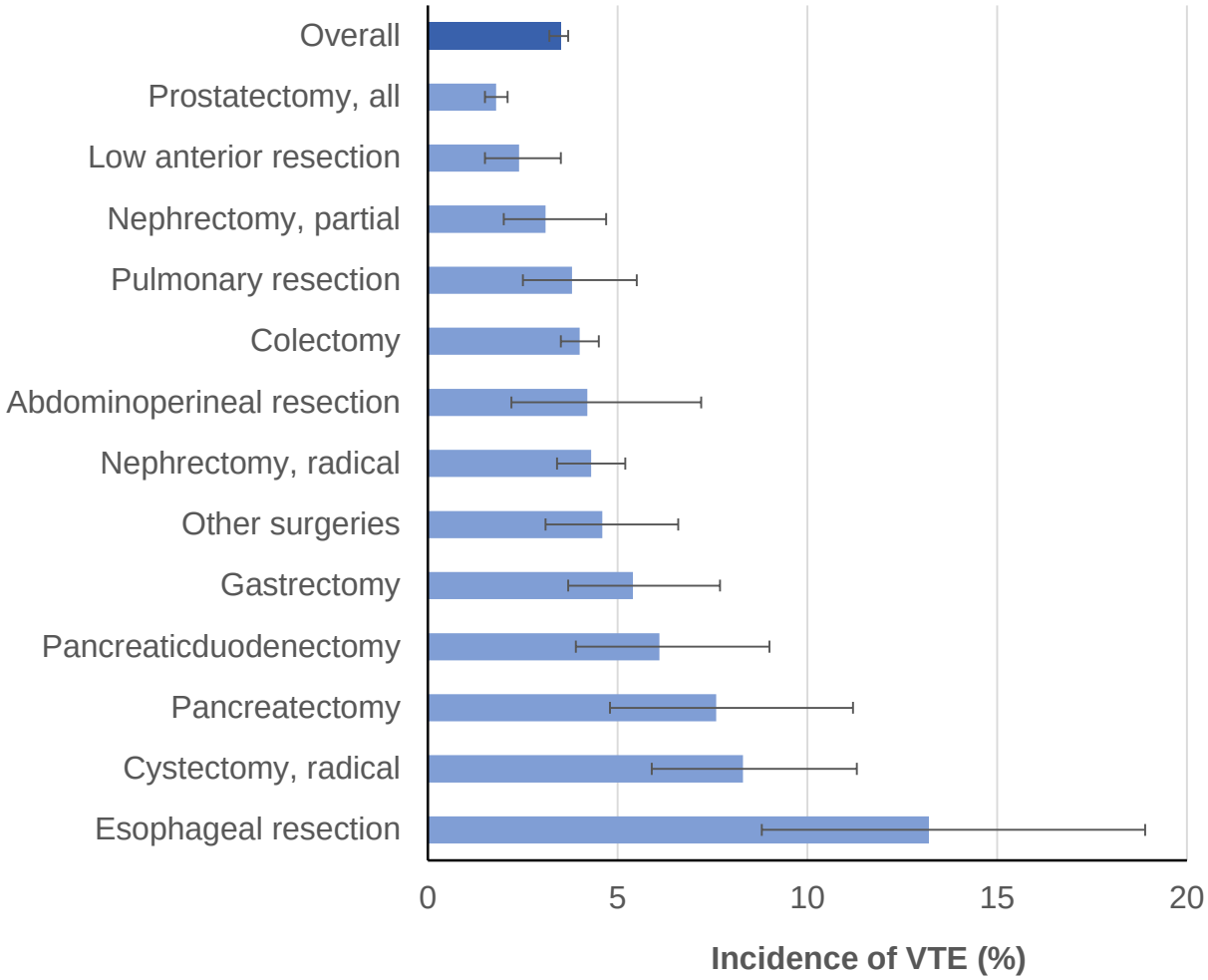
Treatment-related factors

- Major surgery
- Hospitalization
- Chemotherapy
- Central venous catheters
- Hormonal therapy
- Antiangiogenic agents
- ESAs
- Transfusions

Khorana et al., Cancer. 2007;110(10):2339-46

Incidence of VTE after Cancer Surgery

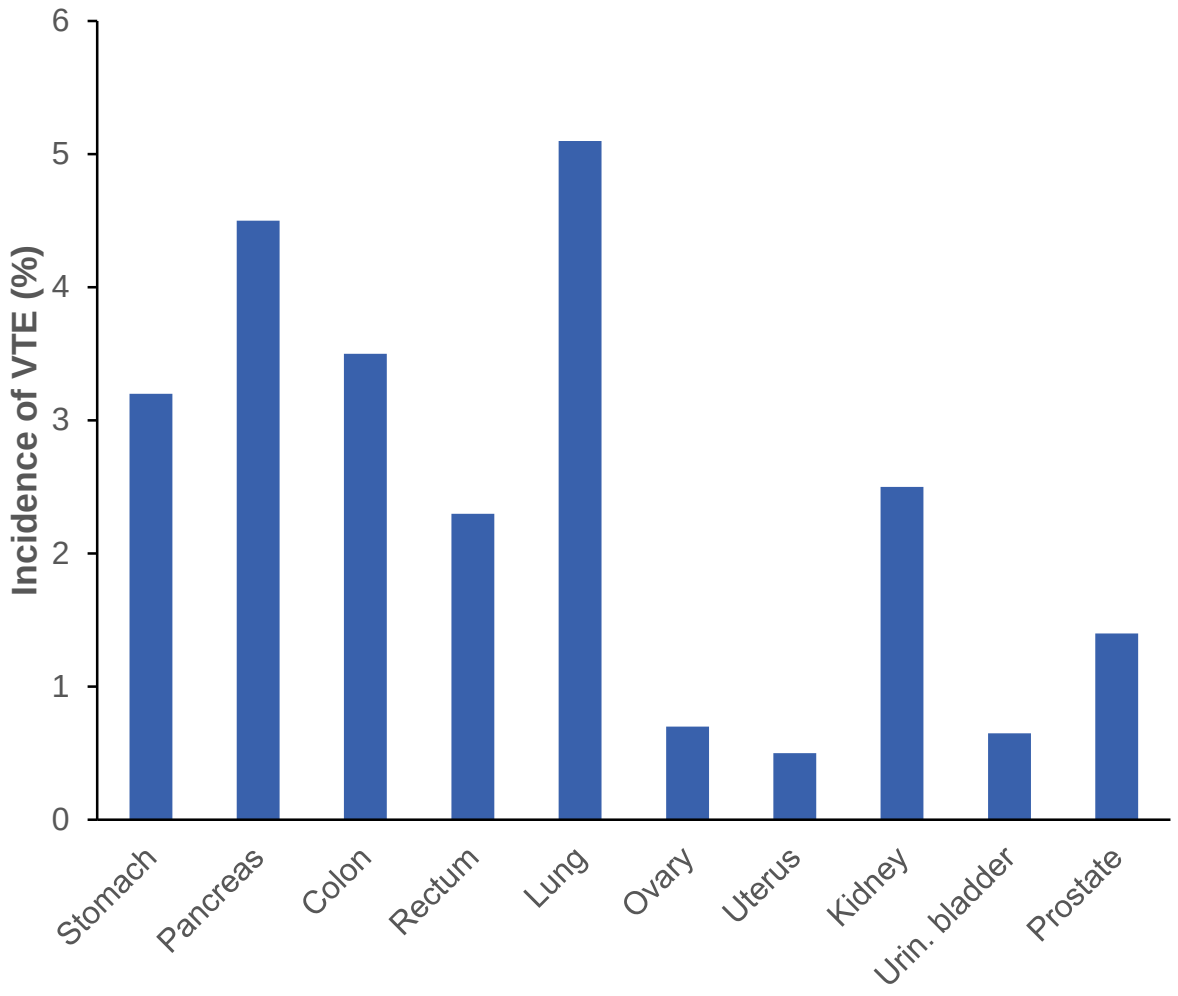
- 20,762 patients undergoing major cancer surgery
- Overall 30-day VTE rate 3.5%



Hammond J *et al*, *Ann Surg Oncol* 2011;18:3240–3247

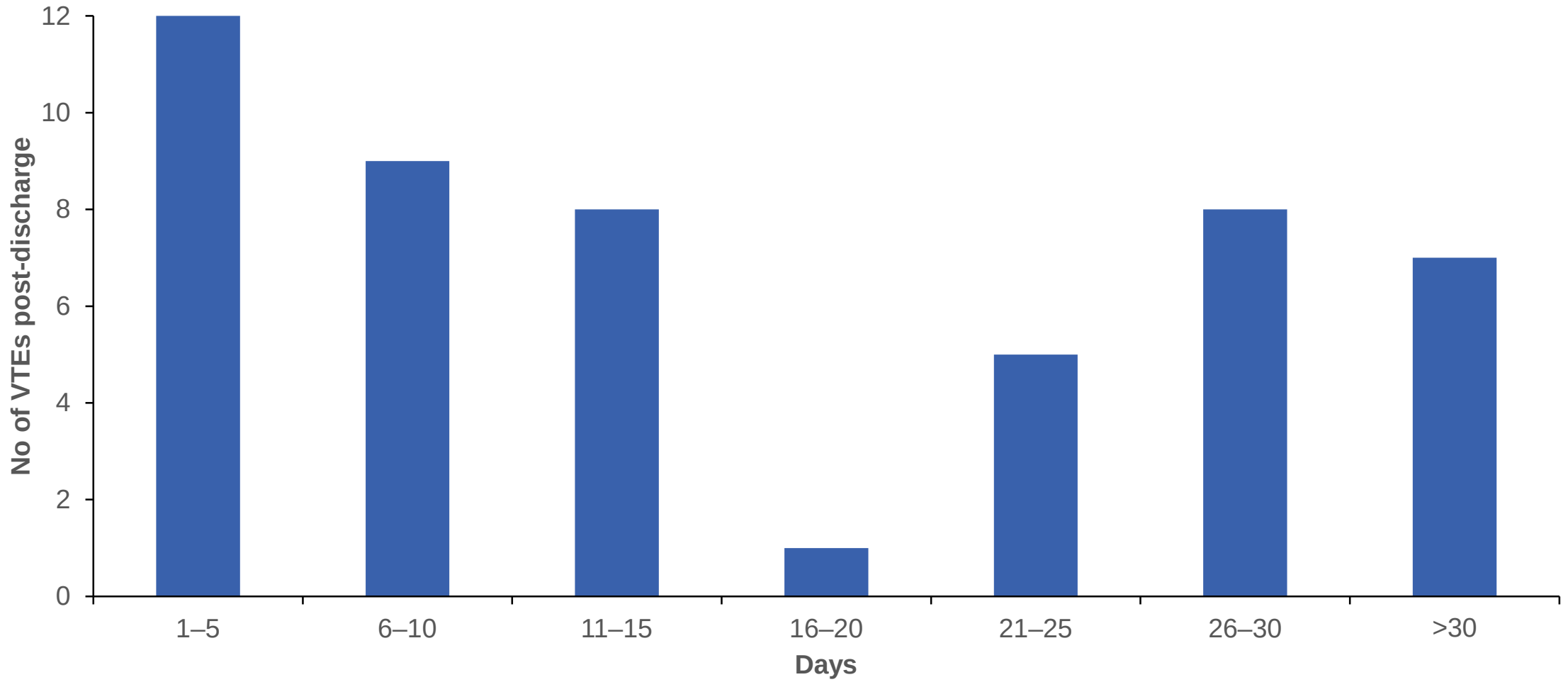
Incidence of VTE by Site

- Prospective study, 2373 patients undergoing general, urologic or gynecologic surgery
- Clinical VTE up to 30±5 days or more if hospital stay was >35 days
- Overall incidence = 50 patients (2.1%)



Agnelli G *et al*, *Ann Surg* 2006;243:89–95

Incidence of post-op VTE – Timing



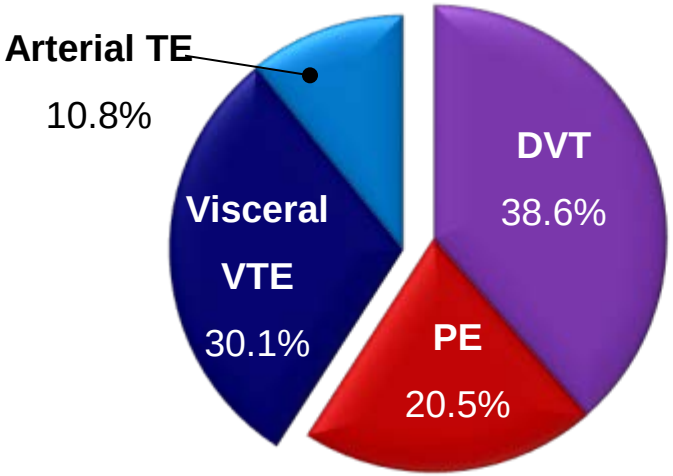
Agnelli G *et al*, *Ann Surg* 2006;243:89–95

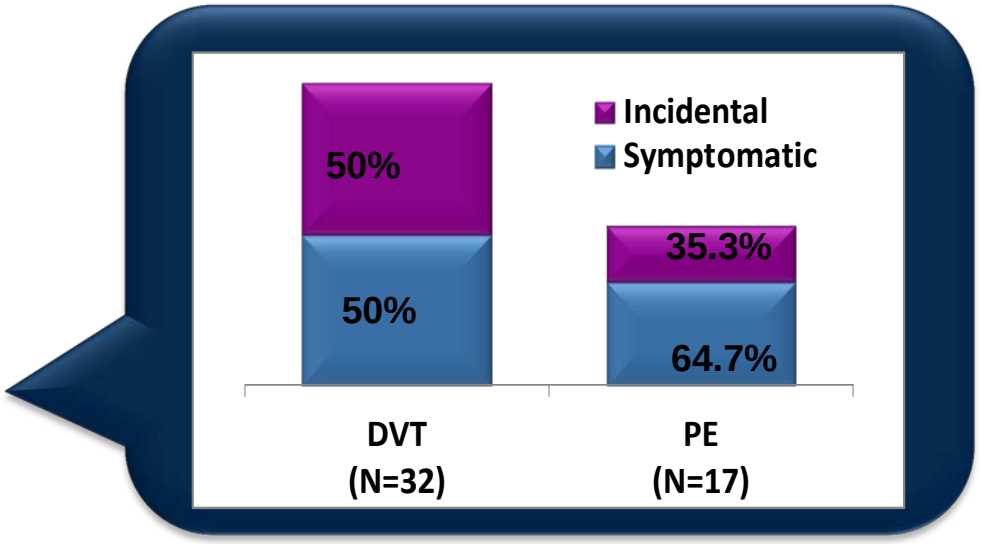
VTE in Cancer Patient: High prevalence of silent forms

Gastrointestinal Cancer Program Study (Rochester Medical Center)

Retrospective cohort study (N = 220)*

- Approximately 24% of the patients had VTE
- "Typical" localisation accounted for ~60% of the cases
- However, unsuspected DVT/PE accounted for ~ 40% of the VTE (DVT = 7.3% ; PE = 2.7%)





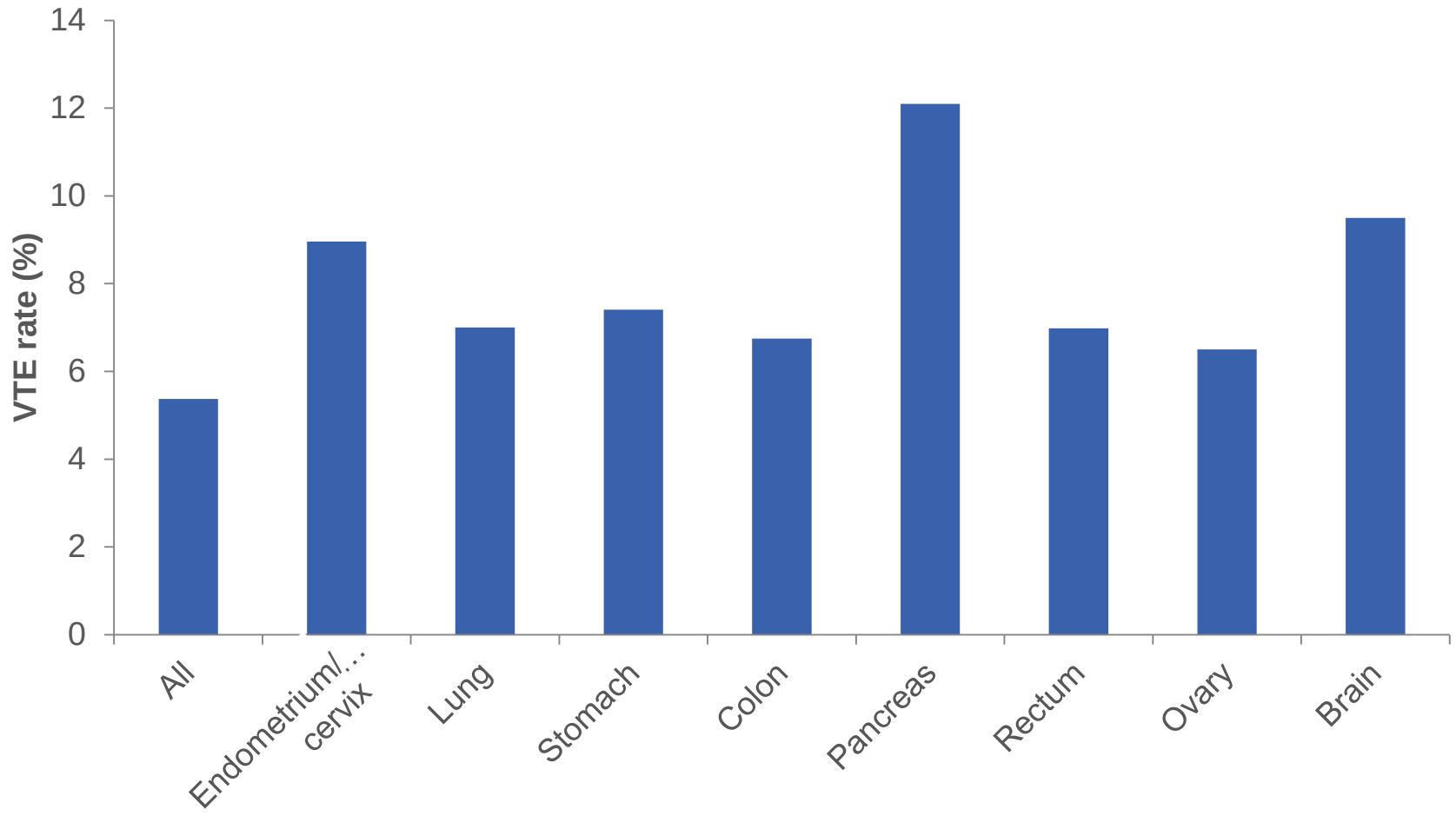
Visceral VTE: Visceral Vein Thromboembolism

Arterial TE: Arterial Thromboembolism

- * Consecutive patients with gastrointestinal cancers receiving systemic chemotherapy
- Cancer localization = esophageal, gastric, liver, biliary tract, pancreatic, small bowel, colon, rectum, anal

Singh R et al. J Thromb Haemost.2010; 8(8):1879-81

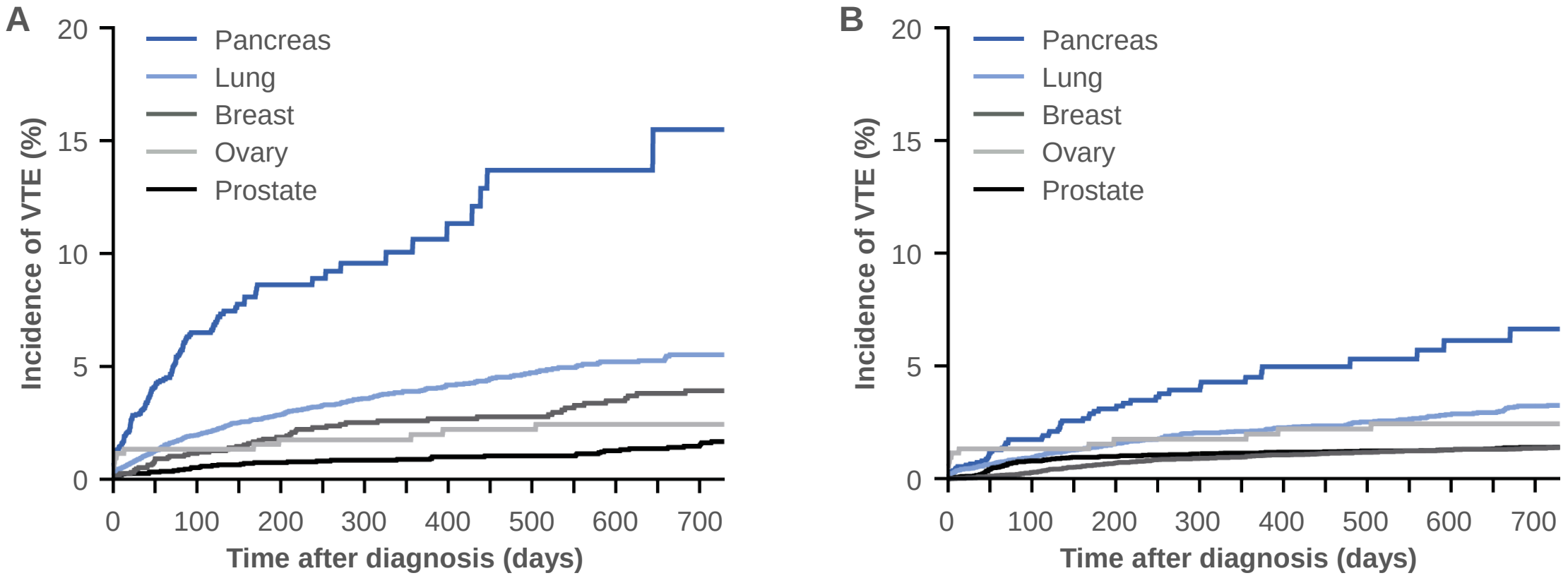
Risk of Inpatient VTE by Site/Type of Cancer



Khorana AA *et al*, *J Clin Oncol* 2006;24:484–490

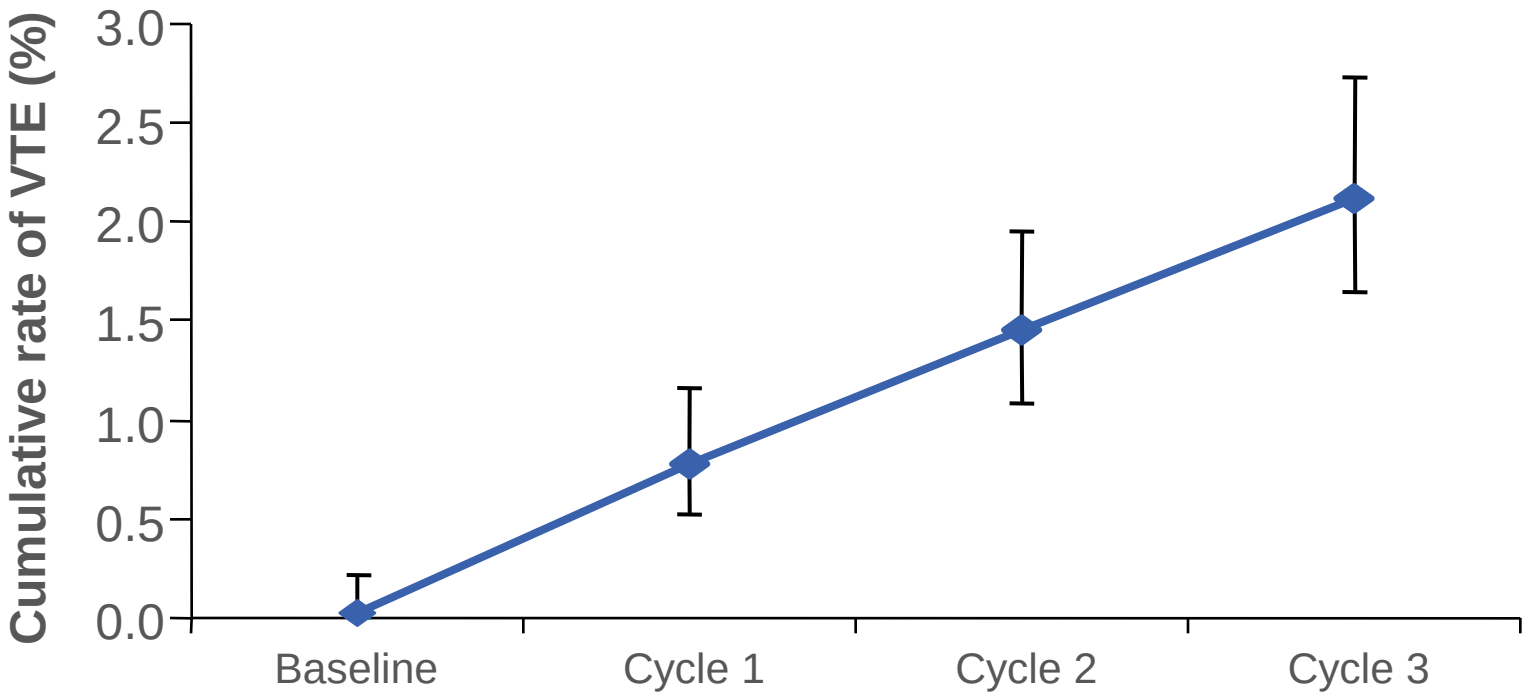
Impact of Stage on VTE

Kaplan–Meier plot of the incidence of VTE ≤2 years of diagnosis of five different types of cancer with (A) metastatic-stage and (B) regional-stage disease at the time of diagnosis



Chew HK *et al*, *Arch Intern Med* 2006;166:458–464

Incidence of VTE in Ambulatory Cancer Patients Initiating a New Chemotherapy Regimen



VTE / 2.4 months	VTE/month	VTE /cycle	Cumulative rate (95% CI)
1.93%	0.8%	0.7%	2.2% (1.7–2.8)

Khorana AA *et al*, *Cancer* 2005;104:2822–2829

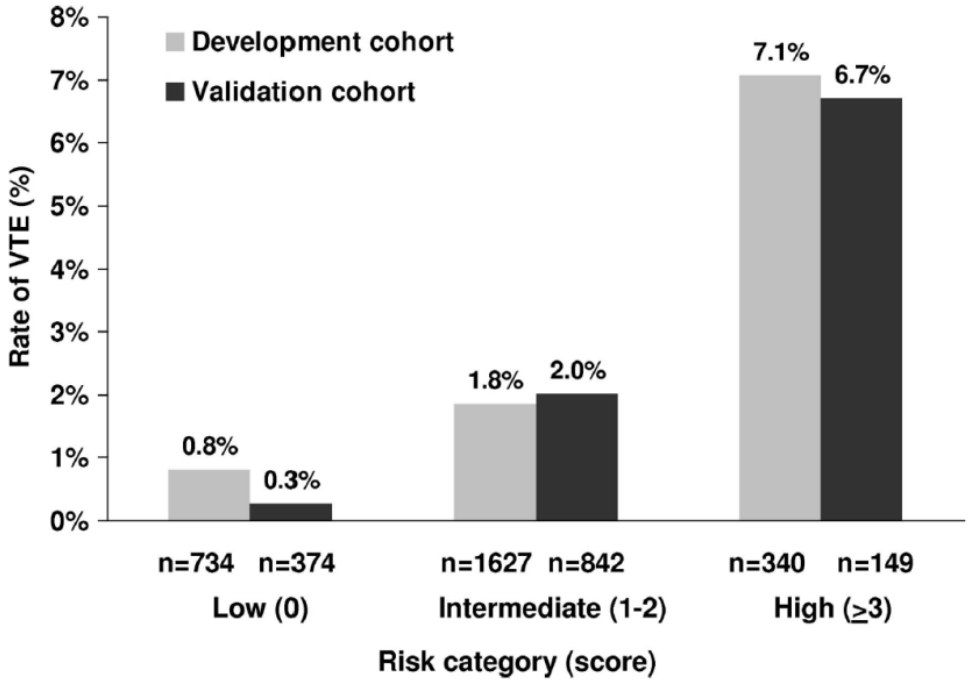
Identifying Patients at Risk of Chemotherapy-Associated Thrombosis

Predictors of chemotherapy-associated VTE

Patient characteristic	β	Odds ratio* (95% CI)
Site of cancer		
Very high risk (stomach, pancreas)	1.46	4.3 (1.2-15.6)
High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate)	0.43	1.5 (0.9-2.7)
Low risk (breast, colorectal, head and neck)	0.0	1.0 (reference)
Prechemotherapy platelet count 350 × 10^9/L or more	0.60	1.8 (1.1-3.2)
Hemoglobin level less than 100 g/L or use of red cell growth factors	0.89	2.4 (1.4-4.2)
Prechemotherapy leukocyte count more than 11 × 10^9/L	0.77	2.2 (1.2-4)
BMI 35 kg/m^2 or more	0.90	2.5 (1.3-4.7)

*Odds ratios are adjusted for stage.

Rates of VTE according to Khorana risk scores

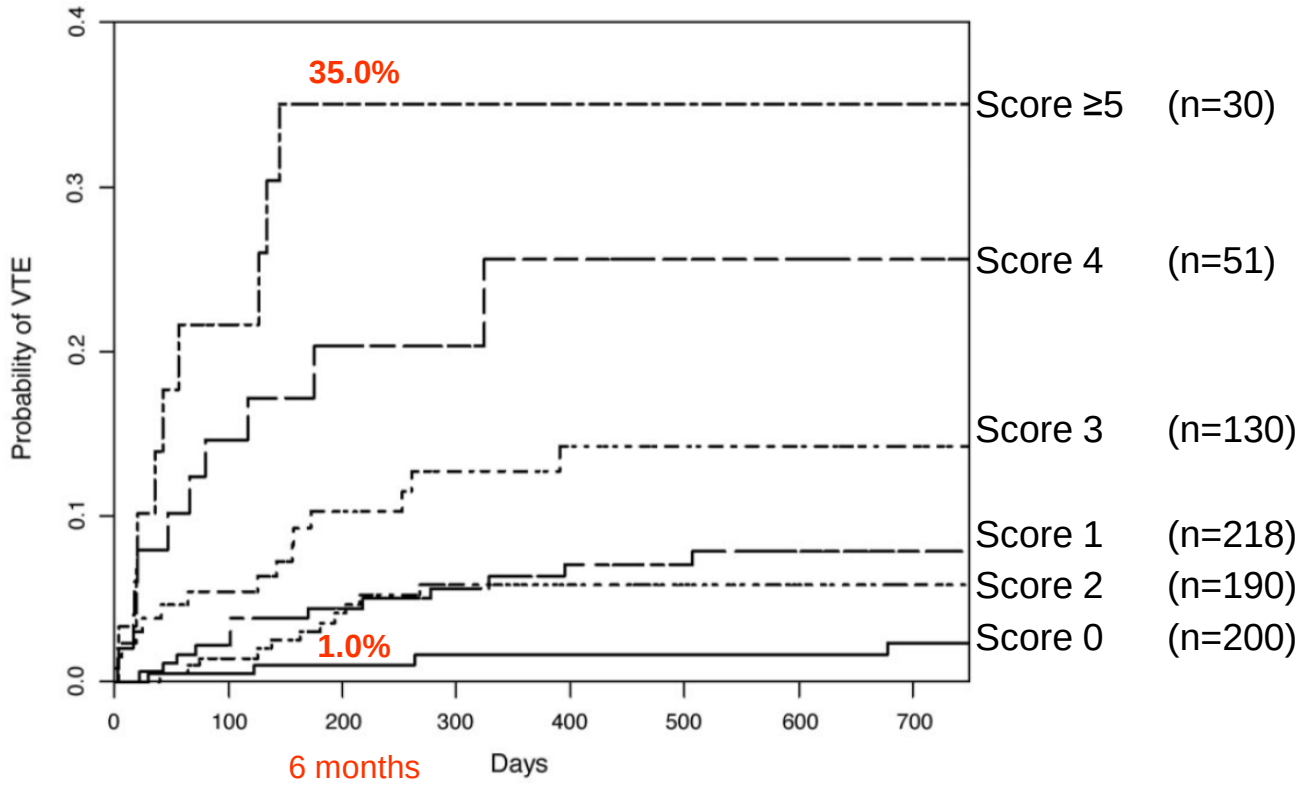


Khorana AA *et al*, *Blood* 2008;111:4902–4907

The Vienna CATS Score

- Khorana score plus biomarkers (D-dimer and sP-selectin)

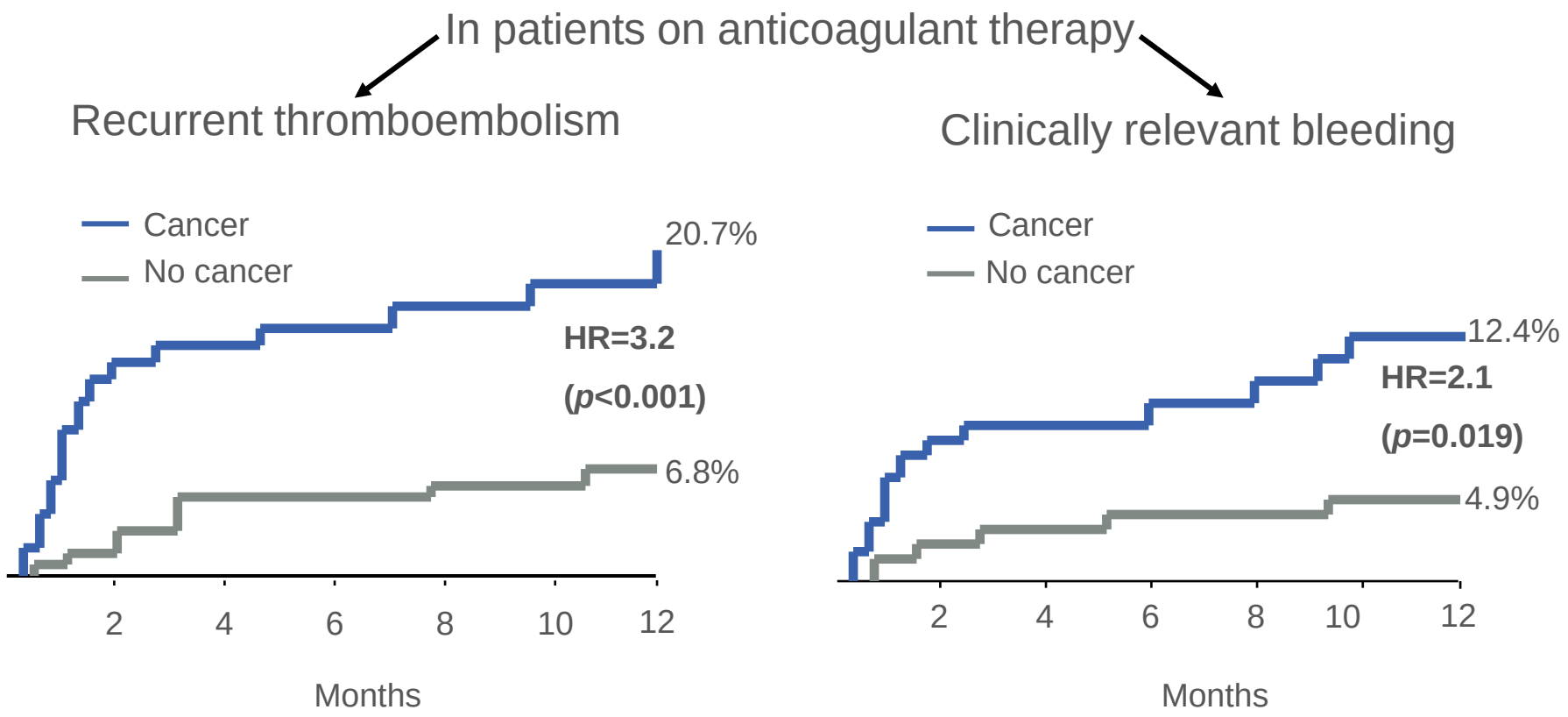
Kaplan-Meier estimates of the risk of VTE according to Vienna CATS score



