Debate: Viable Role in ACS or PCI Patients Yes, Combination of Anticoagulant & Antiplatelet is Still Attractive Approach

Angioplasty Summit – TCTAP 2012

Seoul, Korea

April 2012

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Mayo Clinic
Rochester, MN

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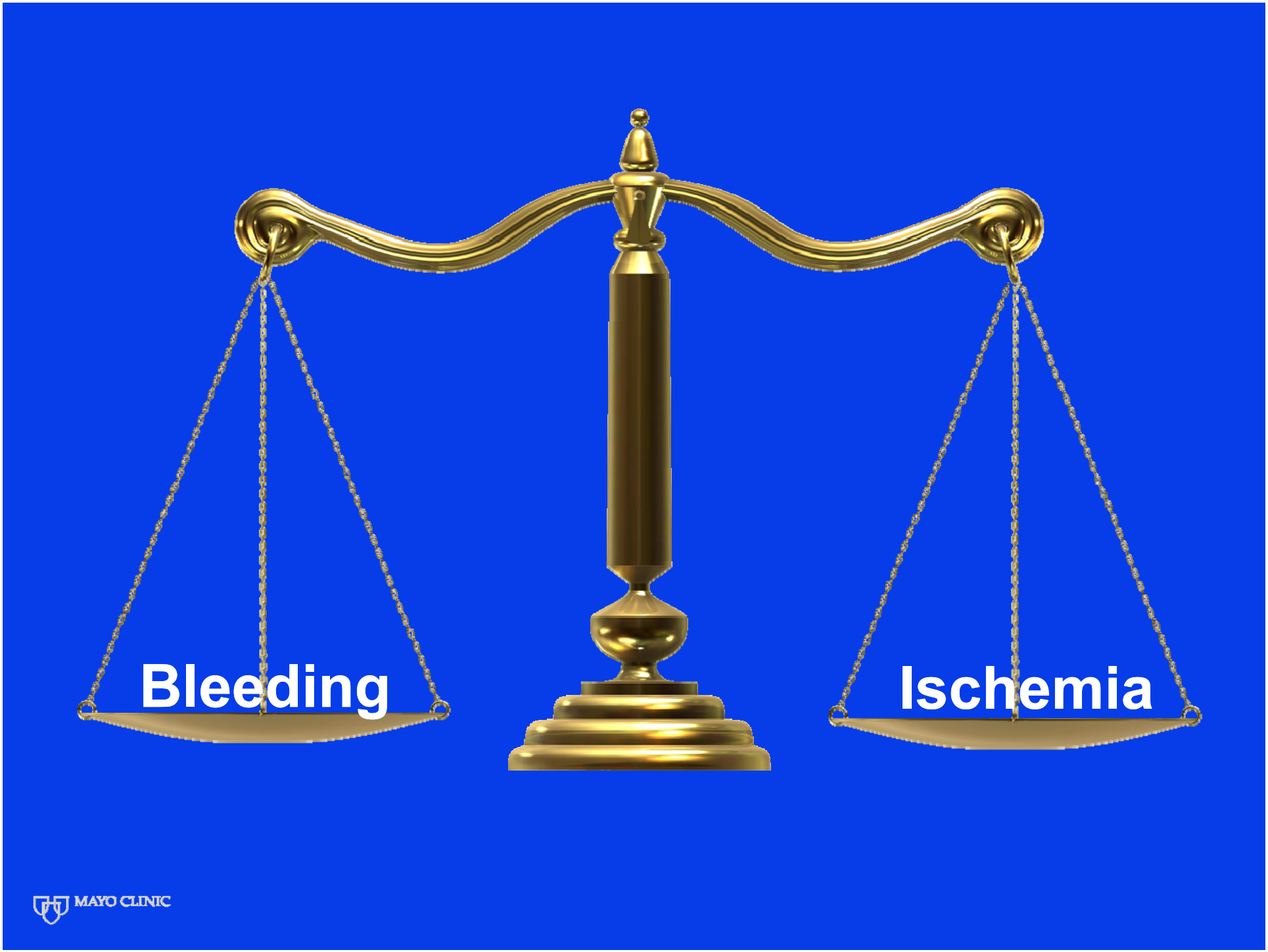
Presenter Disclosure Information

David R. Holmes, Jr., M.D.

"Debate: Viable Role in ACS or PCI Patients Yes, Combination of Anticoagulant & Antiplatelet is Still Attractive Approach"

The following relationships exist related to this presentation:

Immediate Past President ACC


Bleeding
Ischemia

NCDR Action Registry
Anticoagulants and Bleeding

- Analysis of
  - 72,699 patients with NSTEMI
  - 48,943 patients with STEMI
- Patients categorized in anticoagulant strategy selected and CRUSADE bleeding risk category

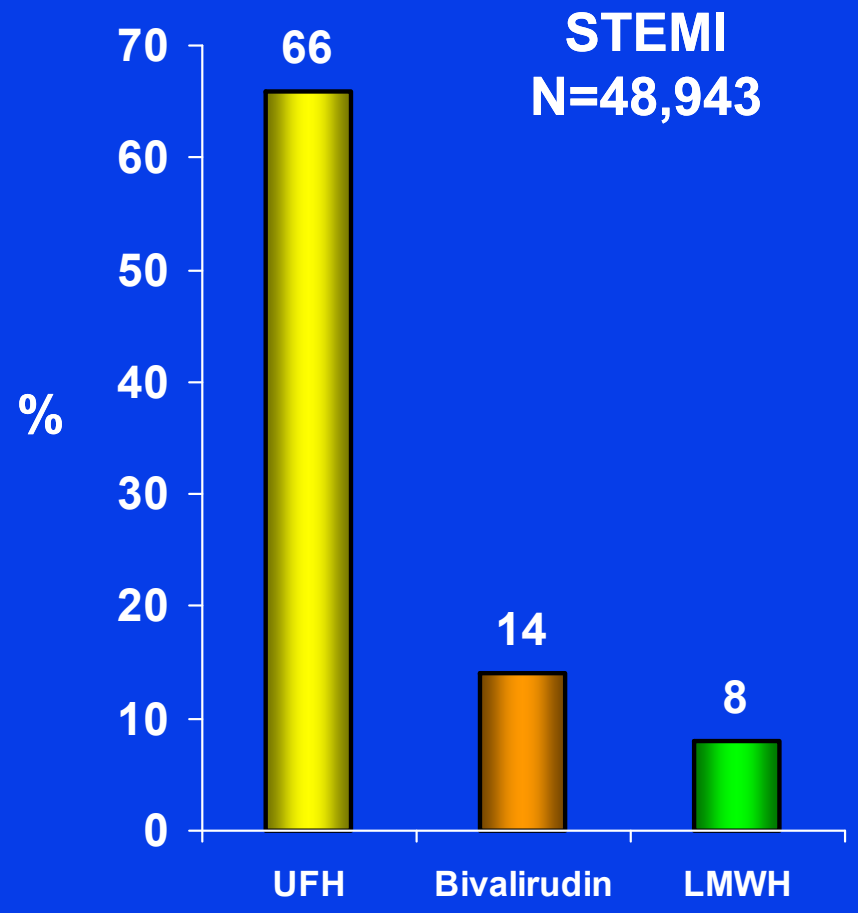
Kadakia MB et al: J Am Coll Cardiol Intv 3:1166-77, 2010

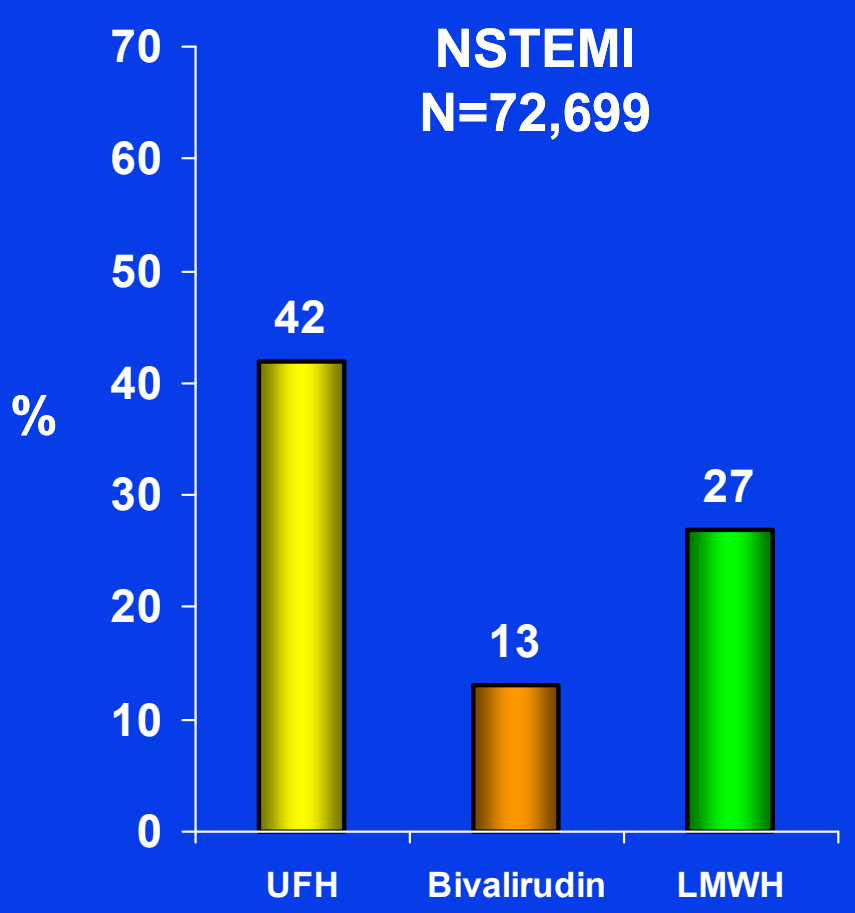
CRUSADE Bleeding Score

- Baseline HCT
- CR clearance
- Heart rate
- Sex
- CHF
- Systemic BP
- Prior vascular disease
- Diabetes

NCDR Bleeding
NSTEMI and STEMI

Jan. 2007 – June 2009





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Kadakia MB et al: J AM Coll Cardiol Intv 3:1166-77, 2010

Bleeding Risk Scores

STEMI n=42,918	CRUSADE Bleeding Score	N (%)	Major Bleeding Events (%)
	≤20	19,050 (44.4)	1,036 (5.4)
	21-30	9,864 (23.0)	1,002 (10.2)
	31-40	6,565 (15.3)	956 (14.6)
	41-50	4,250 (9.9)	857 (20.2)
	>50	3,189 (7.4)	928 (29.1)

Kadakia MB et al: J AM Coll Cardiol Intv 3:1166-77, 2010

Bleeding Risk Scores

NSTEMI n=61,540	CRUSADE Bleeding Score	N (%)	Major Bleeding Events (%)
	≤20	19,803 (32.2)	605 (3.1)
	21-30	11,134 (18.1)	670 (6.0)
	31-40	9,831 (16.0)	822 (8.4)
	41-50	8,944 (14.5)	1,099 (12.3)
	>50	11,828 (19.2)	2,314 (19.6)

Kadakia MB et al: J AM Coll Cardiol Intv 3:1166-77, 2010

CLINICAL RESEARCH

Use of Anticoagulant Agents and Risk of Bleeding Among Patients Admitted With Myocardial Infarction

A Report From the NCDR ACTION Registry–GWTG (National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines)

Mitul B. Kadakia, MD,*† Nihar R. Desai, MD, MPH,*† Karen P. Alexander, MD,‡ Anita Y. Chen, MS,‡ JoAnne M. Foody, MD,† Christopher P. Cannon, MD,*† Stephen D. Wiviott, MD,*† Benjamin M. Scirica, MD, MPH,*† on behalf of the National Cardiovascular Data Registry

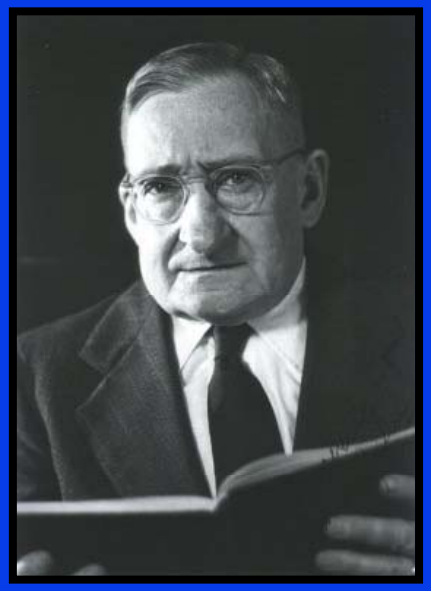
Boston, Massachusetts; and Durham, North Carolina

Conclusions: There is a wide variability in the use of anticoagulant regimens with significant differences according to baseline characteristics and concomitant therapies. Major bleeding is common, though a great degree of the variability in the rate of bleeding is largely based on differences in baseline characteristics, comorbidities, and invasive treatment strategies, rather than specific anticoagulant regimens.

Conclusions There is a wide variability in the use of anticoagulant regimens with significant differences according to baseline characteristics and concomitant therapies. Major bleeding is common, though a great degree of the variability in the rate of bleeding is largely based on differences in baseline characteristics, comorbidities, and invasive treatment strategies, rather than specific anticoagulant regimens. (J Am Coll Cardiol Intv 2010;3:1166–77)

BACKGROUND: Thrombin In ACS

- There is excess thrombin generation that persists for 6 months following an index ACS event.
- Thrombin is the most potent stimulant of platelet aggregation.
- Reduction of thrombin generation by warfarin reduces recurrent MI by 44% in a meta-analysis of 10 ACS trials.

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Marquette
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Ashland
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Antithrombotic Therapy
Treatment of ACS

- 1950 – VKA
  - 1970 – Heparin + VKA
    - 1980 – lytic + ASA + Hep + VKA
      - 1990 – PTCA + ASA + Hep + VKA
        - 2000 – Stenting + DAPT
          - 2005 – DAPT + VKA → Bleeding
            - 2011 – DAPT + Apixaban
              - APPRAISE Trial – bleeding
                - 2012 – DAPT → Rivaroxaban

Adapted from Braunwald

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APPRAISE 2

- Randomized double-blind placebo controlled trial
- Patients with ACS within 7 days who had ≥2 additional high risk factors (e.g. age >65, EF <40%)
- Randomization
  - Apixaban 5 bid or placebo + standard antiplatelet Rx
- Primary efficacy outcome:
  - CV death, MI or ischemic stroke
- Primary safety outcome:
  - Major bleeding

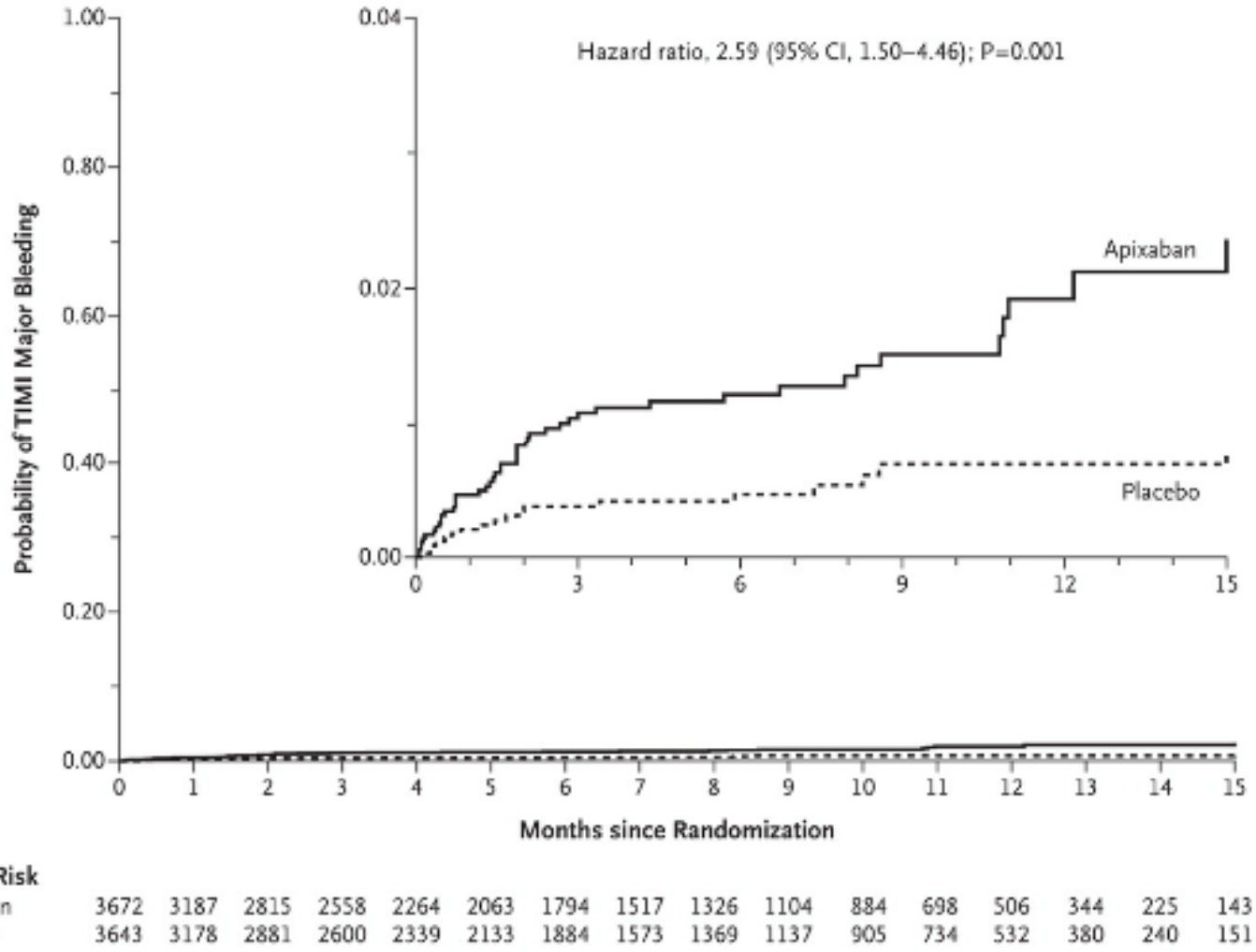
Alexander, N Engl J Med, 365:699-708, 2011

APPRAISE 2

- 7,392 patients enrolled
- Stopped prematurely
- Primary efficacy composite
  - 7.5% Apixaban
  - 7.9% control
- Primary safety endpoint – major bleeding
  - 1.3% Apixaban
  - 0.5% control p=0.001

Alexander, N Engl J Med, 365:699-708, 2011

Primary Safety Outcome



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Alexander, N Engl J Med, 365:699-708, 2011

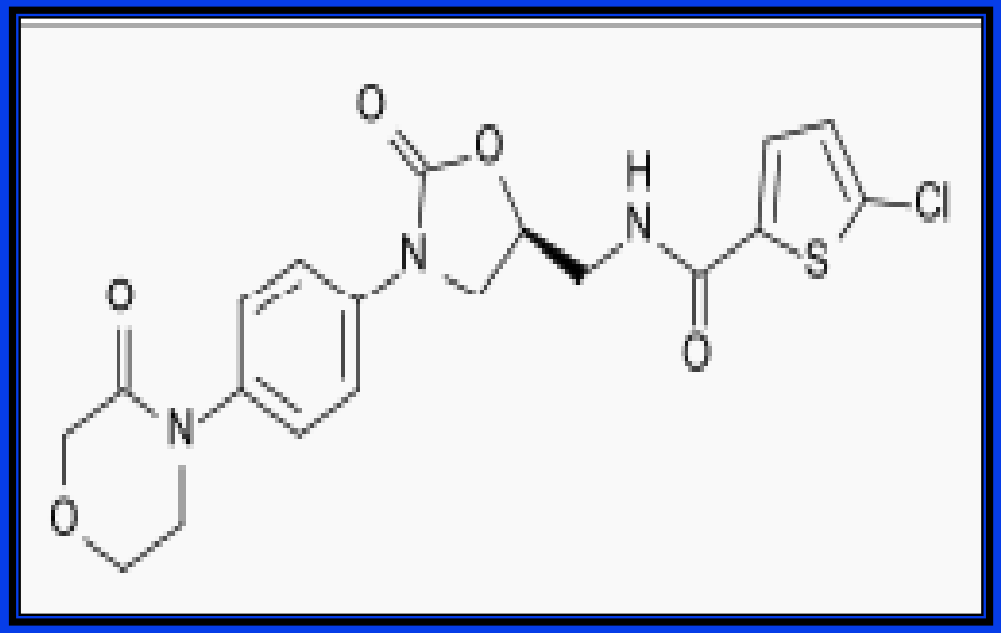
Conclusions

The addition of Apixaban, at a dose of 5 mg twice daily, to antiplatelet therapy in high-risk patients after an acute coronary syndrome increased the number of major bleeding events without a significant reduction in recurrent ischemic events.

Alexander, N Engl J Med, 365:699-708, 2011

ATLAS ACS-2 – TIMI 51

- Double-blind placebo controlled trial of 15,526 patients with recent ACS within 7 days after admission



Gibson, N Engl J Med, 366:9-19, 2012

Recent ACS: STEMI, NSTEMI, UA

No increased bleeding risk, No warfarin, No ICH, No prior stroke if on ASA + Thienopyridine

Stabilized 1-7 Days Post-Index Event

Stratified by Thienopyridine use at MD Discretion

+ ASA 75 to 100 mg/day

Placebo
N=5,176
ASA + Thieno, n=4,821
ASA, n=355

RIVAROXABAN
2.5 mg BID
n=5,174
ASA + Thieno, n=4,825
ASA, n=349

RIVAROXABAN
5.0 mg BID
N=5,176
ASA + Thieno, n=4,827
ASA, n=349

PRIMARY ENDPOINT:

EFFICACY: CV Death, MI, Stroke* (Ischemic + Hemg.)

SAFETY: TIMI major bleeding not associated with CABG

Event driven trial of 1,002 events in 15,342 patients**

* Stroke includes ischemic stroke, hemorrhagic stroke, and uncertain stroke

** 184 subjects were excluded from the efficacy analyses prior to unblinding

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ATLAS ACS-2 – TIMI 51

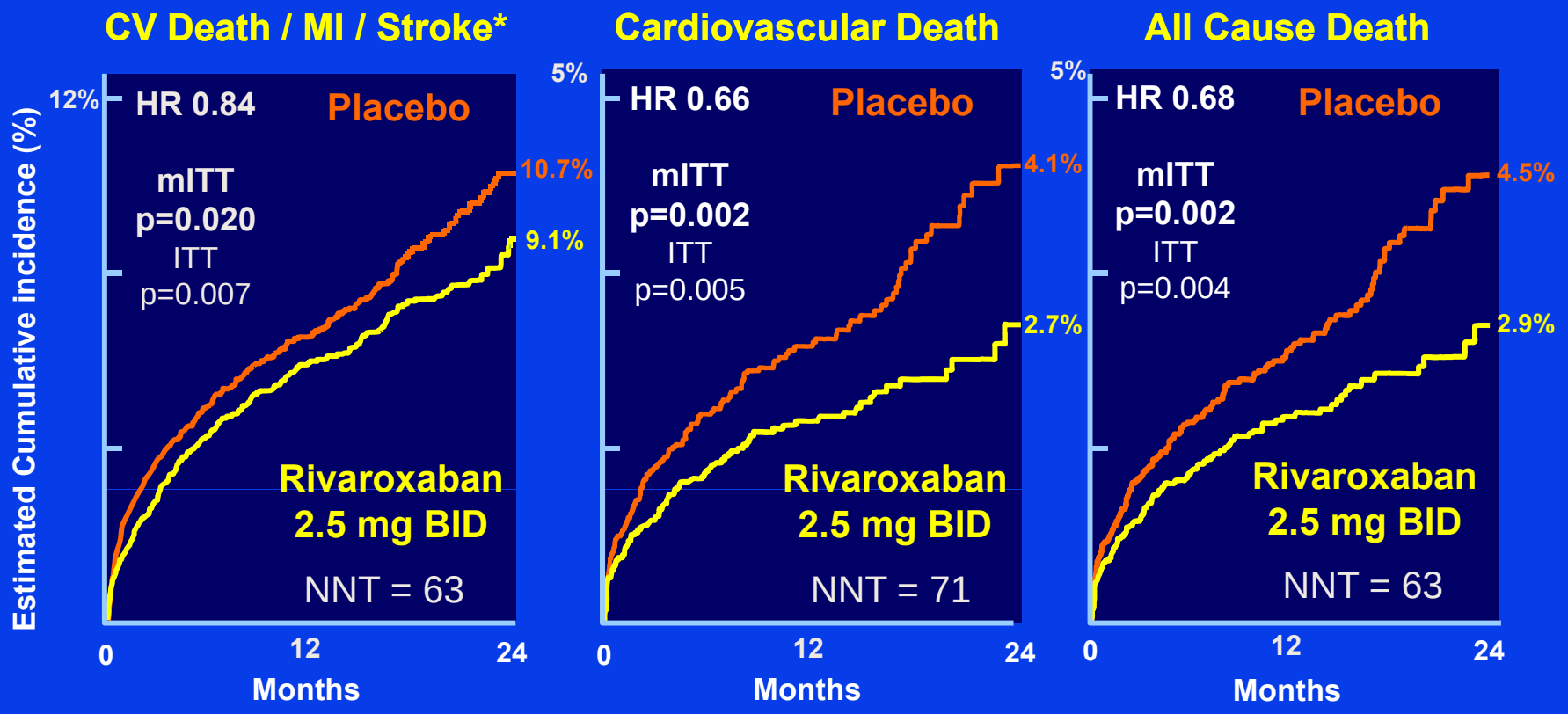
- Background therapy
  - Thienopyridine 93%
  - Mean duration 13.3 months
- Discontinuation of drug
  - Placebo – 26.4%
  - Rivaroxaban – 26.9%, 29.4%

Gibson, N Engl J Med, 366:9-19, 2012

Baseline Characteristics

	Placebo	Rivaroxaban 2.5 mg BID	Rivaroxaban 5.0 mg BID
Age, mean (SD)	61.5 (± 9.4)	61.8 (± 9.2)	61.9 (± 9.0)
Sex, male n (%)	75.0%	74.9%	74.2%
Prior MI, n (%)	27.3%	26.3%	27.1%
Diabetes, n (%)	31.8%	32.3%	31.8%
STEMI, n (%)	50.9%	50.3%	49.9%
NSTEMI, n (%)	25.6%	25.5%	25.8%
UA, n (%)	23.6%	24.2%	24.3%
PCI at Index Hosp, n (%)	59.9%	60.2%	60.0%

Primary Efficacy Endpoint*: 2.5 mg PO BID



* First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC across thienopyridine use strata
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach;
Stratified log-rank p-values are provided for both mITT and ITT approaches; NNT=Number needed to treat.

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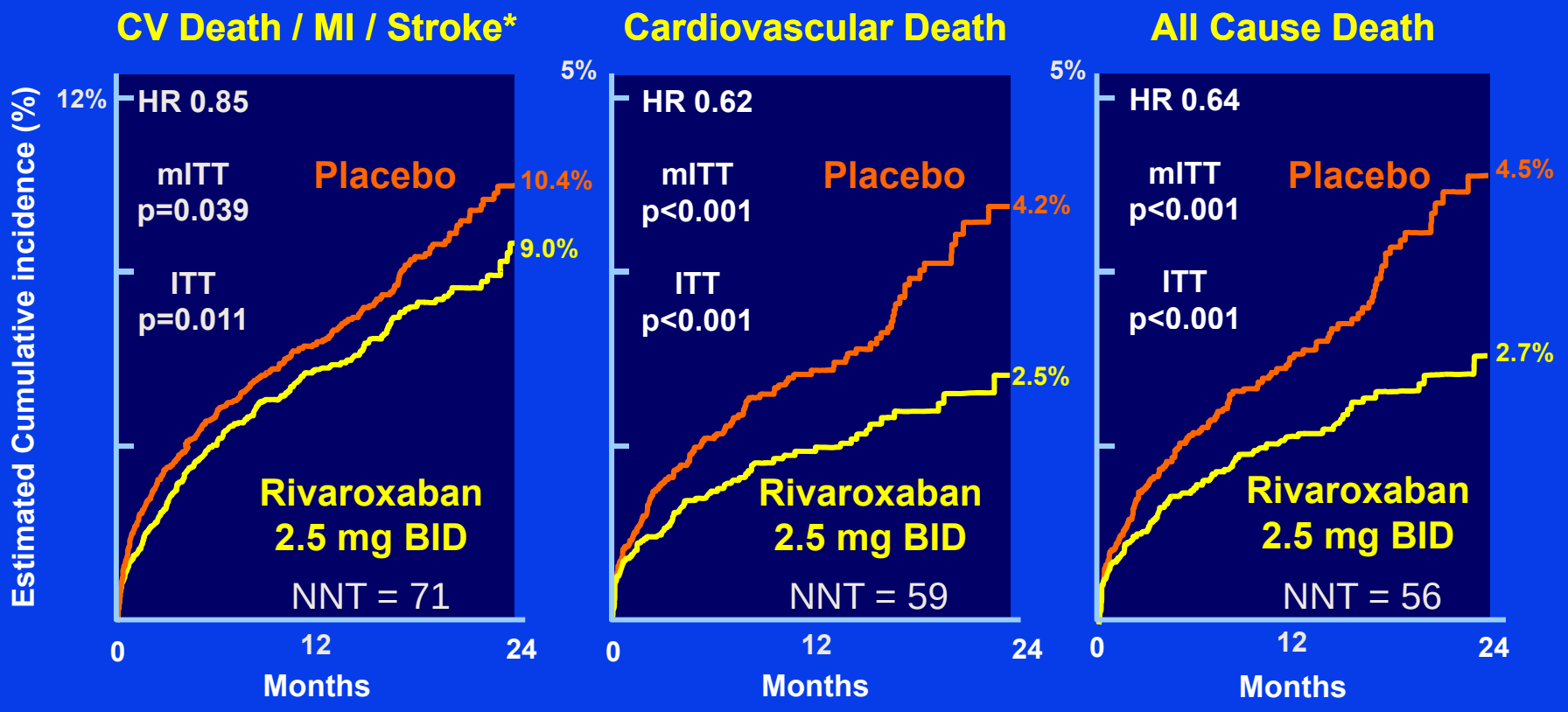
Primary Efficacy Endpoint*: 2.5 mg PO BID
In Patients Treated with ASA + Thienopyridine



* First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; NNT=Number needed to treat.

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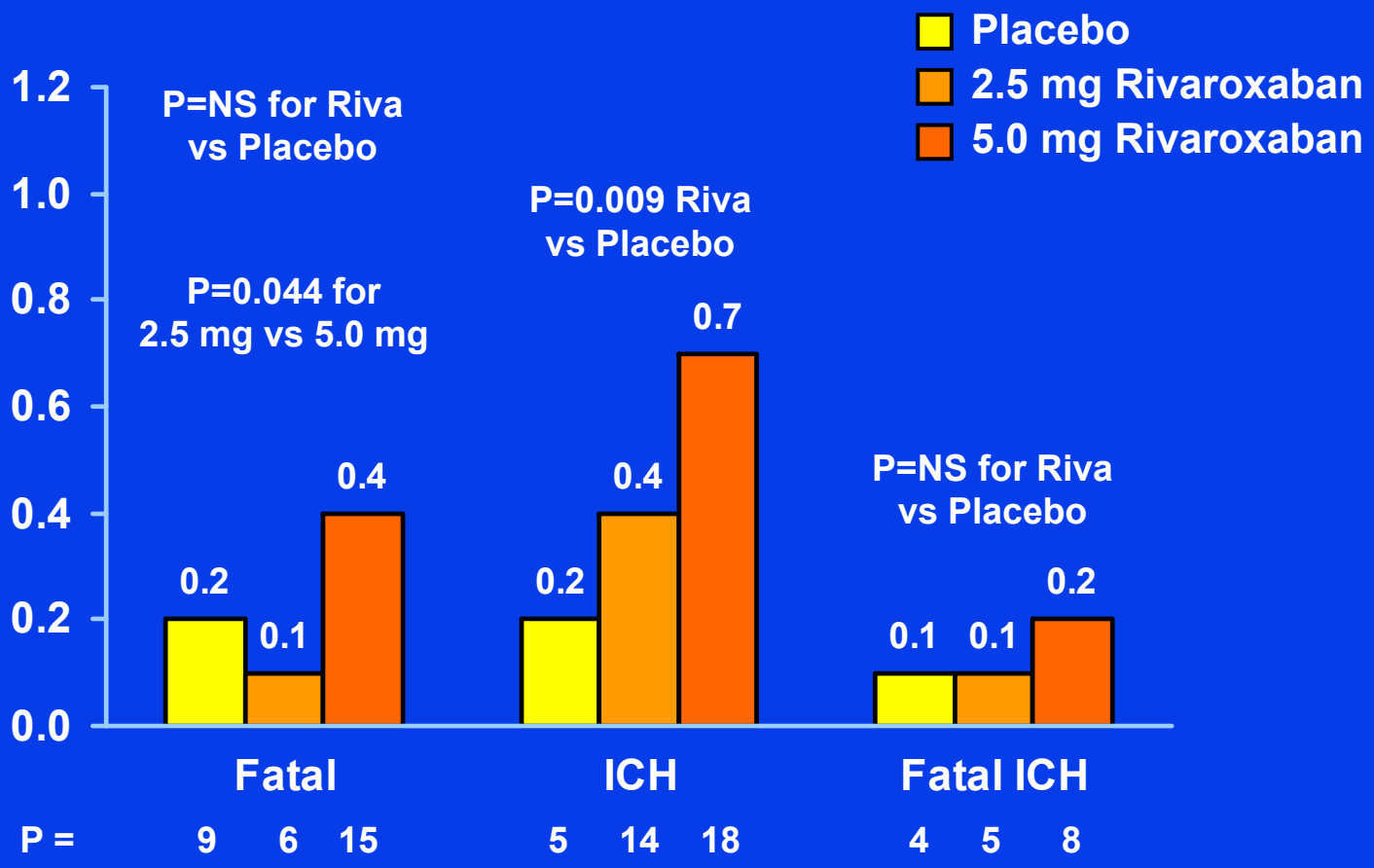
Treatment-Emergent Fatal Bleeds and ICH