Ay C *et al*, *Blood* 2010;116:5377–5382

VTE Treatment in Cancer Patients

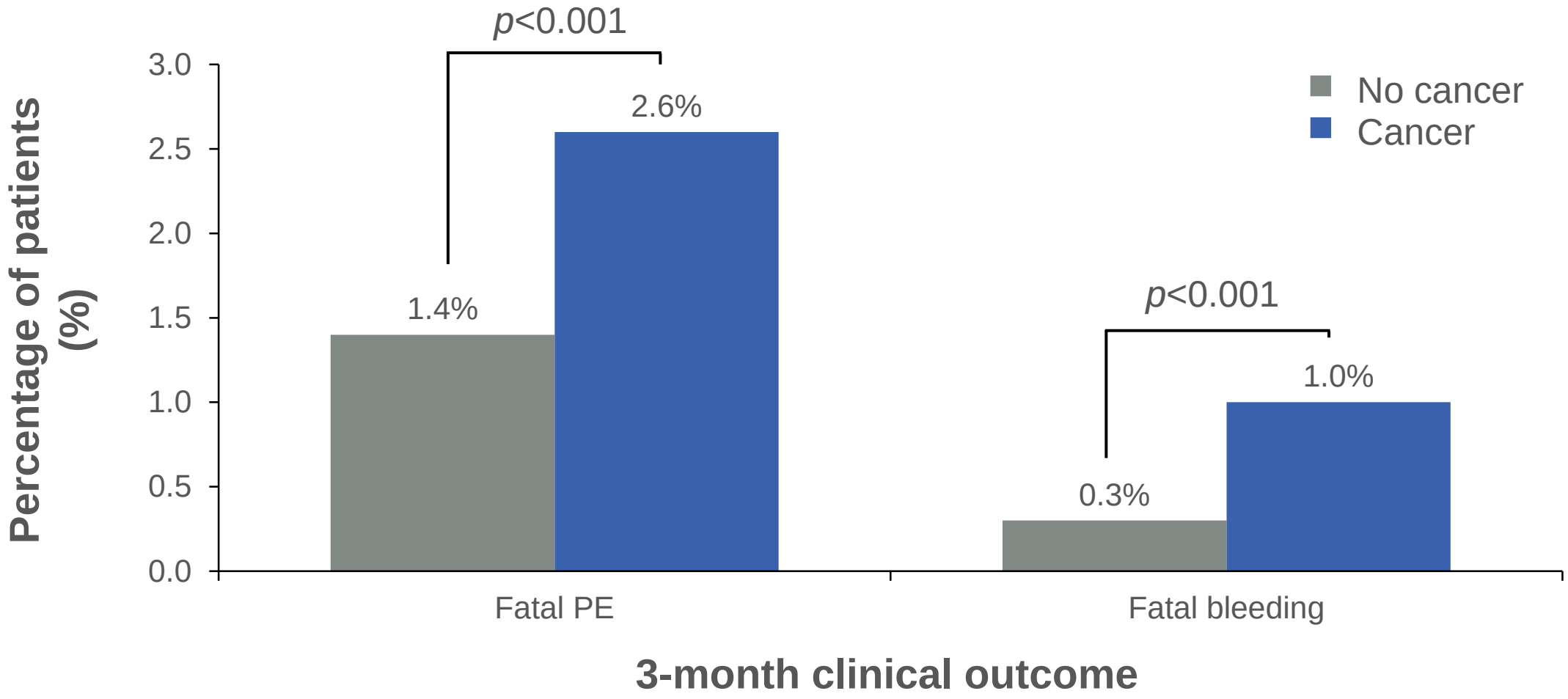
Benefit and risk balance more difficult to achieve



Prandoni P *et al*, *Blood* 2002;100:3484–3488

Higher Rates of Fatal PE and Fatal Bleeding in Patients with Cancer

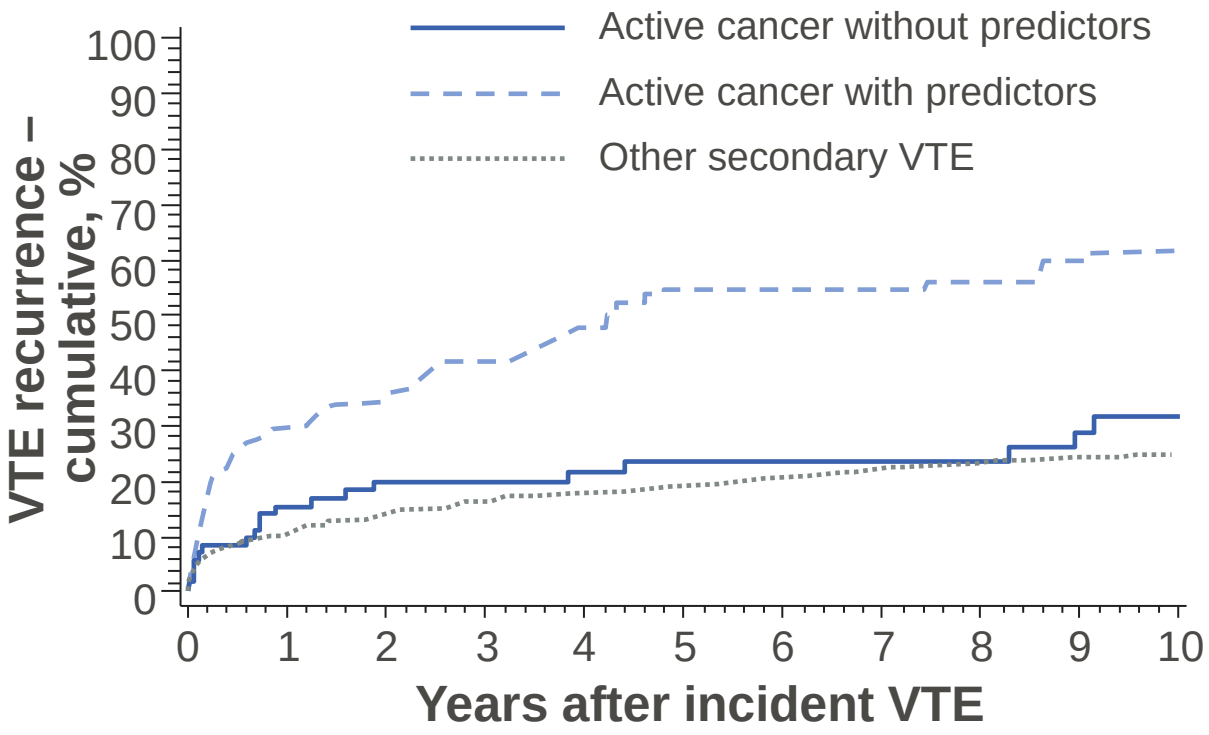
Risk of fatal PE or fatal bleeding in the RIETE registry[1]



1. Monreal M *et al*, *J Thromb Haemost* 2006;4:1950–1956

Predicting VTE Recurrence Among Olsted County Residents with Active-Cancer-Related Incident DVT or PE

Cumulative incidence of first VTE recurrence



Multivariate predictors of VTE recurrence

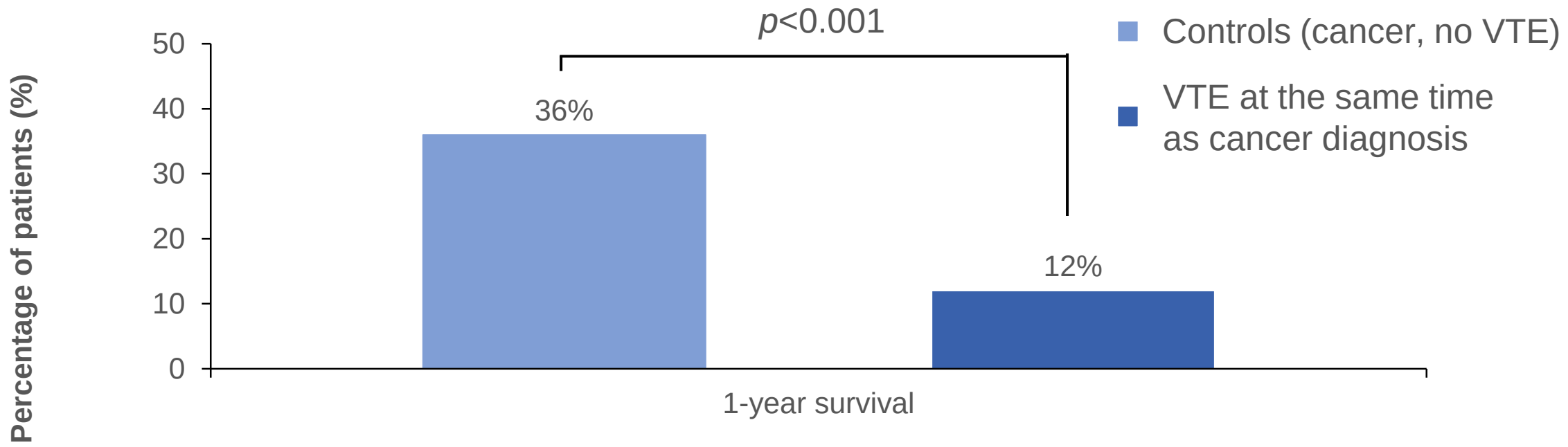
Characteristic	HR	95% CI	*p*-value
Stage IV pancreatic cancer	6.38	2.69–15.13	<0.0001
Brain cancer	4.57	2.07–10.09	0.0002
Myeloproliferative or myelodysplastic disorder	3.49	1.59–7.68	0.002
Ovarian cancer	3.22	1.57–6.59	0.001
Stage IV cancer (non-pancreas)	2.85	1.74–4.67	<0.0001
Lung cancer	2.73	1.63–4.55	0.0001
Neurological disease with leg paresis	2.38	1.14–4.97	0.02
Cancer stage progression	2.14	1.30–3.52	0.003
Warfarin therapy	0.43	0.28–0.66	<0.0001

Chee CE *et al*, *Blood* 2014;123:3972–3978

Cancer and VTE Predict Poor Outcome

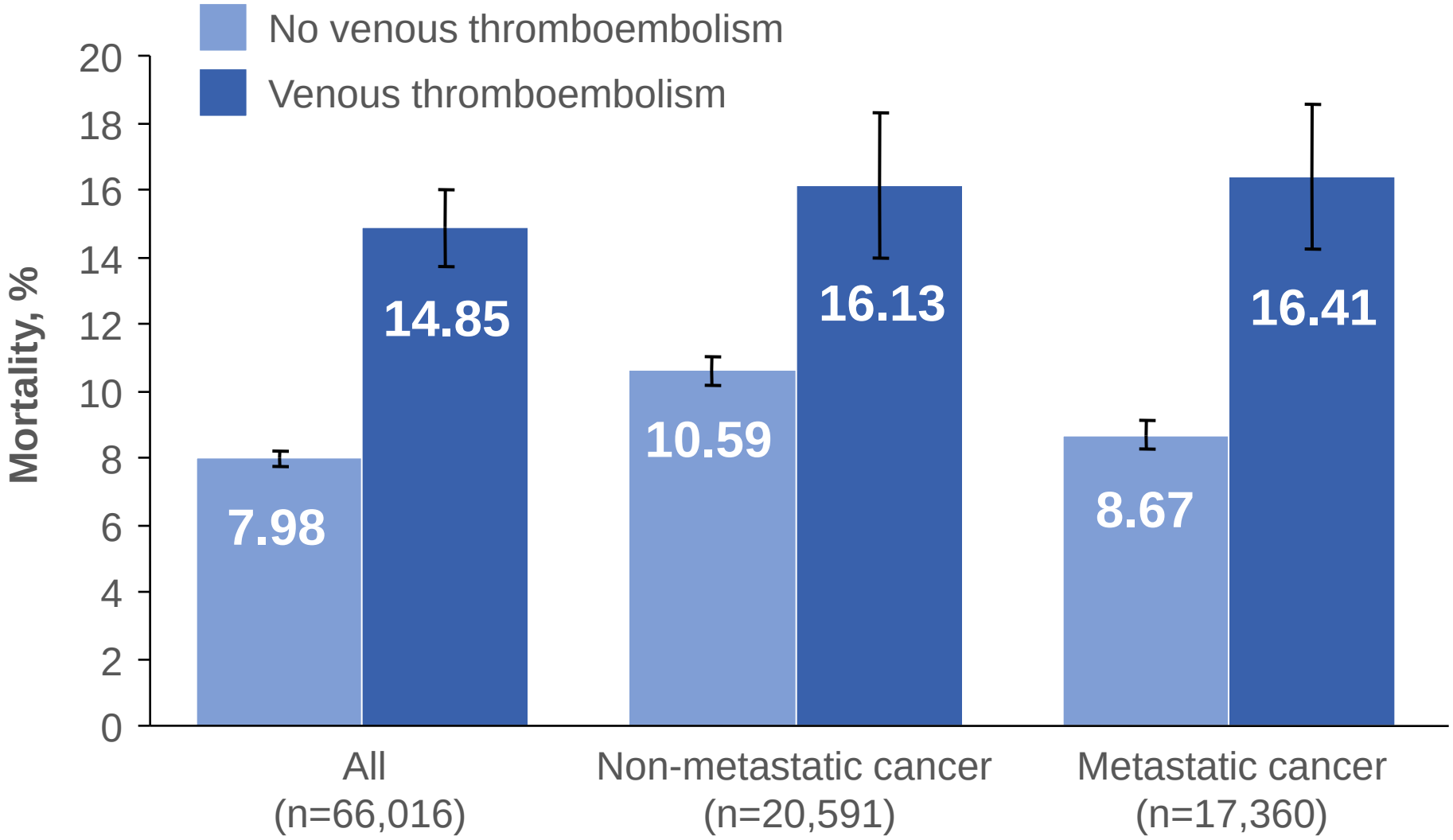
- Patients with a diagnosis of cancer at the time of an episode of VTE were more likely to have distant metastases and had poorer 1-year survival than matched controls with cancer but no VTE

1-year survival in patients with cancer and VTE versus matched controls



Sørensen HT *et al*, *N Engl J Med* 2000;343:1846–1850

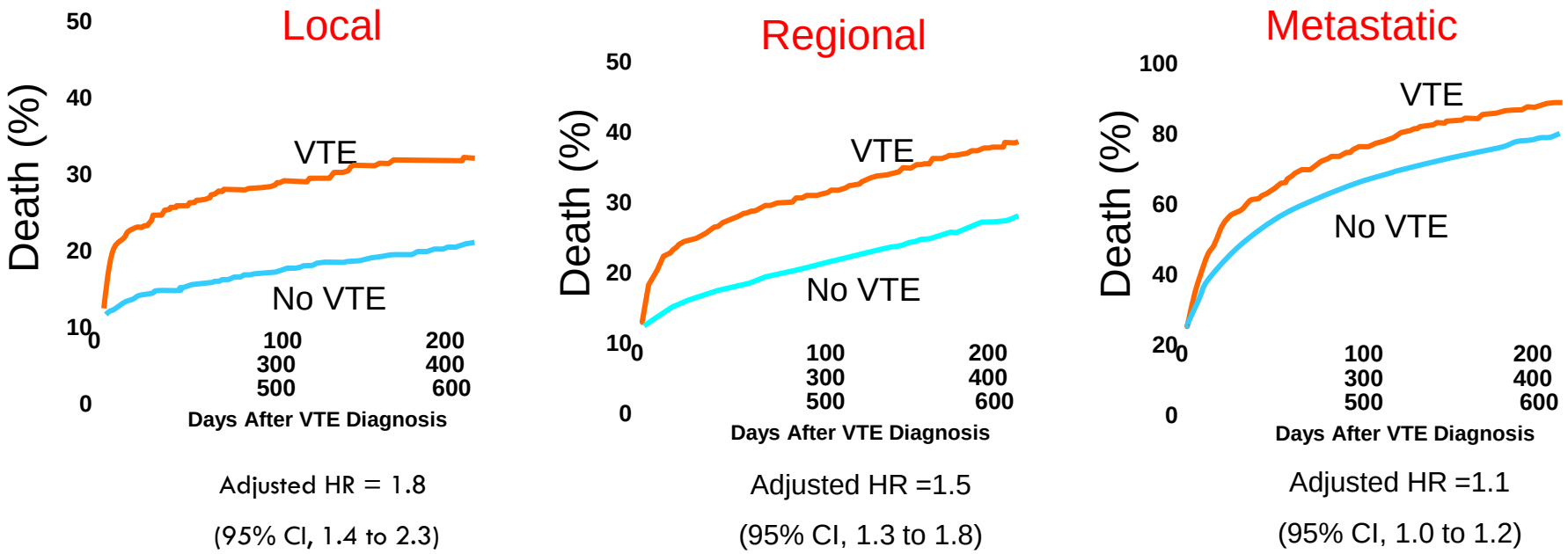
VTE and Inpatient Mortality



Khorana AA *et al*, *J Clin Oncol* 2006;24:484–490

Impact of VTE on Survival according to Cancer Site and Stage

Occurrence of VTE has more deleterious effect on localized or regional cancer



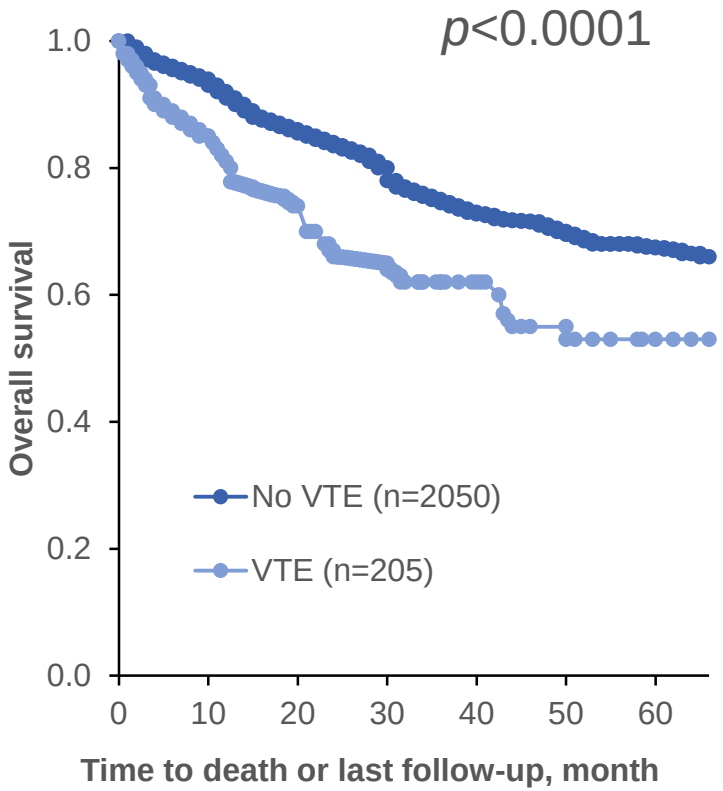
In risk-adjusted models

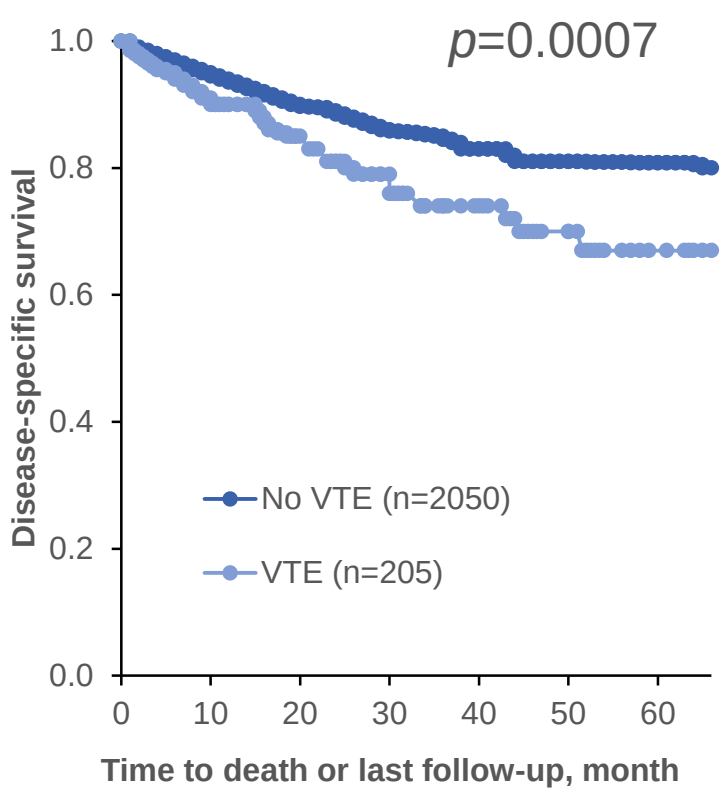
VTE is a significant predictor of death within 1 year of cancer diagnosis among patients with local or regional-stage disease but not among patients with metastatic disease

Alcalay A et al. *J Clin Oncol.* 2006; 24:1112-1118.

Postoperative VTE and Survival

- Impact of VTE on 5-year survival following cancer resection in patients with and without VTE
- Matched for:
  - Gender
  - Age
  - Year of surgery
  - Type of cancer
  - Stage
  - Procedure
- Worse disease-specific survival in patients with VTE





Auer RAC *et al*, *Ann Surg* 2012;255:963–970

Outcomes in the First Month and Over the Following 2–6 Months After Diagnosis of VTE

	Month 0–1		Months 2–6	
	Events	Rate per 100 person-years (95% CI)	Events	Rate per 100 person-years (95% CI)
Primary endpoints				
All-cause mortality	108	13.0 (10.7–15.6)	352	7.4 (6.7–8.2)
Major bleed	46	5.5 (4.2–7.4)	60	1.3 (1.0–1.7)
Recurrent VTE	35	4.2 (3.0–5.9)	134	2.9 (2.4–3.4)
Secondary endpoints				
Any bleed	239	29.0 (25.6–32.9)	383	8.4 (7.6–9.3)
Myocardial infarction	11	1.3 (0.7–2.4)	31	0.7 (0.5–0.9)
Stroke/TIA	9	1.1 (0.6–2.1)	29	0.6 (0.4–0.9)

Date of analyses: 24th April 2017.

GARFIELD-VTE. Unpublished data.

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Causes of Death Over 6 Months After VTE

	n	%
Cancer-related	250	54.3
Cardiac	32	7.0
VTE-related events (including PE)	22	4.8
Bleed	15	3.3
Stroke	5	1.1
Other	82	17.8
Unknown	54	11.7
Total	460	100

Date of analyses: 24th April 2017.

Turpie AGG, et al. Presented at ISTH Congress 2017. Poster PB1196.

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

A New Diagnosis of Cancer in VTE patients

- **A new diagnosis of cancer was made in 195 patients in the first 6 months after VTE diagnosis**
- Equivalent to a rate of 4.1 (3.6–4.8) events per 100 person-years

Date of analyses: 24th April 2017.

Turpie AGG, et al. Presented at ISTH Congress 2017. Poster PB1196.

The GARFIELD-VTE registry is funded by an unrestricted research grant from Bayer AG

Conclusion

- Cancer is an important risk factor for VTE
- Impact on medical and surgical cancer patients
- Attended by higher risk for bleeding and recurrence
- Impacts mortality
- A two way association

TREATING AND PREVENTING VTE IN CANCER PATIENTS

HOWARD A. LIEBMAN MD
DONALD I. FEINSTEIN PROFESSOR OF MEDICINE
JANE ANN NOLH DIVISION OF HEMATOLOGY
UNIVERSITY OF SOUTHERN CALIFORNIA- KECK SCHOOL OF MEDICINE

Disclosures

- **CONSULTING:** PfIZER, BMS, JANSSEN, RIGEL, AMGEN, NOVARTIS, SANOFI, GENZYME

- **RESEARCH SUPPORT:** JANSSEN, PROTOLEX, SYNTIMMUNE

Educational Need/Practice Gap

Gap = Despite randomized clinical trials demonstrating clinical superiority of LMW heparin vs. warfarin for the secondary prophylaxis of cancer-associated DVT, warfarin continues to be used in this patient population.

DOACs in preliminary studies show promise in this patient population, but without randomized clinical data to support their equivalence or superiority to LMW heparins.

Need = Cost of LMW heparins and both patient and clinician hesitancy to prescribe long-term injection therapy.

Objectives

Upon completion of this educational activity, you will be able to:

1. **Know the clinical data supporting the preferred use of LMW heparin in the initial treatment and secondary prophylaxis of VTE in cancer patients.**
2. **Know the present status on VTE prophylaxis in ambulatory high-risk cancer patients.**
3. **Know the present status of clinical trials on the use of DOACs for treatment and ambulatory prophylaxis of VTE in cancer patients.**

Expected Outcome

- Clinicians will be more likely to prescribe and encourage their patients to use LMWH for initial treatment and secondary VTE prophylaxis.
- They will remain alert to ongoing randomized trials of DOACs versus LMWH for VTE treatment in cancer patients. The outcomes of these trials may change the treatment algorithm in cancer-associated VTE.

- Clinicians will consider the use of ambulatory VTE prophylaxis in high risk cancer patients. They will remain alert to ongoing VTE prophylaxis trials in high risk cancer patients.

TREATING CANCER-ASSOCIATED VTE

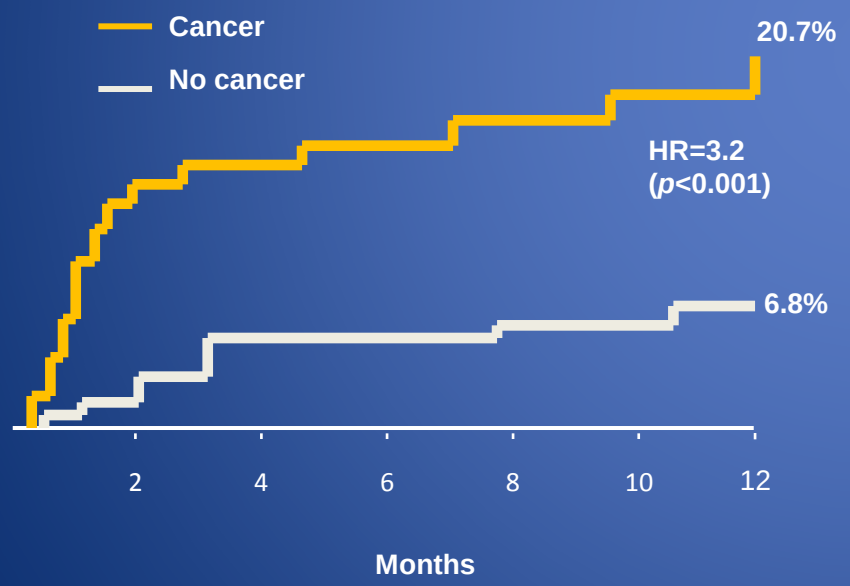
WHAT IS THE STANDARD IN 2017?

VTE Treatment in Cancer Patients

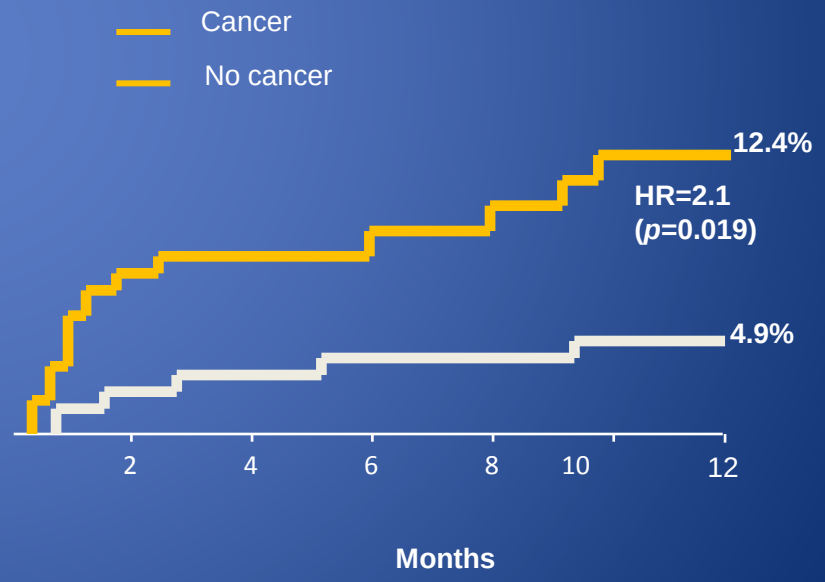
Benefit and risk balance more difficult to achieve

In patients on VKA anticoagulant therapy

Recurrent thromboembolism



Clinically relevant bleeding



Prandoni P, *et al*. *Blood* 2002;100:3484–3488

Risk of Bleeding Is Unrelated to INR in Cancer Patients:

Analysis from 2 Multicenter Clinical Treatment Trials

INR (range)	Recurrent VTE		Major Bleeding	
	Cancer	No Cancer	Cancer	No Cancer
< 2.0	54	15.9	30.6	0
2.0–3.0	18.9	7.2	11.2	0.8
> 3.0	18.4	6.4	0	6.3
Overall	**27**	**9**	**13.3**	**2.1**
Number of events per 100 patients/yrs				

Hutten BA, et al. J Clin Oncol 2000; 18: 3078-3083

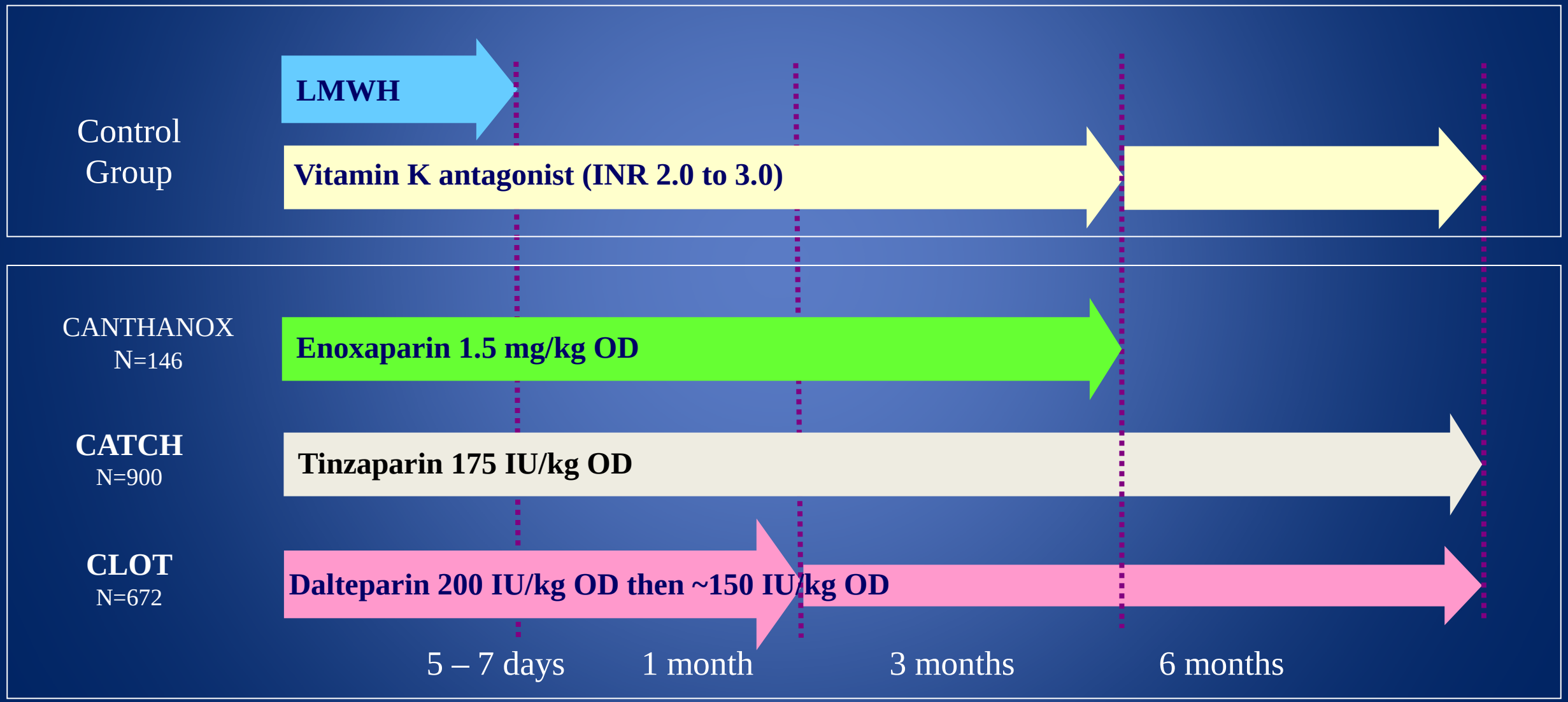
Treatment of VTE in Oncology

LMWH vs warfarin

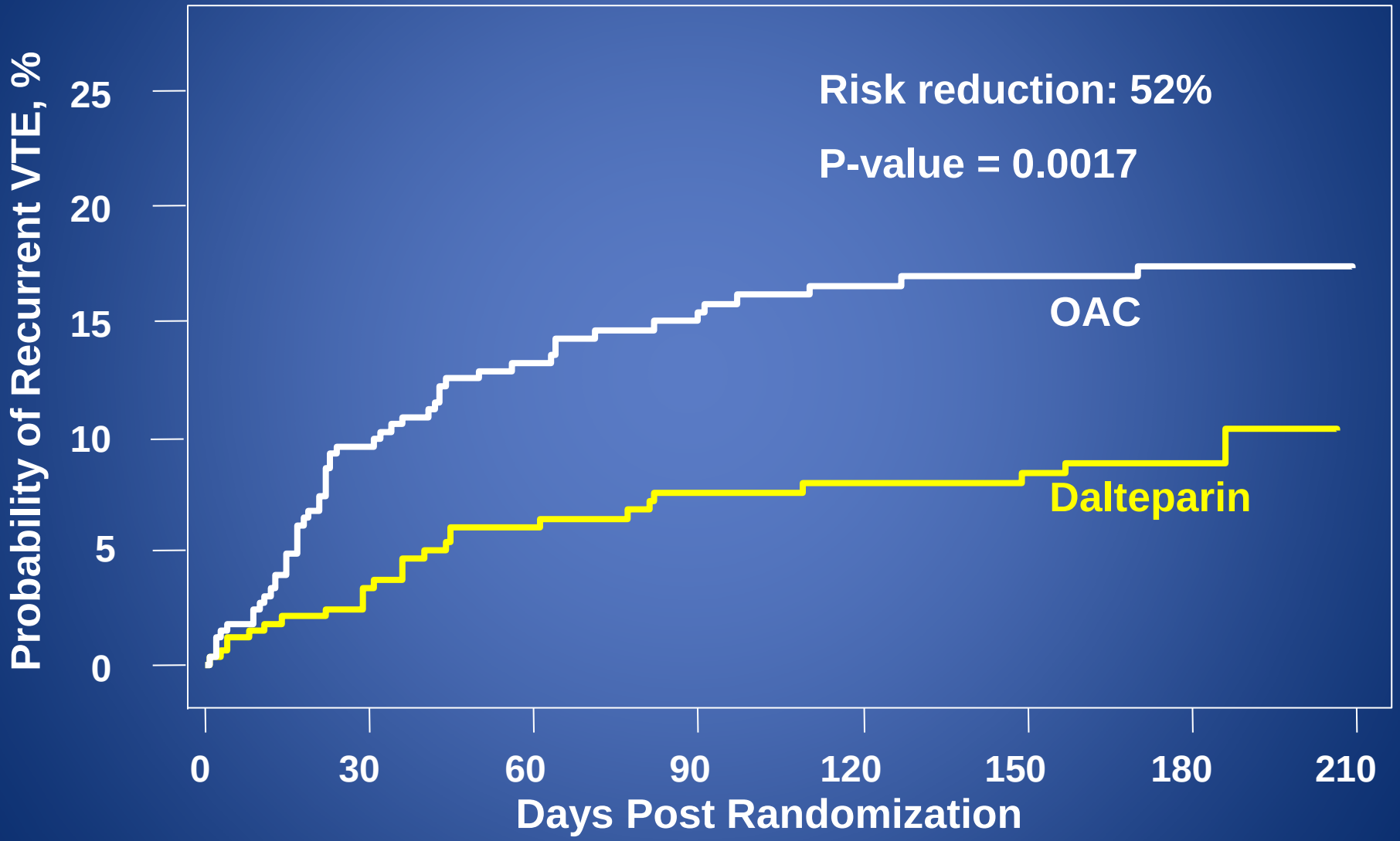
- **CANTHANOX**
- **CATCH**
- **CLOT**
- **LITE***
- **ONCENOX***