* Among patients treated with aspirin + thienopyridine, there was an increase in fatal bleeding among patients treated with 5.0 mg of Rivaroxaban (15/5110) vs 2.5 mg of Rivaroxaban (5/5115) (p=0.02)

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ATLAS ACS-2 – TIMI 51

	Rivaroxaban	Placebo	P
Primary efficacy			
Endpoint	8.9	10.7	0.008
2.5 mgm R, bid	9.1	10.7	0.02
5 mgm R, bid	8.8	10.7	0.03
Mortality	2.5		
CV	2.7	4.1	0.002
All	2.9	4.5	0.002

Gibson, N Engl J Med, 366:9-19, 2012

ATLAS ACS-2 – TIMI 51

	Rivaroxaban	Placebo	P
Major bleeding			
Not from CABG	2.1	0.6	<0.001
ICH	0.6	0.2	0.009
Fatal	0.3	0.2	0.66

Gibson, N Engl J Med, 366:9-19, 2012

Rates of Ischemic Bleeding Events in Drug Trials for ACS

Event	TRITON-TIMI 38		PLATO		APPRAISE-2*		ATLAS ACS 2-TIMI 51†	
	Pras-ugrel	Clopid-ogrel	Tica-grelor	Clopid-ogrel	Apix-aban	Pla-cebo	Rivaroxban (2.5 mg)	Pla-cebo
Death, MI, or stroke	10.7	12.7	10.2	12.3	8.8	8.9	9.1	10.7
Death from CV causes	2.1	2.4	4.0	5.1	2.8	3.0	2.7	4.1
Bleeding								
Major TIMI (non-CABG)	2.4	1.8	2.8	2.2	1.3	0.5	1.8	0.6
Fatal	0.4	0.1	0.3	0.3	0.1	0.0	0.1	0.2
Intracranial	0.3	0.3	0.3	0.2	0.3	0.1	0.4	0.2

*Approximately 81% of pt were Rx with a thienopyridine at time of randomization

†Approximately 93% of pt were Rx with a thienopyridine at time of randomization

Ohman et al: NEJM, 2012

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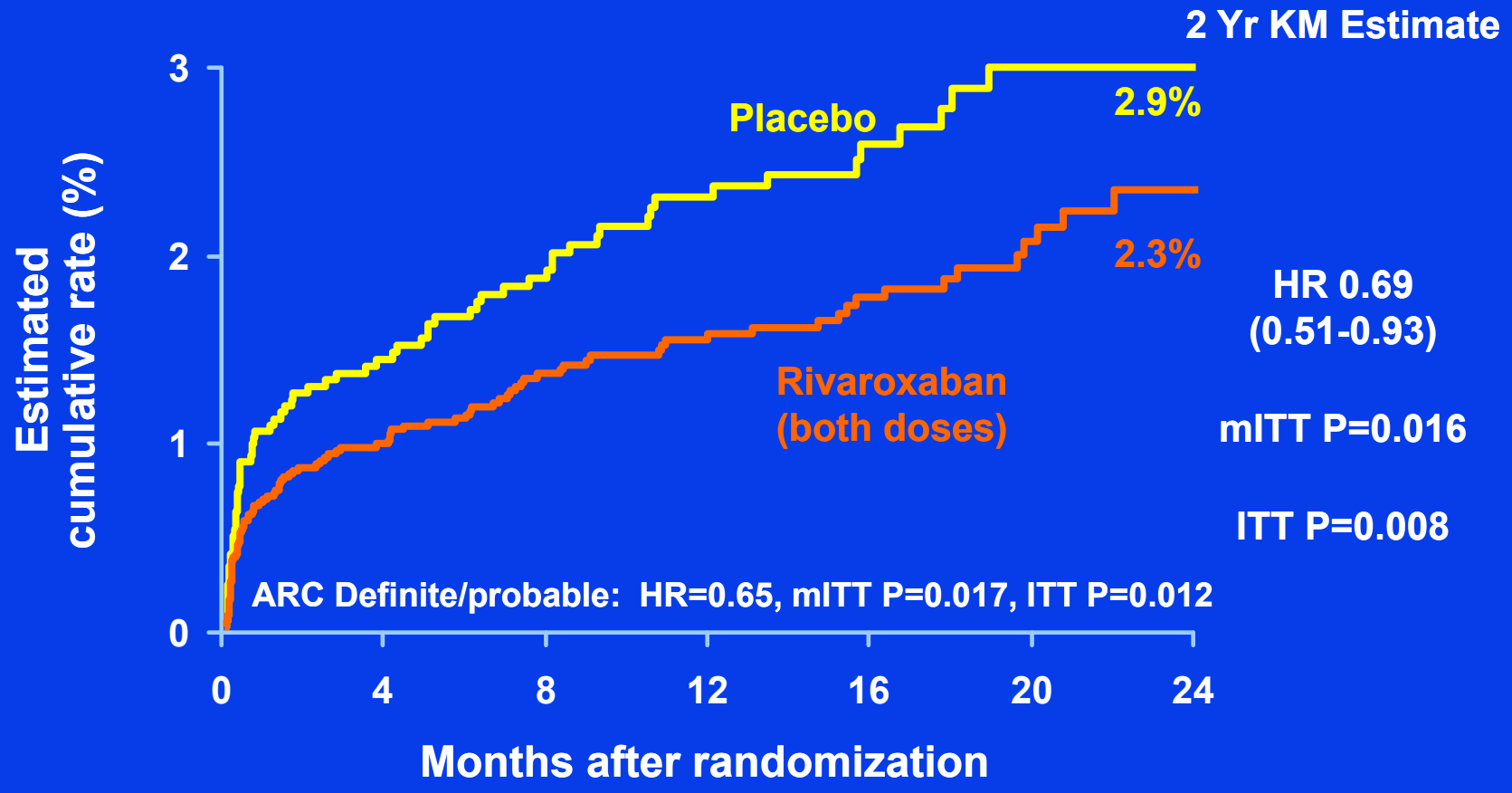
Stent Thrombosis*
ARC Definite, Probable, Possible



* **End point events are as adjudicated by the CEC across thienopyridine use strata Two year Kaplan-Meier estimates,** HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; Rivaroxaban=Pooled Rivaroxaban 2.5 mg BID and 5 mg BID.

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Summary-Efficacy

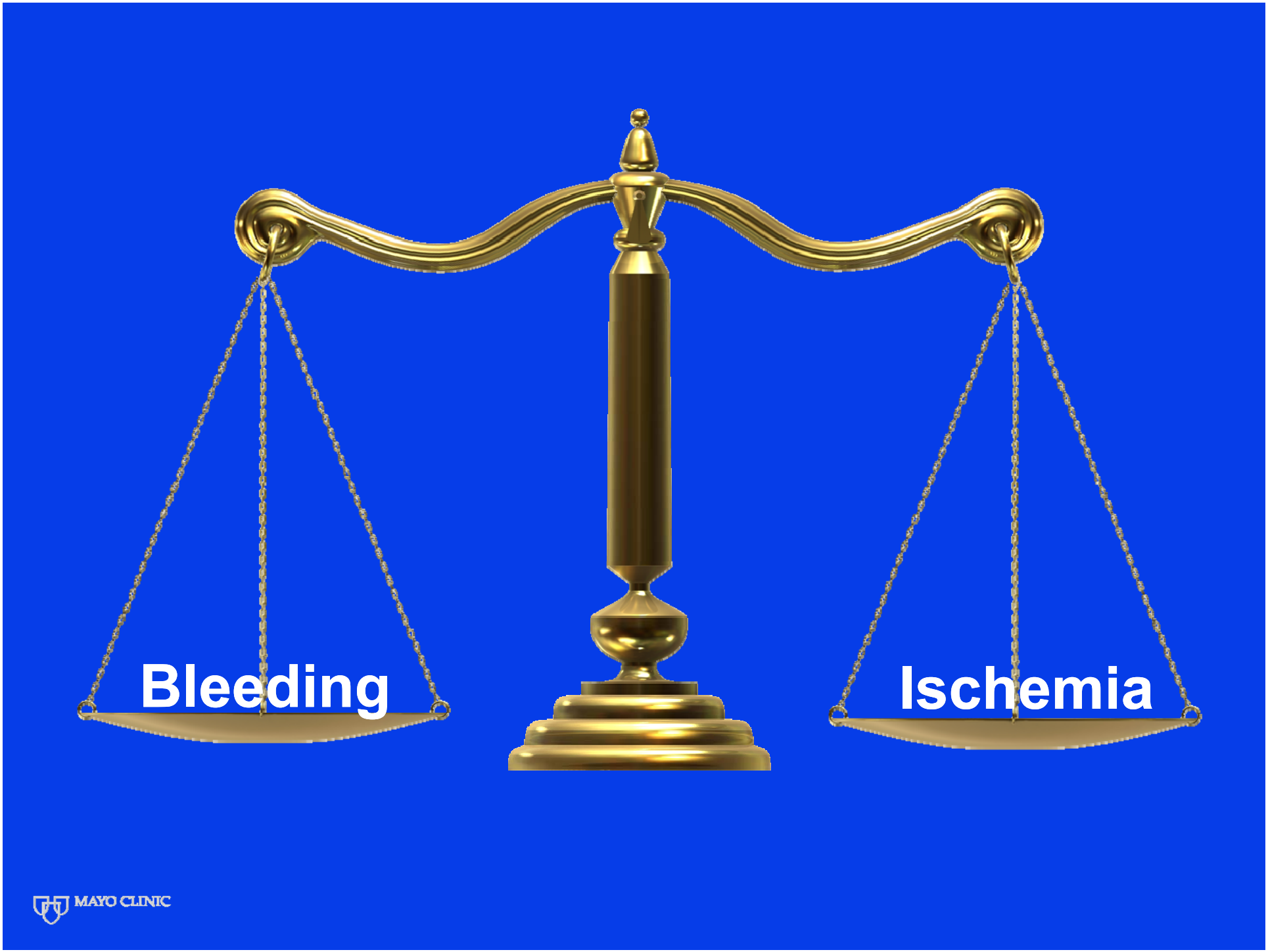
- The primary efficacy endpoint of CV death, MI and stroke was reduced when added to standard therapy for both Rivaroxaban doses combined, and for the 2.5 and 5.0 mg BID doses separately
- CV and all cause death were reduced for both Rivaroxaban doses combined, and for the 2.5 mg BID dose in both mITT and ITT analyses

Summary-Efficacy (cont.)

- When 2.5 mg PO BID of Rivaroxaban was added to ASA + thienopyridine, cardiovascular death was reduced by 38% and all cause death by 36%
- One death prevented if 56 patients treated for two years with 2.5 mg BID of Rivaroxaban

Summary-Safety

- There was a dose dependent increase in bleeding associated with Rivaroxaban (2.5 mg ↓ 5.0 mg)
- Although ICH was increased with Rivaroxaban, there was no excess risk of fatal ICH or fatal bleeding associated with Rivaroxaban compared to placebo
- No evidence of drug induced liver injury or rebound (post-treatment) ischemic events


Bleeding
Ischemia

Neither my friend nor I are perfect;

We suit each other admirably

Alexander Pope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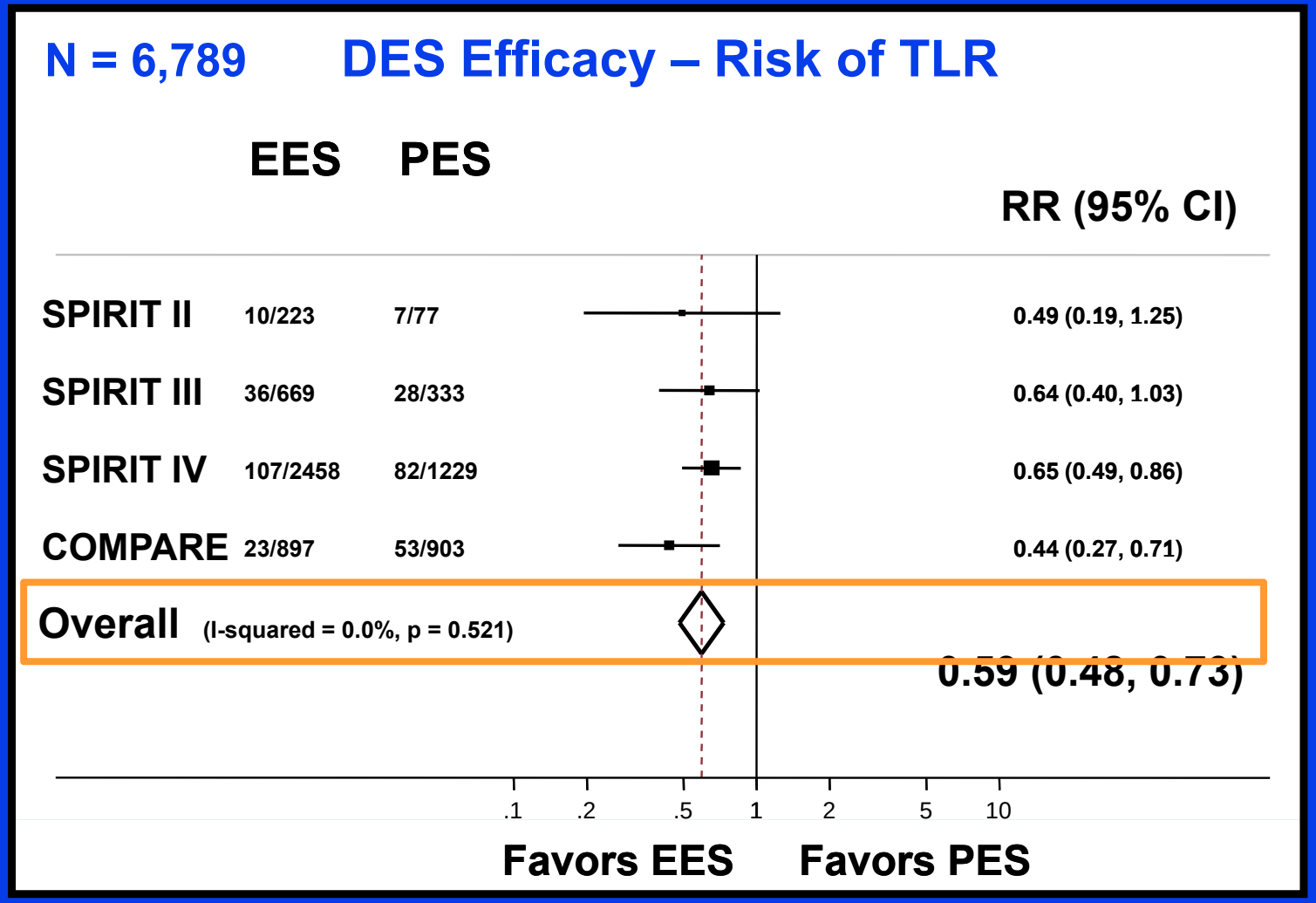
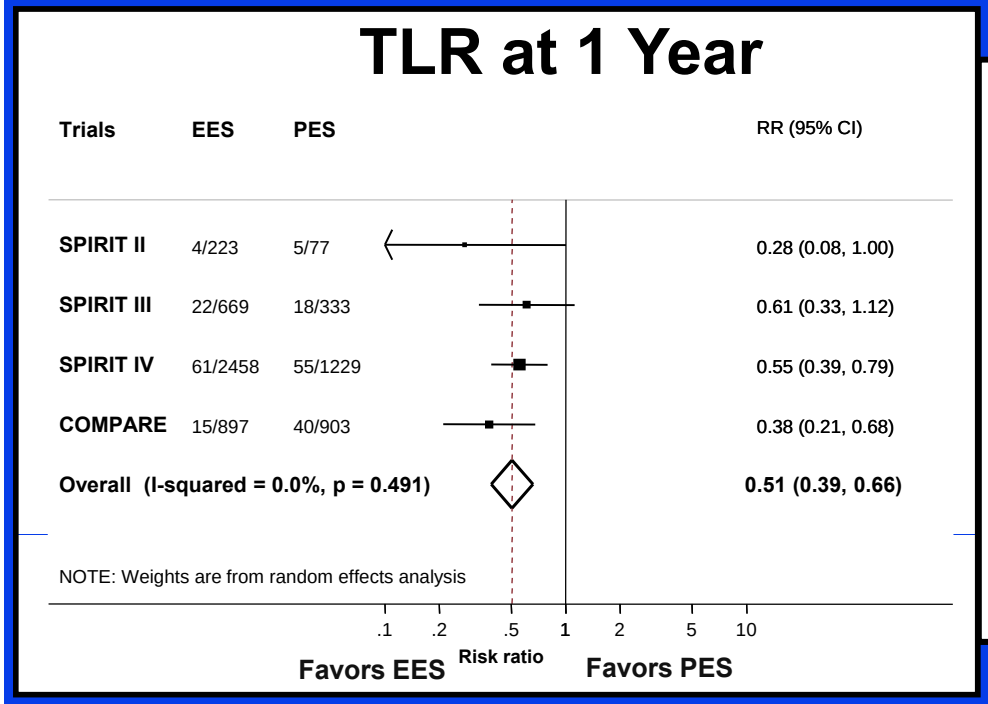
Everolimus-Eluting vs Paclitaxel-Eluting Stents