* Abstract only

Treatment of Acute VTE in Cancer

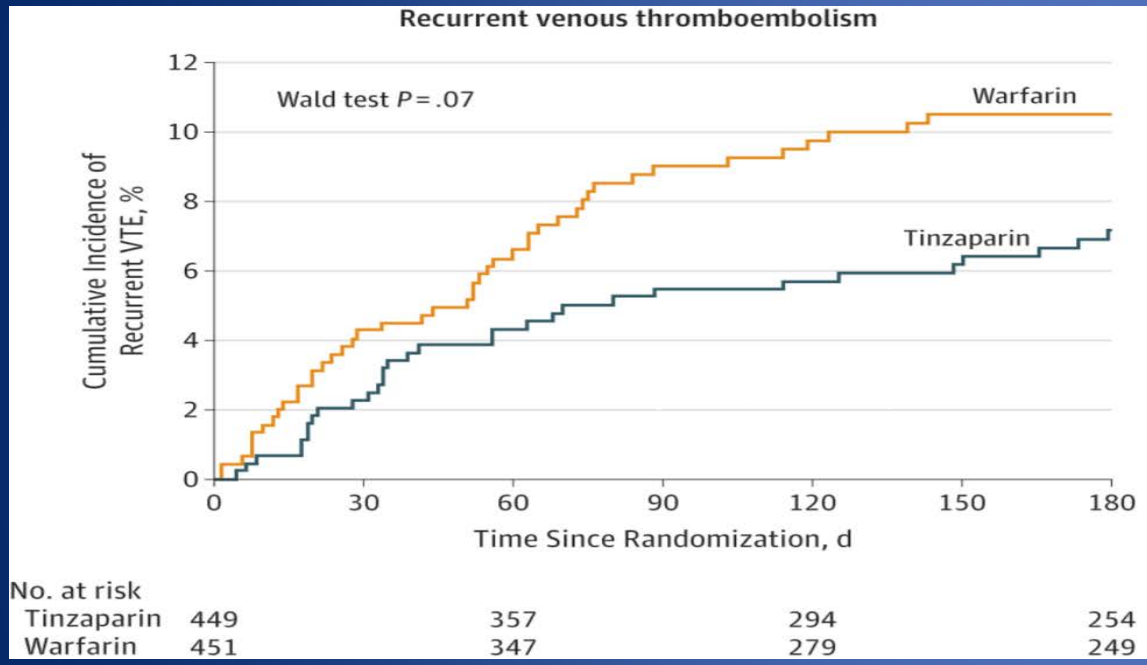


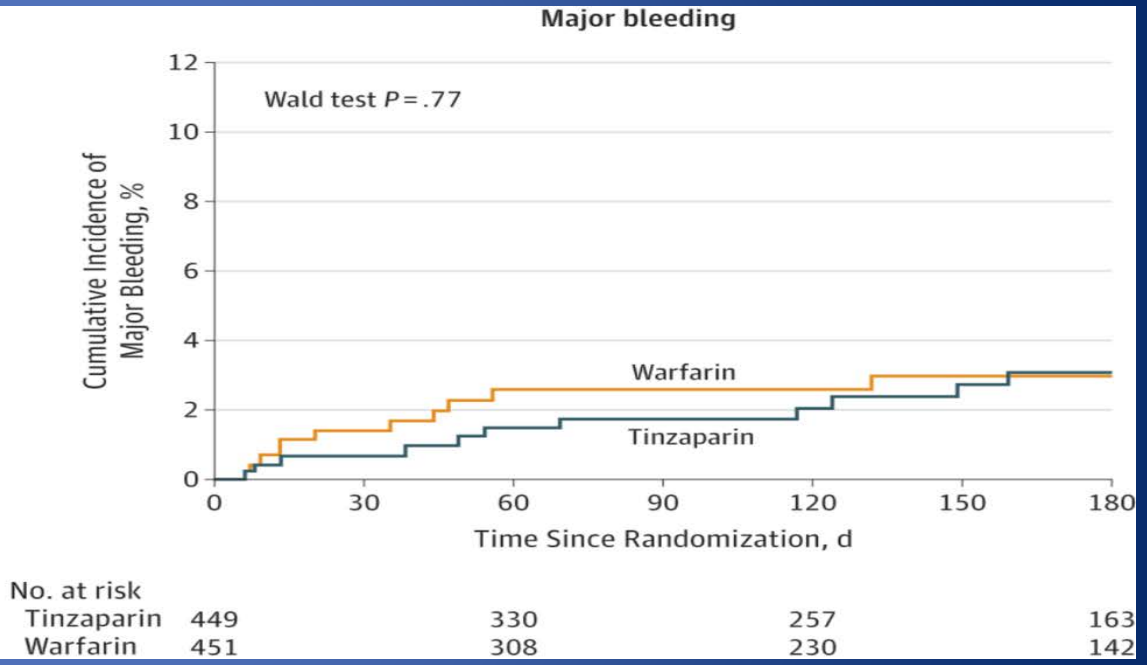
CLOT Recurrent VTE



Lee et al. New Engl J Med 2003;349:146-153

Tinzaparin vs Warfarin for Treatment of VTE in Patients With Active Cancer



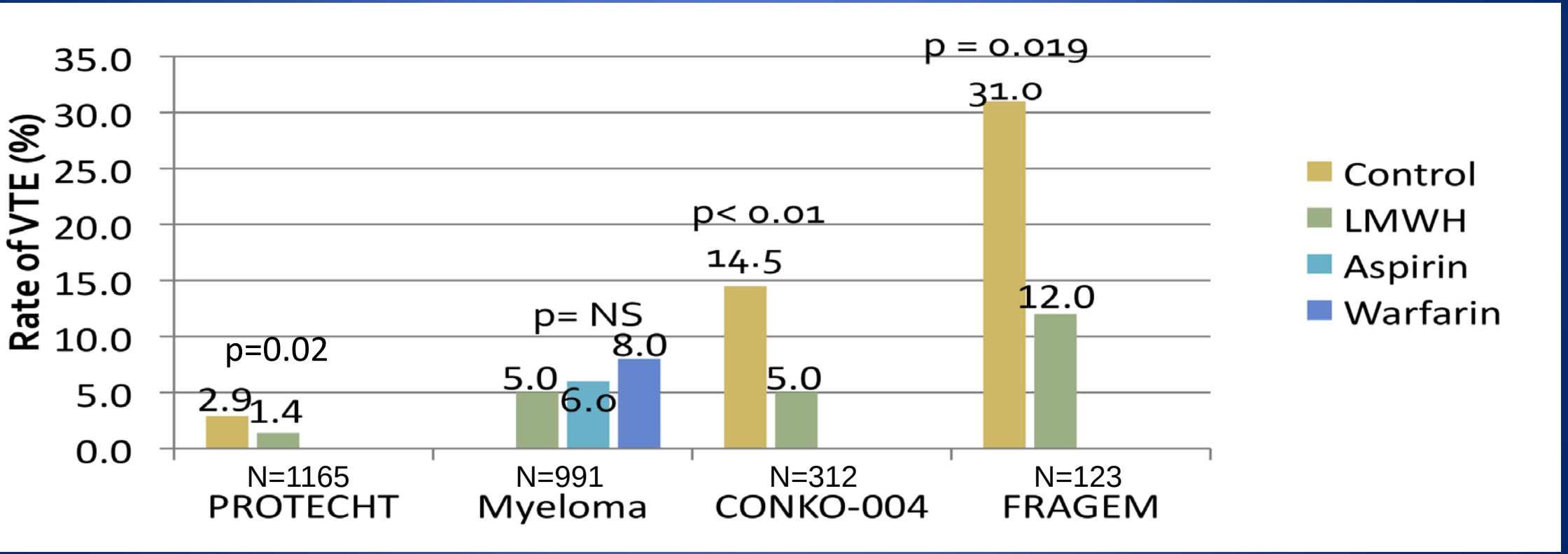


Lee AYY, et al for the CATCH Investigators. *JAMA*. 2015;314:677-686.

IT IS BETTER TO PREVENT THAN TO TREAT

PREVENTION OF VTE IN CANCER PATIENTS

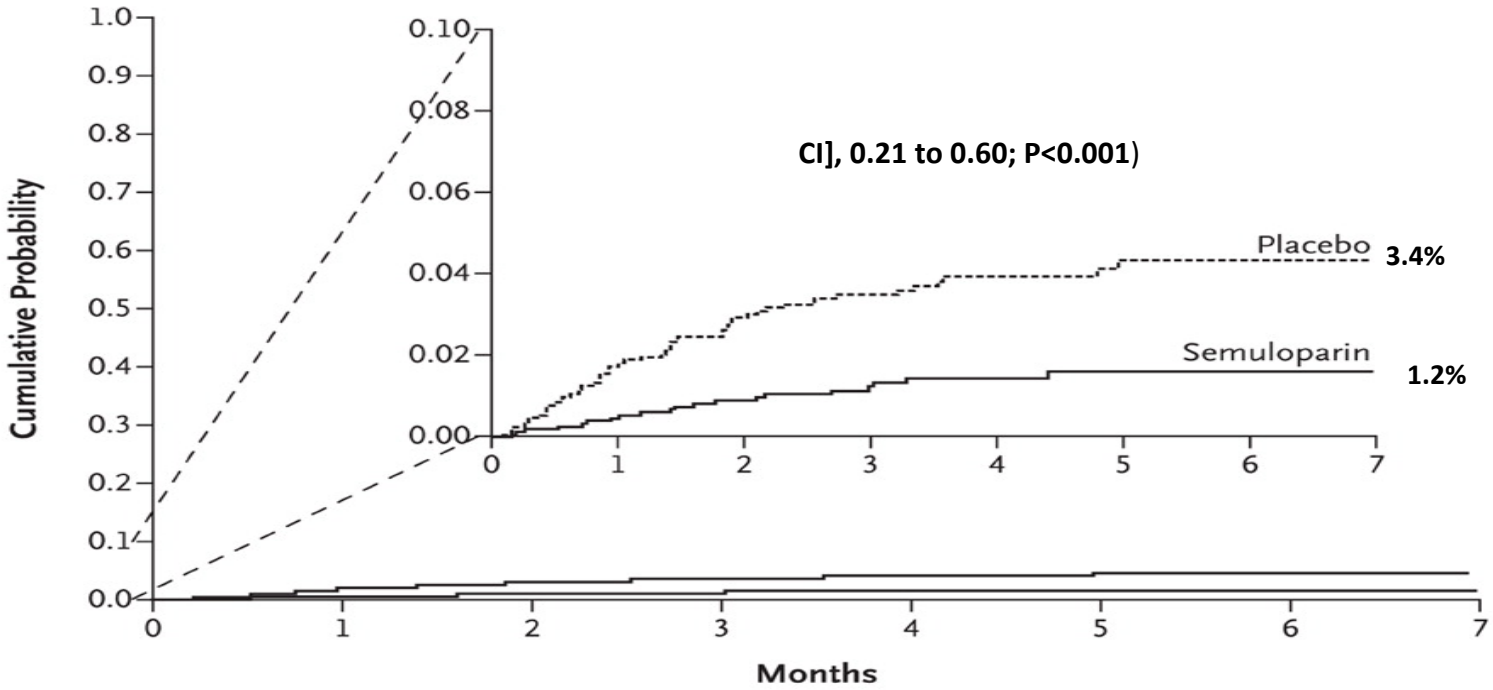
Rates of VTE in Recent Prophylaxis Studies



Agnelli G, et al. *Lancet Oncol.* 2009;10:943-9; Palumbo A, et al. *J Clin Oncol.* 2011;29:986-993
Petzer U et al. *Dtsch Med Wochenschr. 2013*;138:2084-8; Maraveyas A ,et al *Eur J Cancer.* 2012;48:1283-1292.

SEMULOPARIN FOR VTE PROPHYLAXIS IN AMBULATORY CANCER PATIENTS RECEIVING CHEMOTHERAPY

Kaplan–Meier Curves for the Primary Efficacy Outcome in the Intention-to-Treat Population, According to Study Group.



No. at Risk								
Semuloparin	1608	1410	1227	986	681	384	197	77
Placebo	1604	1375	1212	985	689	403	201	92
No. of Events								
Semuloparin	0	7	13	17	19	20	20	20
Placebo	0	26	42	49	53	55	55	55

Agnelli G et al. N Engl J Med 2012;366:601-609.

CAN WE SELECT FOR AMBULATORY CANCER PATIENTS AT HIGH RISK OF VTE?

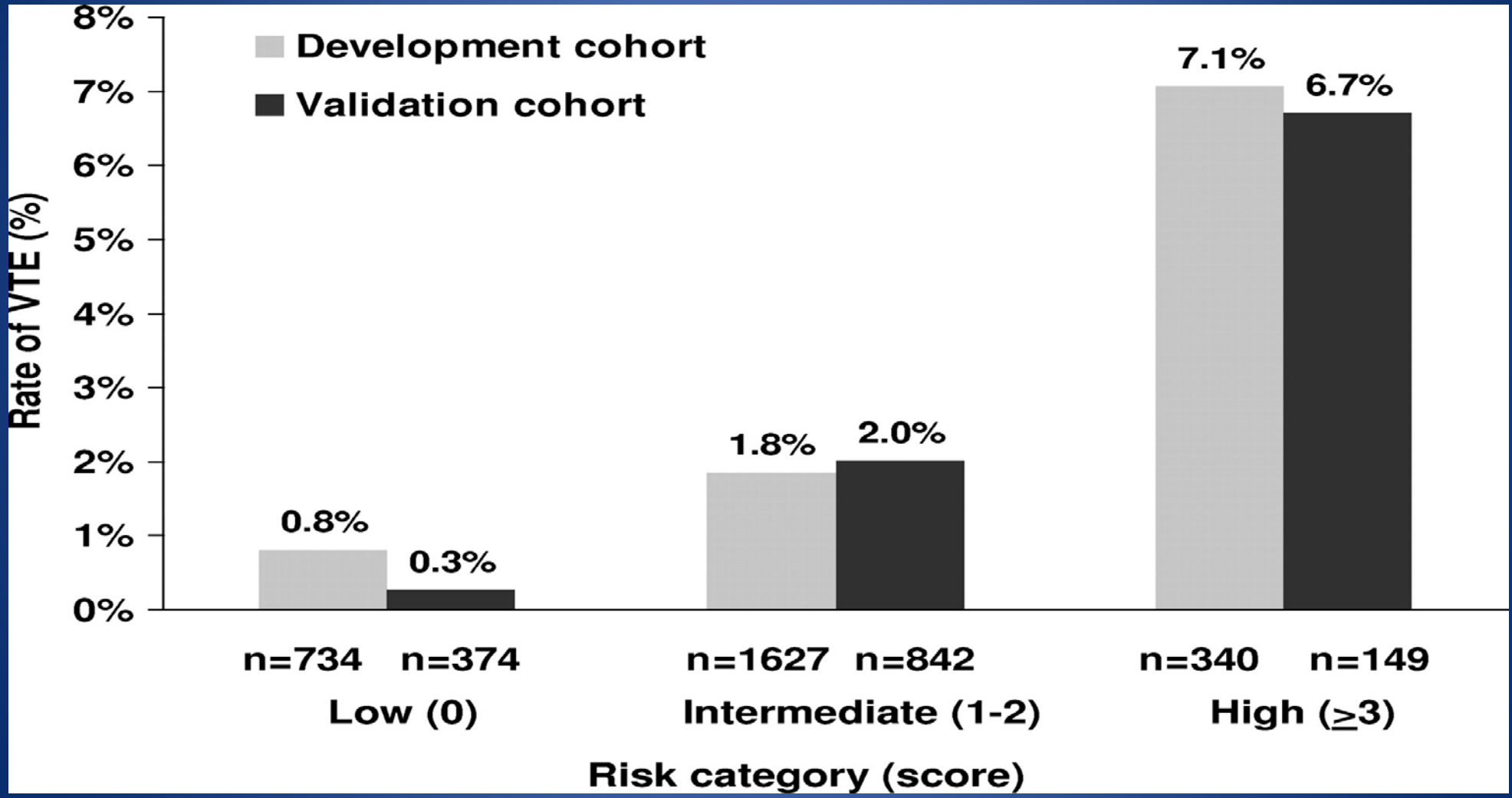
Khorana Clinical Risk Model

Patient Characteristic	Score
Site of Cancer	
• Very high risk (stomach, pancreas)	2
• High risk (lung, lymphoma, gynecologic, GU excluding prostate)	1
Platelet count $\geq$ 350,000/mm^3	1
Hb < 10g/dL or use of ESA	1
Leukocyte count > 11,000/mm^3	1
BMI $\geq$ 35 kg/m^2	1

*Risk for patients receiving systemic chemotherapy

Khorana AA et al. Blood 2008;111:4902-4907

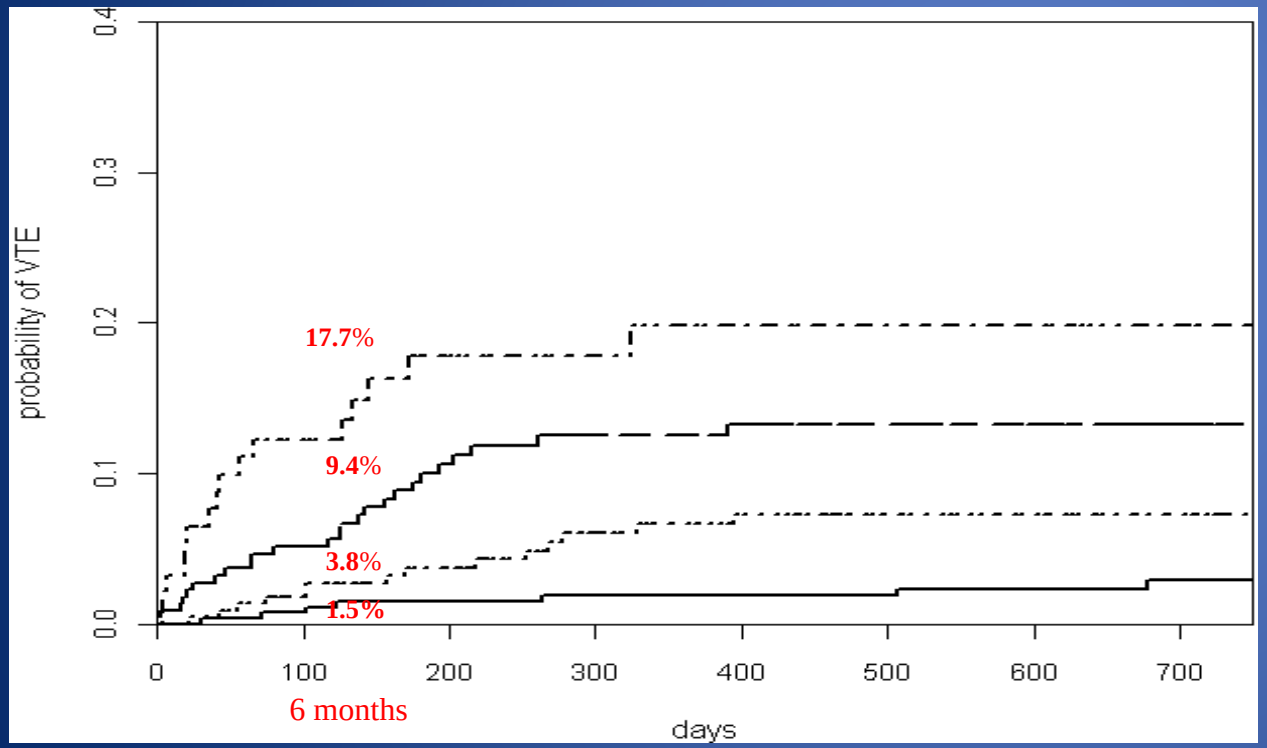
Rates of VTE according to scores from the risk model in the derivation and validation cohorts



Khorana AA et al. Blood 2008;111:4902-4907

Vienna CATS validation

- **Full data available in 839 patients**
- **Median observation time/follow-up: 643 days**



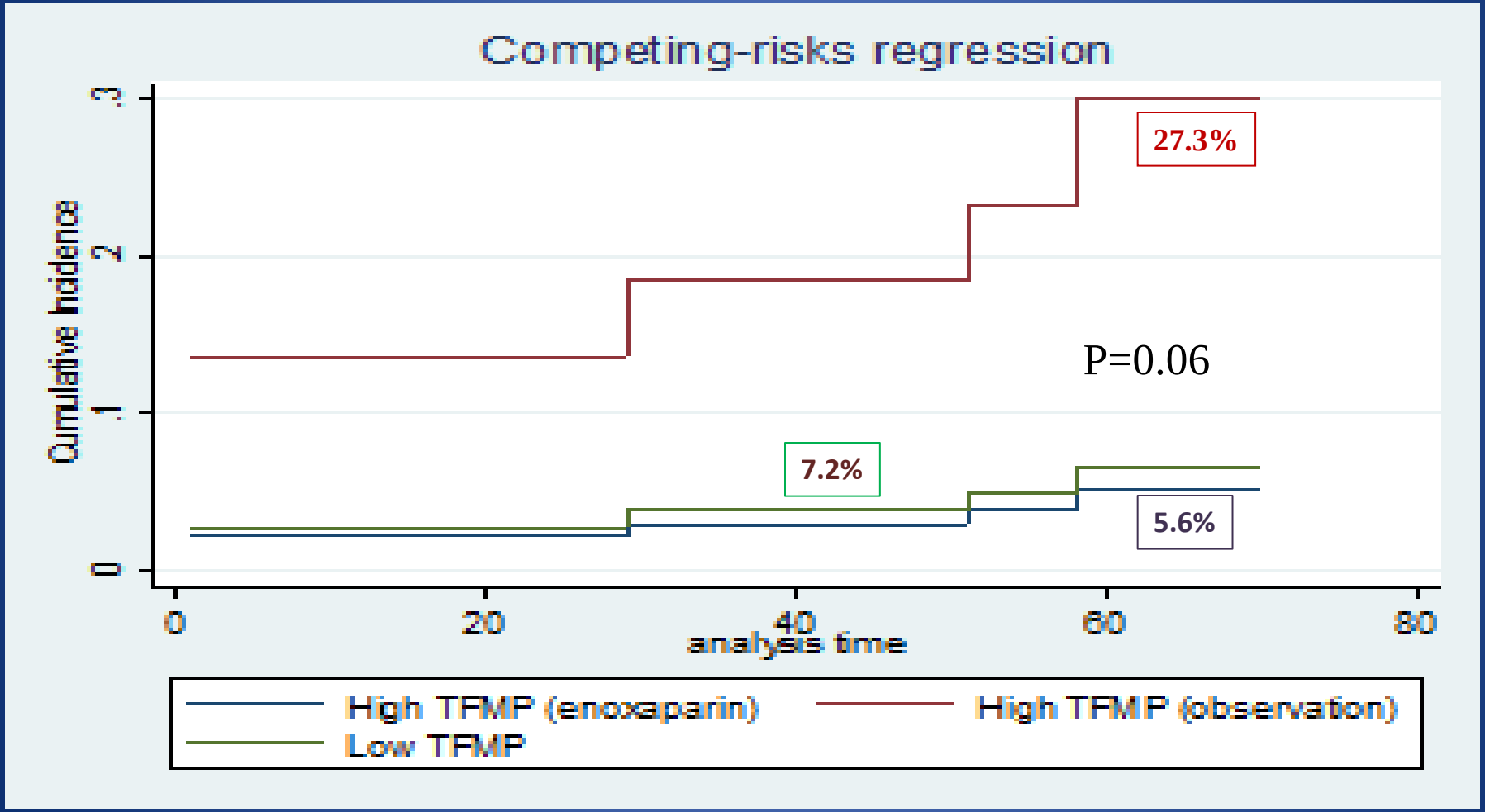
	Number of Patients n	Number of Events n (%)
Score ≥3	96	16 (17%)
Score 2	231	25 (11%)
Score 1	233	14 (6%)
Score 0	279	7 (3%)

Ay C, *et al*. *Blood* 2010;116:5377–5382

Validated Biomarkers

- D-DIMER (D-D)
- Soluble P-selectin
- Factor VIII
- Tissue Factor (TF)
- Interleukin 6 (Il-6)
- TF bearing micro-particles

MICROTEC Outcome

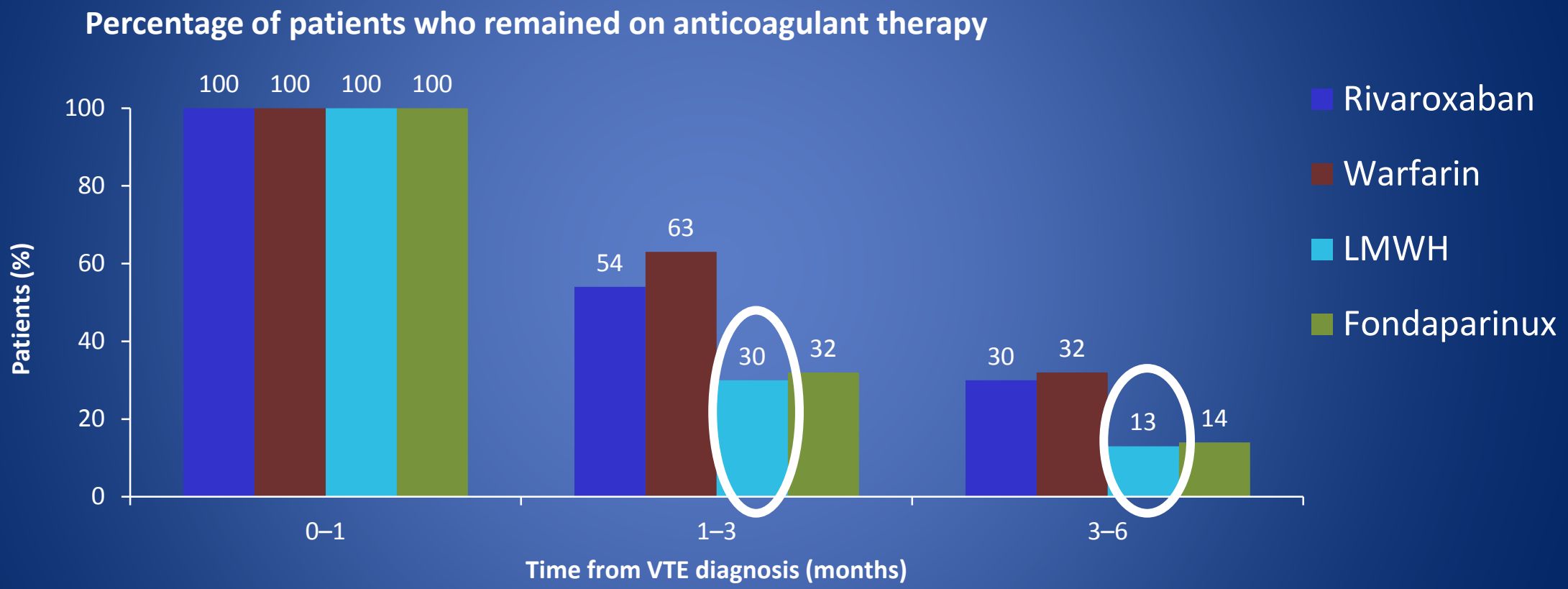


Zwicker JI, et al. Br J Haematol 2013;160: 530-537

WHAT ABOUT THE NOACS?
ARE THEY AS EFFICACOUS AS LMWH ?

Real-World Anticoagulant Use: Duration

52,911 cancer patients with VTE in the USA (2009–2014)



LMWH, low molecular weight heparin; VTE, venous thromboembolism

Khorana AA *et al, Throm Res* 2016;145:51–53

Comparative features of Direct Oral Anticoagulants

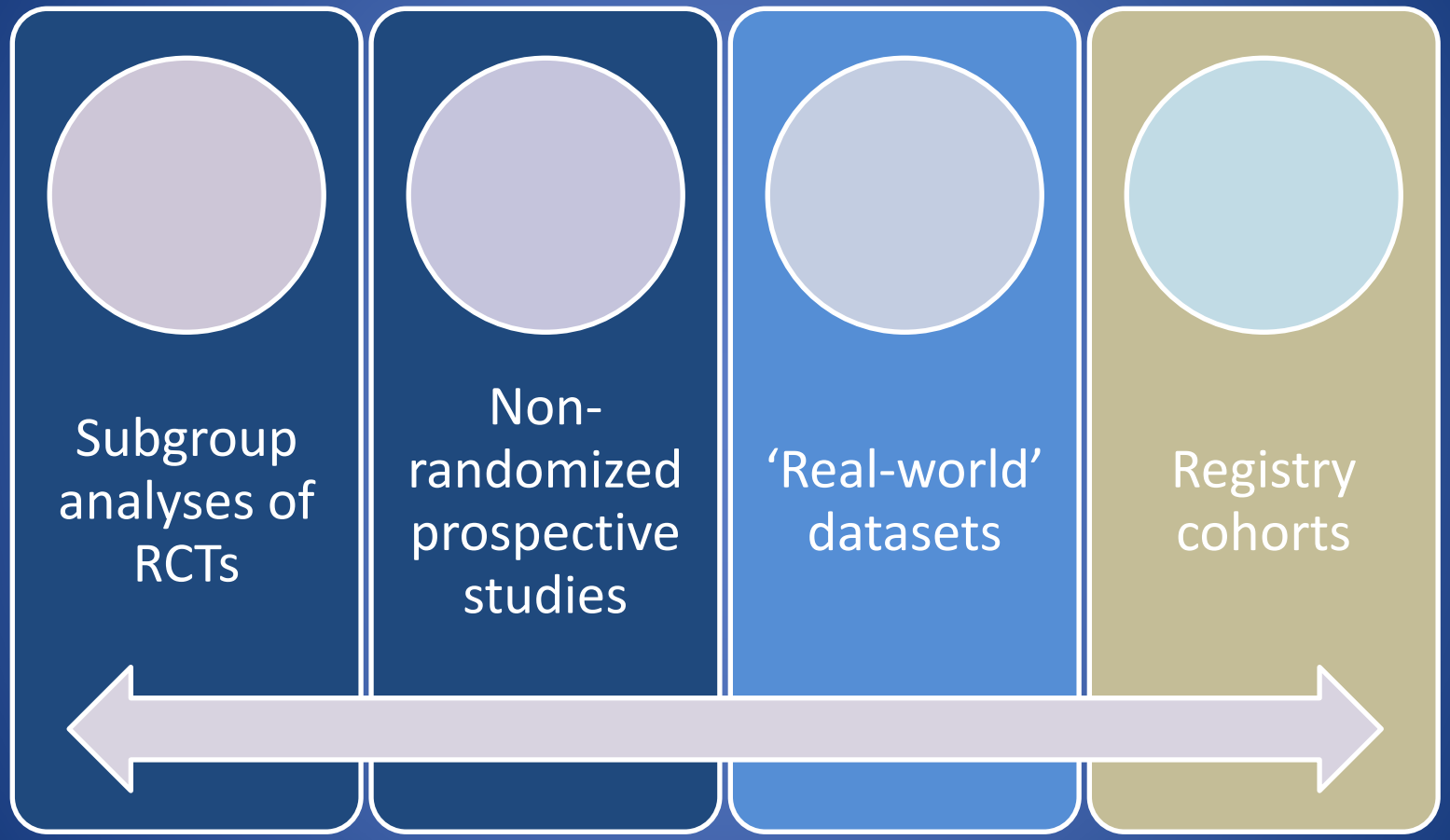
	Edoxaban	Dabigatran etexilate	Rivaroxaban	Apixaban
Target	Factor Xa	Thrombin	Factor Xa	Factor Xa
Oral bioavailability	45%	3–7%	66–100%	50%
T (max)	1-1.5 h	1 h	2–4 h	3–4 h
Half-life	9-11 h	12–17 h	5–9 h healthy, 11–13 h elderly	12 h
Monitoring	Not needed	Not needed	Not needed	Not needed
Administration	QD	BID	QD or BID	BID
Metabolism/ Elimination	33% renal 67% biliary	80% renal 20% biliary	66% renal 28% biliary	27% renal 73% biliary
Antidote or treatment of bleeding	factor replacement; prothrombinase complex concentrates		factor replacement; prothrombinase complex concentrates	factor replacement; prothrombinase complex concentrates
Assay	Anti-factor Xa	Ecarin clotting time	Anti-factor Xa, PiCT®, HepTest®	Anti-factor Xa
Drug interactions	Potent P-gp inhibitors/inducers	Potent P-gp inhibitors/inducers	Potent P-gp inhibitors/inducers; CYP3A4 inhibitors	Potent P-gp inhibitors/inducers; CYP3A4 inhibitors

Revolade summary of product characteristics. October 2013; Pradaxa Prescribing information. April 2013; Xarelto prescribing information. August 2013; Eliquis Prescribing information. March 2014; Heidbuchel *et al. Europace* 2013;15:625–51; Samama *et al. Thromb Haemost* 2010;103:815–25

Cancer Drugs with Important Interactions with P-gp and Cyp3A4

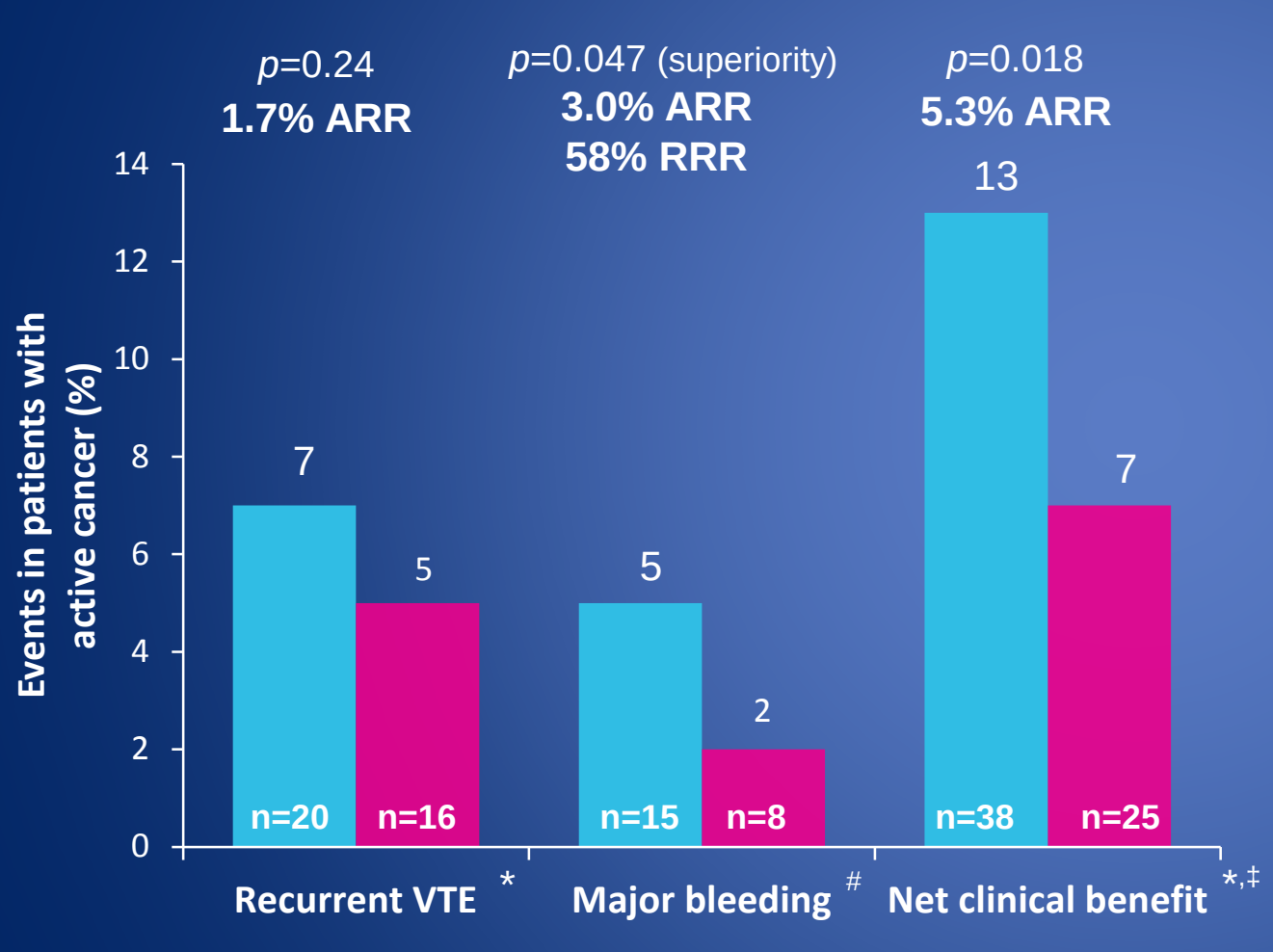
Cyp3A4	P-gp
• Cyclophosphamide • Ifosfamide • doxorubicin • Imatinib • Dasatinib • Sorafenib • Sunitinib • Carbozantinib • Ibrutinib • Afatinib • Erlotinib • Ponatinib • Regorafenib	• Vinblastine • Vincristine • Paclitaxel • Sorafenib • Carbozantinib

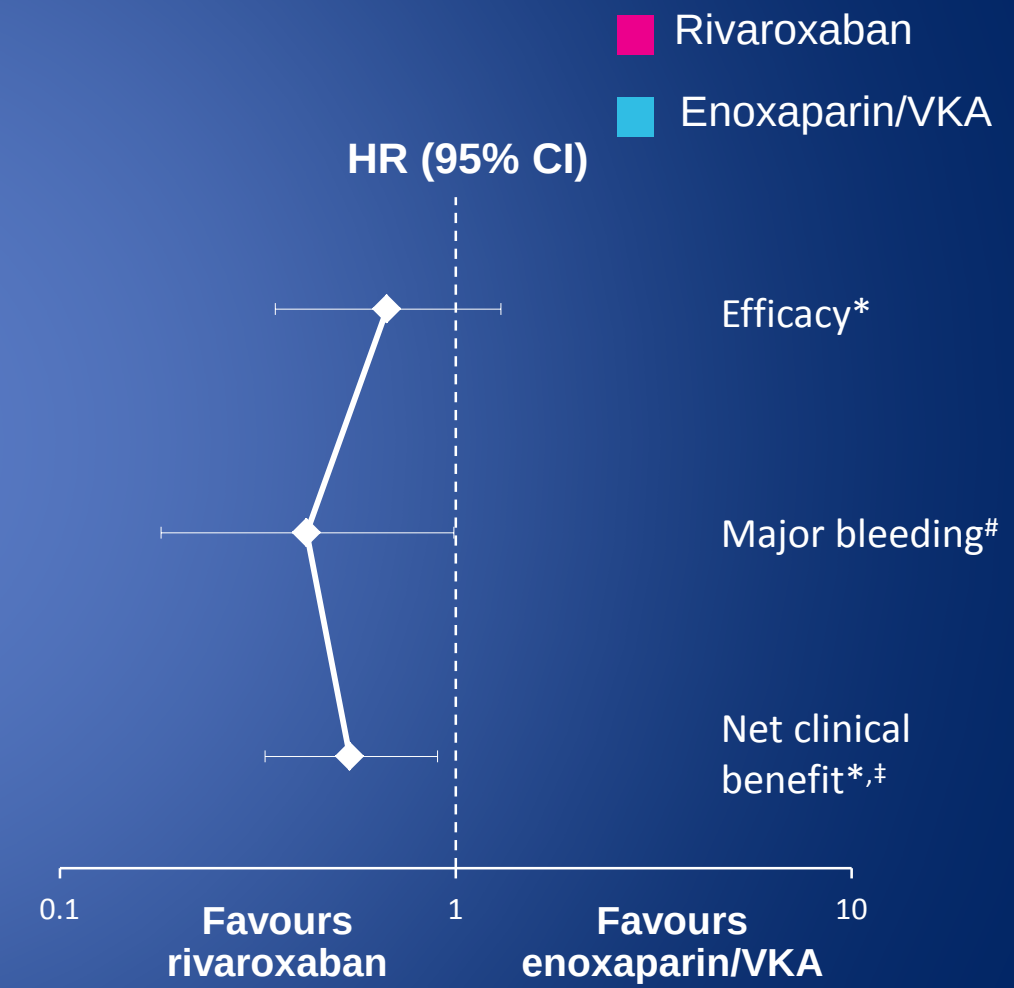
DOACs in CAT: Emerging Data



EINSTEIN DVT/PE Pooled Analysis:

Active Cancer at Inclusion or Diagnosed During the Study





*ITT population: N=8281; patients with active cancer, n=655;
#safety population: N=8246; patients with active cancer, n=651; ‡composite of recurrent VTE and major bleeding
ARR, absolute risk reduction; RRR, relative risk reduction; VKA, vitamin K antagonist; VTE, venous thromboembolism

Prins MH et al. *Lancet Haematol* 2014;1:e37–e46

Cancer Patients in VTE Trials with VKA vs DOACs

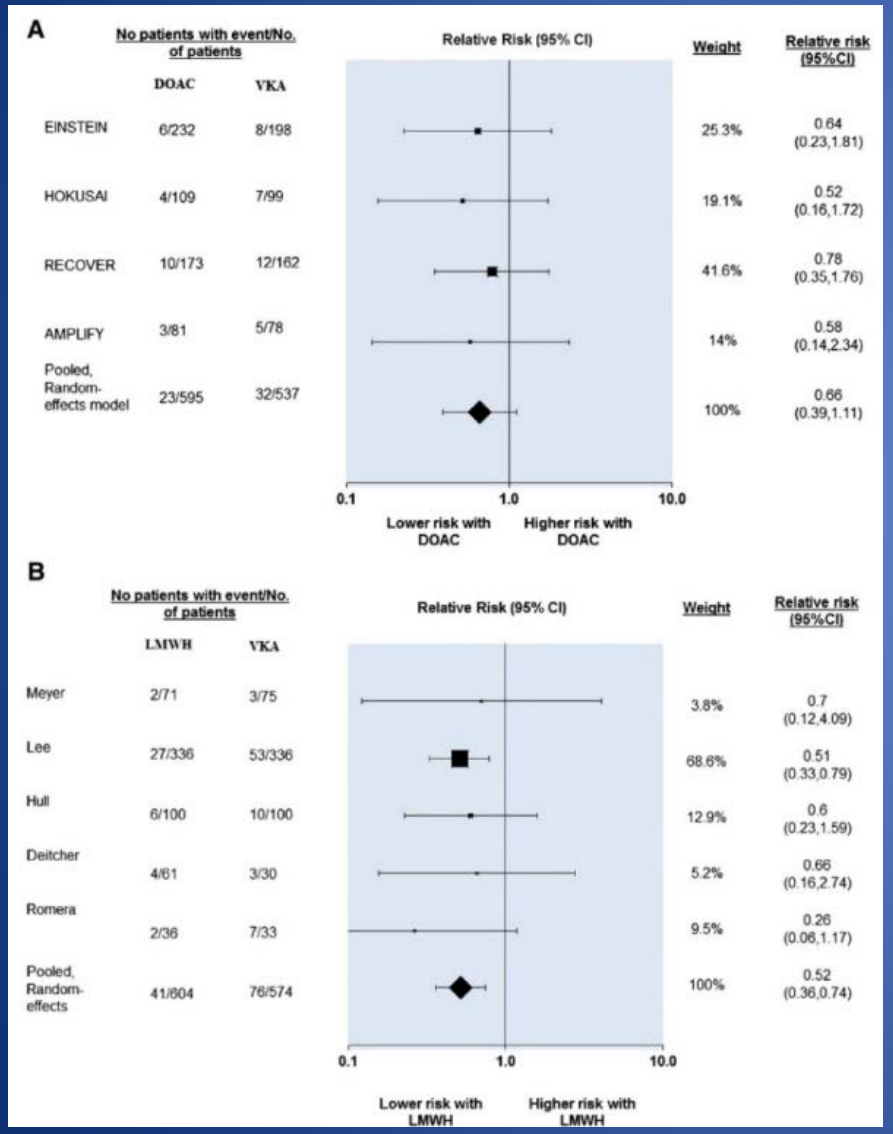
Subgroup analysis of:	EINSTEIN PE and EINSTEIN DVT[1,a]		AMPLIFY[2,b,c]		Hokusai-VTE[3,b]		RE-COVER and RE-COVER II[4,a,c]	
Treatment group (n)	Rivaroxaban (n = 354)	SOC (n = 301)	Apixaban (n = 81)	SOC (n = 78)	Edoxaban (n = 109)	SOC (n = 99)	Dabigatran (n = 173)	SOC (n = 162[a])
Patients with VTE, %	5.0	7.0	3.7	6.4	4.0	7.0	5.2	7.4
	HR = 0.67 95% CI 0.35–1.30 P = 0.24[d]		RR = 0.56 95% CI 0.13–2.37 P interaction = 0.07[d]		HR = 0.55 95% CI 0.16–1.85 P value NR		P = NS	
Treatment group (n)	Rivaroxaban (n = 353)	SOC (n = 298)	Apixaban (n = 87)	SOC (n = 80)	Edoxaban (n = 109)	SOC (n = 99)	Dabigatran (n = 159[a])	SOC (n = 152[a])
Patients with major bleeding event, %	2.0	5.0	2.3	5.0	5.0	3.0	3.8	4.6
	HR = 0.42 95% CI 0.18–0.99 P = 0.047[d]		HR = 0.45 95% CI 0.08–2.46 P interaction = 0.83[d,e]		HR = 1.52 95% CI 0.36–6.43 P value NR		P = NS	

***p*-interaction = the interaction of treatment across the cancer subgroups**
CI, confidence interval; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant; NR, not reported; NS, not significant; SOC, standard of care; VKA, vitamin K antagonist; VTE, venous thromboembolism

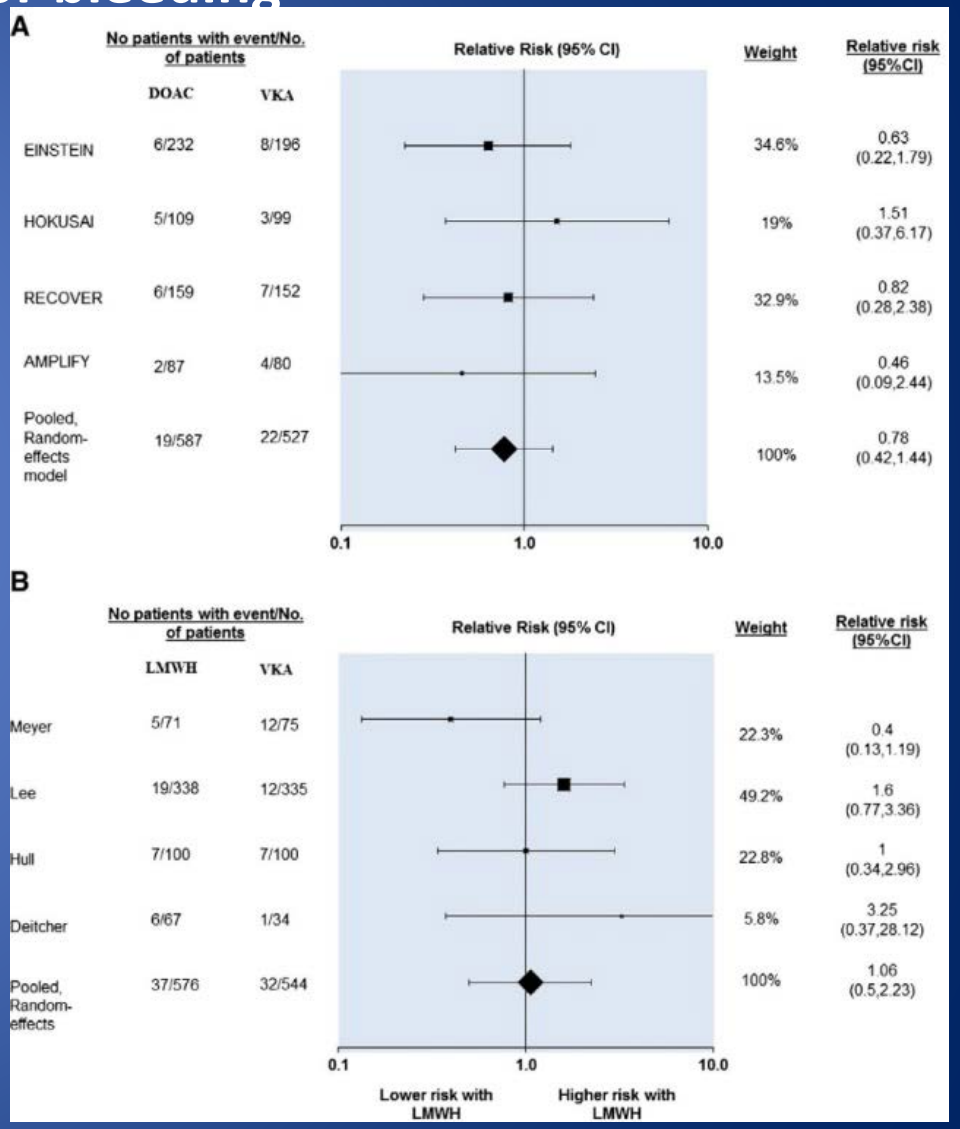
1. Prins MH *et al, Lancet Haematol* 2014;1:e37–e46; 2. Agnelli G *et al. J Thromb Haemost* 2015;13:2187–2191; 3. Raskob GE *et al, Lancet Haematol 2016;e379–87*;
4. Schulman S *et al. Thromb Haemost* 2015;114:150–157

DOACs and LMWHs Versus VKAs in CAT

Recurrent VTE



Major bleeding



DOAC, direct oral anticoagulant; LMWH, low molecular weight haeparin; VKA, vitamin K antagonist; VTE, venous thromboembolism

Carrier M *et al, Thromb Res* 2014;134:1214–1219

Emerging Data: Mayo Clinic Experience

Mayo Thrombophilia Clinic DOAC Registry (2013–2015)

- Consecutive patients treated with rivaroxaban for DVT or PE and had ≥3 months of follow-up (N=296)
  - n=118 with active cancer*
- Genitourinary (23.6%), gastrointestinal (20.3%) and lung (13.5%)
- Recurrent VTE rate: 3.3%
  - n=4 only

Variable	Cancer (n=118)	No cancer (n=178)	*p*-value
VTE recurrence, n (%)	4 (3.3)[#]	5 (2.8)	0.53
DVT, n	3	4	1.00
PE, n	1	1	1.00
Major bleeding, n (%)	3 (2.5)	0	0.06
NMCR bleeding, n (%)	4 (3.4)	1 (0.6)	0.08
Major and NMCR bleeding, n (%)	7 (5.9)	1 (0.6)	0.008
Minor bleeding, n (%)	3 (2.5)	3 (1.7)	0.69
Death, n (%)	37 (31.0)	0	<0.0001

Mean follow up of 1.36±0.5 years

*Active cancer was not defined in the publication; [#]two events occurred during anticoagulation interruption for an invasive procedure
DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; NMCR, non-major clinically relevant; PE, pulmonary embolism; VTE, venous thromboembolism

Bott-Kitslaar DM *et al*, *Am J Med* 2016;129:615–619

Emerging Data: MSKCC Experience

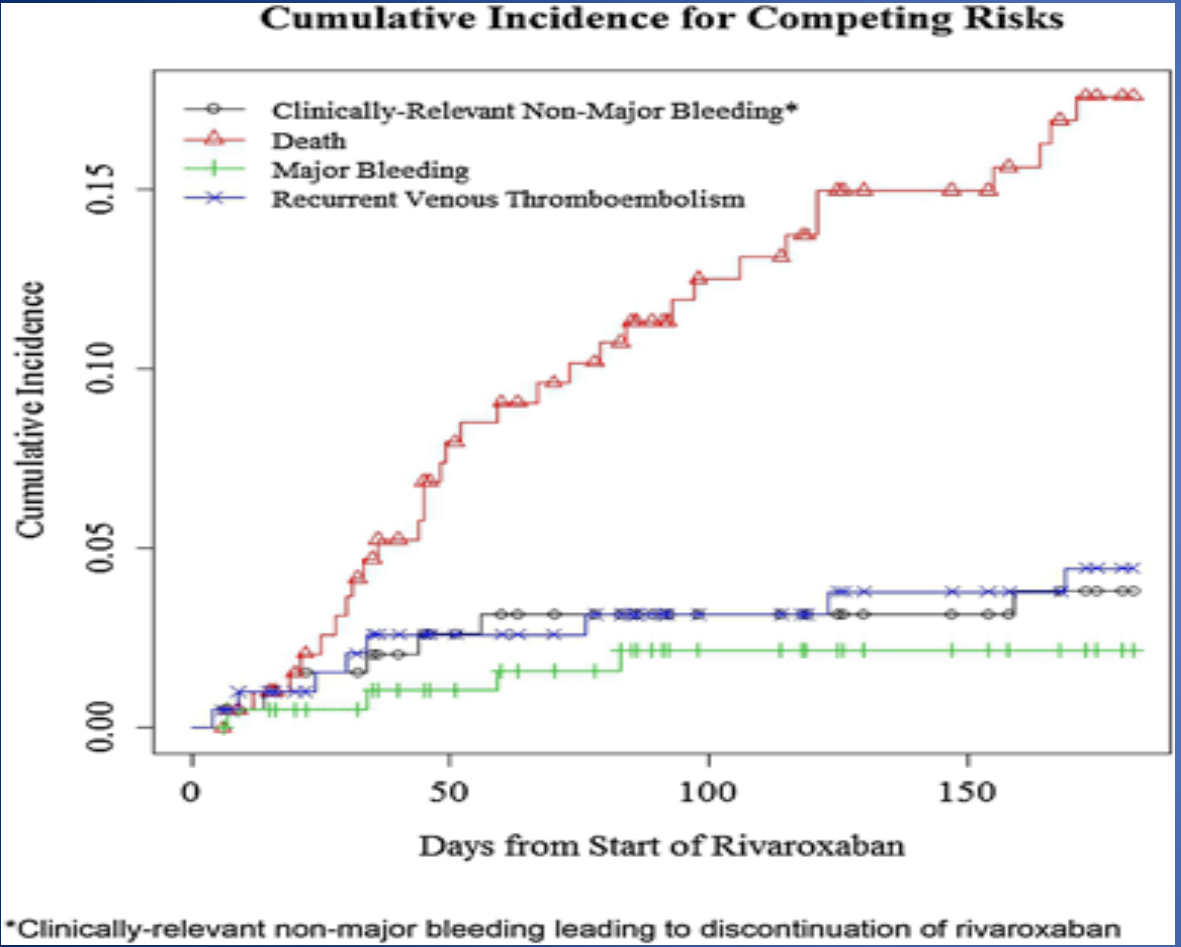
Quality assessment initiative

- 200 patients with active cancer and CAT treated with rivaroxaban
  - Intended to receive ≥6 months of therapy
- Several exclusions:
  - CrCl <30 ml/min
  - Liver function tests >3× ULN
  - Expected malabsorption at stomach or small bowel
  - Active GU or GI lesions
  - Untreated primary CNS neoplasm
  - A body weight <50 or >150 kg
  - Any antiplatelet agent other than ASA 81 mg daily and any significant drug interaction
- Empirically dose-reduced: patients ≥75 years old received rivaroxaban 10 mg bid for 3 weeks followed by 15 mg od

ASA, acetylsalicylic acid; CAT, cancer-associated thrombosis; CNS, central nervous system; CrCl, creatinine clearence; GI, gastrointestinal; GU, gastrouritary; MSKCC, Memorial Sloan Kettering Cancer Center; ULN, upper limit of normal

Mantha S *et al, J Thromb Thrombolysis* 2017;43:166–171

Clinical Pathway Evaluation of the Use of Rivaroxaban in 200 Patients with Cancer-Associated VTE



In competing risk analysis, 6-month cumulative incidence

Recurrent VTE	4.4 %	(95 % CI	1.4 to 7.4 %)
Major bleeding	2.2 %	(95 % CI	0.0 to 4.2 %)
All-cause mortality	17.6 %	(95 % CI	11.7 to 23.0 %)

Mantha S, *et al,.J Thromb Thrombolysis* 2017;43:166–171

Active Clinical Trials in Cancer-Associated VTE: Prophylaxis and Treatment

PROPHYLAXIS

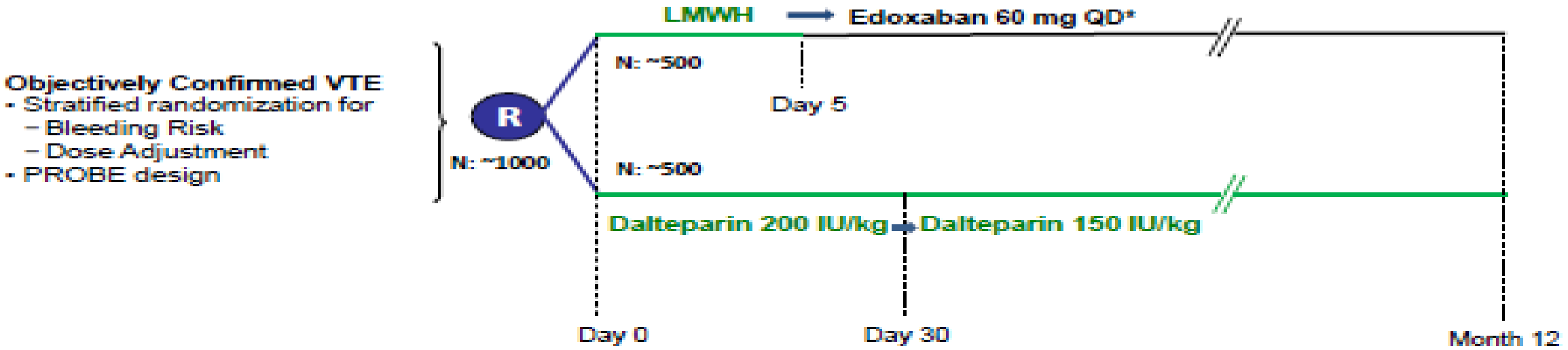
- Anti-Platelet and Statin Therapy to Prevent Cancer-Associated Thrombosis
- Cancer Associated Thrombosis and Isoquercetin (CAT IQ)
- Apixaban for prevention of VTE in high risk cancer patients (AVERT Trial)
- Efficacy and safety of rivaroxaban prophylaxis compared to placebo in high risk cancer patients receiving systemic chemotherapy (CASSINI Trial)

TREATMENT

- Edoxaban in VTE associated with cancer (Hokusai VTE Cancer)
- Rivaroxaban for the treatment of cancer-associated thrombosis (SELECT-D Trial)
- Apixaban for the treatment of venous thromboembolism in patients with cancer: a prospective randomized open blinded end-point (PROBE) study (Caravaggio Trial)
- A Phase III, randomized, double-blind study evaluating the safety of 2 doses of Apixaban for secondary prevention of cancer related VTE after 6 months of anticoagulation therapy

Edoxaban in Venous Thromboembolism Associated with Cancer

Hokusai VTE CANCER



12 months of treatment or shorter (intention for at least 6 months) ~ mitigating factors in subject's clinical status

Efficacy and safety data will need to be collected during the entire 12 month study period

Expected Outcome

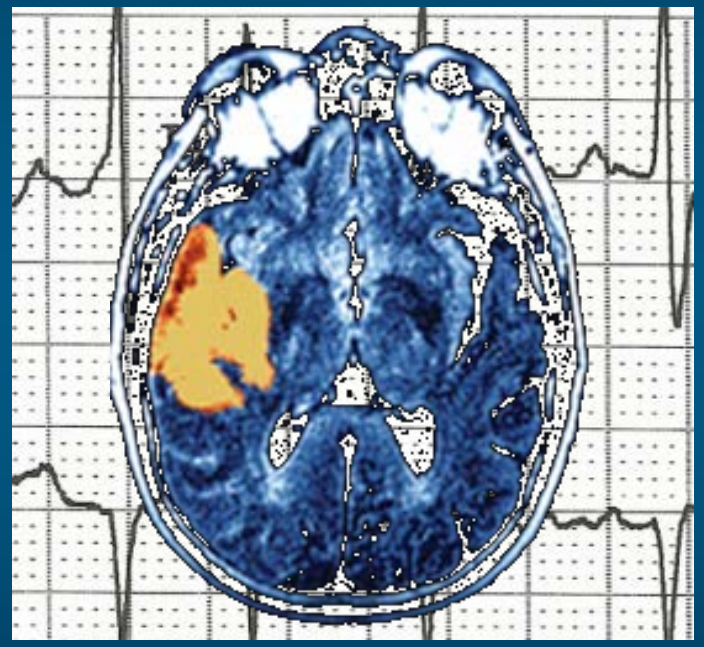
- Clinicians will be more likely to prescribe and encourage their patients to use LMWH for initial treatment and secondary VTE prophylaxis.
- They will remain alert to ongoing randomized trials of NOACs versus LMWH for VTE treatment in cancer patients. The outcomes of these trials may change the treatment algorithm in cancer-associated VTE.

- **Clinicians should consider the use of ambulatory VTE prophylaxis in high risk cancer patients. They will remain alert to ongoing VTE prophylaxis trials in high risk cancer patients.**

TRI Sponsored Friday Satellite Symposia at 59th ASH

Anticoagulation: Applying Innovation in Clinical Practice

8th December 2017, Marriott Marquis Atlanta, Atlanta, GA



Anticoagulation and Atrial Fibrillation Current Perspectives "The Real World"

A. John Camm MD

St. George's University of London and Imperial College, United Kingdom

Declaration of Competing Interests

Chairman: ESC Guidelines on Atrial Fibrillation, 2010 and Update, 2012; ACC/AHA/ESC Guidelines on SVT, 2003 and VAs and SCD, 2006; NICE Guidelines on ACS and NSTEMI, 2012; NICE Guidelines on Heart Failure, 2008; **Member:** NICE Guidelines on AF, 2006; ESC VA and SCD Guidelines, 2015; **Reviewer:** ESC AF Guidelines, 2016.

Steering Committees: multiple trials involving antiarrhythmic agents, heart failure drugs and novel anticoagulants.

DSMBs: multiple trials of devices and drugs.

Events Committees: one trial of novel oral anticoagulants and multiple trials of miscellaneous agents with CV adverse effects.

Editorial Role: Editor-in-Chief, European Heart Journal - Case Reports and Clinical Cardiology; Editor, European Textbook of Cardiology, European Heart Journal, Electrophysiology of the Heart, and Evidence Based Cardiology

Consultant/Advisor/Speaker: Astellas, Astra Zeneca, Gilead, Huya, Incarda, Merck, Menarini, Milestone, Omeicos, Otsuka, Sanofi, Servier, Xention, **Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Boston Scientific**, Biotronik, Medtronic, Sorin, St. Jude Medical, Actelion, GlaxoSmithKline, InfoBionic, Johnson and Johnson, Mitsubishi, Novartis, Takeda

Educational Need/Practice Gap

Gap = there remains a substantial gap between guideline mandated anticoagulant therapy and clinical practice

Need = physicians need to understand that bleeding adverse events are mostly remediable but stroke represents irretrievable harm

Objectives

Upon completion of this educational activity, you will be able to:

1. Know the difference between data from the “real world” and randomized clinical trials
2. Comprehend the current status of anticoagulant therapy for thromboprophylaxis in AF
3. Understand the gap between guideline mandated therapy and treatment provided in the real world

Expected Outcomes

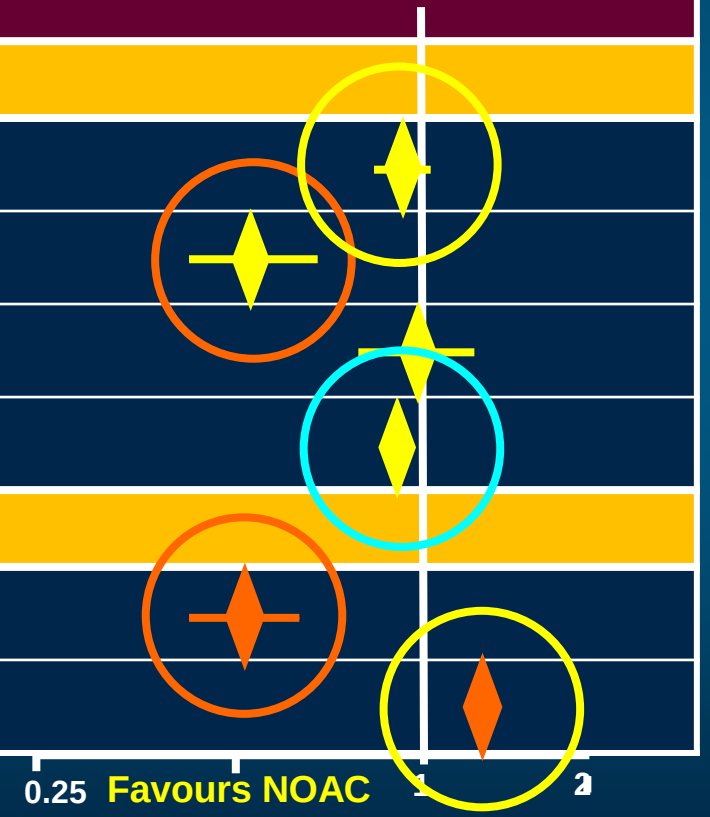
- Increased education of physicians and patients about the net clinical benefit of anticoagulant therapy for thromboprophylaxis in high stroke risk atrial fibrillation patients
- Closer adherence to guideline mandated therapy for these patients
- In the long-term less strokes and other thromboembolic events due to atrial fibrillation

Efficacy vs Safety

NOAC 4-trial Meta-analysis Full Dose

Warfarin vs placebo /control: 54% stroke RRR stroke and 26% RRR ACM (Hart meta-analysis)

Result	Pooled DOAC Events/Total	Pooled Warfarin Events/Total	Risk Ratio	95% CIs	p
Efficacy					
Ischaemic Stroke	665 / 29292	724 / 29221	0.92	0.83-1.02	0.10
Hemorrhagic stroke	130 / 29292	263 / 29221	0.49	0.38-0.64	<0.0001
Myocardial Infarction	413 / 29292	432 / 29221	0.97	0.78-1.20	0.97
All Cause mortality	2022 / 29292	2245 / 29221	0.90	0.851-0.95	0.0003
Safety					
Intra-cranial hemorrhage	204 / 29287	425 / 29211	0.48	0.39-0.59	<0.0001
Gastrointestinal bleeding	751 / 29287	591 / 29211	1.25	1.01-1.55	0.043



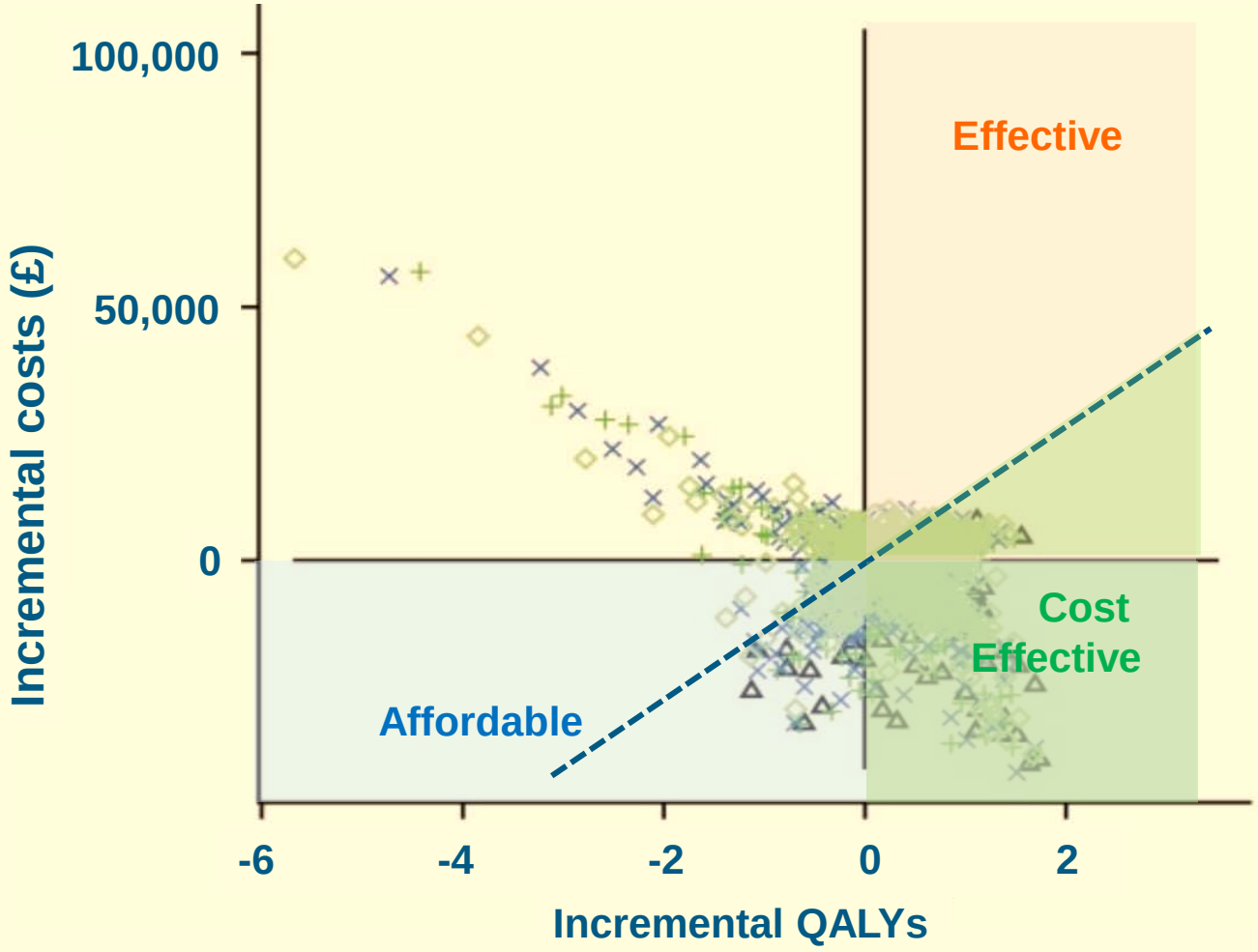
Imputational analysis: NOAC versus no therapy:

72% stroke RRR stroke and 33% RRR ACM (McMurray meta-analysis)

Ruff C, et al. Lancet 2014 Mar 15;383(9921):955-62.