Drug-Eluting Stents vs CABG
Repeat Revascularization

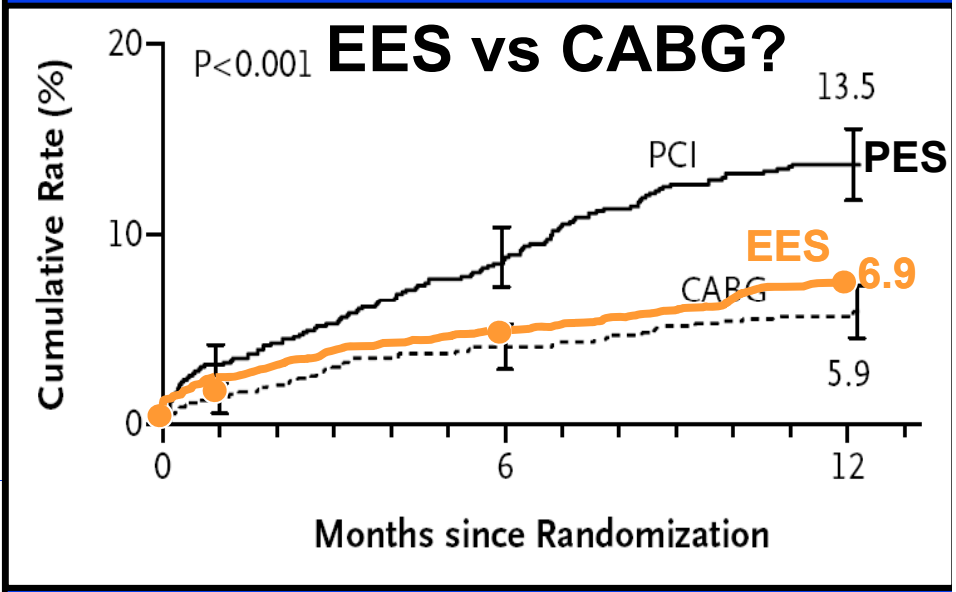
Meta-Analysis EES vs PES

HR=0.51, 95% CI 0.39-0.66



SYNTAX

HR=2.3, 95% CI 1.7-3.1



Kalesan, Juni – Updated 8/2011

Serruys PW et al: NEJM 2009

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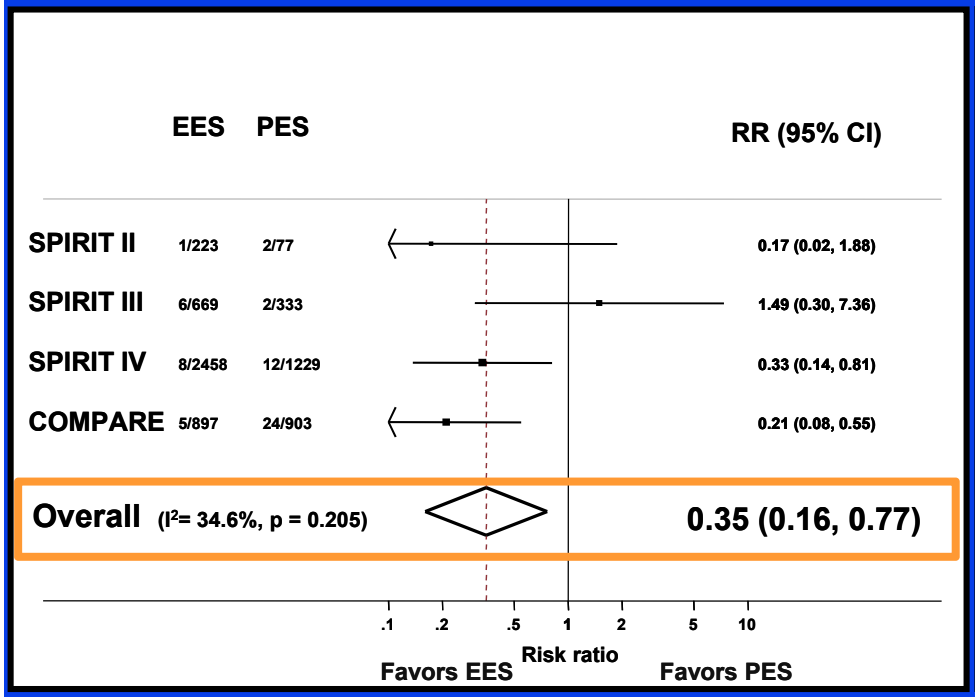
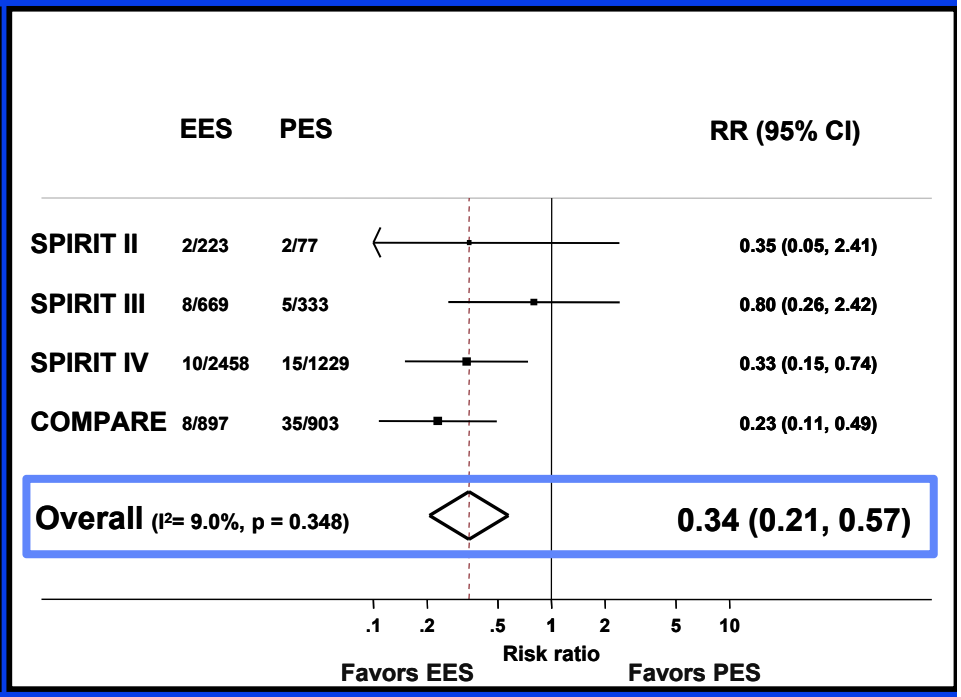
Everolimus-Eluting vs Paclitaxel-Eluting StentsDES Safety - Risk of Stent Thrombosis

Definite ST

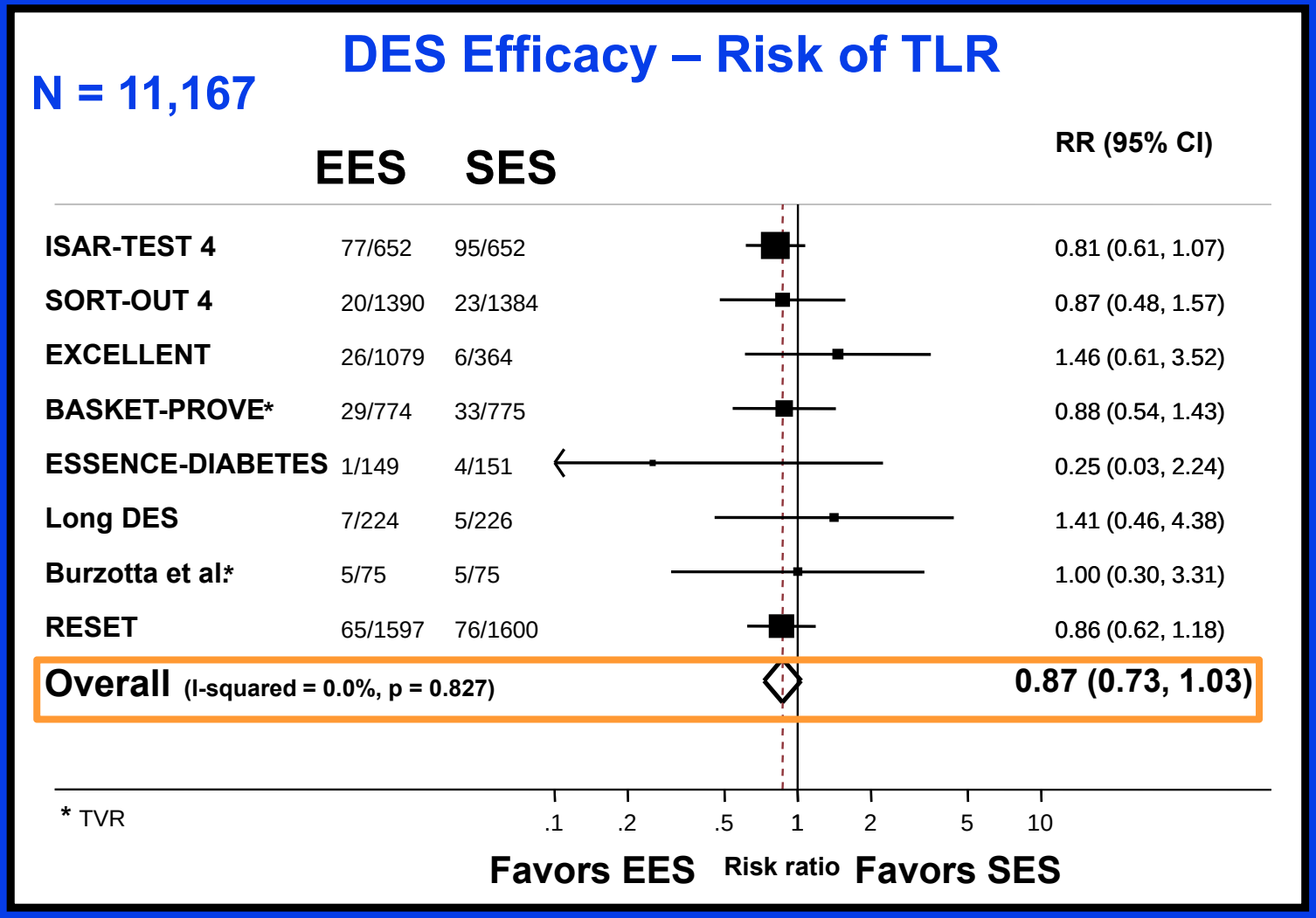


Definite or Probable ST

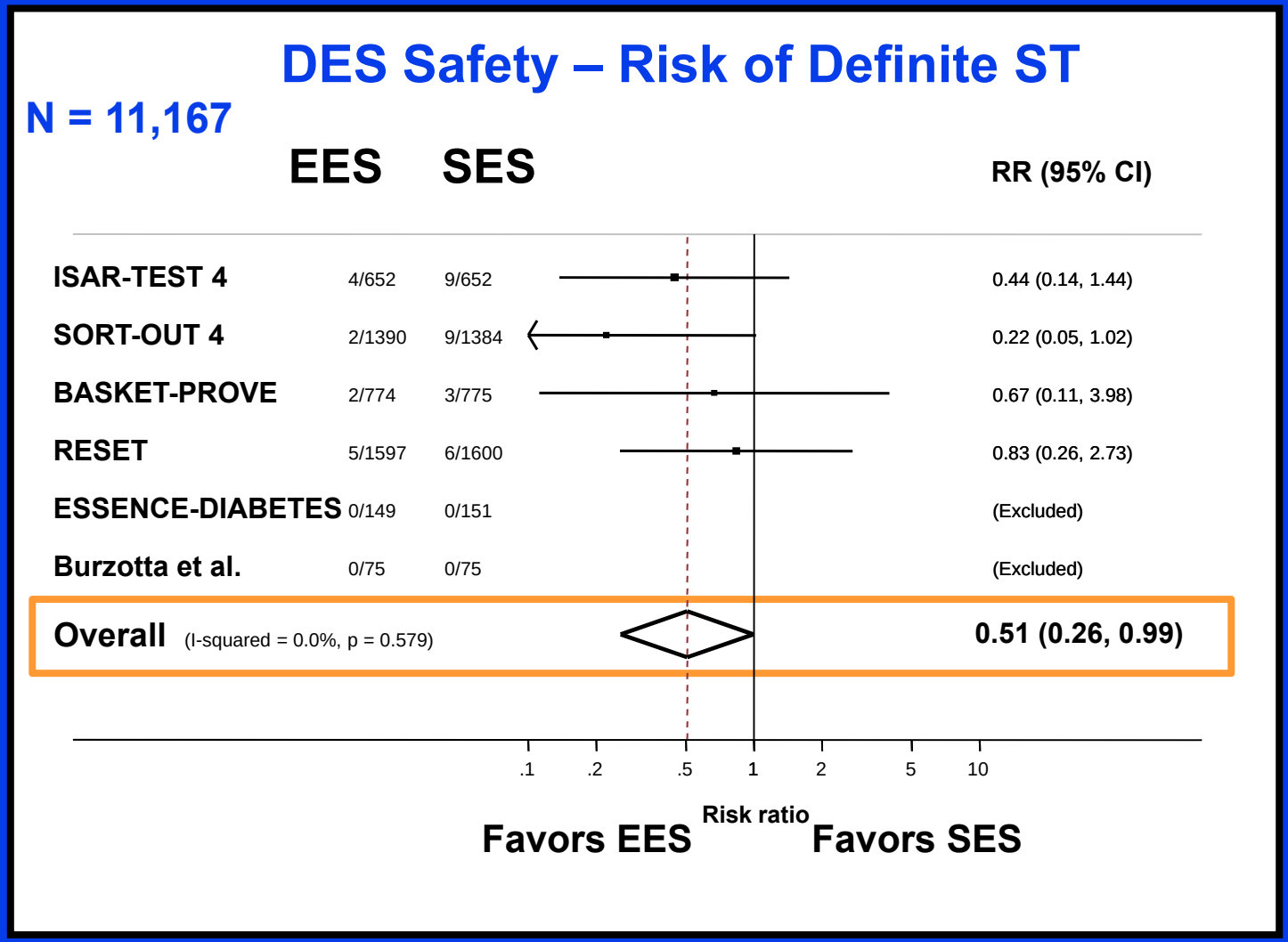


N = 6,789

Everolimus-Eluting versus Sirolimus-Eluting Stents



Everolimus-Eluting vs Sirolimus-Eluting Stents



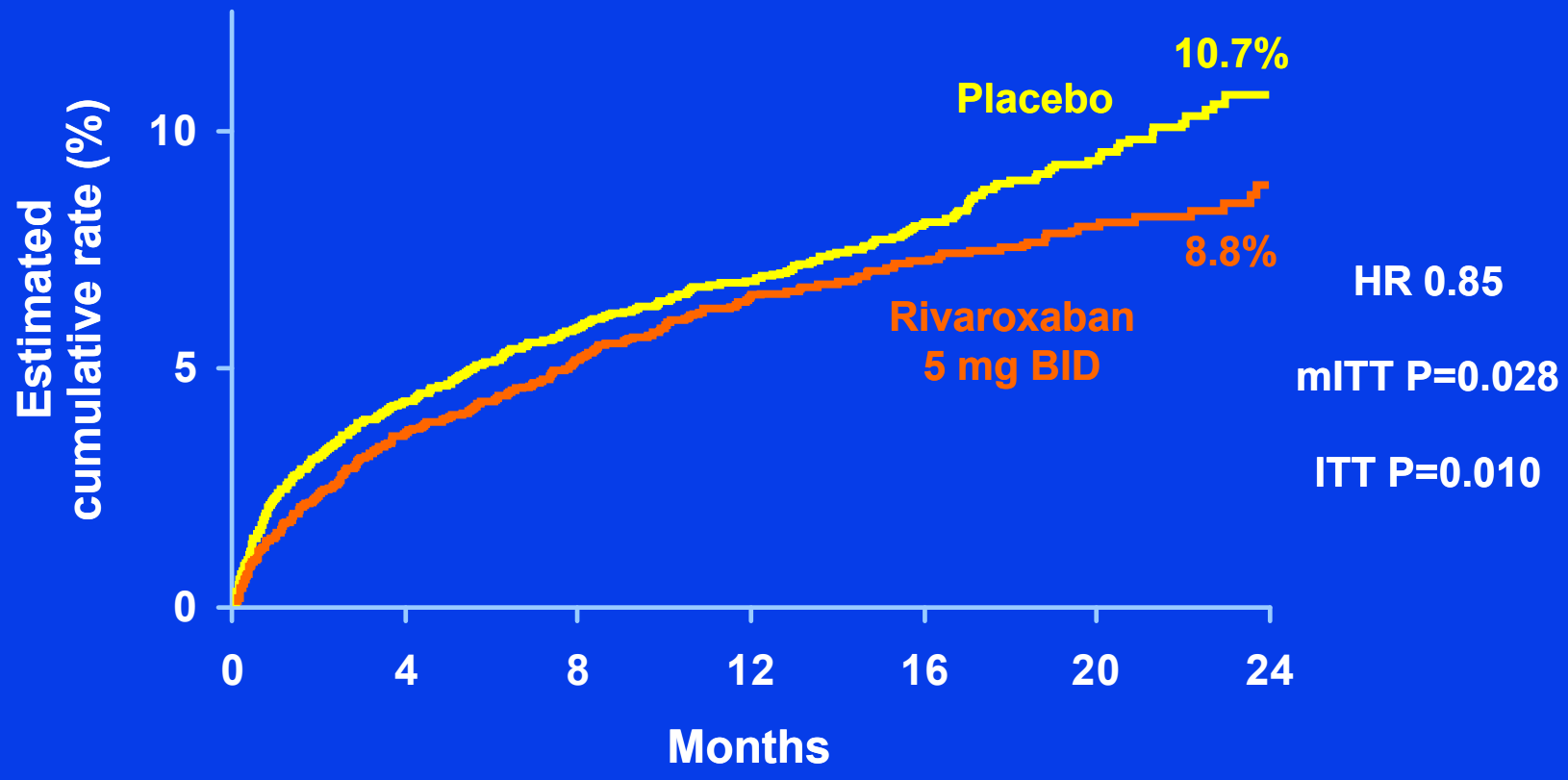
BACKGROUND: Thrombin In ACS

- There is excess thrombin generation that persists for 6 months following an index ACS event.[1]
- Thrombin is the most potent stimulant of platelet aggregation.[2]
- Reduction of thrombin generation by warfarin reduces recurrent MI by 44% in a meta-analysis of 10 ACS trials.[3]
- Rivaroxaban is a direct factor Xa inhibitor which blocks initiation of the final common pathway leading to thrombin generation.
- Based upon safety and efficacy in Phase II, 5.0 mg bid and 2.5 mg bid doses of Rivaroxaban were chosen for Phase III evaluation in ATLAS TIMI 51.[4]

1. Merlini PA et al. *Circulation.* 1994;90:61-68. 2. Coughlin S. Thrombin signaling and protease-activated receptors. Nature 2000;407(6801):258-64.
3. Rothberg MB et al *Ann Intern Med*. 2005 Aug 16;143(4):241-50. 4. *Lancet. 2009;374(9683):29-38.*

Primary Efficacy Endpoint: 5.0 mg BID

CV Death/MI/Stroke* (Ischemic + Hemg)



Rivaroxaban at 5 mg PO BID was associated with a numerical but not statistically significant reduction in mortality.