Cost-Effectiveness of Non-VKA OAC Therapy

Recent Comprehensive Health Technology Assessment



Data based on phase III RTS

- Apixaban (5 mg bd)
- Dabigatran (150 mg bd)
- Edoxaban (60 mg od)
- Rivaroxaban (20 mg od)

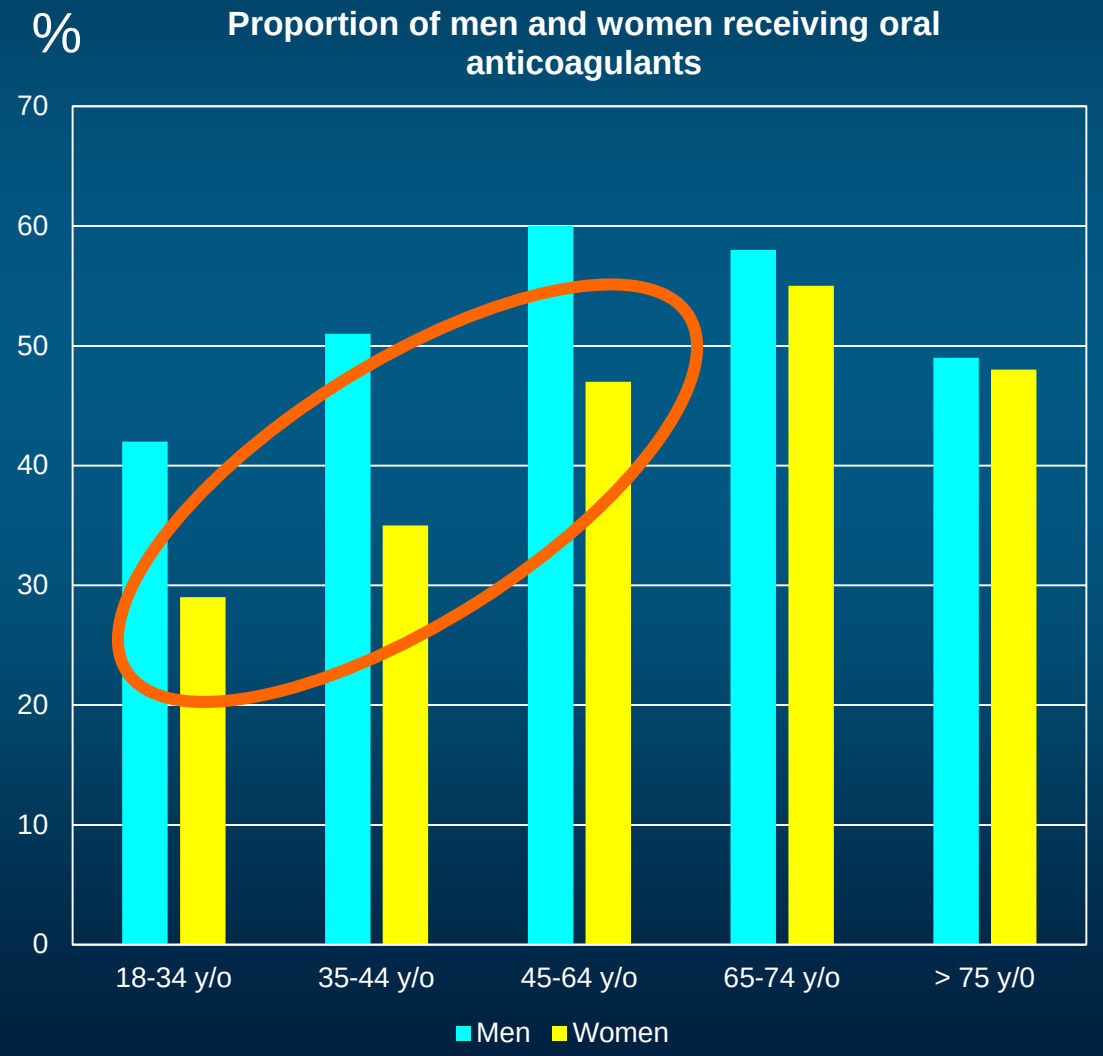
10,000 iterations of the model for 120 cycles (each iteration representing a simulation from the joint distribution of the model parameters)

Sterne J, et al. NICE Health Technology Assessment, No. 21.9 NIHR Journals Library; 2017 Mar

Introduction to the Real World
Anticoagulation for AF

Criteria	Patients
Total number of patients (Aetna, Humana, Harvard Pilgrim)	16.2 million
Patients with AF	231,696 (1.4% of all pts)
AF pts with CHA_2DS_2-VASc ≥ 2	201,882 (87% of AF pts)
Patients with at least one oral anti-coagulation fill	52%
Proportion of days covered by anti-coagulation in AF patients	32%

Pokorney S, et al. J Am Coll Cardiol 2016;67:886



Real World Registry/Database Challenges

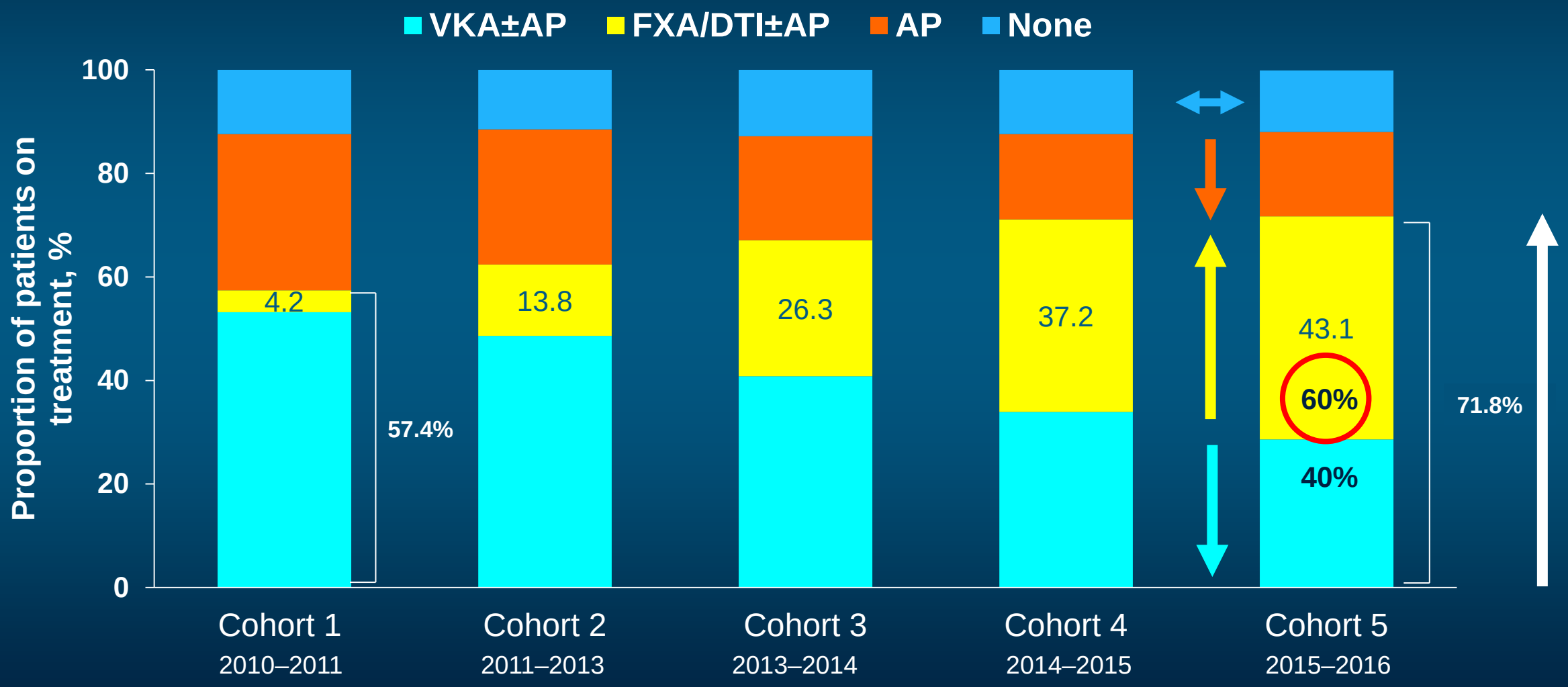
- **Selected patient populations**
  - May not be generally representative: single country / one health insurer / only hospitalised patients / particular clinics
- **Retrospective studies**
  - Reliance on **coded outcome** events; many choices
  - Registry designed for another purpose
  - Variable quality, and usually unaudited data
  - Outcome measures inconsistent, ill-defined - **not adjudicated**
  - No design publication, registry of studies, or **prospective commitment** to details of study
  - Survival bias
- **Prospective studies**
  - Lack of training/quality control, ? recruitment discipline
  - Failure to enrol consecutive patients - **selection bias** on part of patient or physician
  - Incomplete follow-up with many drop outs – **reporting bias**

Large AF Prospective Registries

Registry	Population size	Patient enrolment – key design features	Follow-up duration
GARFIELD-AF[1]	Target: 57,000	• Prospective patients (approx.52,000) enrolled <6 weeks after AF diagnosis in 5 sequential cohorts • Retrospective patients (approx. 5,000) enrolled 6–24 months after diagnosis • ≥1 additional investigator-determined stroke risk factor	≥2 years, up to 8 years Garfield-AF unique study design
GLORIA-AF[2]	Target: 56,000	• Prospective patients enrolled <3 months after AF diagnosis in 3 phases • CHA_2DS_2-VASc score ≥1	0–3 years Phase 1 (pre-NOAC): none Phase 2 (Dabigatran): 2 years Phase 3 (VKA/NOAC): 3 years
ORBIT-AF I[3]	Target 10,000 10,132 enrolled	• Incident or prevalent AF • Patients excluded if life expectancy <6 months	≥2 years
ORBIT-AF II[4]	Target: 15,000	• Prospective patients enrolled <6 months after AF diagnosis; or enrolled <3 months after initiation or transition to a NOAC • Pts excluded if anticipated life expectancy <6 months	≤2 years
PREFER in AF[5]	Target: 7,000 7243 enrolled	• Prospective patients enrolled <12 months after AF diagnosis	1 year

1. Kakkar AK et al. Am Heart J. 2012;163:13-19 e1; 2. Huisman MV et al. Am Heart J. 2014 Mar;167(3):329-34; 3. Piccini JP et al. Am Heart J. 2011;162:606-612.e1; 4. Steinberg BA. Am Heart J. 2014;168:160-7. 5. Kirchhof P et al. Europace. 2014;16:6-14.

Evolution in Baseline Treatment for Patients Enrolled in GARFIELD-AF



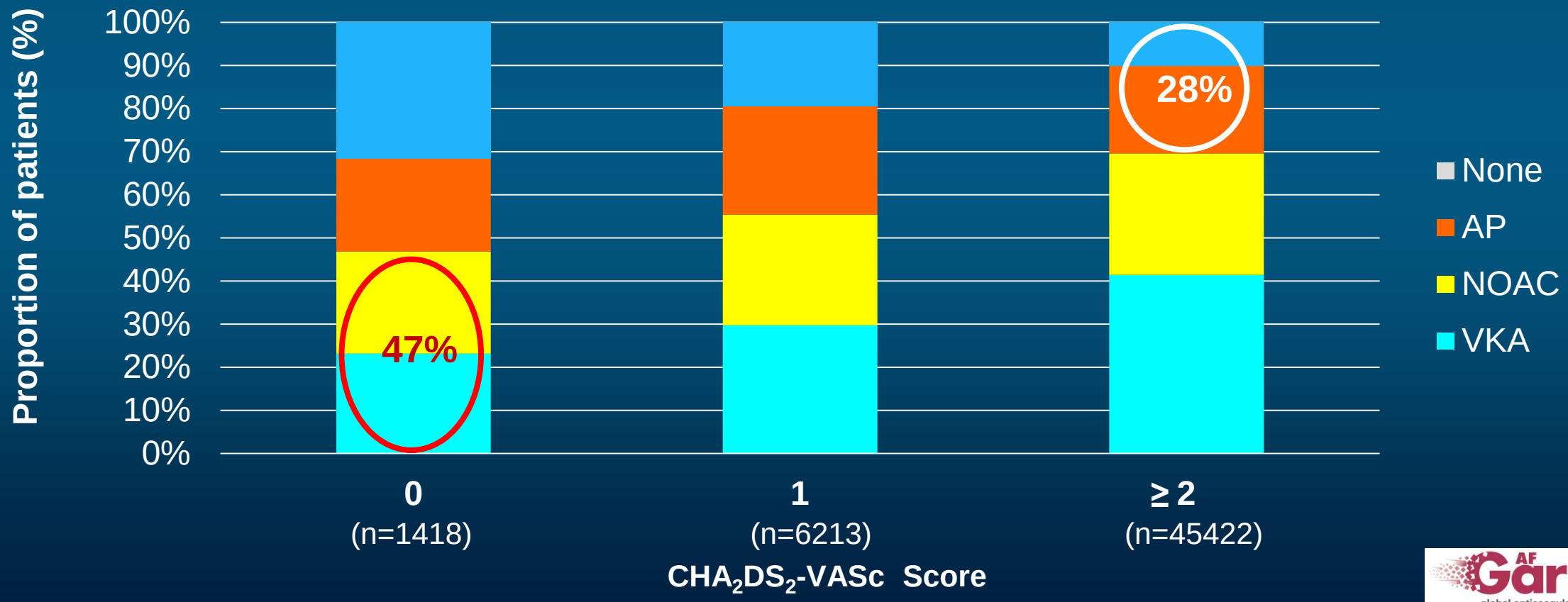
Modified from Camm AJ, et al. Heart. 2017;103:307-314.

Cohorts 1–5, N=51,270

How Are Low- and High-Risk AF Patients Managed in Practice?

Contrary to international guideline recommendations:

- 28% of high-risk patients (CHA_2DS_2-VASc ≥2) are not anticoagulated
- 47% of very low-risk patients (CHA_2DS_2-VASc = 0) are anticoagulated



AF Garfield
global anticoagulant registry in the field

GI Bleeding: 86% of all Major Bleeds
US DoD Database Analysis

- 51,842 NVAF patients taking rivaroxaban were included

		Major Bleed (MB) Cases N=1613
MB Incidence Rate per 100 person-years (95% CI)*		2.71 (2.58–2.84)
MB Site, n (% of those who bled)	Gastrointestinal	1386 (85.9)
	Intracranial	133 (8.2)
	Genitourinary	14 (0.9)
	Other/Unspecified	80 (5.0)
Fatal MB Incidence Rate per 100 person-years (95% CI)#		0.08 (0.06–0.11)

*The MB incidence rate was calculated using person-time for the denominator value (exposure time at risk) for all first major bleeding events within the study period; #Occurred during hospitalization for the MB event

Tamayo S et al, Circulation 2016:134:A15047

Dabigatran: Favourable Benefit-Risk Profile
FDA study of >134 000 Medicare patients

Dabigatran was associated with a lower risk of ischaemic stroke, ICH and death than warfarin

	Incidence rate per 1000 person-years		Adjusted HR (95% CI)
	Dabigatran etexilate	Warfarin	
Ischaemic stroke	* 11.3	13.9	0.80 (0.67–0.96)
Intracranial haemorrhage	* 3.3	9.6	0.34 (0.26–0.46)
Major GI bleeding	34.2	26.5	1.28 (1.14–1.44)
Acute MI	15.7	16.9	0.92 (0.78–1.08)
Mortality	* 32.6	37.8	0.86 (0.77–0.96)

Comparison of matched new-user cohorts treated with dabigatran etexilate 150 mg or 75 mg* or warfarin for non-valvular AF based on 2010–2012 Medicare data. Primary findings are based on analysis of both doses (no stratification by dose)

Graham DJ, et al. Circulation. 2014 Oct 30. pii: CIRCULATIONAHA.114.012061

Outcome Events in New-User Cohorts of Dabigatran and Rivaroxaban for NVAF

Outcome event counts, and crude and adjusted hazard ratios comparing inverse probability of treatment-weighted new-user cohorts of dabigatran and rivaroxaban for non-valvular atrial fibrillation [a]

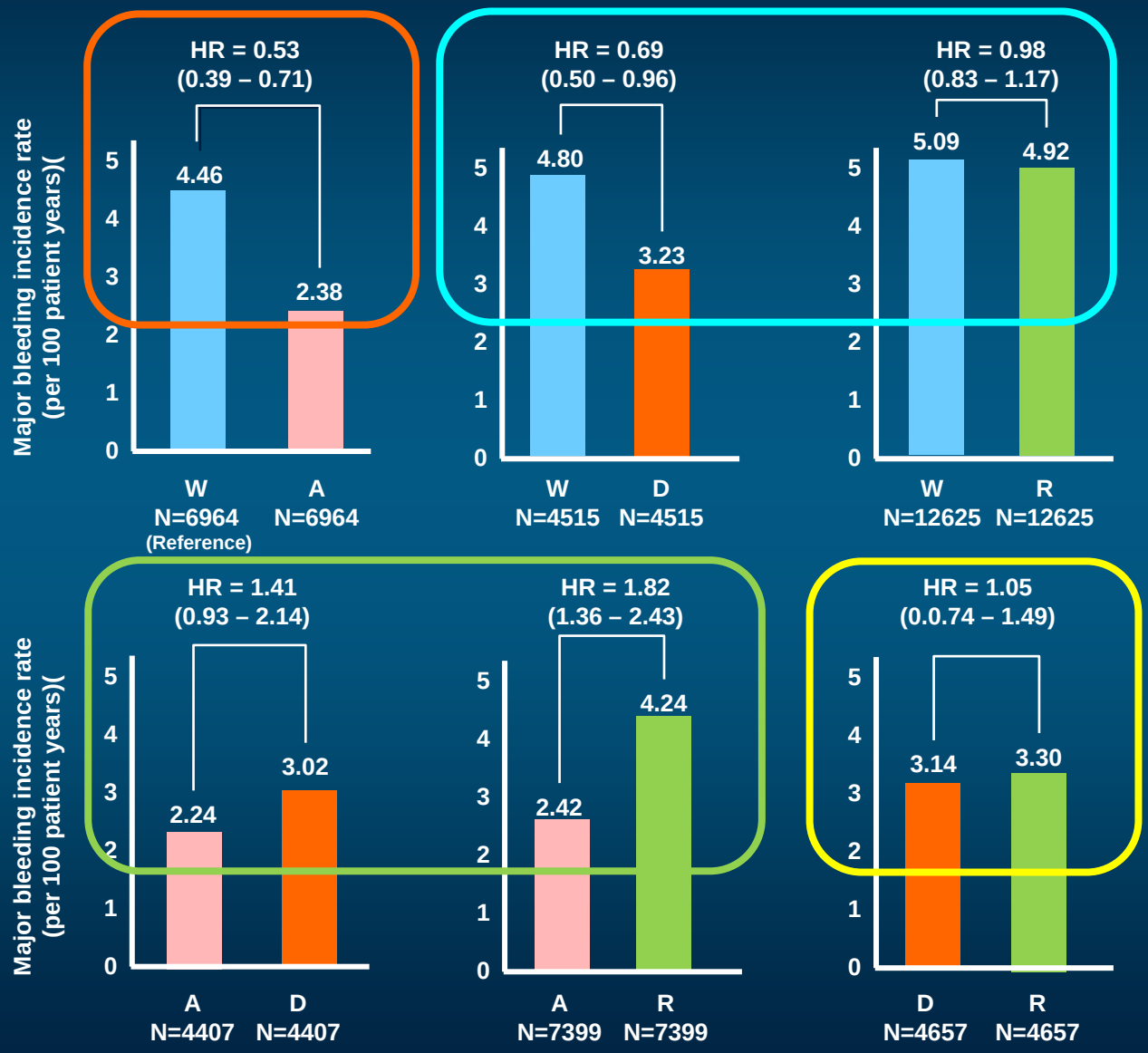
Outcome	Crude (Unadjusted) Incidence Rate per 1,000 person-years (No.of Events)		Hazard Ratio (95% CI)	Hazard Ratio (95% CI) Adjusted Data	
	Dabigatran (n=52,240)	Rivaroxaban (n=66,651)	Crude	Adjusted	*p Value*
Primary Outcomes					
Thromboembolic stroke	9.7 (150)	7.7 (156)	0.80 (0.64–1.00)	0.81 (0.65–1.01)	0.07
Intracranial hemorrhage	3.7 (58)	5.8 (118)	1.58 (1.15–2.16)	1.65 (1.20–2.26)	0.002
Major extracranial bleeding	26.6 (413)	39.4 (796)	1.47 (1.31–1.66)	1.48 (1.32–1.67)	<0.001
Gastrointestinal	23.3 (362)	32.5 (656)	1.39 (1.22–1.58)	1.40 (1.23–1.59)	<0.001
Mortality	22.2 (346)	24.7 (500)	1.12 (0.98–1.29)	1.15 (1.00–1.32)	0.051
Secondary Outcomes					
Hospitalized extracranial bleeds	39.2 (608)	54.0 (1,091)	1.38 (1.25–1.52)	1.39 (1.25–1.53)	<0.001
Acute myocardial infarction	12.9 (200)	11.0 (223)	0.86 (0.71–1.05)	0.88 (0.72–1.06)	0.18

[a] Dabigatran served as the reference group.

Graham DJ, et al. JAMA Intern Med. doi:10.1001/jamainternmed.2016.5954

Major Bleeding with NOACs

- Truven MarketScan® US claims database
- NVAF patients
- Aged ≥18 years
- Newly prescribed oral anticoagulant
- 01Jan2013–31Dec2014
- 1-year baseline period
- Major bleeding: bleeding requiring hospitalization
- Propensity score matching
- No efficacy data



Lip GYH, et al. Thromb Haemost 2016; 116

Major Bleeding in Selected Real-World Studies
Rivaroxaban Studies

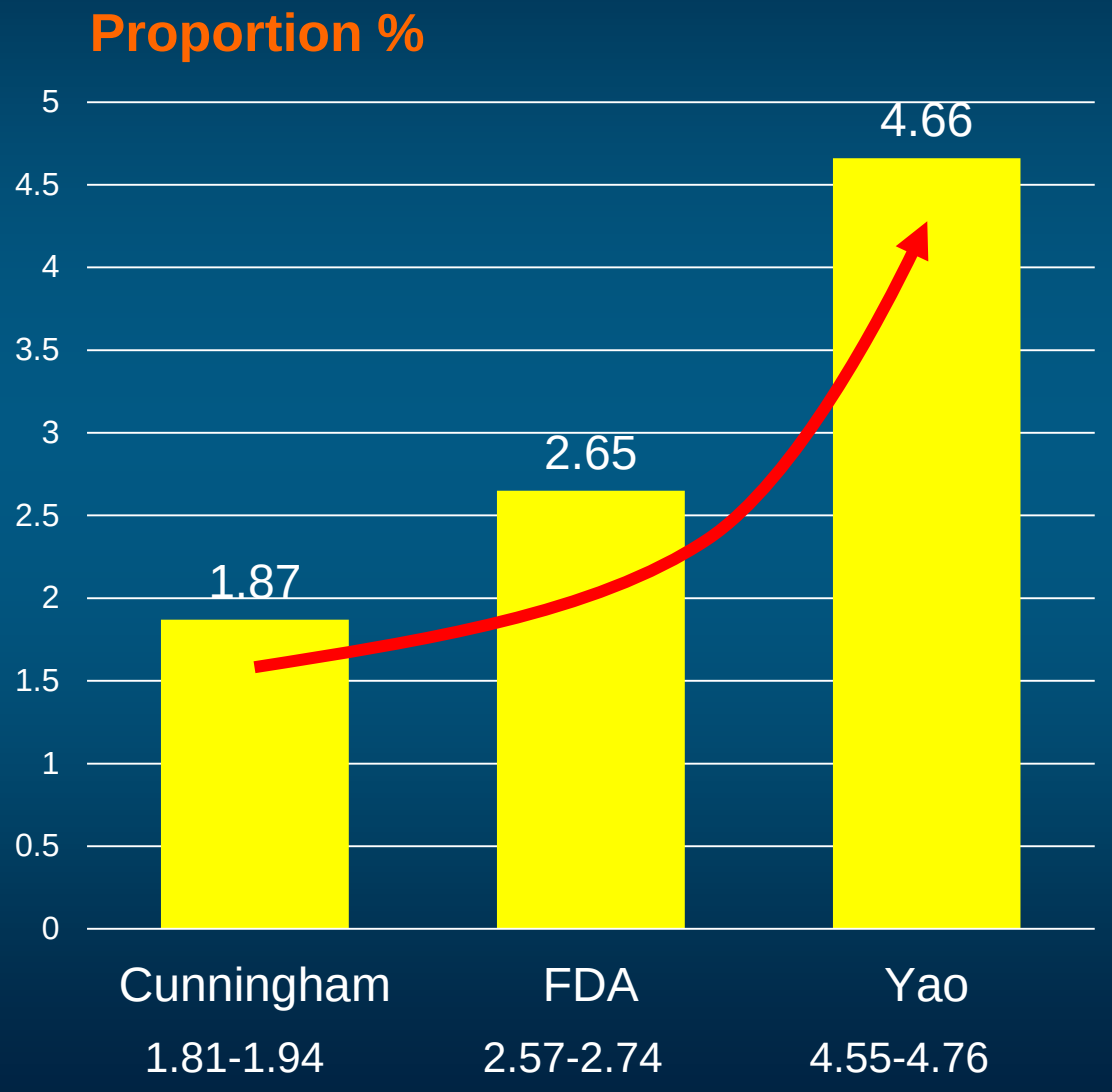
	XANTUS 2015[1]*	Dresden 2014[2]	REVISIT 2016[3]	Tamayo 2015[4]	Laliberté 2014[5]	Tepper 2015[6]
Design	Prospective registry	Prospective registry	Retrospective claims	Retrospective claims	Retrospective claims	Retrospective claims
Definition of major bleeding	ISTH	ISTH	FDA mini-sentinel	Cunningham algorithm	Author determined	?
ICD-9/10 code position	N/A	N/A	Primary	Primary (occasionally 2^0)	Primary and secondary	?
Rate of major bleeding, %/year	2.1	3.1	NR	2.86	12.79	20.2
Rate of ICH, %/year	0.4	NR	0.49	0.22	1.8	2.4
Rate of GI bleeding, %/year	0.9	NR	NR	2.53	9.5	6.2

*Adjudicated events; FDA, US Food and Drug Administration; GI, gastrointestinal; ICH, intracranial haemorrhage; N/A, not applicable; NR, not reported

1. Camm AJ *et al*, *Eur Heart J* 2016;37:1145–1153; 2. Beyer-Westendorf J *et al*, *Blood* 2014;124:955–962; 3. Coleman CI *et al*, *JICE* 2016;45:253 3–5; abstract 15-48; 4. Tamayo S *et al*, *Clin Cardiol* 2015;38:63–68; 5. Laliberté F *et al*, *Curr Med Res Opin* 2014;30:1317–1325; 6. Tepper P *et al*, *Eur Heart J* 2015;36:338; abstract 1975

Inconsistency in Major Bleeding Definitions

- Schemas to identify bleeding-related hospitalizations in claims data differ in both the **specific codes used** and **coding positions allowed**
- Within MarketScan claims data, identified adults with NVAF and newly started on an OAC from 1/2012 to 6/2015
- 151,738 new users of OACs with NVAF (median CHA_2DS_2-VASc score=3, HAS-BLED score=3)



Coleman CI et al, Data on file

NSAIDs and Upper Gastrointestinal Bleeding Risk
Danish National Registry Data

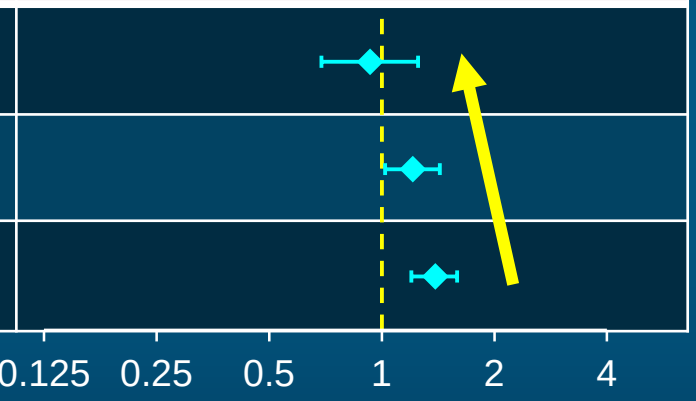
Periods of drug use	Number	Person-years	Observed (O)	Expected (E)	O/E	95% CI
Current use of NSAID	156,138	107,305	515	124.9	4.12	3.8–4.5
NSAID only	152,882	94,987	365	101.2	3.61	3.3–4.0
NSAID + glucocorticoids	17,875	5908	58	8.0	7.24	5.5–9.4
NSAID + glucocorticoids + other drug*	1593	464	7	1.1	6.41	2.6–13.2
NSAID + anticoagulants	1001	340	8	0.7	11.46	4.9–22.6
NSAID + anticoagulants + other drug#	178	35	0	0.1	-	-
NSAID + glucocorticoids + anticoagulants ± other drugs	154	29	1	0.1	18.74	0.2–10.4
NSAID ± low-dose ASA ± high-dose ASA	10,246	5542	76	13.8	5.52	4.3–6.9
Former use of NSAID	145,877§	314,278	370	264.4	1.40	1.3–1.5
Non-use of any other drug	144,584	294,676	267	224.9	1.19	1.0–1.3
Current use of any other drug‡ (not NSAID)	28,455	19,062	103	39.6	2.60	2.1–3.2

*Not anticoagulants; #Not glucocorticoids; ‡Includes drugs suspected to predispose to UGIB (low and high dose ASA, anticoagulants and glucocorticoids; §Among the 156,138 NSAID users, 145,877 were followed during periods of non-use ≥90 days after a non-renewed prescription

Mellemkjaer L et al, Br J Clin Pharmacol 2002:53:173–181

Gastro-Intestinal Bleeding Events
Rivaroxaban versus Warfarin

	Rivaroxaban	Warfarin	HR (95% CI) Rivaroxaban vs warfarin	HR (95% CI) Rivaroxaban vs warfarin
	Rate (%/year)	Rate (%/year)		
Abraham *et al*, 2015[1]	2.84	3.06	0.93 (0.69–1.25)	
Yao *et al*, 2016[2]	3.26	2.53	1.21 (1.02–1.43)	
Hohnloser *et al*, 2017[3]	4.5	3.5	1.39 (1.20–1.59)	



- Only Abraham *et al* used propensity score matching based on ICD-9-CM code-identified comorbid conditions that are known predictors of GI bleeding, including[1]
  - History of previous GI bleed, diverticulosis and *Helicobacter pylori* infection, and specific concomitant medications including NSAIDs

1. Abraham NS et al, BMJ 2015:350:h1857 2, Yao X et al, J Am Heart Assoc 2016:5:pii: e003725 3. Hohnloser SH et al, Clin Res Cardiol 2017 DOI 10.1007/s00392-017-1098-x

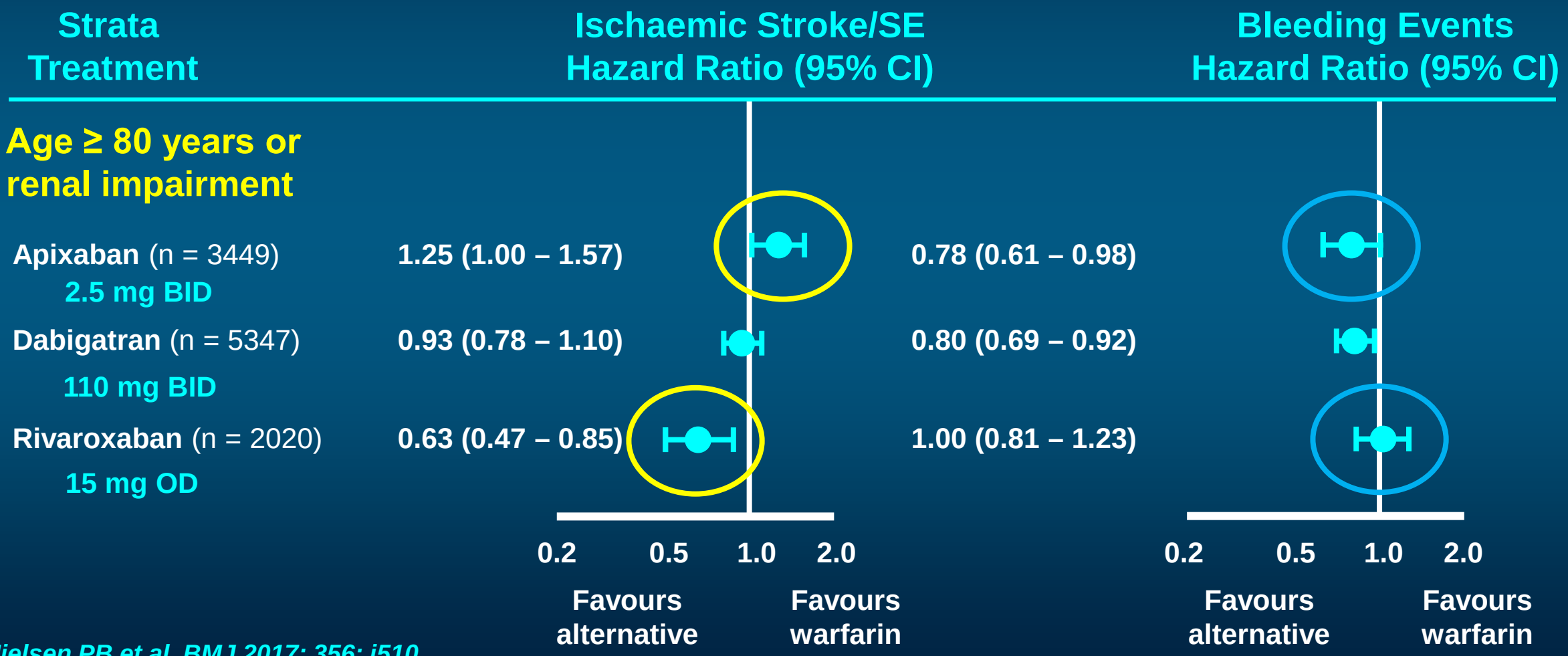
Prescribing Patterns of NOACs Globally

Country	Apixaban[1]		Dabigatran[1]			Rivaroxaban[1]		
	2.5 mg	5 mg	75 mg	110 mg	150 mg	10 mg	15 mg	20 mg
United States	25	75	16	0	84	5	19	76
Japan	46	54	28	72	0	45	55	0
Germany	43	57	1	60	39	3	33	63
Canada	37	63	1	50	49	4	25	71
Australia	40	60	0	63	36	2	29	69
United Kingdom	37	62	2	51	48	4	21	75
Spain	39	61	2	59	39	4	31	65
Belgium	31	69	0	59	41	2	40	58
Italy	37	63	0	62	37	1	36	63
%	ARISTOTLE[2]		RE-LY[3]			ROCKET AF[4]		
Phase III studies	4.7		50 (29)			21		
Real world	37		50			31		