* First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC

Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches.

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Expertise

- Myeloid related protein
- Osteoprotegerin
- Placental growth factor
- Adiponectin
- Mid-region proadrenomedullin

Title/drp–author: WT/BK – Holmes, David
Sub/drp–Job#: YW105/BK – 3189182

Subject: Ohman Editorial NEJM 2012

Background: BU3
Banner/brdr: 0-40-159/BU41
Side title: YW105
• /colhdgs: YW105
Text: WT/BK
Highlight: YO114
Subdue: BU31
Footnotes: BU41

Plot/brdr: open/BU41
x, y only

PPT shooting instructions
PPT File to Server
(1 image)

Artist: mls Due Date: 4-20-2012

COLOR REFERENCE ONLY

Match: Mayo2bu-2002 (CP1111378)

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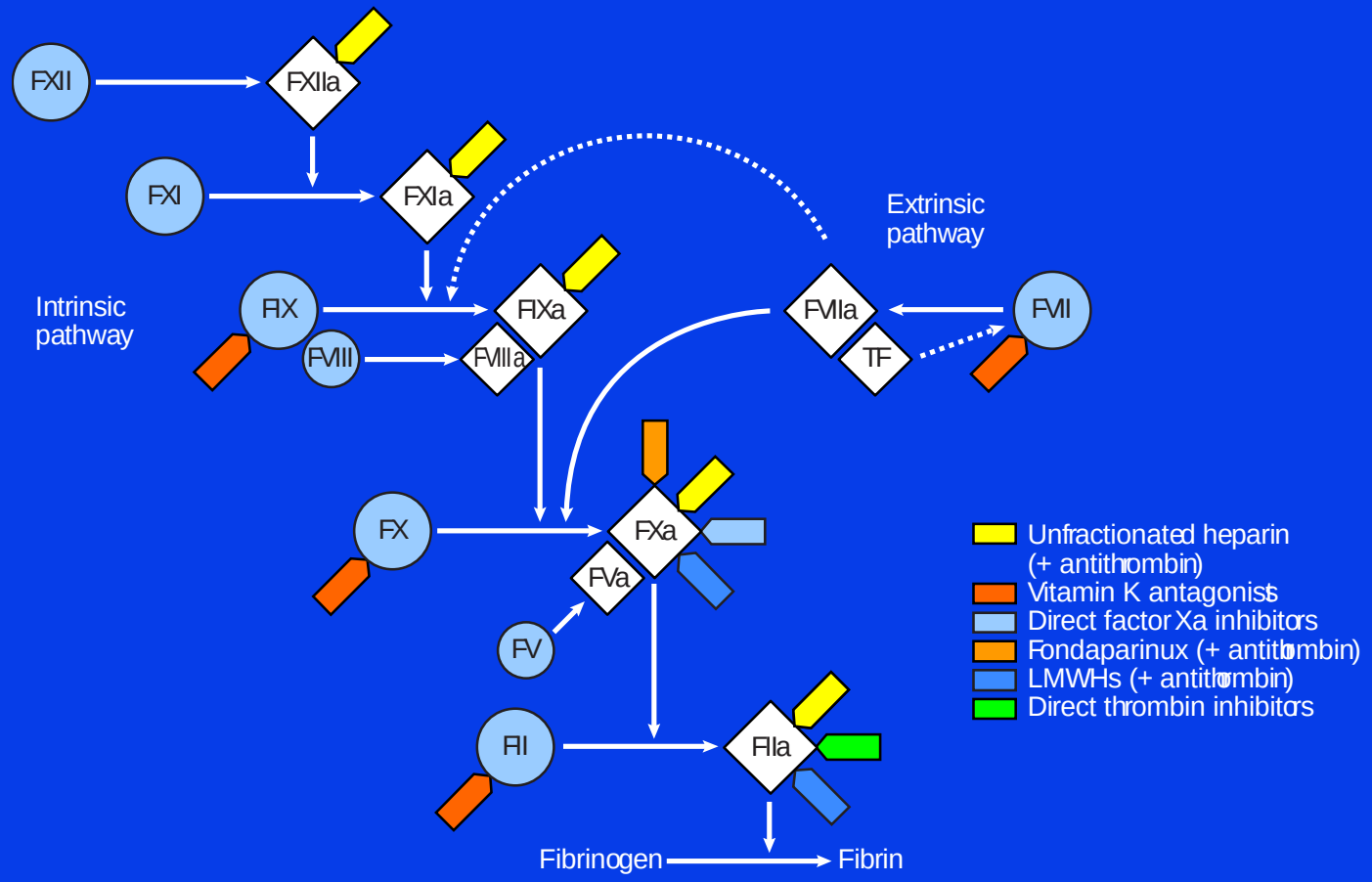
Simplified Schematic for the Blood Coagulation Cascade



Perzborn E et al: Nature Reviews 10:63-75, 2011

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Title/drp–author: WT/BK – Holmes, David
Sub/drp–Job#: YW105/BK – 3189183

Subject: Rivaroxaban Factor Xa Inhibitor, Perzborn

Background: BU3
Banner/brdr: 0-40-159/BU41
Plot/brdr: open/BU41
x, y only

Side title: YW105
- **/colhdgs: YW105**

Text: WT/BK
Highlight: YO114
Subdue: BU31
Footnotes: BU41

PPT shooting instructions
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(23 images)

Artist: RK Due Date: 4-20-2012

COLOR REFERENCE ONLY

Match: Mayo2bu-2002 (CP1111378)

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C. Michael Gibson, M.S., M.D.,
Jessica Mega, M.P.H., M.D., & Eugene Braunwald, M.D.
on behalf of the ATLAS ACS 2 TIMI 51 Investigators

Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome – Thrombolysis in Myocardial Infarction 51 Trial (ATLAS-ACS 2 TIMI 51): A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects with Acute Coronary Syndrome

Funded by a Research Grant from Johnson and Johnson and Bayer to Brigham & Women's Hospital. Dr. Gibson has received honoraria & consulting fees from J&J and Bayer.

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Trial Organization

Trial Leadership: TIMI Study Group

Chairman: Eugene Braunwald, Principal Investigator: C. Michael Gibson

Investigator: Jessica Mega, Statisticians: Sabina Murphy, Charles Contant

Executive Committee

Jean-Pierre Bassand, Deepak Bhatt, Christoph Bode, Keith Fox, Marc Cohen, Shinya Goto, David Schneider, Freek Verheugt

Sponsors: Johnson & Johnson and Bayer Health Care

J&J: Paul Burton, Peter DiBattiste, Alexei N. Plotnikov, Linda DeCaprio, Xiang Sun

Bayer: Nancy Cook Bruns, Scott Berkowitz, Frank Misselwitz

Data Safety Monitoring Board

Douglas Weaver (Chair) , Christian Hamm, Judith S. Hochman, Jeffrey Anderson, Hiroyuki Daida, Statistician: Allan Skene

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PHILIPPINES (38)

44 Countries **766 Sites**

MAYO CLINIC

3157424-49

Title/drp–author: WT/BK – Holmes, David
Sub/drp–Job#: YW105/BK – 3157424

Subject: ATLAS2, Gibson, AHA2011

Background: BU3
Banner/brdr: 0-40-159/BU41
Plot/brdr: open/BU41
x, y only

Side title: YW105
- **/colhdgs: YW105**

Text: WT/BK
Highlight: YO114
Subdue: BU31
Footnotes: BU41

PPT shooting instructions
PPT File to Server
(18 images)

Artist: JS Due Date: 11-15-2011

COLOR REFERENCE ONLY

Match: Mayo2bu-2002 (CP1111378)

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3157424-50

DAPT Duration

Review of Completed Trials & Insights from DAPT Trial Enrollment

MAYO CLINIC

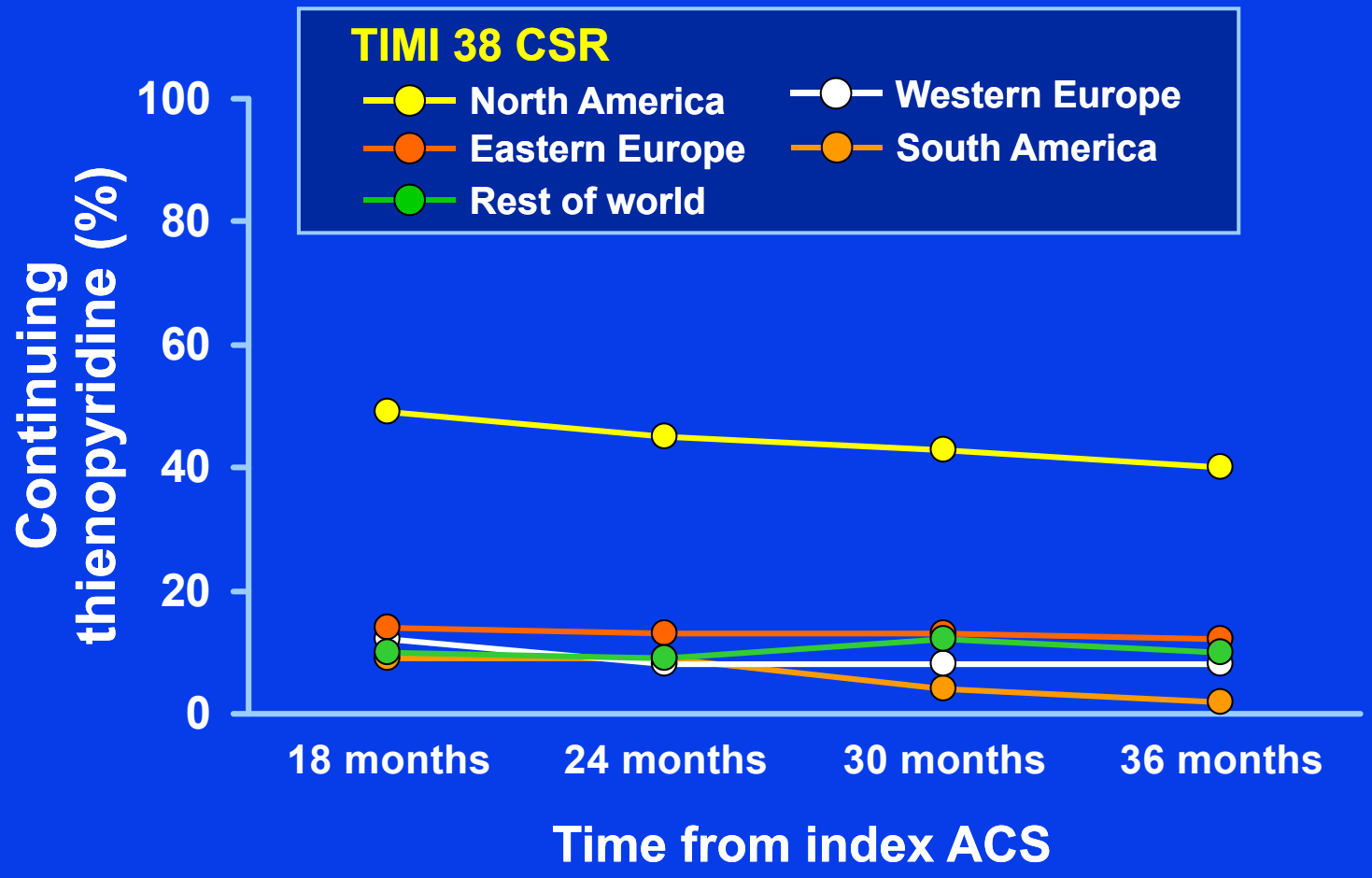
Disclosures

- Research support for DAPT Study is being provided to Harvard Clinical Research Institute from

  Abbott, Boston Scientific Corporation, Cordis Corporation, Medtronic, Inc., Bristol-Myers Squibb/Sanofi-Aventis Pharmaceuticals Partnership, Eli Lilly and Company and Daiichi Sankyo Company Limited

  Additional funding from U.S. Department of Health and Human Services and National Institutes of Health
- Consulting: Abbott, Cordis Corporation, Medtronic

Prescription of DAPT after 12 Months is Highly Variable Across Regions



Bonaca M:ACC, 2011

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- There is broad variation in practice regarding actual duration of therapy within the U.S., and worldwide
- Until recently, all data regarding duration of therapy were observational, not randomized

Randomized Antiplatelet Rx Duration Trials

	Inclusion group, N	DAPT duration	DES Type	1º Endpoint	2º Endpoint
REAL+ ZESTLATE	2701 12-month event free	~12 vs 24	All DES	2-year cardiac death/MI	Presented ACC 2010
EXCELLENT	1443 Non-STEMI	6 vs 12	SES or EES	1-year cardiac death/MI/TVR	Presented ACC 2011
PRODIGY	1357 12-month event free	6 vs 24	DES and BMS	2-year death/MI	Presented ESC 2011
ITALIC	3200	6 vs 12	EES	1-year death/MI/ revasc/stroke/n	Enrolling
ISAR-SAFE	6000 6-month event free	6 vs 12	All DES	Death/MI/stroke/ TIMI major bleed at 15 months	Enrolling
OPTIMIZE	3120 non-STEMI	3 vs 12	ZES	1-year death/MI/ stroke/bleed	Enrolling
DAPT	20,645 12-month event free	12 vs 30	1. DES 2. BMS	1. Death/MI/stroke at 33 months 2. Def/prob ST at 33 months	Enrollment complete

PES=paclitaxel-eluting stent; ZES=zotarolimus-eluting stent; SES=siroliumus-eluting stent; EES=everolimus-eluting stent

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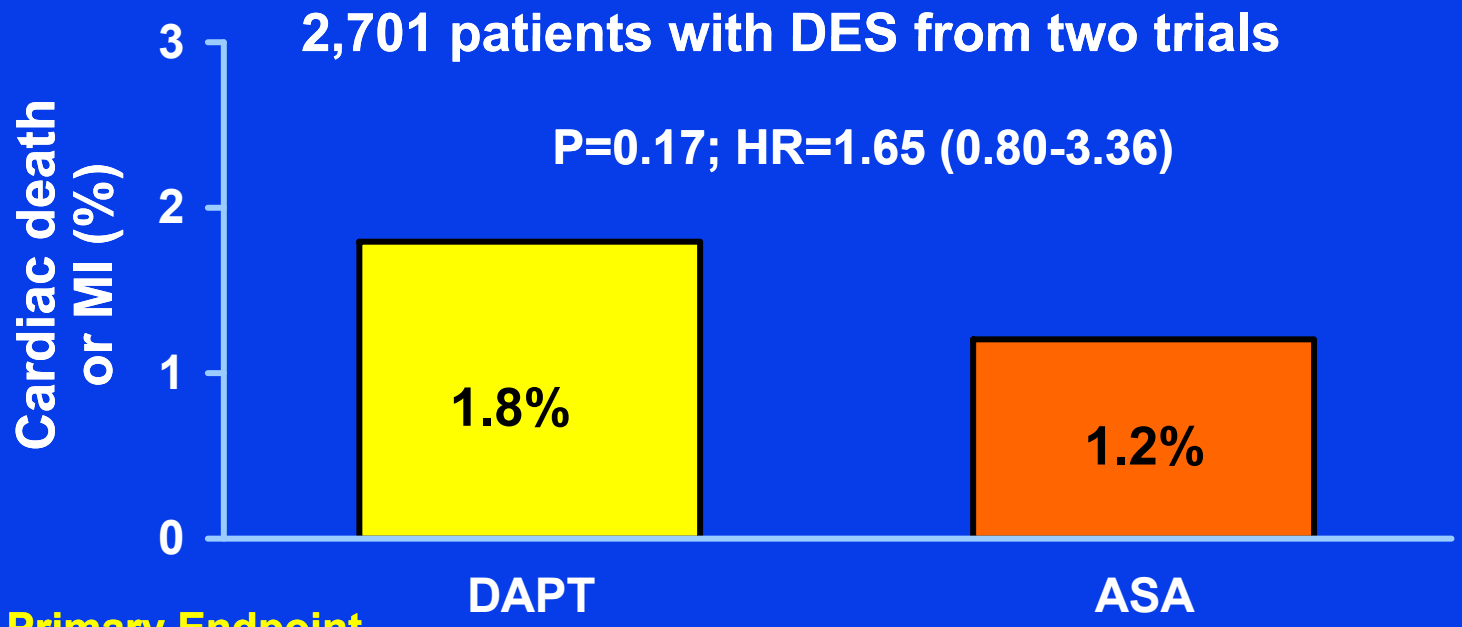
REAL-Late/ZEST-Late
2-Year Endpoints



Primary Endpoint

No. at risk	Baseline	1 year	2 year
DAPT	1,357	1,122	299
ASA	1,344	1,100	301

Lack of difference not interpretable because of insufficient power and follow-up: <1/4 reached 2-year follow-up

Park SJ et al: NEJM 362:1374-1382, 2010

MAYO CLINIC

3157427-56

REAL-Late/ZEST-Late
Timing of Randomization

Characteristic	Clopidogrel + Aspirin (n=1,357)	Aspirin Alone (n=1,344)	P
Time to randomization			0.86
12 mo-18 mo after procedure	87.6	88.3	
18 mo 24 mo after procedure	12.3	11.6	
>24 months after procedure	0.1	0.1	
Median (interquartile range)	12.8 (12.2–14.6)	12.8 (12.2–14.8)	

Time of randomization varied from 12-24 months post PCI

Park SJ et al: NEJM 362:1374-1382, 2010

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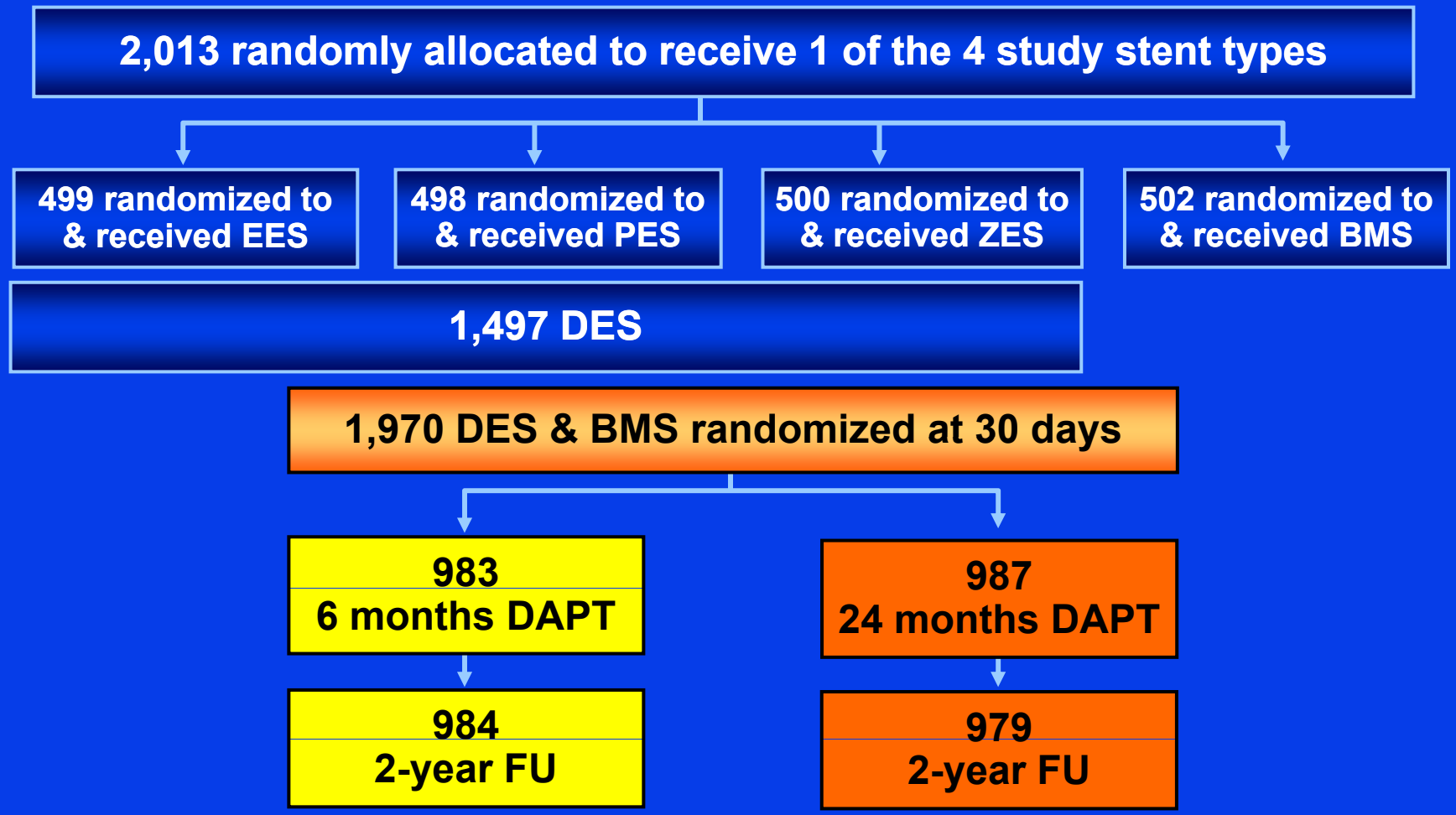
3157427-57

Prodigy Study: 6 vs 24 months DAPT after DES or MBS

Randomized at 30 Days



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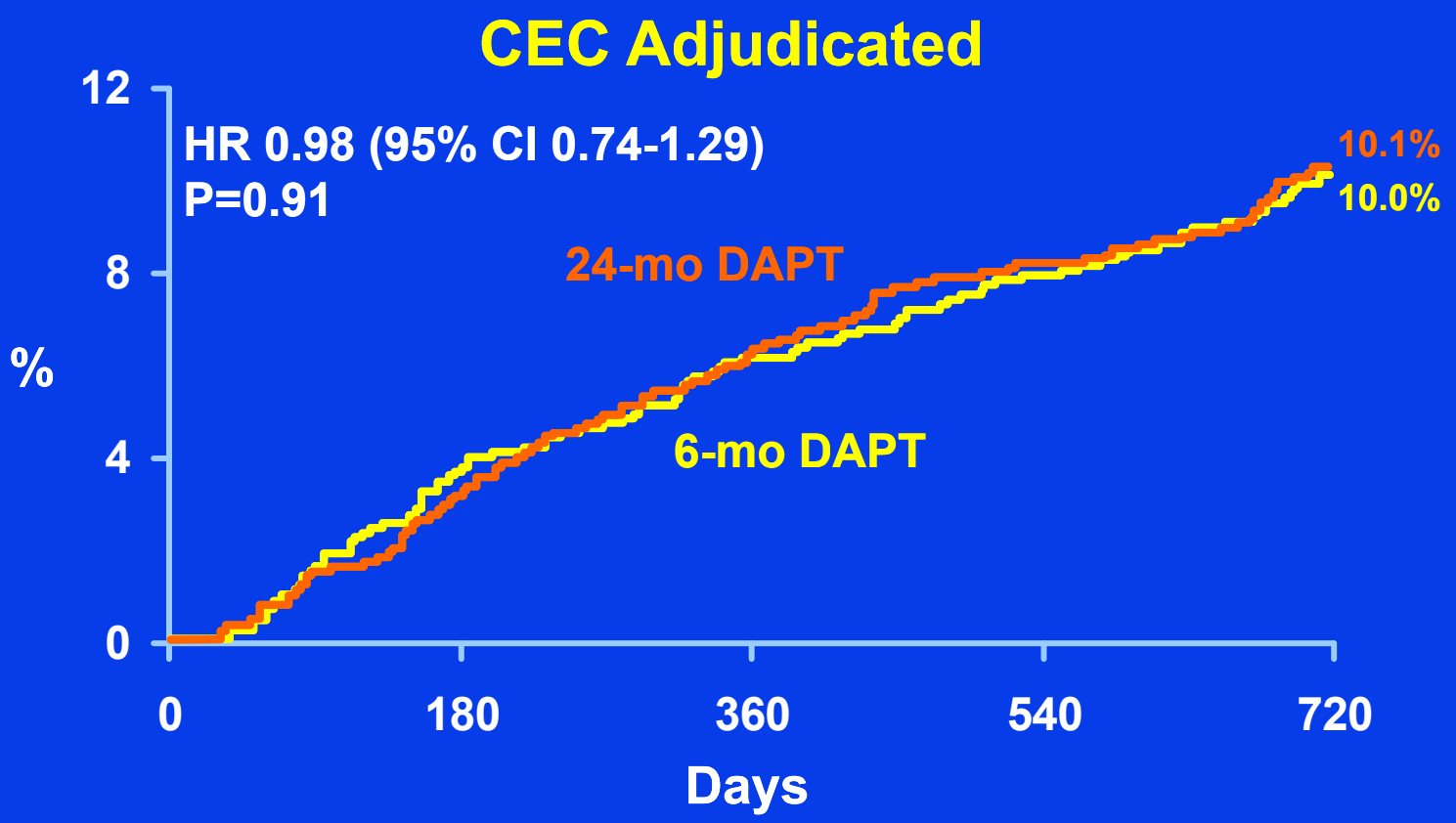
Primary Endpoint
Overall Death, MI or CVA



No. at risk			
24-mo clopidogrel	987	925	884
6-mo clopidogrel	983	919	881

Valgimigli: ESC, 2011

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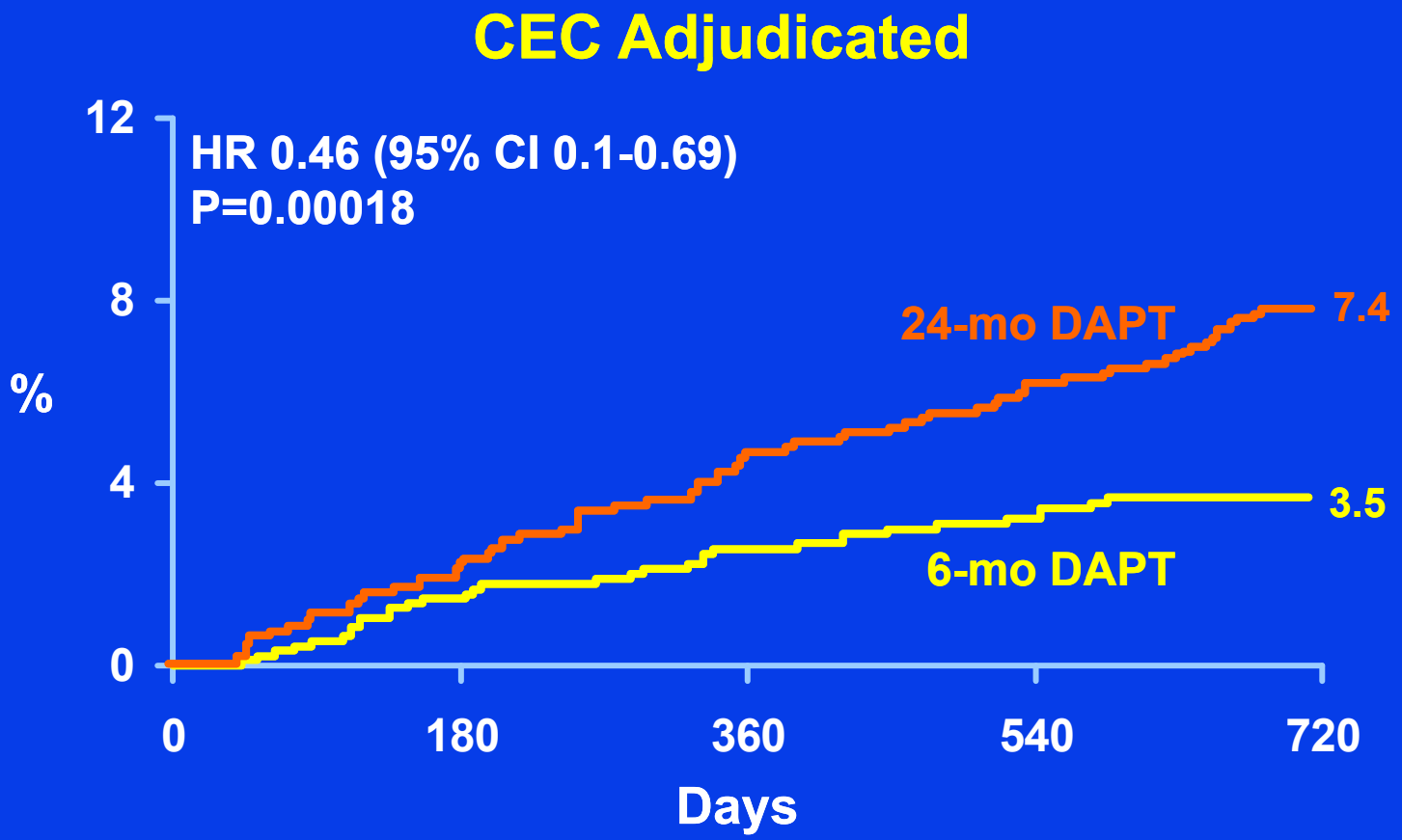
3157427-59

Type II, III or V BARC Bleeding



No. at risk			
24-mo clopidogrel	987	925	884
6-mo clopidogrel	983	919	881

Valgimigli: ESC, 2011

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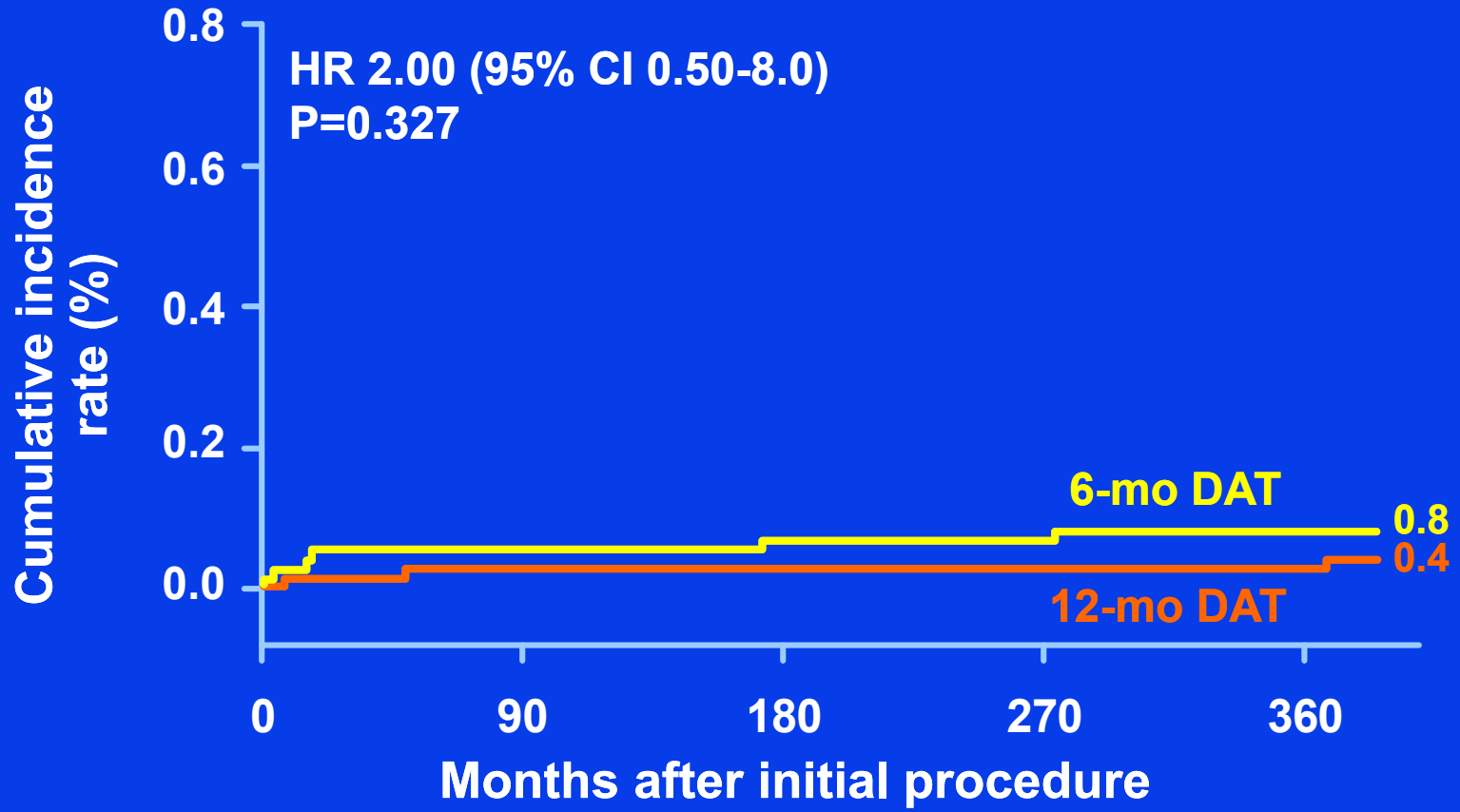
3157427-60