In practice, prescriptions for apixaban at the lower 2.5 mg dose are disproportionately high. Similar but less-marked patterns are seen with dabigatran and rivaroxaban

1. IMS MIDAS; 2. Granger CB et al, N Engl J Med 2011;365:981-92; 3. Connolly SJ et al, N Engl J Med 2009;361:1139–1151; 4. Fox KAA et al, Eur Heart J 2011;32:2387–2394

Outcomes Associated with Reduced Dose NOAC Treatment in Focused Populations

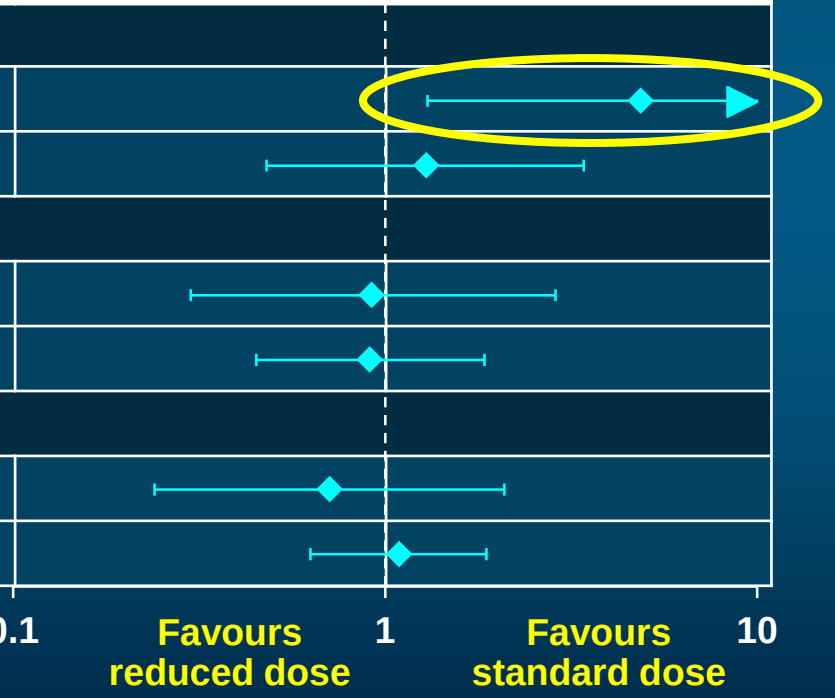


Nielsen PB et al. BMJ 2017; 356: j510

Inappropriate Reduced Dose of a NOAC Might Increase the Risk of Stroke/SE

Patients with no renal indication for dose reduction

	Reduced dose	Standard dose	HR (95% CI)	*p*-value	HR (95% CI)
	Event rate per 100 person-years				
Apixaban	N=550	N=550			
Stroke/SE	2.57	0.54	4.87 (1.30–18.26)	0.02	
Major bleeding	6.01	4.64	1.29 (0.48–3.42)	0.61	
Dabigatran	N=412	N=412			
Stroke/SE	1.64	1.75	0.92 (0.30–2.87)	0.89	
Major bleeding	4.99	5.54	0.91 (0.45–1.85)	0.80	
Rivaroxaban	N=815	N=815			
Stroke/SE	1.23	1.65	0.71 (0.24–2.09)	0.54	
Major bleeding	5.42	4.90	1.09 (0.63–1.87)	0.76	



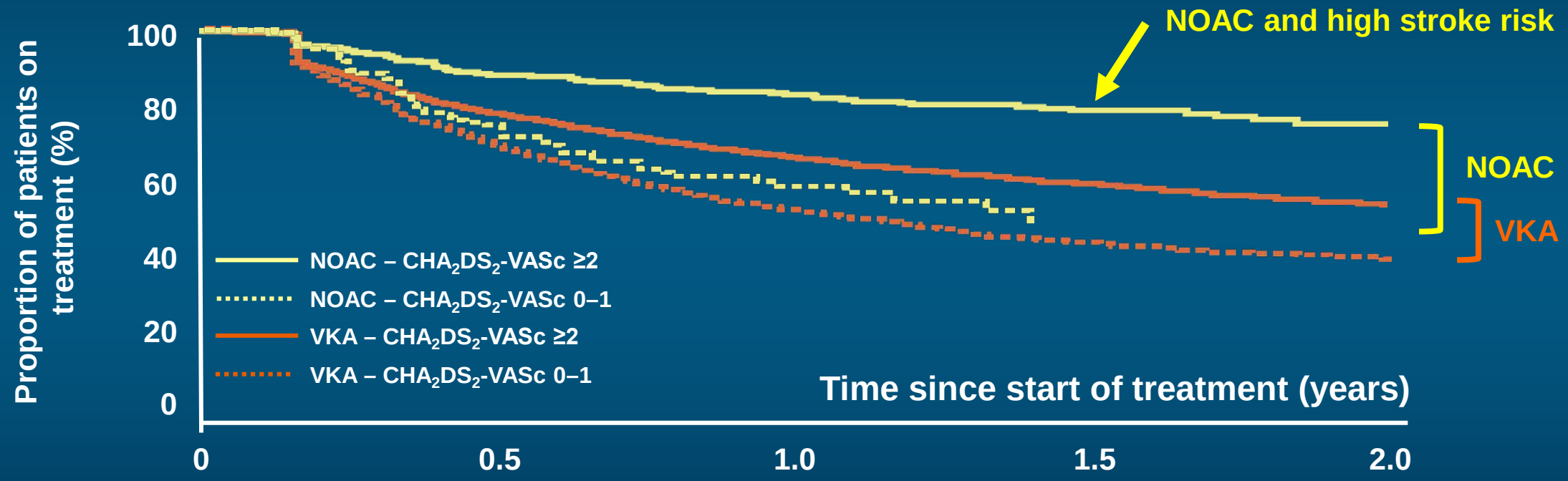
Median follow-up: 4.0 months (IQR 1.0–9.6 months)

Propensity score matching used to account for differences in baseline characteristics between patients receiving reduced and standard doses

Yao X et al, J Am Coll Cardiol 2017;69:2779–2790

Without Routine Coagulation Monitoring, NOAC Use Showed Higher Persistence Versus VKA at All Time Points

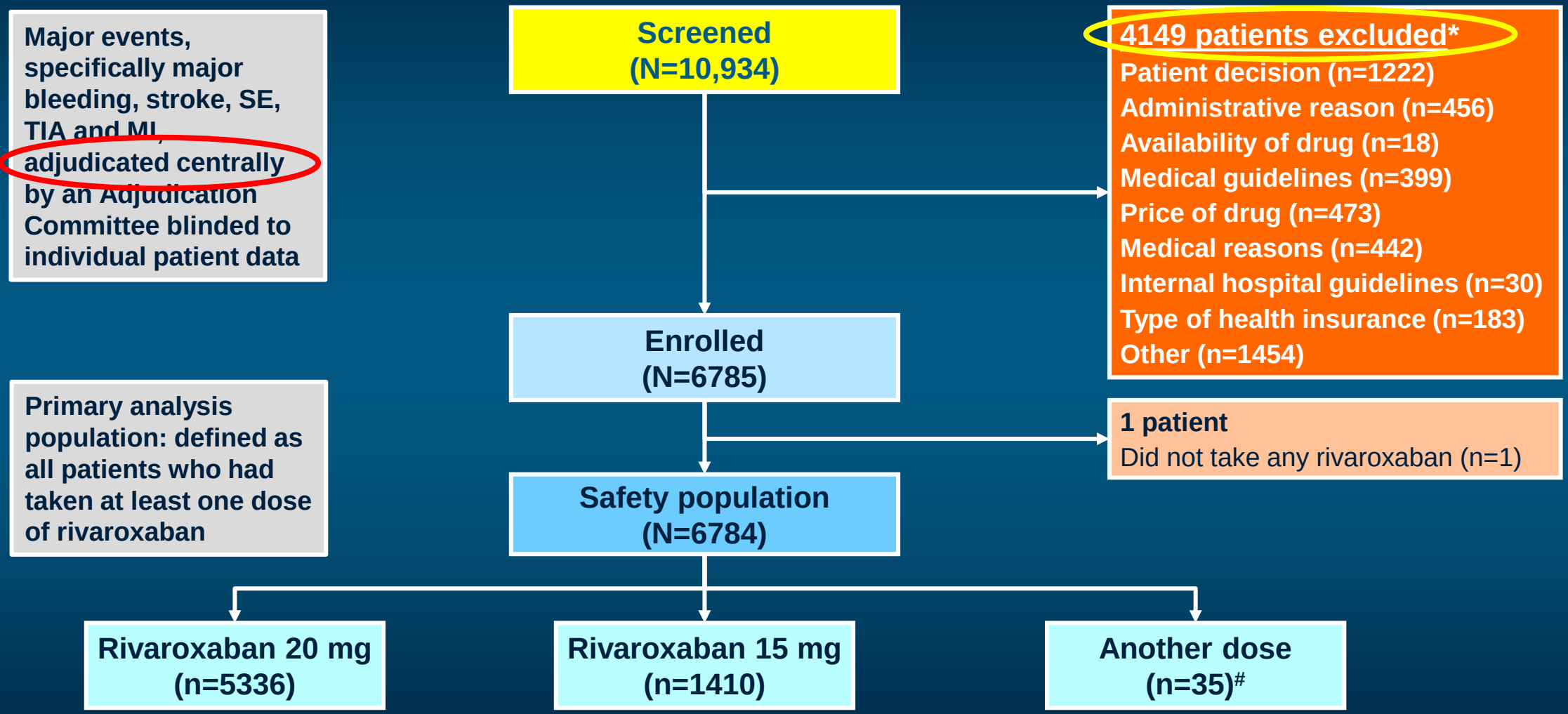
Therapy persistence according to CHA_2DS_2-VASc score



Retrospective study (UK primary care database): OAC-naïve patients starting on a NOAC or VKA ≤90 days after incident AF (N=13,221)

Martinez C et al, Thromb Haemost 2015;115:31–39

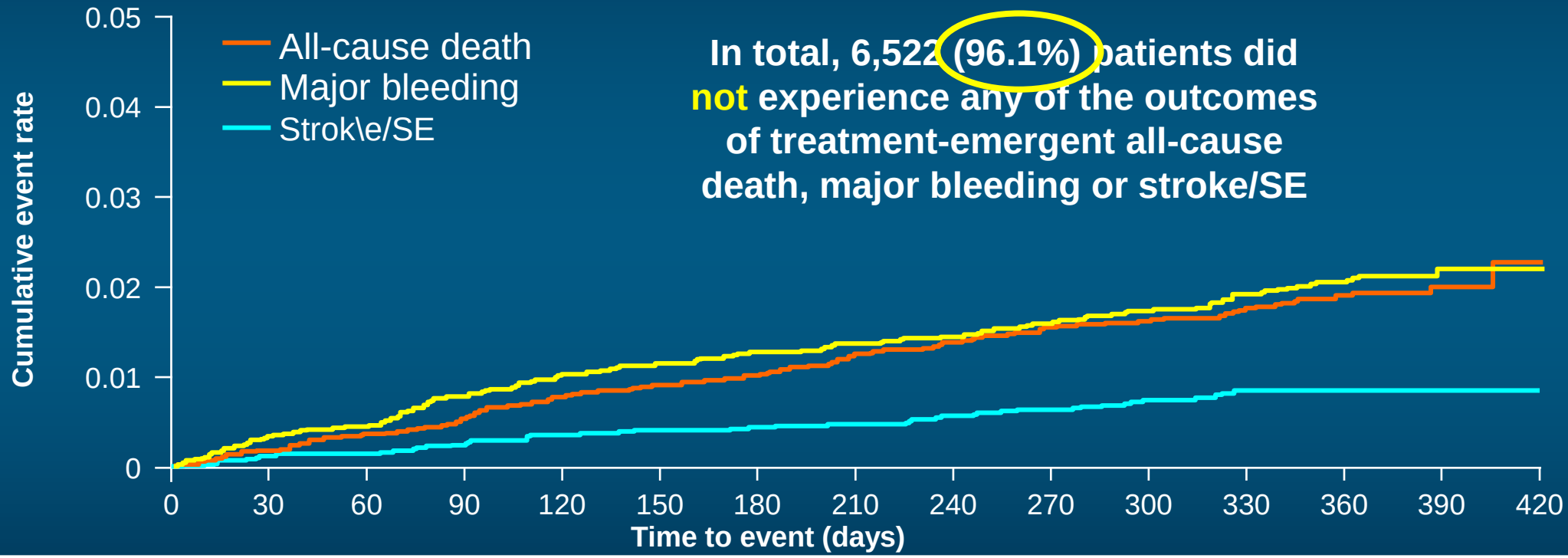
XANTUS: Patient Disposition



*Reasons for not continuing in the study included, but were not limited to, patient decision, administrative or medical reasons. Some patients could have more than one reason for exclusion;
#other dose includes any initial daily rivaroxaban dose besides 15/20 mg od (excluding missing information, n=3)

Camm AJ, et al. Eur Heart J 2015; doi: 10.1093/eurheartj/ehv466

Cumulative Rates (Kaplan–Meier) for Treatment-Emergent Primary Outcomes



Patients at risk															
All-cause death	6,784	6,530	6,349	6,211	6,054	5,938	5,853	5,754	5,679	5,597	5,512	5,295	4,307	1,153	514
Major bleeding	6,784	6,522	6,340	6,197	6,033	5,909	5,824	5,726	5,649	5,559	5,471	5,256	4,273	1,144	513
Stroke/SE	6,784	6,532	6,353	6,216	6,053	5,933	5,848	5,752	5,674	5,587	5,499	5,282	4,296	1,149	513

Camm AJ, et al. Eur Heart J. 2016;37:1145–53

Conclusions

- RCT data are indispensable (the gold standard) for drug approval
- RCT data suggest that DOAC therapy is more effective, safer and more cost-effective that VKA thrombo-prophylaxis in high risk AF patients
- Real world data exist, should be evaluated, and may strengthen, extend or challenge data derived from RCTs
- Real world data confirm the safety and effectiveness of DOAC therapy
- Comparative data are difficult to asses without formal randomised head-to-head trials of DOAC treatments, but bleeding may be more with rivaroxaban and strokes more with reduced dose apixaban
- Comprehensive understanding of the value of a specific therapy should be assessed using RCT and RWE, appropriately weighted for its likely accuracy

Thank you for your attention

St George's
University of London

Is there a Rationale for Anticoagulation in Patients with Arterial Disease?

Freek W.A. Verheugt

Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG)

Amsterdam, The Netherlands

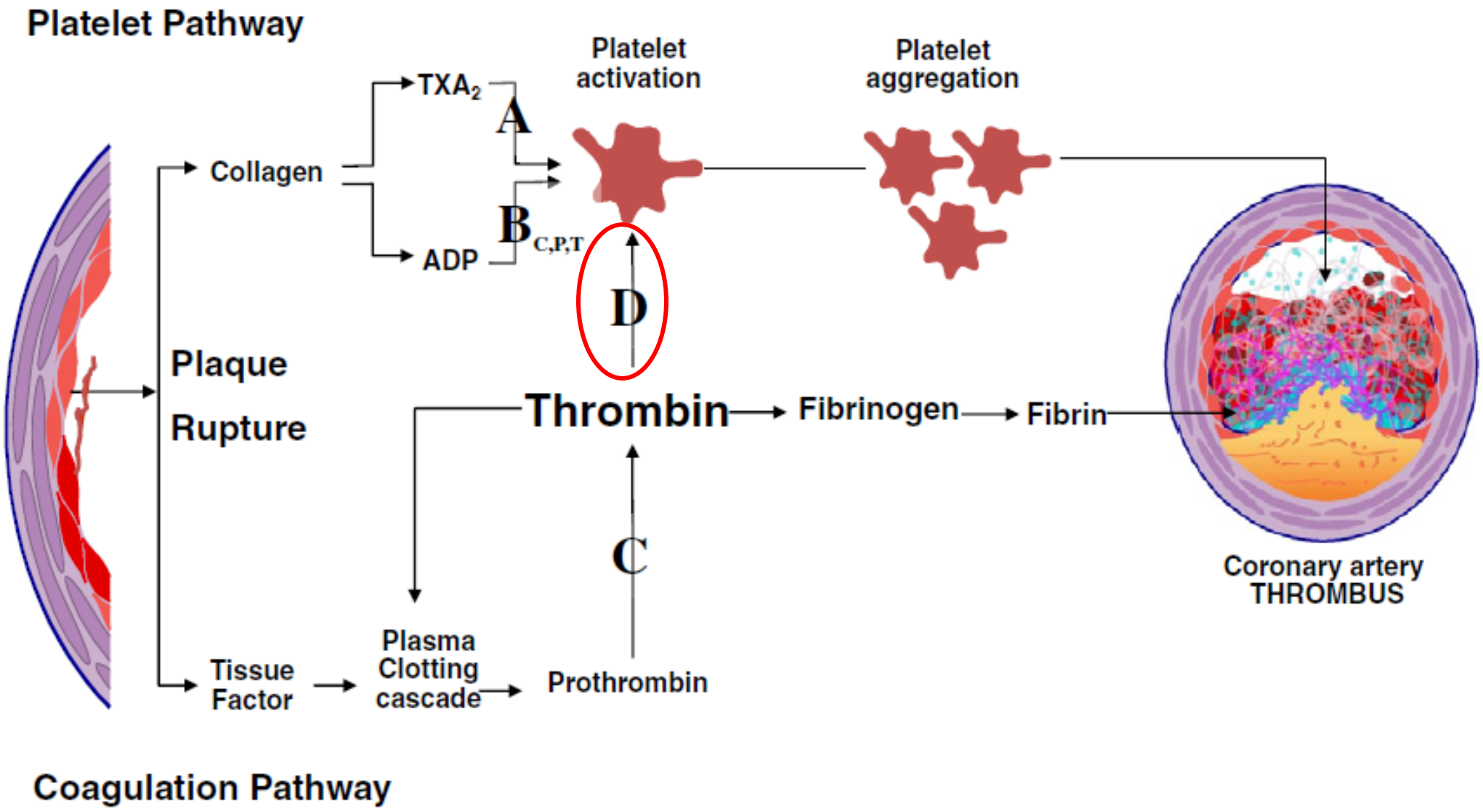
olvg

Onze Lieve Vrouwe Gasthuis, Amsterdam

Disclosures for Freek W. A. Verheugt

Research support/ principal investigator	Bayer HealthCare, Boehringer Ingelheim, Eli Lilly and Roche
Consultant	Bayer Healthcare, Eli Lilly, Daiichi-Sankyo, and Merck
Speakers' bureau	none
Honoraria	Bayer Healthcare, Eli Lilly, Daiichi-Sankyo and Merck
Scientific advisory board	AstraZeneca and Cardialysis B.V.

Role of Thrombin in Coronary Clot Formation



First Randomized Controlled Trial of Warfarin in Cardiac Disease

THE USE OF THE ANTICOAGULANTS IN THE TREATMENT OF DISEASES OF THE HEART AND BLOOD VESSELS *

By Irving S. Wright, M.D., F.A.C.P., *New York, N. Y.*

The Treatment and Prophylaxis of Thrombophlebitis and Pulmonary Embolism

Ann Intern Med 1949;30:80-91

olvg

Onze Lieve Vrouwe Gasthuis, Amsterdam

First Randomized Controlled Trial of Warfarin in Cardiac Disease

ANTICOAGULANTS IN HEART AND BLOOD VESSEL DISEASES

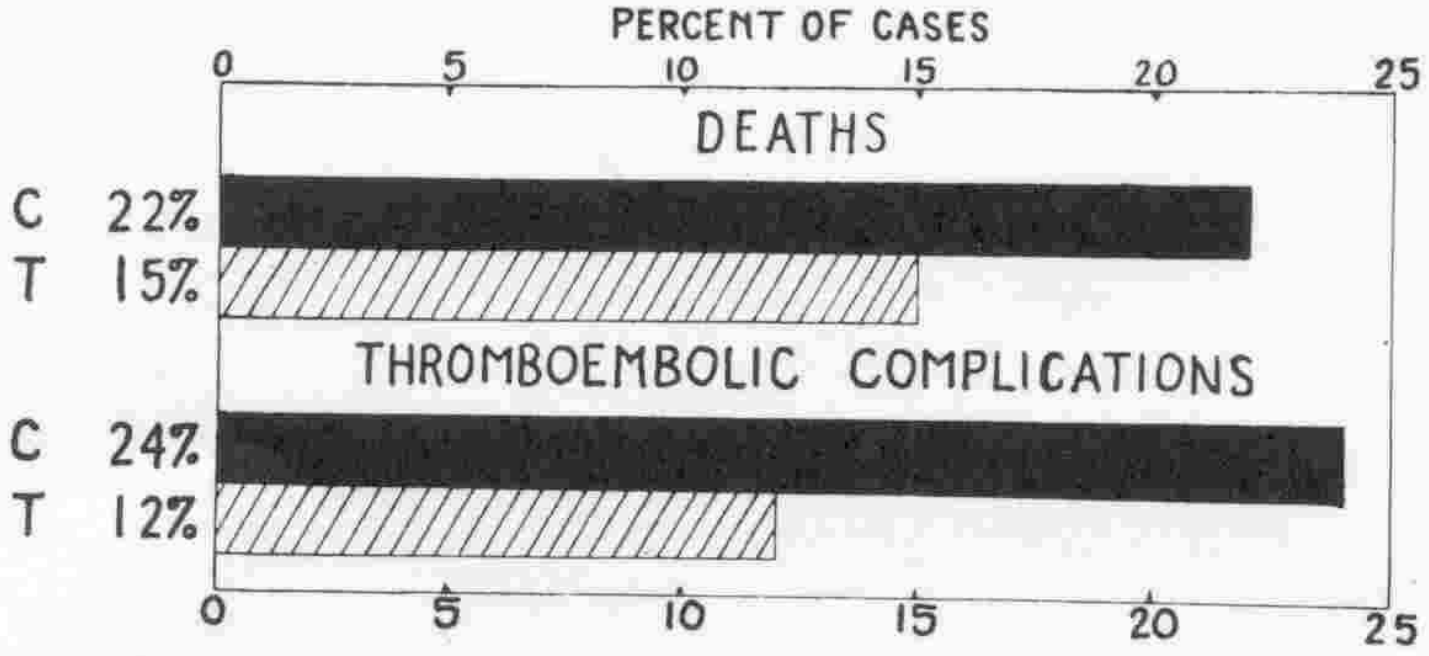


Chart I. Anticoagulants in coronary occlusion with myocardial infarction (800 cases)

Ann Intern Med 1949;30:80-91

First Randomized Placebo-Controlled Trial of Warfarin after MI

A DOUBLE-BLIND TRIAL TO ASSESS LONG-TERM ORAL ANTICOAGULANT THERAPY IN ELDERLY PATIENTS AFTER MYOCARDIAL INFARCTION

Report of the Sixty Plus Reinfarction Study Research Group*

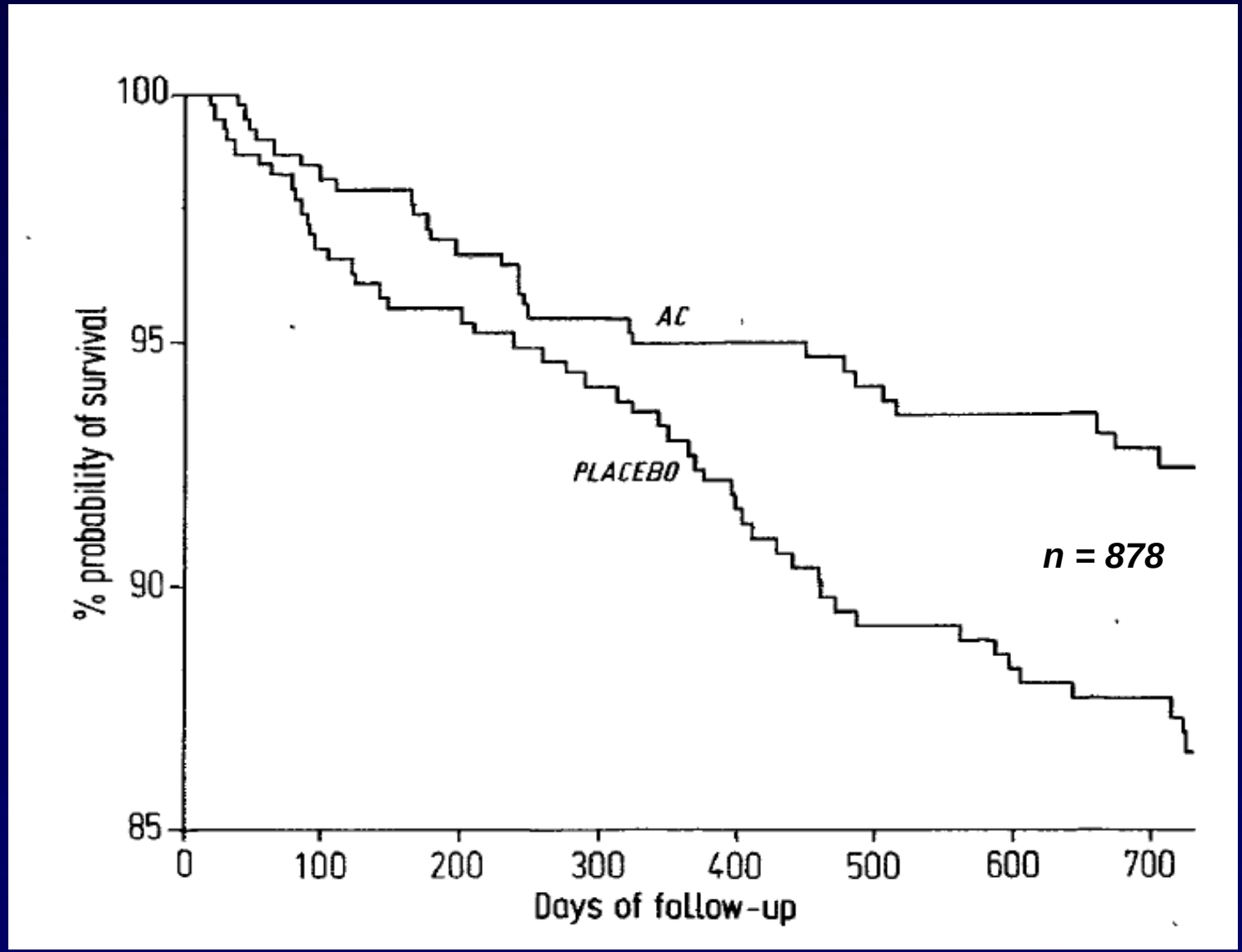
Summary In a randomised double-blind multicentre clinical trial the effect of continued oral anticoagulant therapy after a myocardial infarction was assessed in a group of patients over 60 years of age. Half of the 878 patients who had been on anticoagulants ever since their primary myocardial infarction received placebos instead of the anticoagulant; the others continued anticoagulant therapy. All were followed for 2 years. The levels of hypocoagulability reached in the group on anticoagulants were such that, of the registered prothrombin times ('Thrombotest'), 72% were between 107 and 180 s. 2-year total mortality was 13·4% in the placebo group and 7·6% in the group treated