EXCELLENT Trial – Stent Thrombosis

Definite or Probable Stent Thrombosis by ARC Definition



Pt (no. at risk)					
6 mo	722	713	712	712	706
12 mo	721	716	712	710	705

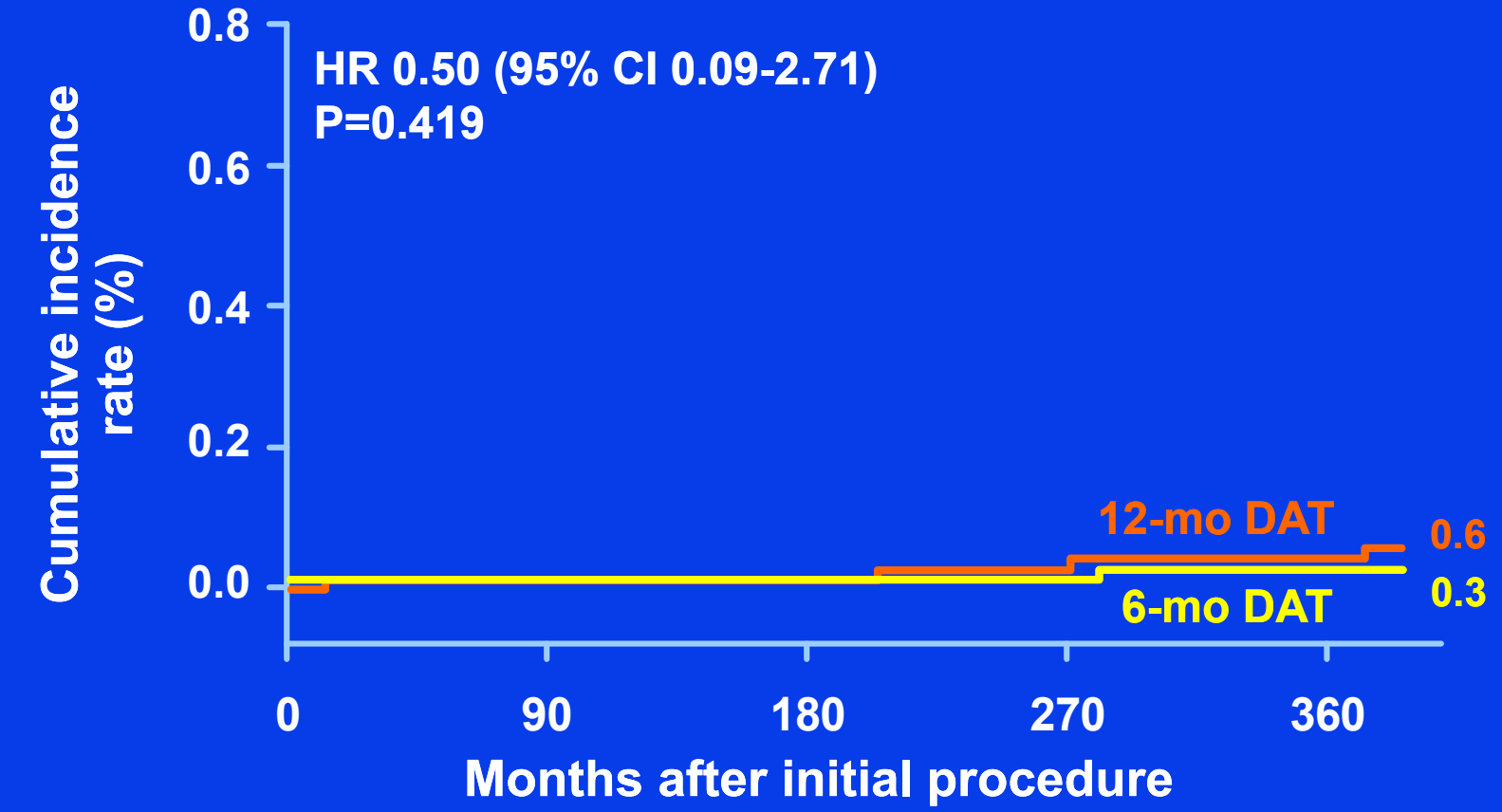
Gwon HC: ACC, 2011

MAYO CLINIC

3157427-61

EXCELLENT Trial – TIMI Major Bleeding

Overt Clinical Bleeding with Drop of Hb >5 g/dL or HCT >15%



Pt (no. at risk)					
6 mo	722	717	717	716	710
12 mo	721	716	712	711	703

Gwon HC: ACC, 2011

MAYO CLINIC

3157427-62

Recent Studies in Context

- Recent studies show that questions continue regarding benefit vs risk of longer thienopyridine therapy on MACCE
- Recent study results have not been definitive

  Not powered to determine differences in stent thrombosis

  Variable treatment durations

  Not blinded

- Yet each of these studies highlights the remaining clinical question regarding DAPT: Is there a benefit (stent thrombosis or MACCE prevention) that outweighs the risk (bleeding) or cost

Study Design

Eligible for enrollment after PCI

- Any PCI with DES or BMS
- ≥18 years of age
- No contraindications to dual antiplatelet therapy
- Able and willing to provide written informed consent

Not Eligible for randomization at 12 months

- Death
- MI or repeat PCI at >6 weeks
- CABG
- Stroke
- Major bleed

Total 33 month follow-up

Eligible for randomization at 12 months stratified by DES vs BMS, drug-type and complexity (ACS or lesion based)

12 mo DAPT Arm
Aspirin + blinded placebo

30 mo DAPT Arm
Aspirin + blinded thienopyridine

Study treatment period 12-30 mo

Study observational period 30-33 mo

Total 33 month follow-up

- Primary analysis of DES treated subjects, 12-33 mo
- Secondary analysis of propensity matched BMS to DES subjects 0-33 mo
- 2 co-primary endpoints: stent thrombosis and MACCE (death, MI, or stroke)
- Powered safety endpoint major bleeding (GUSTO)

Mauri, Kereiakes et al: AHJ 160(6):1038-1041, 2010

Principal Investigators

PI: Laura Mauri, MD, MSc, Brigham and Women's Hospital, Boston, MA, USA

Co-PI: Dean Kereiakes, MD, Christ Hospital, Cincinnati, OH, USA

National Coordinating Investigators

P.Gabriel Steg, MD, Hospital Bichat, France

Anthony Gershlick, MD, University Hospitals of Leicester, United Kingdom

Wolfgang Rutsch, MD, Charite Univeitaetsmedizin Berlin, Germany

Andrzej Hoffman, MD, Wielospecj Szpital Miedjski im.dr. E Warminsigo –SPZOZ, Poland

Ian Meredith, MD, Monash Cardiovascular Research Centre, Australia

John Ormiston, MD, Mercy Angiography, New Zealand

www.daptstudy.org; www.clinicaltrials.gov – NCT00977938

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DAPT Top Enrollers

Site Name	Investigator	Subjects Enrolled
United States		
Washington Hospital Center	Lowell Satler	340
Providence St. Vincent Medical Center	Todd Caulfield	242
Conemaugh Valley Memorial Hospital	Samir Hadeed	230
Europe		
NZOZ Centr. Med. Beluga-Med (PL)	Jaroslaw Trebacz	205
Instit. Inimii Niculae Stancioiu Cluj-Napoca (RO)	Adrian Corneliu Iancu	160
InstytutKardiologiiKardynalaWyszynskiego (PL)	Cezary Sosnowski	129
Australia/New Zealand		
Wellington Hospital (NZ)	Scott Harding	57
Sir Charles Gairdner Hospital (AU)	Peter Thompson	55
Ascot Integrated Hospital (NZ)	Warwick Jaffe	54

Study Leadership

Principal investigators

PI: Laura Mauri, MD, MSc, Brigham & Women's Hospital, Boston, MA, USA

Co-PI: Dean Kereiakes, MD, Christ Hospital, Cincinnati, OH, USA

Data Coordinating Center

Harvard Clinical Research Institute, Boston, MA, USA

Executive Committee

Donald Cutlip, MD, Beth Israel Deaconess Medical Center, Boston, MA, USA

Sharon Lise Normand, PhD, Dept of Health Care Policy, Harvard Medical School, Boston, MA, USA

P. Gabriel Steg, MD, Université Paris-VII, France

Advisory Committee

Chairman: Eugene Braunwald, MD Brigham & Women's Hospital, Boston, MA, USA

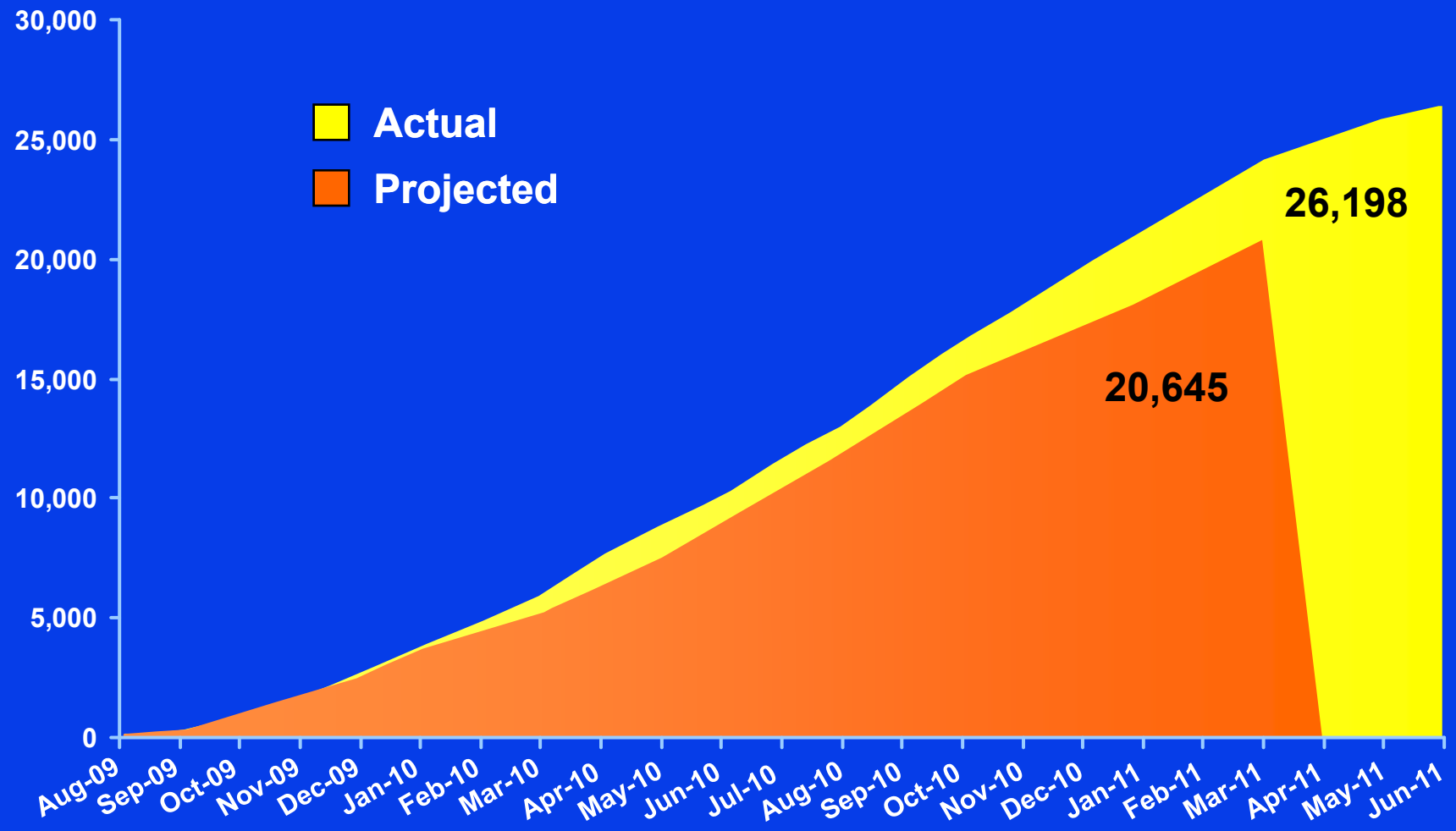
Members: Steven Wiviott, David Holmes, David Cohen, Mike Linkoff, Ralph Brindis, Alice Jacobs, Doug Weaver, Dan Simon, Jean-Francois Tanguay, Stephan Windecker, Anthony Gershlick, Paul Gurbel

Data Safety Monitoring Board

Chairman: Robert Bonow, MD

Members: Charles Davidson, William Wijns, Eric Bates, Jim Neaton

Total Enrollment
August 2009-July 1, 2011



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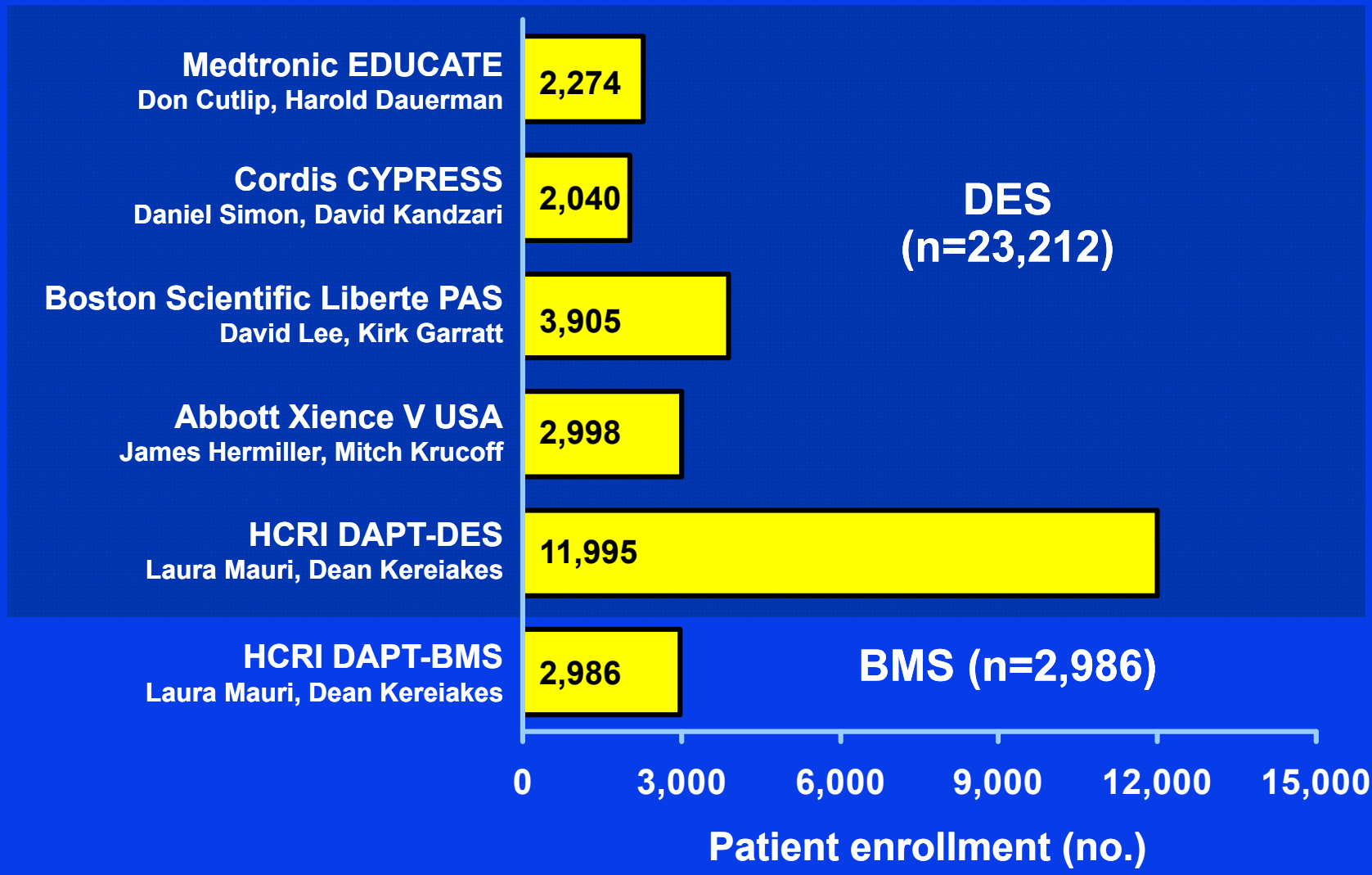
Total Subject Enrollment