Lancet 1980;ii:989-994

olvg

Onze Lieve Vrouwe Gasthuis, Amsterdam

First Randomized Placebo-Controlled Trial of Warfarin after MI

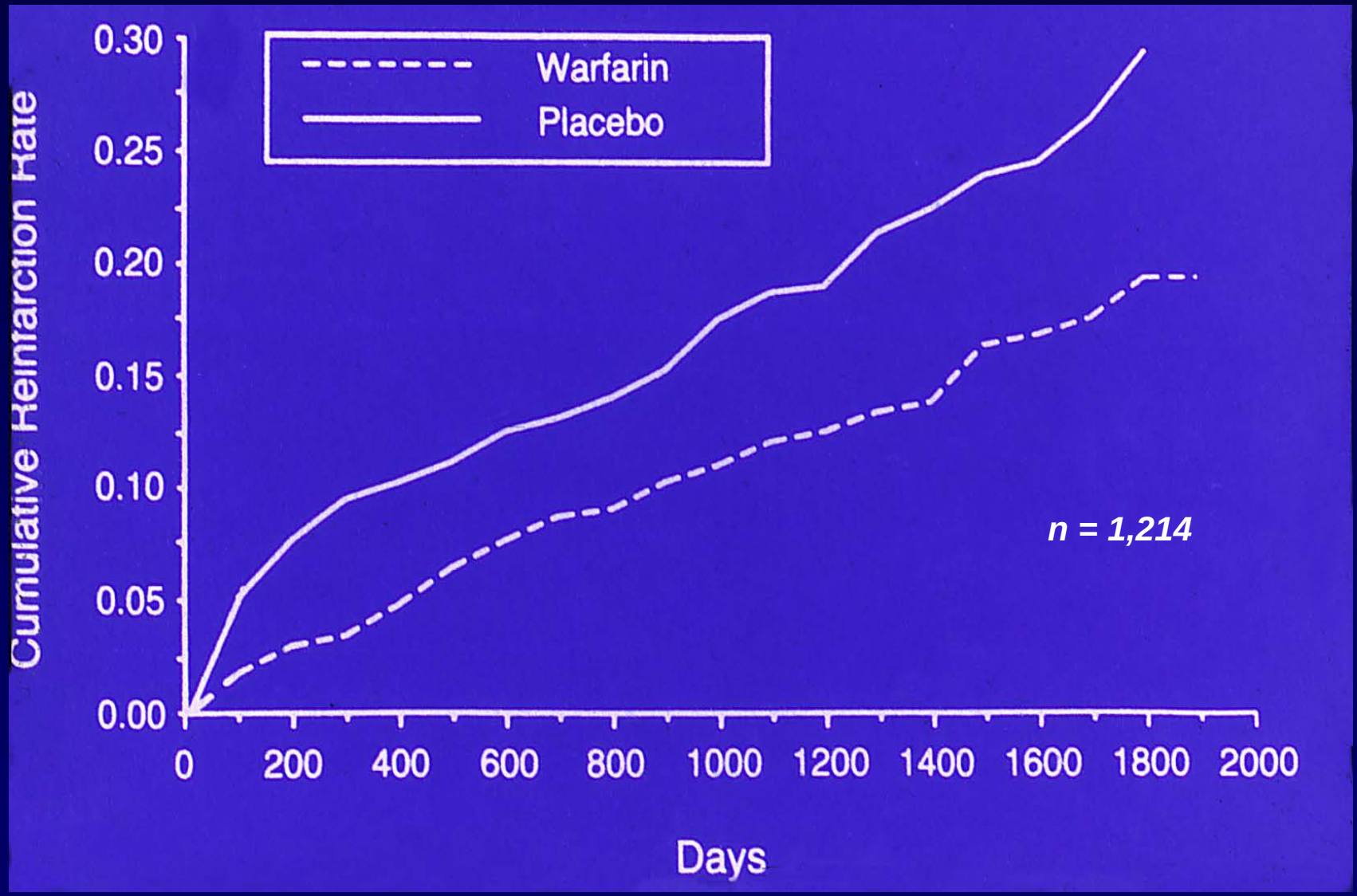


Lancet 1980;ii:989-994

olvg

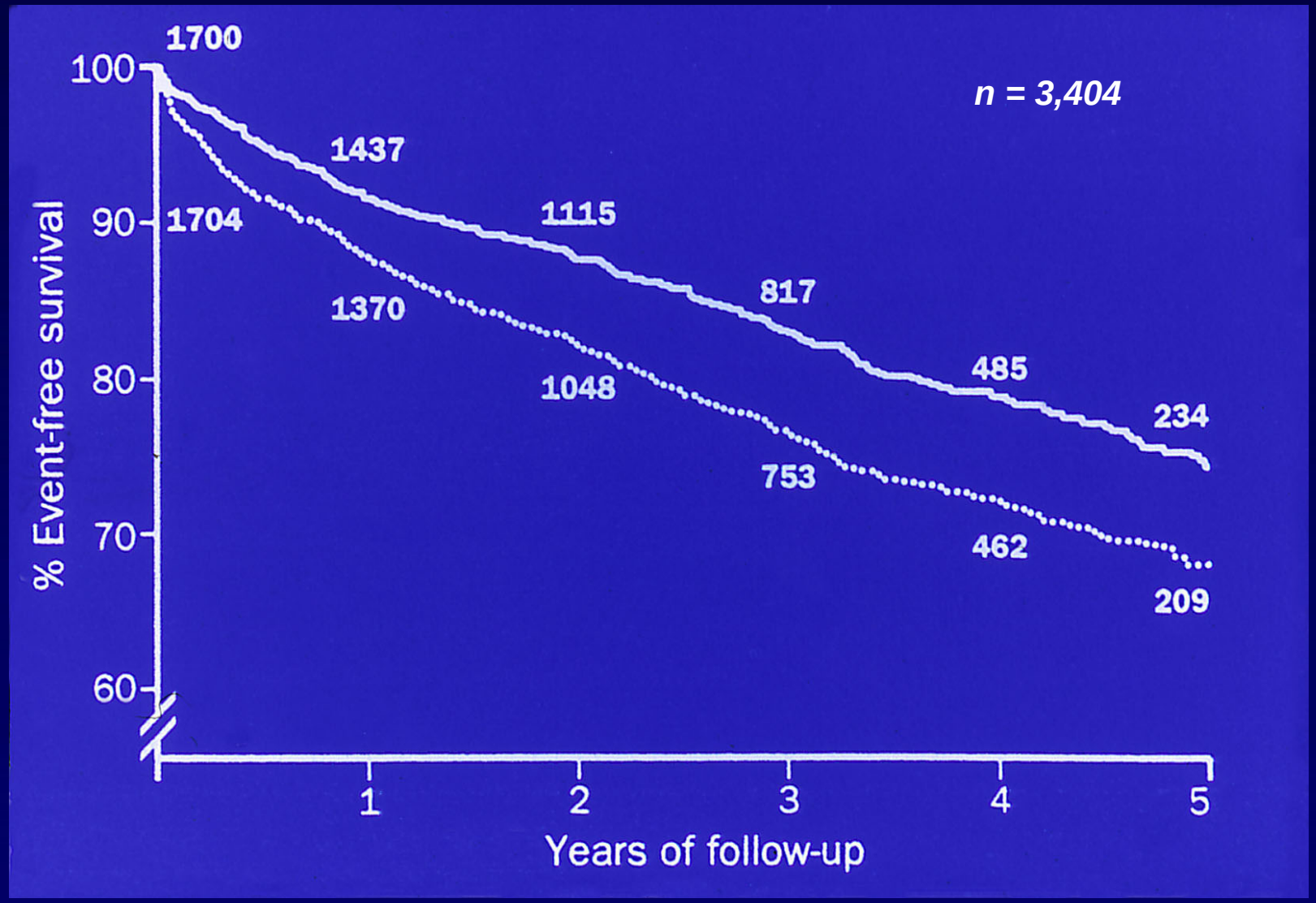
Onze Lieve Vrouwe Gasthuis, Amsterdam

Second Randomized Placebo-Controlled Trial of Warfarin after MI



WARIS. N Engl J Med 1990;323:147-152

Third Randomized Controlled Trial of Warfarin after MI

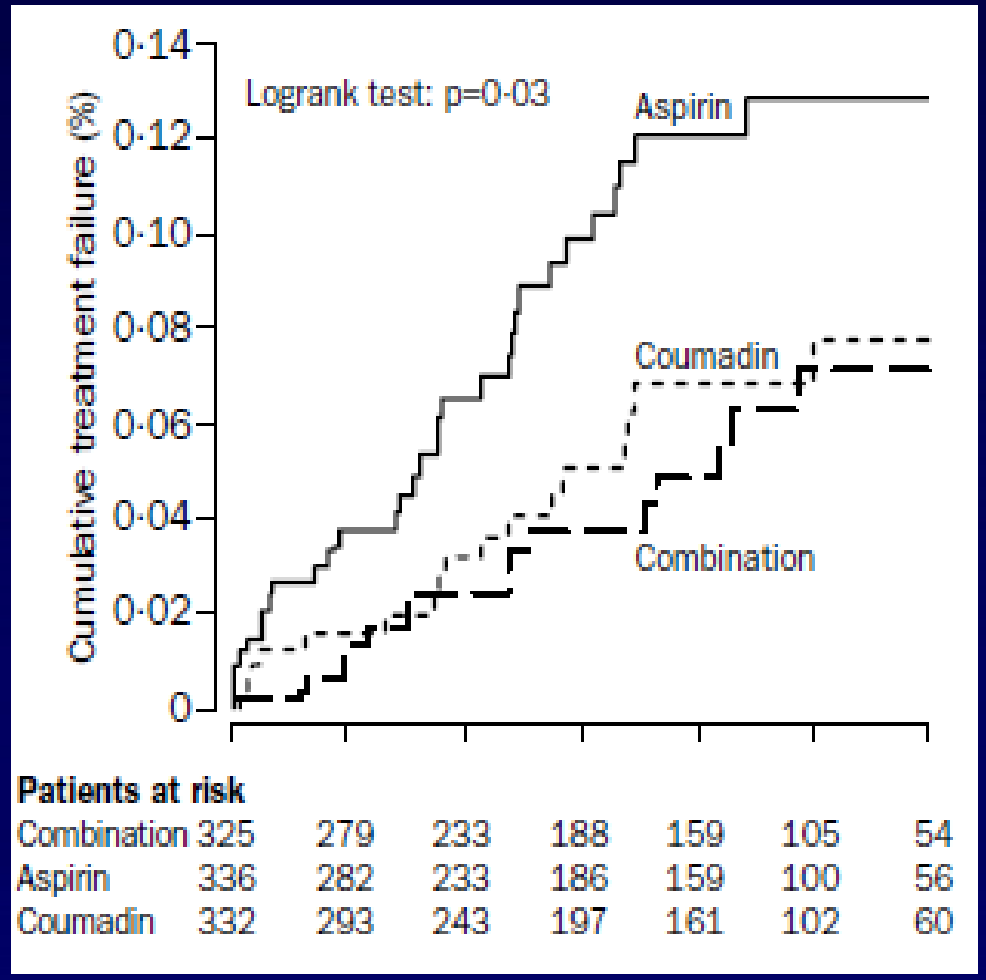


ASPECT. Lancet 1994;343:499-503

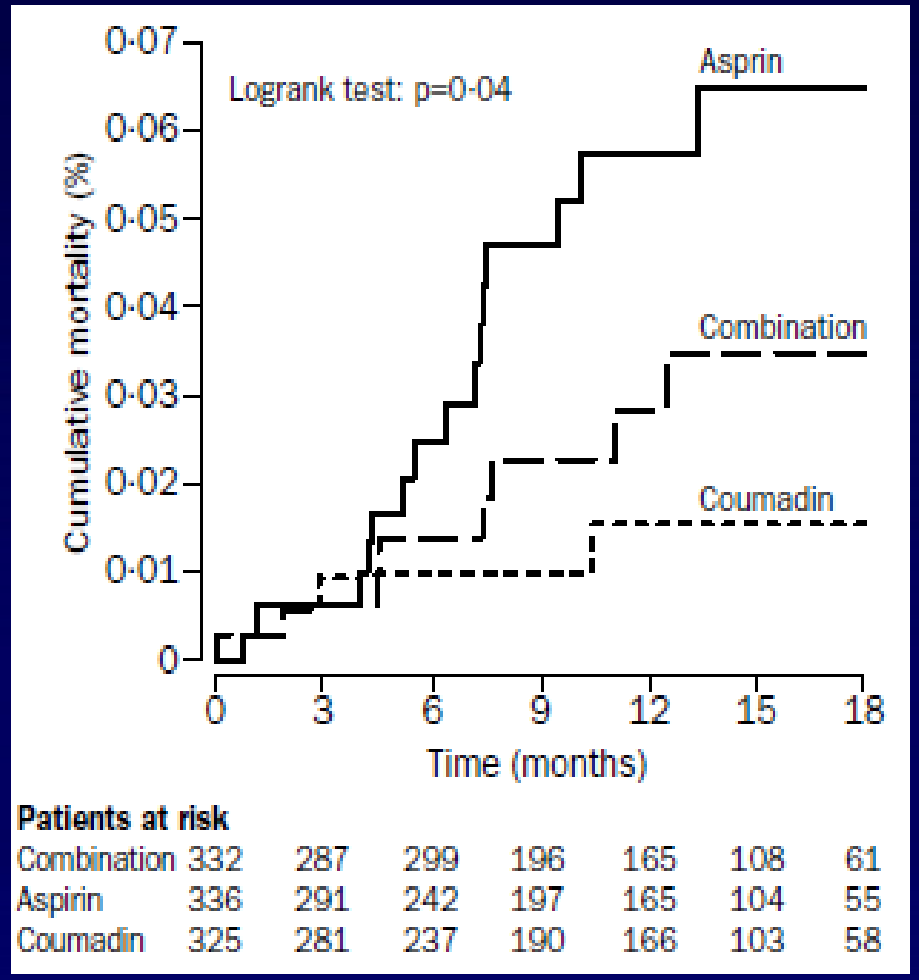
olvg

Onze Lieve Vrouwe Gasthuis, Amsterdam

Aspirin vs Acenocoumarol vs Both after MI



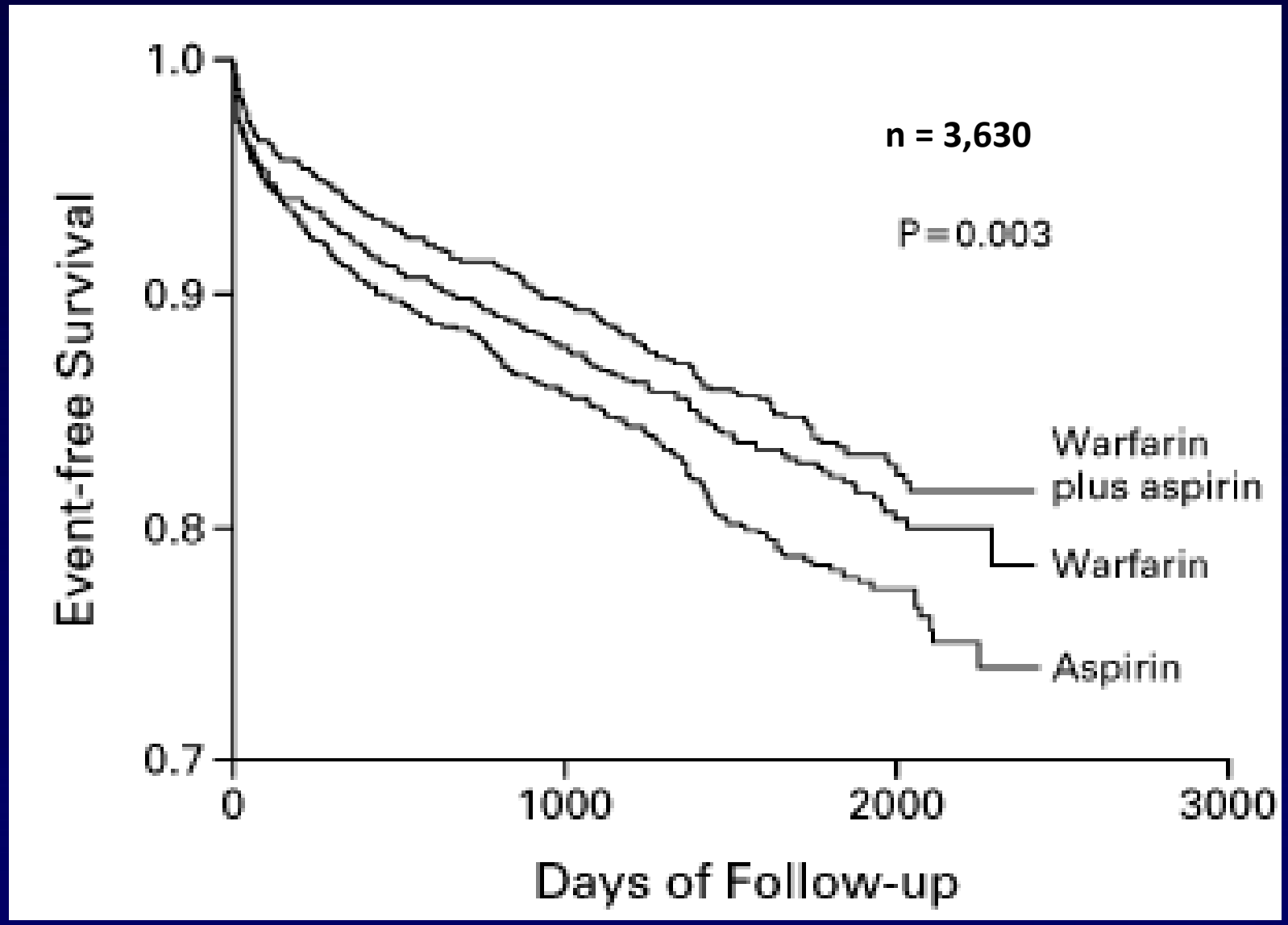
death, reMI, stroke



mortality

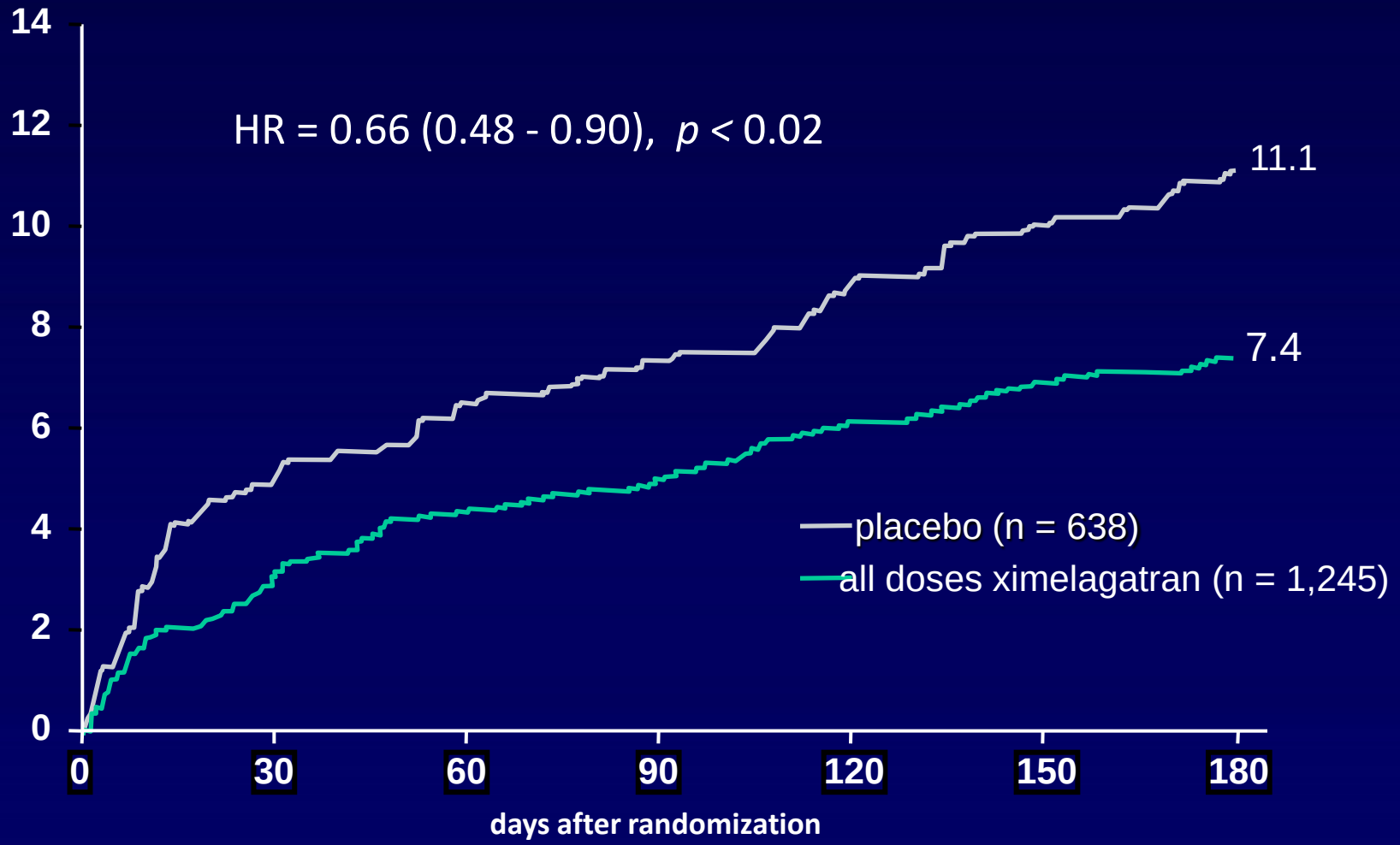
ASPECT-2. Lancet 2002:360:109-113

Aspirin vs Warfarin vs Both after MI



WARIS-2. N Engl J Med 2002; 347:969-974

NOAC plus aspirin vs aspirin alone after ACS: death, MI or stroke

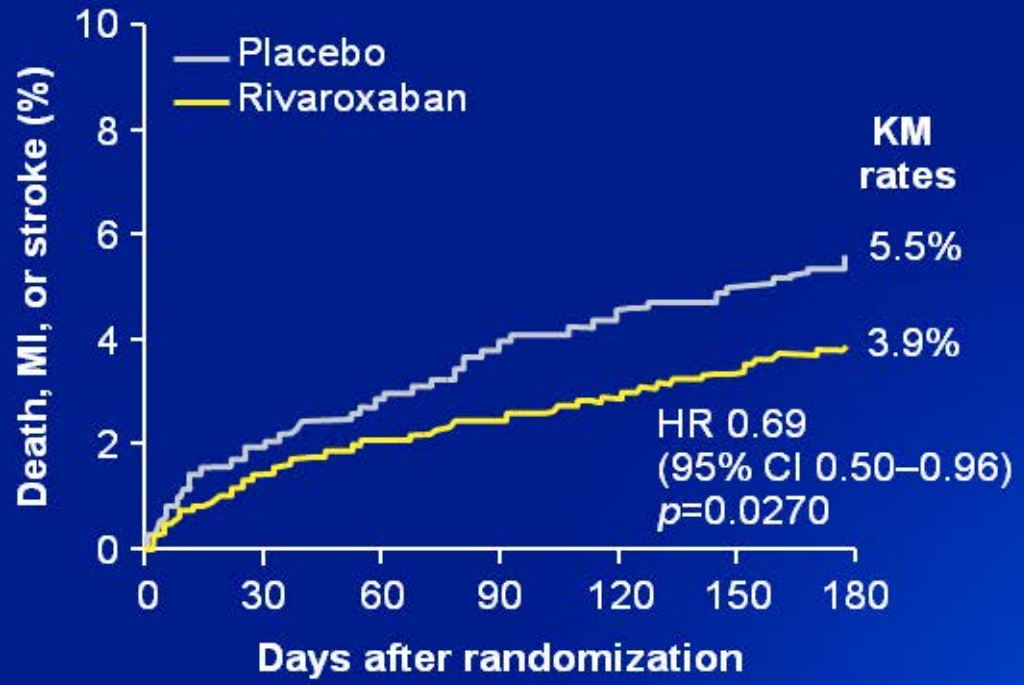


ESTEEM. Lancet 2003;362:789-797

olvg

Onze Lieve Vrouwe Gasthuis, Amsterdam

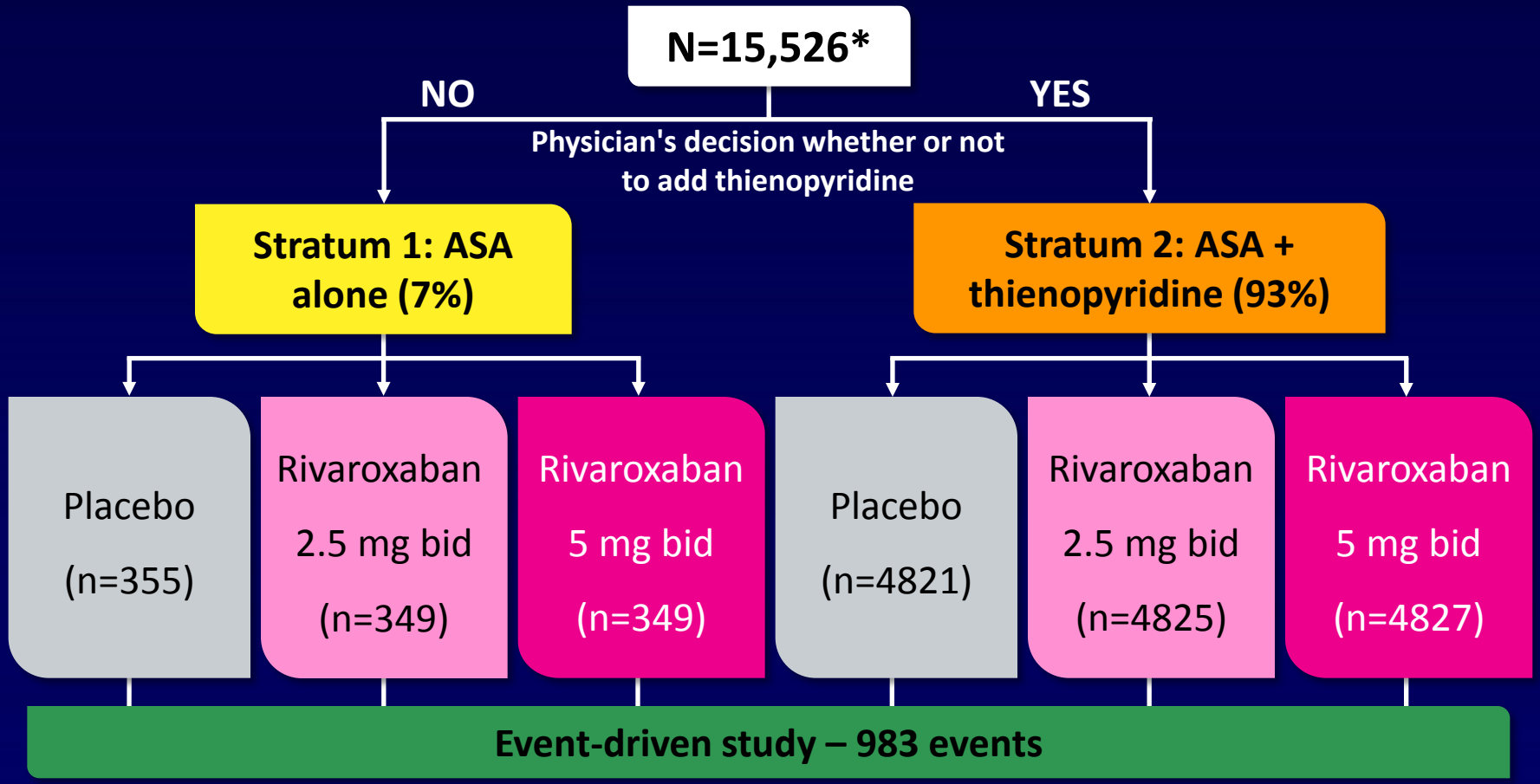
ATLAS ACS TIMI 46:
Secondary efficacy endpoint – total doses



Number at risk							
Placebo	1,160	1,119	1,094	1,073	1,051	1,036	1,020
Rivaroxaban	2,331	2,246	2,193	2,161	2,119	2,084	2,052

Mega *et al*. *Lancet* 2009;374:29–38

NOAC plus DAPT vs DAPT alone after ACS: ATLAS ACS-2



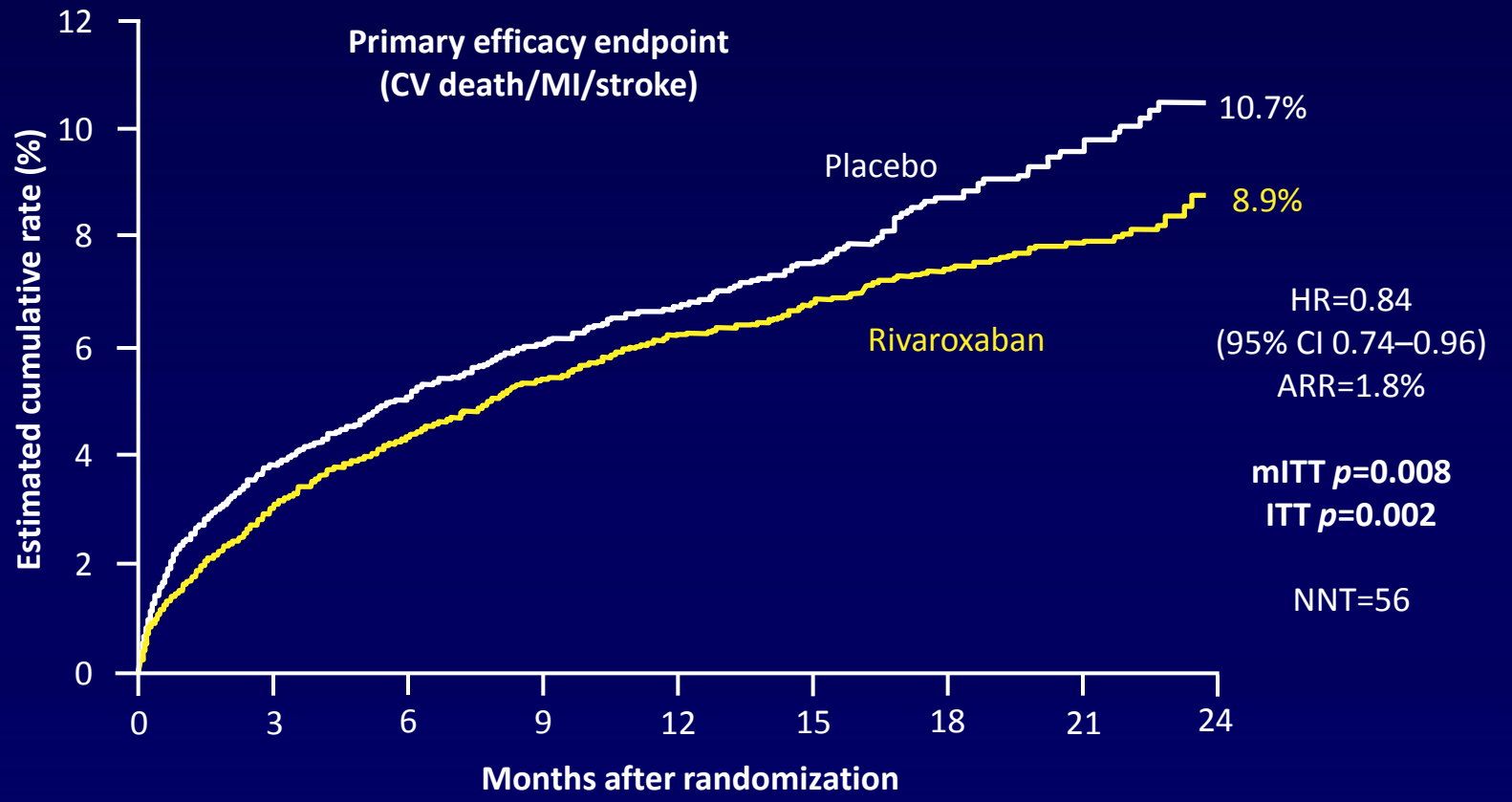
ASA dose: 75–100 mg, prior stroke excluded

olvg

N Engl J Med 2012;366:9-19

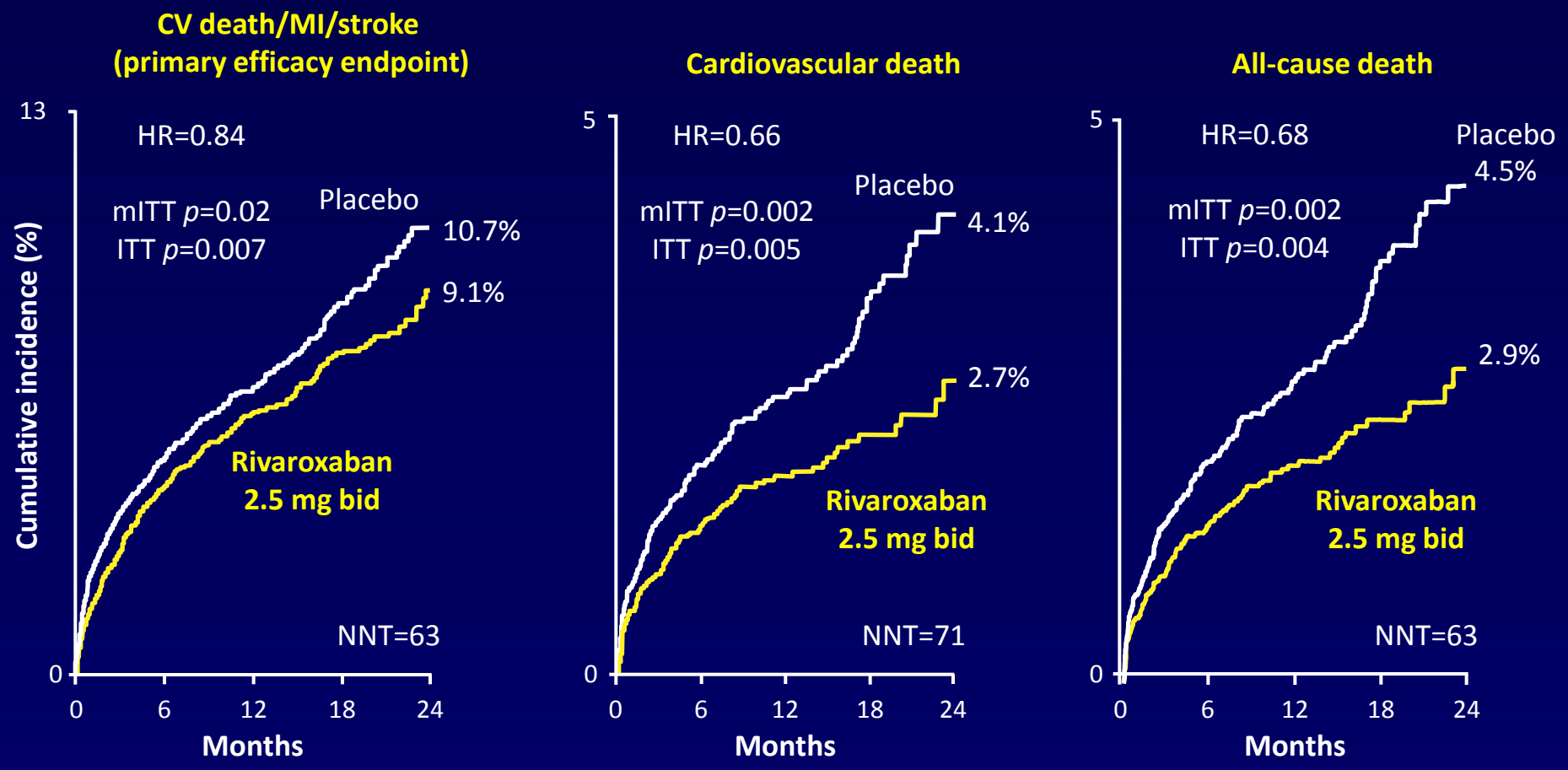
Onze Lieve Vrouwe Gasthuis, Amsterdam

NOAC plus DAPT vs DAPT alone after ACS in ATLAS ACS-2: efficacy



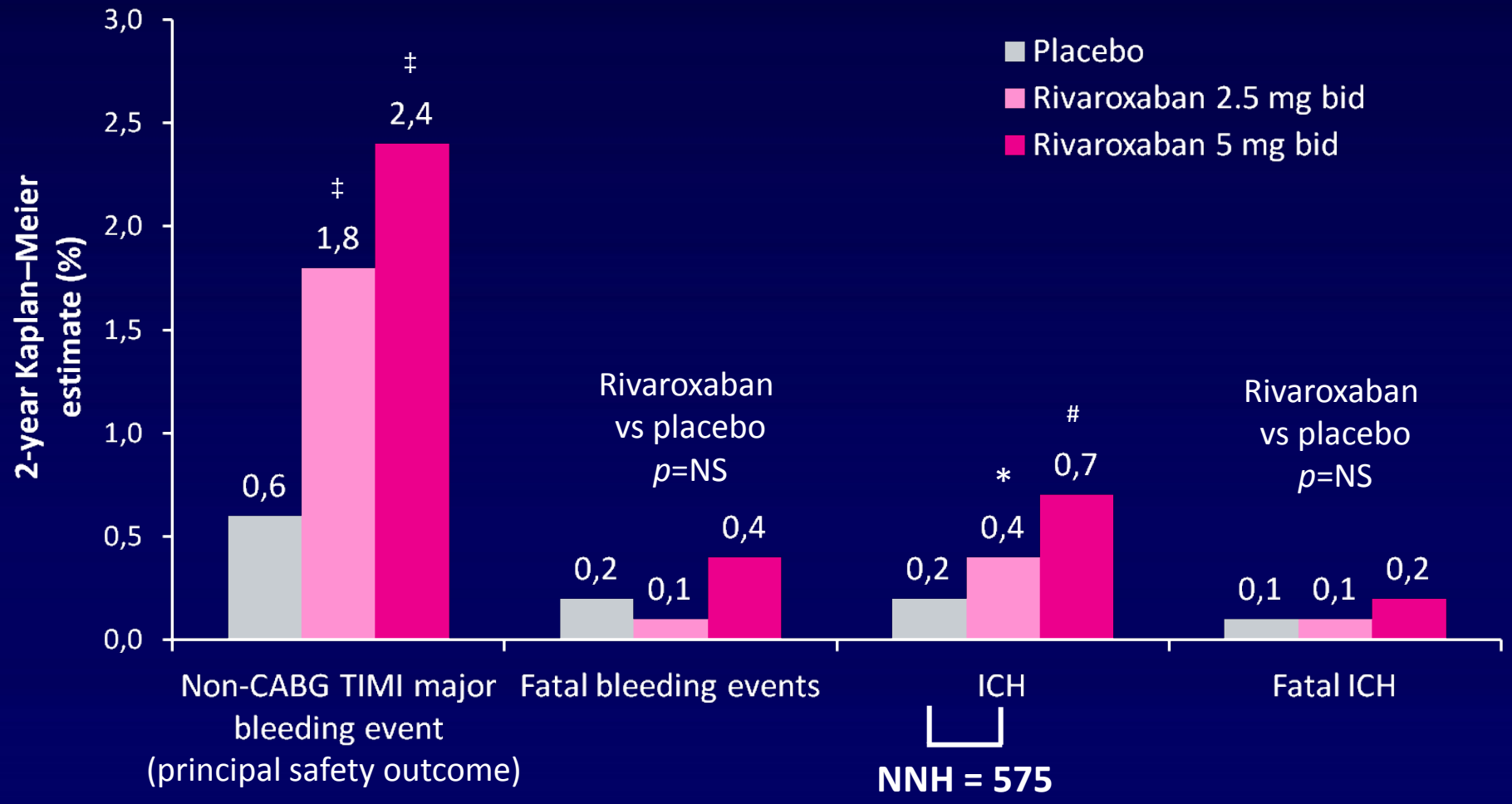
N Engl J Med 2012;366:9-19

Low-dose NOAC plus DAPT vs DAPT alone after ACS in ATLAS ACS-2: efficacy



N Engl J Med 2012;366:9–19

NOAC plus DAPT vs DAPT alone after ACS in ATLAS ACS-2: bleeding



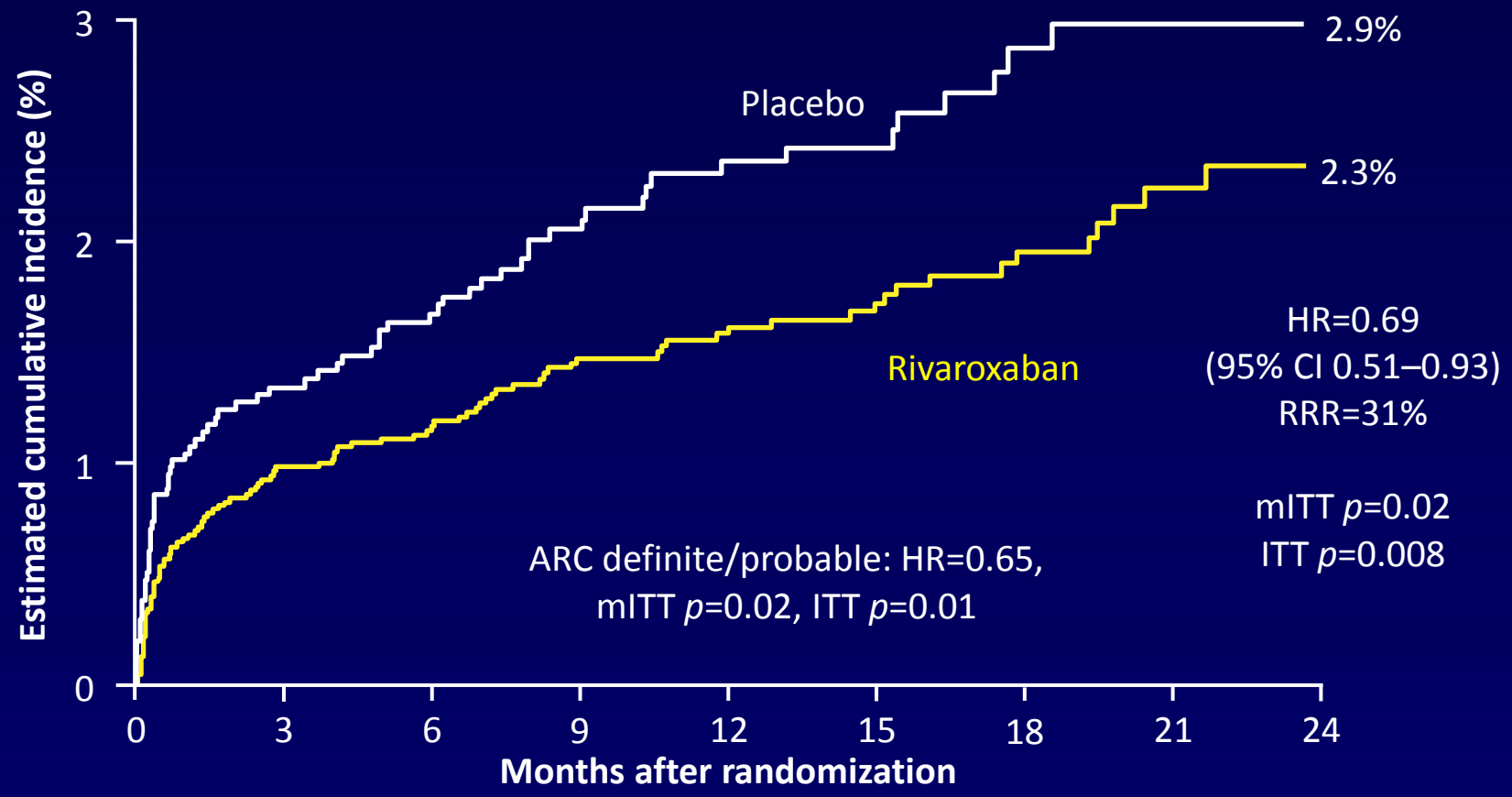
*p=0.04 vs placebo; #p=0.005 vs placebo; ‡p<0.001 vs placebo.

N Engl J Med 2012;366:9-19

olvg

Onze Lieve Vrouwe Gasthuis, Amsterdam

Stent Thrombosis NOAC plus DAPT vs DAPT alone in ATLAS ACS 2



Gibson CM . J Am Coll Cardiol 2013;62:286–290

STENT THROMBOSIS WITH NOACS AFTER ACS

trial	f/u (m)	n	reported stent thrombosis (%) NOAC	reported stent thrombosis (%) placebo	RR 95% CI)	NNT
APPRAISE-2	8	7,392	0.9	1.3	0.73 (0.47 - 1.12)*	250
ATLAS-2[1]	13	15,526	2.3	2.9	0.69 (0.51 - 0.93)**	250

[1] *both doses*

* *p = 0.15*

** *p = 0.02*

Verheugt FWA. Eur Heart J 2013;34:1618-1620

COMPASS

(n = 27,395)

CAD without indication for DAPT*,or PAD after 3w ASA run-in

rivaroxban 5 mg bid	rivaroxaban 2.5 mg bid + aspirin 100 mg qd	aspirin 100 mg qd
PPI / no PPI	PPI / no PPI	PPI / no PPI
30d washout	30d washout	30d washout

*previous MI < 20y, or
*MVD with or without PCI or CABG

primary efficacy endpoint: CV death/MI/stroke
safety endpoint: ISTH major bleeding

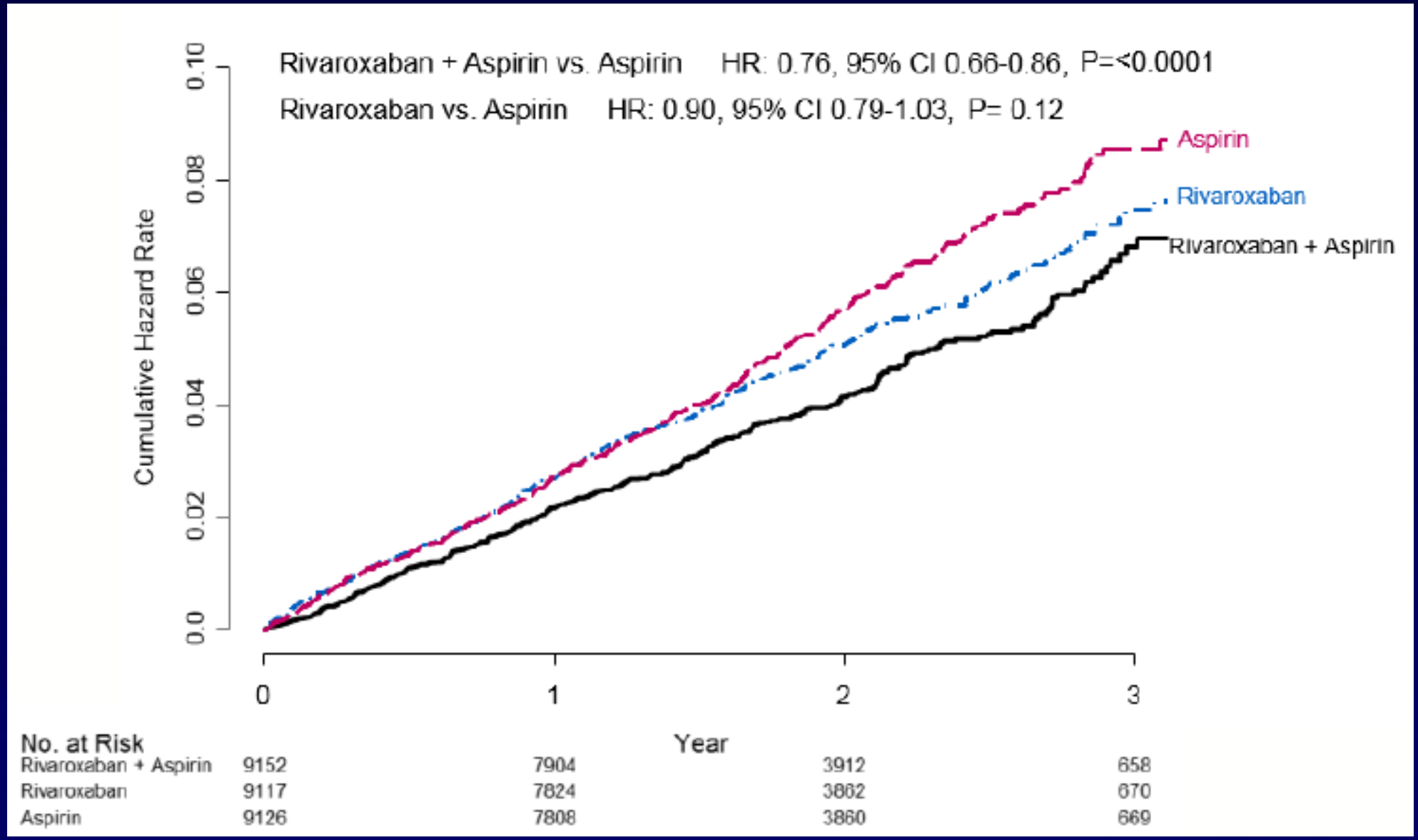
Substudies: COMPASS CABG (n = 2,000) and COMPASS MIND (n = 1,500)

olvg

N Engl J Med 2017;377:1319-1330

Onze Lieve Vrouwe Gasthuis, Amsterdam

COMPASS: Primary Endpoint



N Engl J Med 2017;377:1319-1330

COMPASS: Primary Endpoint

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	p
CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9%)	142 (1.6%)	0.58 (0.44-0.76)	<0.0001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

olvg

N Engl J Med 2017;377:1319-1330

Onze Lieve Vrouwe Gasthuis, Amsterdam

COMPASS: Secondary Endpoints

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P*
CHD death, IS, MI, ALI	329 (3.6%)	450 (4.9%)	0.72 (0.63-0.83)	<0.0001
CV death, IS, MI, ALI	389 (4.3%)	516 (5.7%)	0.74 (0.65-0.85)	<0.0001
Mortality	313 (3.4%)	378 (4.1%)	0.82 (0.71-0.96)	0.01

NNT = 143

N Engl J Med 2017;377:1319-1330

olvg

Onze Lieve Vrouwe Gasthuis, Amsterdam

COMPASS: Bleeding Endpoints

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P
Major bleeding	288 (3.1%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001
Fatal	15 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	0.32
Non fatal ICH*	21 (0.2%)	19 (0.2%)	1.10 (0.59-2.04)	0.77
Non-fatal other critical organ*	42 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	0.14

* symptomatic

NNH = 83

COMPASS: Net Clinical Benefit

- **Definition:** composite of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ
- **i.e. irreversible harm**

Outcome	Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152	Aspirin 100 mg N=9126	Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg HR (95% CI)	*p*-value
Net clinical benefit	431 (4.7%)	534 (5.9%)	0.80 (0.70–0.91)	<0.001

NNT = 80

N Engl J Med 2017;377:1319-1330

olvg

Onze Lieve Vrouwe Gasthuis, Amsterdam

Is there a Rationale for Anticoagulation in Patients with Arterial Disease?

Conclusions

1. In patients after surviving ACS addition of low-dose NOAC to DAPT significantly reduces death and stent thrombosis, but at the risk of significant major, but not fatal bleeding.

2. In stable coronary and peripheral artery disease addition of low-dose rivaroxaban to aspirin alone reduces long-term ischemic outcomes: death and stroke are significantly reduced with an acceptable increase in major, but not fatal bleeding.

Interactive discussions

Applying innovation in Clinical Practice

Case

A Case of Secondary Prevention
1 Year After ACS

Freek W.A. Verheugt

CASE

68-year-old male with hypertension and history of bleeding ulcer presents with NSTEMI with a marginal troponin rise.

Ticagrelor 90 mg bid, aspirin.

Cath showed triple vessel-disease.

He received a DES in the proximal LAD and RCA.

Uneventful recovery without symptoms.

ECHO: normal LV, but wide LA.

At 1 year: no symptoms and normal ECG.

Antithrombotic Options at 1 year

What would be your preferred strategy in this case?

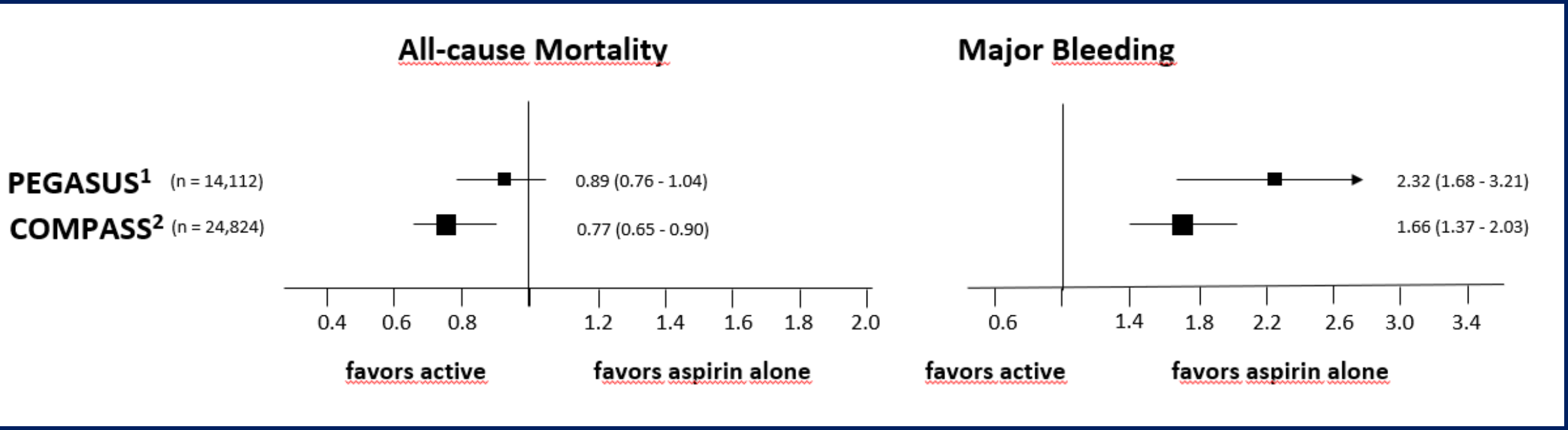
1. **Stop ticagrelor**
2. **Continue ticagrelor at 60 mg b.i.d.**
3. **Stop ticagrelor and start rivaroxaban 2.5 mg b.i.d.**
4. **Stop ticagrelor and start clopidogrel *(de-escalation)***

Antithrombotic Options at 1 year

What would be your preferred strategy in this case?

1. Stop ticagrelor
2. **Continue ticagrelor at 60 mg b.i.d.** (standard of care in high risk)
3. **Stop ticagrelor and start rivaroxaban 2.5 mg b.i.d.** (COMPASS)
4. Stop ticagrelor and start clopidogrel *(de-escalation)*

A Case of Secondary Prevention ≥ 1 Year After ACS



1. Bonaca MP. Long-Term use of ticagrelor in patients with prior myocardial Infarction. N Engl J Med 2015;372:1791-1800

2. Connolly SJ,. Rivaroxaban with or without aspirin in patients with stable coronary artery disease. Lancet 2017, November 10: http://dx.doi.org/10.1016/S0140-6736(17)32458-3

Case:

Managing this “not uncommon” case of incidental pulmonary embolism in a cancer patient

Howard Liebman

Case 2

The patient is a 76-year-old female admitted to an outside emergency room with syncope and 6 to 7 bloody bowel movements. She was found to have a haemoglobin (Hgb) of 10.6 g/dL. A colonoscopy showed a mass of 20 cm and biopsy revealed an infiltrating moderately differentiated adenocarcinoma. CT scan revealed irregularity of the distal sigmoid colon with adjacent enlarged lymph nodes.

Laparotomy resulted in a recto-sigmoid colon resection with pathology revealing a 5.5 cm tumour infiltrating the muscularis propria and subserosal fat with 7/17 lymph nodes positive. After recovery, the patient was treated with 12 cycles of FOLFOX chemotherapy. Upon completion of chemotherapy, a restaging CT scan showed no evidence of cancer, but an isolated subsegmental pulmonary embolism was noted. Patient denied any specific symptoms, except fatigue, which she related to her previous chemotherapy. Her Hgb at that time was 12.8 g/dL.

WHAT WOULD YOU DO?

A. Do nothing since she has no respiratory symptoms and only isolated subsegmental.
B. Start LMW heparin at treatment dose.
C. Give LMW heparin a prophylactic dose.
D. Do a D-dimer assay and only treat if above 500ng/ml.
E. Do lower extremity compression ultrasound and treat if positive.

WHY IS THERE DISCORDANCE BETWEEN AUTOPSY DATA AND REPORTED SYMPTOMATIC VTE?

Symptomatic VTE → **VTE at autopsy**

?

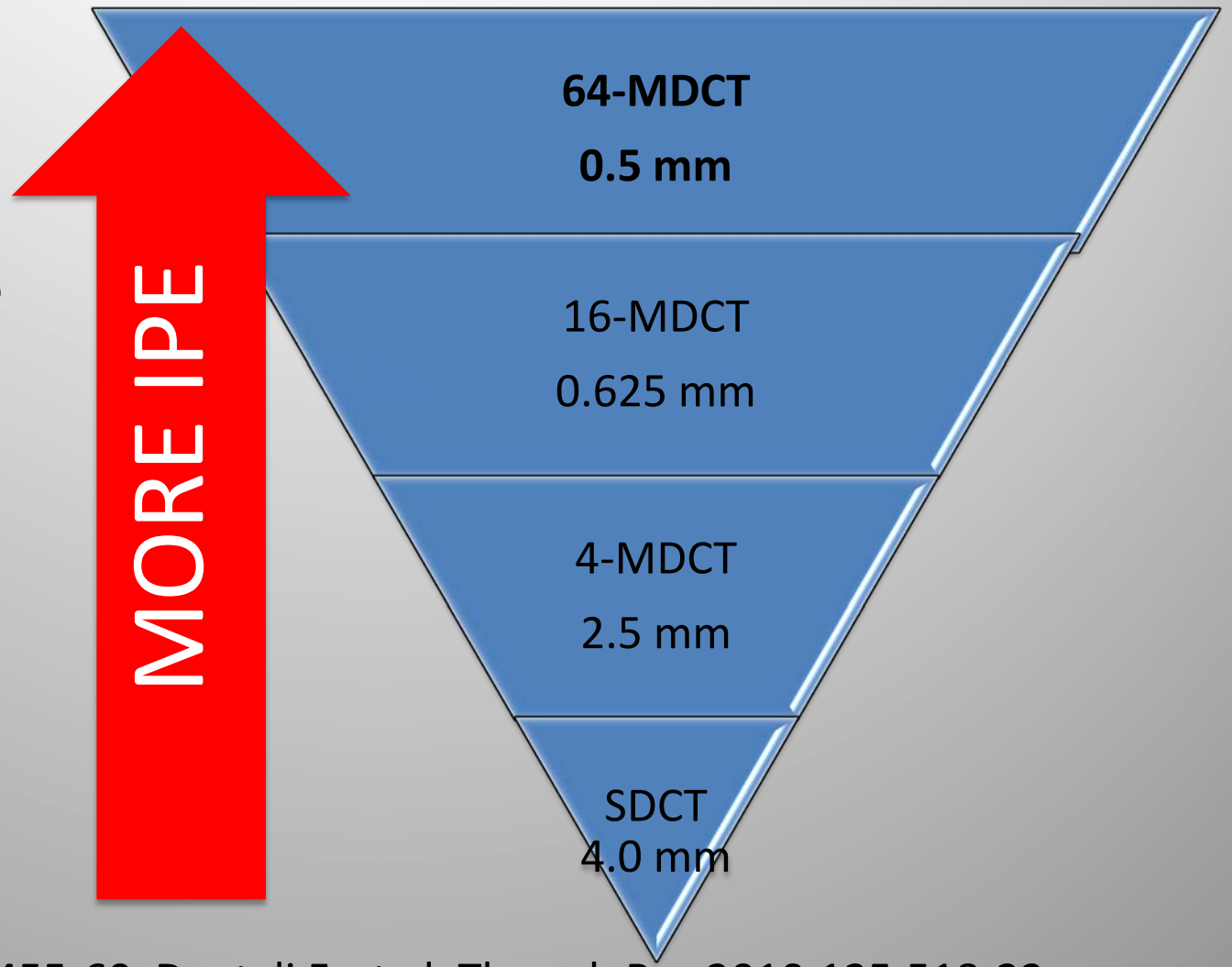
– 1 to 10% [1,2]

– 20 to 50% [2-4]

1. Sallah S, et al. Thromb Haemost 2002; 87: 575-579
2. Rickles FR, Levine MN. Acta Haemat 2001; 106: 6-12.
3. Thompson CM, Rodgers RL. Am J Med Sci 1952; 223: 469-476.
4. Sproul EE. Am J Med Sci 1938; 34: 566-85

Incidental pulmonary embolism: Radiographic Features

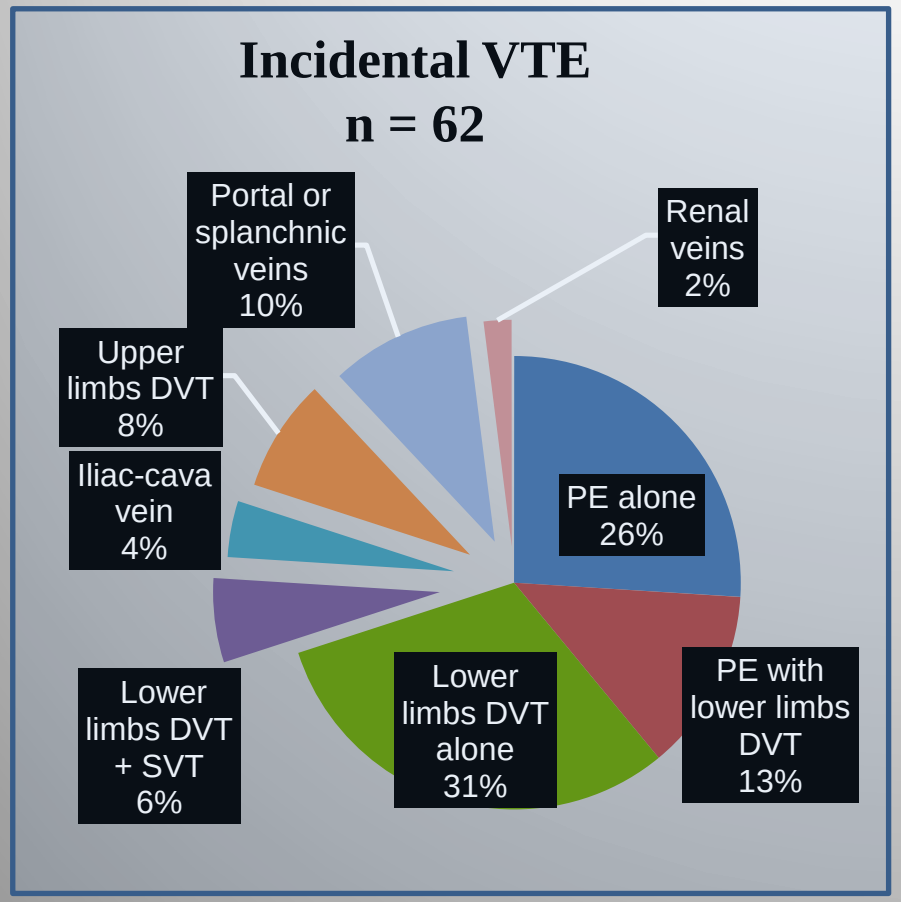
- Smaller slice thickness leads to better visualization of the pulmonary arterial tree

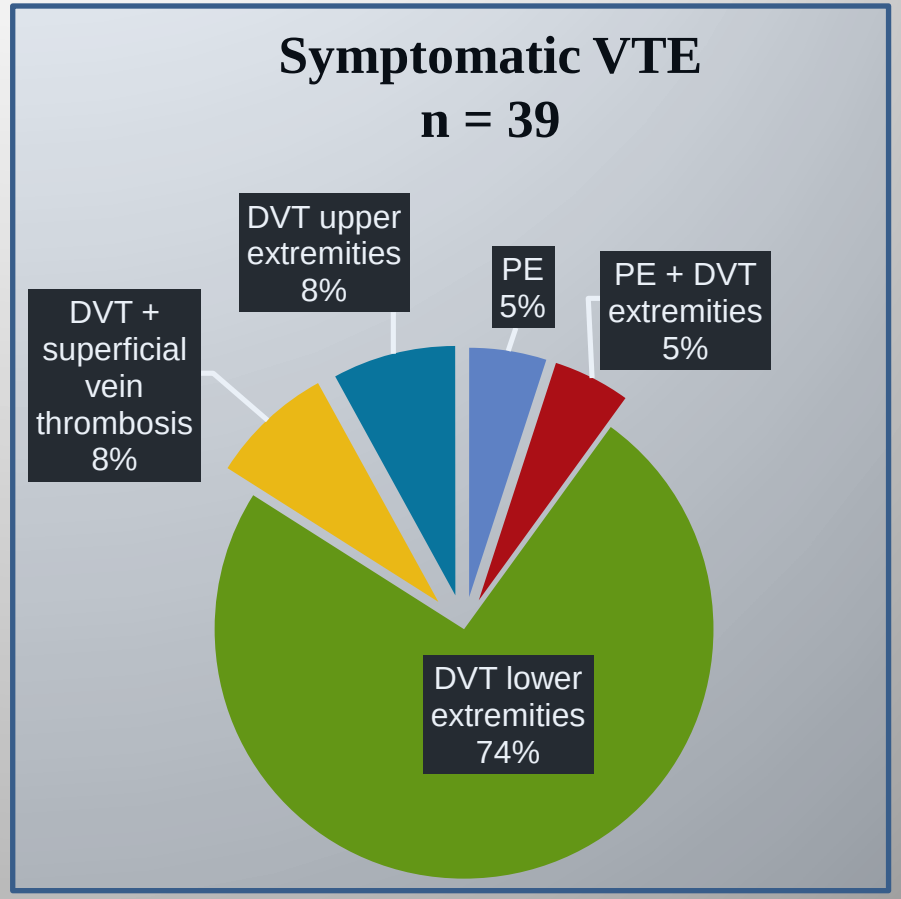


Patel S, et al. Radiology. 2003;227:455-60. Dentali F, et al. Thromb Res 2010;125:518-22

Where do incidental VTE occur in cancer patients?

Retrospective single institution cohort study: solid tumour and chemotherapy (N = 1,921)





SVT = superficial vein thrombosis.

Di Nisio M, et al. Thromb Haemost. 2010;104:1049-54.

Where do incidental PE occur in cancer patients?

Most proximal divisional location of PE per patient	
Main	4 (22)
Lobar	5 (28)
Segmental	6 (33)
Subsegmental	3 (17)

50%

Browne AM, et al. *J Thoracic Oncol* 2010;5:798-803

Main	7 (10%)
Lobar	26 (37%)
Segmental	20 (29%)
Subsegmental	17 (24%)

47%

O'Connell CL, et al. *J Thromb Haemost* 2011:9:305-311

Unsuspected pulmonary emboli: Not so silent!

Table 3. Signs and Symptoms Among Patients With and Without Unsuspected PE

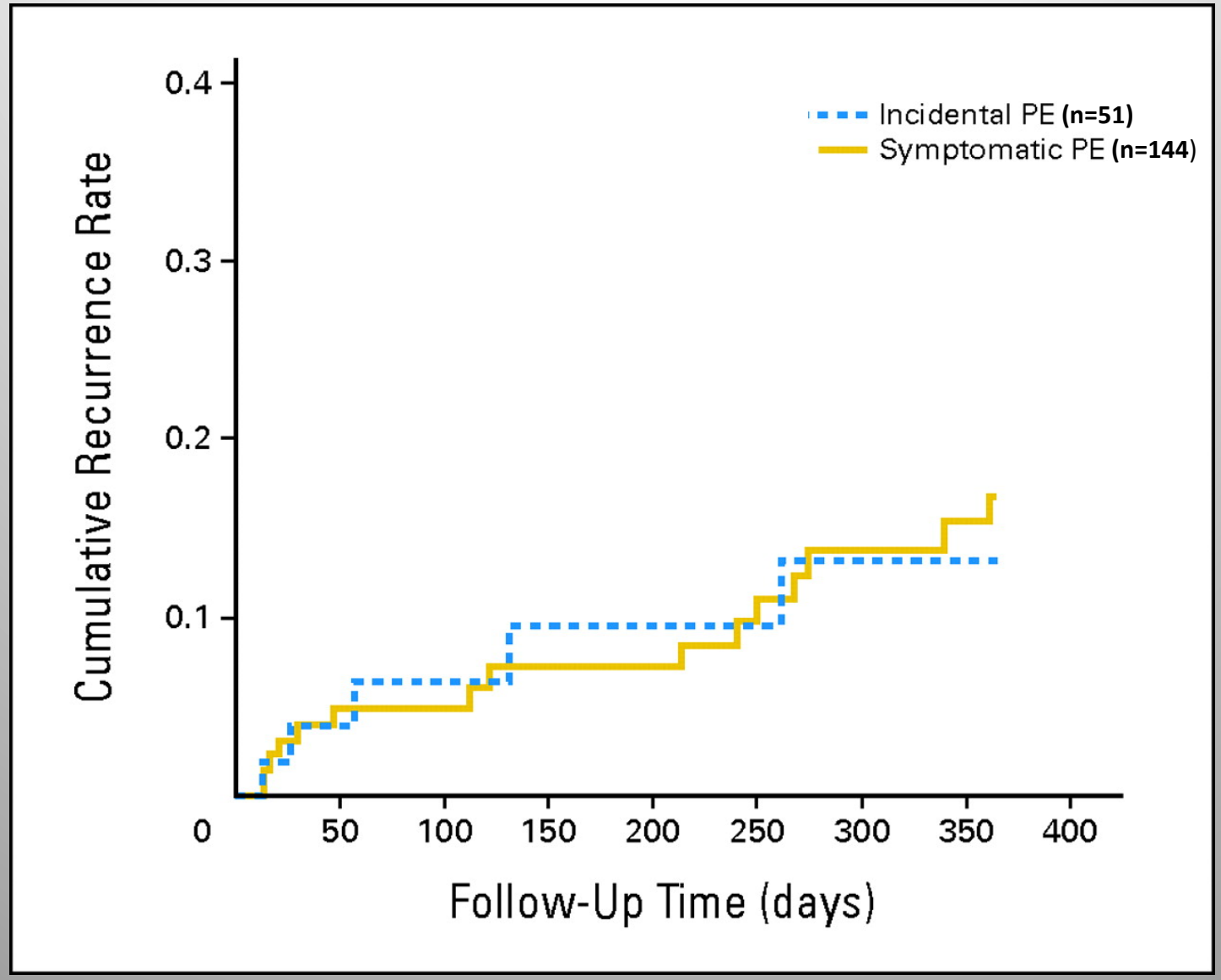
Symptom	Case Patients		Control Patients		Odds Ratio*	*P**
	No.	%	No.	%		
Chest pain	3	7	6	7	0.94	.93
Fatigue	25	54	18	20	4.88	.0002
Limb pain or swelling	7	15	14	15	1.02	.97
Shortness of breath	10	22	7	8	5.03	.02
Tachycardia or palpitations	7	15	12	13	1.21	.72

Abbreviation: PE, pulmonary emboli.

*Calculated using conditional logistic regression matching by age and stage, and using additional adjustment for age within each matched set.

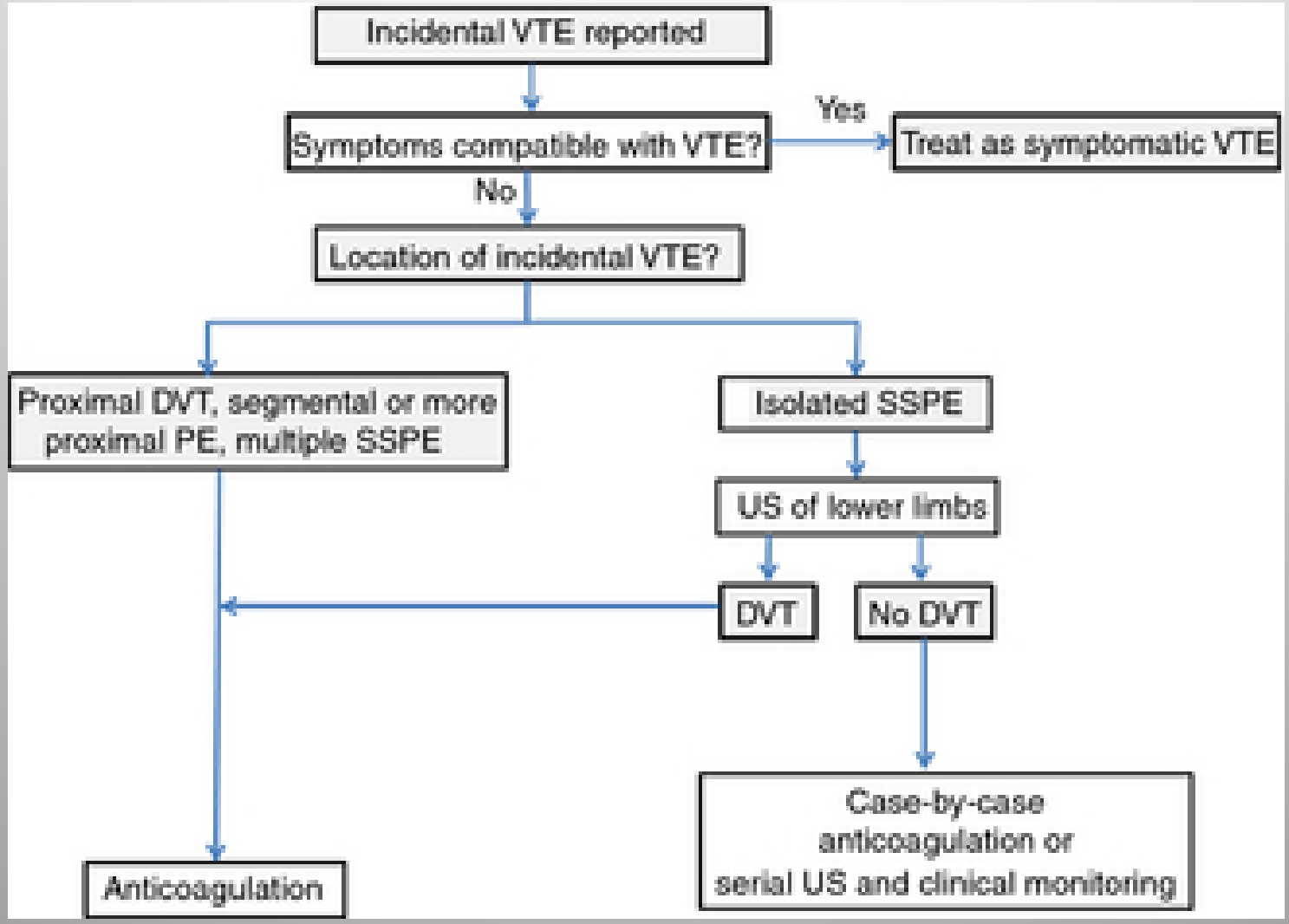
O'Connell CL, et al. J Clin Oncol 2006; 24:4928.

SYMPTOMATIC VERSUS INCIDENTAL PE: RISK OF VTE RECURRENCE



den Exter PL et al. JCO 2011;29:2405-2409

Diagnosis and treatment of incidental VTE in cancer patients: Guidance from the SSC of the ISTH



Di Nisio M; Lee AY; Carrier M; Liebman HA; Khorana AA; Subcommittee on Haemostasis and Malignancy.
J Thromb Haemost 2015; 13(5):880-3.

A pooled analysis of 926 international cancer patients with IPE: Recurrence

6-month cumulative VTE recurrence risk **LMWH**	6-month cumulative VTE recurrence risk **VKA**	6-month cumulative VTE recurrence risk **No treatment**
• 6.2% **(3.7-8.3)**	• 4.7% **(3.5-9.6)**	• 12% **(4.7-23)**

Recurrence for total cohort: 5.8%. Risk of recurrence was similar among treated cancer patients including patients with SSPE.

Van der Hull T, et al. *J Thromb Haemost* 2016; 14: 105-113

A pooled analysis of 926 international cancer patients with IPE: Major bleeding

6-month cumulative VTE recurrence risk **LMWH**	6-month cumulative major bleeding risk **VKA**	6-month cumulative major bleeding risk **No treatment**
• 3.9% **(2.3-5.9)**	• 13% **(6.4-20)**	• 6.4% **(1.3-15)**

Risk of major bleeding was similar among cancer patients with SSPE.

Van der Hull T, et al. *J Thromb Haemost* 2016; 14: 105-113

HOW LONG WOULD YOUR TREAT THIS PATIENT?

A. For 6 months and stop if no evidence of recurrent cancer.
B. For 1 year and stop if no evidence of recurrent cancer.
C. Stop LMW heparin at 6 months and start patient on 10 mg rivaroxaban long-term prophylaxis.
D. Stop LMW heparin at 6 months and start Apixiban 2.5 mg b.i.d. long-term prophylaxis.

PATIENT'S MANAGEMENT

The patient was started on dalteparin as per CLOT study protocol. A lower extremity ultrasound documented a distal clot in the left leg. She tolerated her injections without problems and the injections were stopped at 1 year when studies showed resolution of the LE clot and PE with no evidence of recurrent cancer.

The patient remains free of recurrent cancer now 8 years post completion of her chemotherapy. However, 4.5 years after stopping her anticoagulation she was admitted to an outside hospital with a symptomatic PE. Her primary care physician started her on rivaroxaban treatment, as per prescribed protocol, and she remains on 20 mg today. He performed a hypercoagulable work-up and the patient was found to be heterozygous for the Factor V Leiden mutation

SUMMARY

- Incidental VTE and PE now appear to constitute the majority of newly diagnosed thrombotic events in cancer patients.
- Incidental PE are most often associated with symptoms in cancer patients often missed by the treating oncologists.
- Incidental PE has the same risk of recurrence and similar impact on cancer prognosis as symptomatic PE. They should be treated in a similar way to symptomatic events.
- In clinical trials on the use of the new anticoagulants for VTE treatment or prophylaxis, incidental VTE is now considered a primary outcome event.

Case:
Upper Extremity DVT

Jeffrey I. Weitz

Case

An 86-year-old woman is diagnosed with PICC-associated axillary and subclavian DVT. The PICC was inserted for delivery of parenteral vancomycin for treatment of MSRA osteomyelitis. Other medications include dilantin and carbamazepine for seizures.

How would you treat the PICC-associated DVT?

1. LMWH with transition to warfarin
2. Extended LMWH
3. Rivaroxaban
4. LMWH with transition to edoxaban

Would you remove the PICC?

1. Yes
2. No

How long would you treat for?

1. 3 months
2. 6 months
3. Until the PICC is removed
4. Until the ultrasound normalises

Closing Remarks

Rt Hon Professor the Lord Kakkar
Thrombosis Research Institute and
University College London, UK

TRI Thrombosis Research Institute