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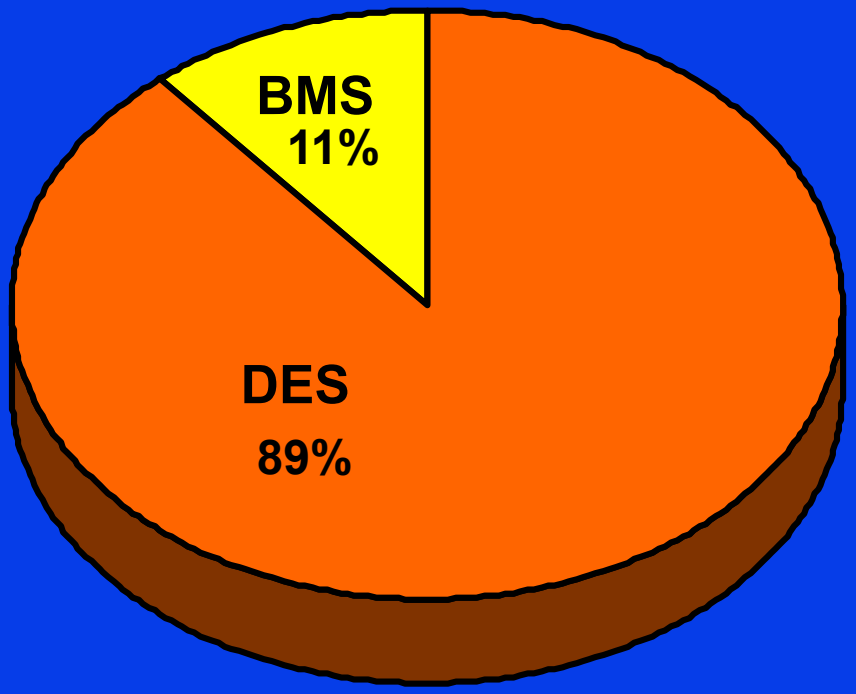
Stent Type

All subjects
n=26,198



	DES type (%)*
CYPHER (n=3,056)	13.2
ENDEAVOR (n=3,458)	14.9
TAXUS (n=5,216)	22.5
Xience/PROMUS (n=11,752)	50.6

*Some pt have received ≥1 DES type

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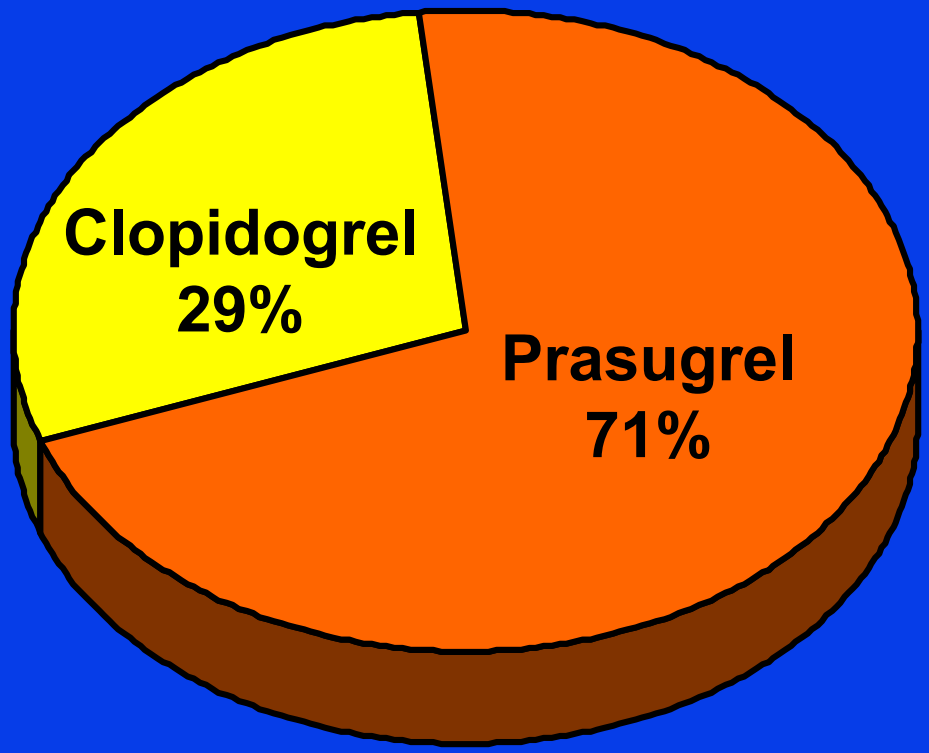
Thienopyridine

All subjects
n=26,198



MAYO CLINIC

Patient Characteristics

	DES N=23,212	BMS N=2,986	All Patients N=26,198
Age			
Mean ± SD	62.1 ± 10.6	59.1 ± 11.3	61.7 ± 10.7
Sex (Female) (%)	28.2	25.9	27.9
Race			
Black or African American (%)	6.6	6.4	6.6
White (%)	88.6	90.9	88.8
Other (%)	3.8	2.8	3.7
Hispanic or Latino (%)	4.2	5.4	4.3

Patient Characteristics

	DES N=23,212	BMS N=2,986	All Patients N=26,198
Diabetes Mellitus (%)	33.0	24.0	32.0
Insulin (%)	10.0	6.4	9.6
Oral Medication (%)	18.3	13.8	17.8
Diet or No Treatment (%)	4.7	3.7	4.6
Hypertension (%)	77.8	66.6	76.6
Current Smoker or within 1 yr (%)	25.3	41.9	27.2
CHF (%)	6.3	5.0	6.2
Previous PCI (%)	34.9	20.4	33.3
Previous CABG	13.9	7.6	13.2

Patient Characteristics

	DES N=23,212	BMS N=2,986	All Patients N=26,198
Any Clinical Complexity Factors	35.2%	66.6%	38.7%
Any Anatomic Complexity Factors	32.3%	38.5%	33.0%
Complexity (any clinical or anatomic)	53.6%	73.2%	55.8%

Clinical Complexity = ACS, renal insufficiency, or EF<30%
Anatomic Complexity = ≥3 vessels stented, in-stent restenosis of DES, prior brachytherapy, unprotected left main, >2 lesions stented per vessel, lesion length ≥30 m, bifurcation lesion with sidebranch >2.5mm, vein bypass graft, or thrombus-containing lesions

Conclusions

- Balance of risk and benefit of varying durations remains unknown
- DAPT Study is well along its way to answer this question
- Sufficient sample size has been enrolled to detect meaningful differences in stent thrombosis, MACCE and bleeding, in patients who tolerate 1 year of DAPT
- Randomization phase with over 6,000 randomized subjects in follow-up
- Study on track to achieve final study results in 2014

Thank You to all Study Investigators and Patients

Australia: David Muller, Ian Meredith, Jamie Rankin, Matthew Worthley, Nigel Jepson, Peter Thompson, Randall Hendriks, Robert Whitbourn, Steven Duffy **Czech Republic**: Josef Stasek, Kamil Novobilsky, Marcela Skvarilova, Robert Naplava, Zdenek Coufal **France**: Pierre Coste, Bressollette Erwan, Riadh Rihani, Gabriel Steg, Emmanuel Teiger, Bruno Vaquette **Germany**: Darius Harald Sekretariat, Martin W. Bergmann, Peter Radke, Ruth Strasser, Sebastian Philipp, Stefan Hoffmann, Steffen Behrens, Sven Moebius-Winkler, Wolfgang Rutsch **Hungary**: Geza Lupkovics, Ivan Horvath, Sandor Kancz, Tamas Forster, Zsolt Koszegi **New Zealand**: Gerry Devlin, Hamish Hart, John Elliott, John Ormiston, Malcolm Abernathy, Nick Fisher, Patrick Kay, Scott Harding, Warwick Jaffe **Poland**: Andrzej Hoffmann, Cezary Sosnowski, Jaroslaw Trebacz, Pawel Buszman, Slawomir Dobrzycki, Zdzislawa Kornacewicz-Jach **Romania**: Adrian Corneliu Iancu, Carmen Doina Ginghina, Costel Matei, Dan Dobreanu, Filip Romi Bolohan, Maria Dorobantu **United Kingdom**: Adam Jacques, Ajay Jain, Anthony Gershlick, Bakhai Ameet, David Newby, Dawn Adamson, Mark de Belder, Dirk Felmeden, Ian Purcell John Irving, John Edmond, Paul Kelly, Peter O'Kane, Piers Clifford, Michael Pitt, Suresh Venkatesan **United States**: Jan Pattanayak, Abdel Ahmed, Abdulhay Albirini, Abel Moreyra, Abram Rabinowitz, Adhir Shroff, Alice Jacobs, Andrew Taussig, Anthony White, Arif Shakir, Arnold Ghitis, Arvind Agarwal, Ash Jain, Atul Chawla, Aylmer Tang, Barry Bertolet, Barry Uretsky, Barry H. Cheek, Bernard Erickson, Bhola Rama, Brent McLaurin, Brian Dearing, Brian Negus, Bruce Bowers, Bruce Watt, Charles Lambert, Charles Shoultz, Christopher Wolfe, Craig Thieling, Daniel Fisher, Daniel Lee, David Eich, David Goldberg, David Mego, David Rizik, David Safley, Dawn Abbott, Dean Kereiakes, Donald Canaday, Donald Cutlip, Donald Myears, Donald Westerhausen, Douglas Ebersole, Douglas Netz, Drew Baldwin Edward Kosinski, Edward Portnay, Ehtisham Mahmud, Elizabeth Holper, Eric Hockstad, Fayaz Shawl, Fayez Shamoon, Gary Schaer, George Kichura, George Myers, Georges Kaddissi, Govind Ramadurai, Gregory Elsner, Guy Piegari, Henry Liberman, Himanshu Agarwal, Hoshedar P. Tamboli, Imran Dotani, James Revenaugh, James Tift Mann, James F. Fleischhauer, Janah Aji, Jay Patel, John Douglas, John Griffin, John Katopodis, John Lopez, John Wang, Jorge Saucedo, Joseph Tuma, Joshua Kieval, Kasi Ramanathan, Kathleen Allen, Keith Atassi, Kevin Clayton, Kevin Croce, Kimberly Skelding, Kiritkumar Patel, Kishore Harjai, Kollagunta Chandrasekhar, Kumar Kalapatapu, Larry Dean, Lawrence Barr, Lowell Satler, Luis Gruberg, Manish Chauhan, Marc Litt, Mark Dorogy, Mark Lurie, Massoud Leesar, Maurice Buchbinder, Mayra Guerrero Core, Michael Del, Michael Kelberman, Michael Lim, Michael Ragosta, Michael Rinaldi, Michael Rosenberg, Michael Tamberella, Miles McClure, Mirle Kellett, Mladen Vidovich Mirza, Mohd Ayoub, Muhammad Khan, Nabil Dib, Nathan Laufer, Neal Kleiman, Niam Farhat, Osvaldo Gigliotti, Patricia Best, Paul Gordon, Paul Gurbel, Paul Luetmer, Paul Tolerico, Peter Kerwin, Peter Ver Lee, Phillip Kraft, Rafael Gonzalez, Rajesh Dave, Rakesh Prashad, Ramon Aycock, Ramon Quesada, Randolph Renzi, Richard Bach, Richard Kettelkamp, Richard Paulus, Richard Waters, Richard Zelman, Robert Applegate, Robert Feldman, Robert Smith, Robert Watson, Roger Gammon, Ronald Caputo, Ronald Stella, Samir Hadeed, Samuel Ledford, Saurabh Gupta, Sergio Waxman, Simon Dixon, Srihari Naidu, Srinivasa Potluri, Stephen Crowley, Stephen Kirkland, Stephen Thew, Steve Marshalko, Steven Guidera, Steve Hearne, Steven Karas, Steven Manoukian, Steven Yakubov, Stewart Pollock, Subhash Banerjee, Suhail Allaqaband, Sung Choi, Suresh Mulukutla, Theodore Schreiber, Thomas Haldis, Thomas K. Pow, Thomas McGarry, Thomas Nygaard, Timothy Larkin, Todd Caulfield, Tomasz Stys, Vishal Gupta, Walt Marquardt, William Ballard, William French, Zafir Hawa, Zubair Jafar

NCDR Action Registry
Anticoagulants and Bleeding

- Analysis of
  - 72,699 patients with NSTEMI
  - 48,943 patients with STEMI
- Patients categorized in anticoagulant strategy selected and CRUSADE bleeding risk category

Kadakia MB et al: J Am Coll Cardiol Intv 3:1166-77, 2010

CLINICAL RESEARCH

Use of Anticoagulant Agents and Risk of Bleeding Among Patients Admitted With Myocardial Infarction

A Report From the NCDR ACTION Registry–GWTG (National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines)

Mitul B. Kadakia, MD,*† Nihar R. Desai, MD, MPH,*† Karen P. Alexander, MD,‡ Anita Y. Chen, MS,‡ JoAnne M. Foody, MD,† Christopher P. Cannon, MD,*† Stephen D. Wiviott, MD,*† Benjamin M. Scirica, MD, MPH,*† on behalf of the National Cardiovascular Data Registry

Boston, Massachusetts; and Durham, North Carolina

Conclusions: There is a wide variability in the use of anticoagulant regimens with significant differences according to baseline characteristics and concomitant therapies. Major bleeding is common, though a great degree of the variability in the rate of bleeding is largely based on differences in baseline characteristics, comorbidities, and invasive treatment strategies, rather than specific anticoagulant regimens.

Conclusions There is a wide variability in the use of anticoagulant regimens with significant differences according to baseline characteristics and concomitant therapies. Major bleeding is common, though a great degree of the variability in the rate of bleeding is largely based on differences in baseline characteristics, comorbidities, and invasive treatment strategies, rather than specific anticoagulant regimens. (J Am Coll Cardiol Intv 2010;3:1166–77)

VARC Bleeding

Type 0

No bleeding

Type 1

Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2

Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4 or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

VARC Bleeding

Type 3 **Type 3a**
Overt bleeding plus hemoglobin drop of 3 to <5g/dL (provided hemoglobin drop is related to bleed)
Any transfusion with overt bleeding
Type 3b
Overt bleeding plus hemoglobin drop of ≥5g/dL (provided hemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/ hemorrhoid)
Bleeding requiring intravenous vasoactive agents
Type 3c
Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
Subcategories confirmed by autopsy or imaging or lumbar puncture
Intraocular bleed compromising vision

VARC Bleeding

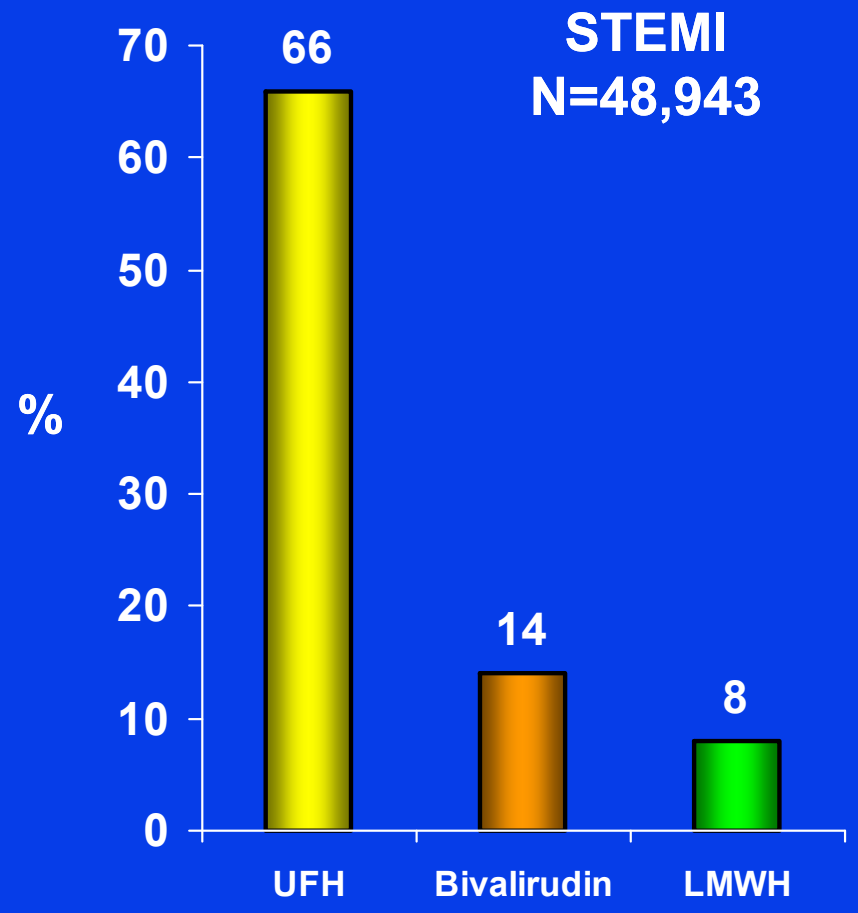
Type 4: CABG-related bleeding
Perioperative intracranial bleeding within 48 hours
Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period
Chest tube output ≥2 L within a 24-hour period
Type 5: Fatal bleeding
Type 5a
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

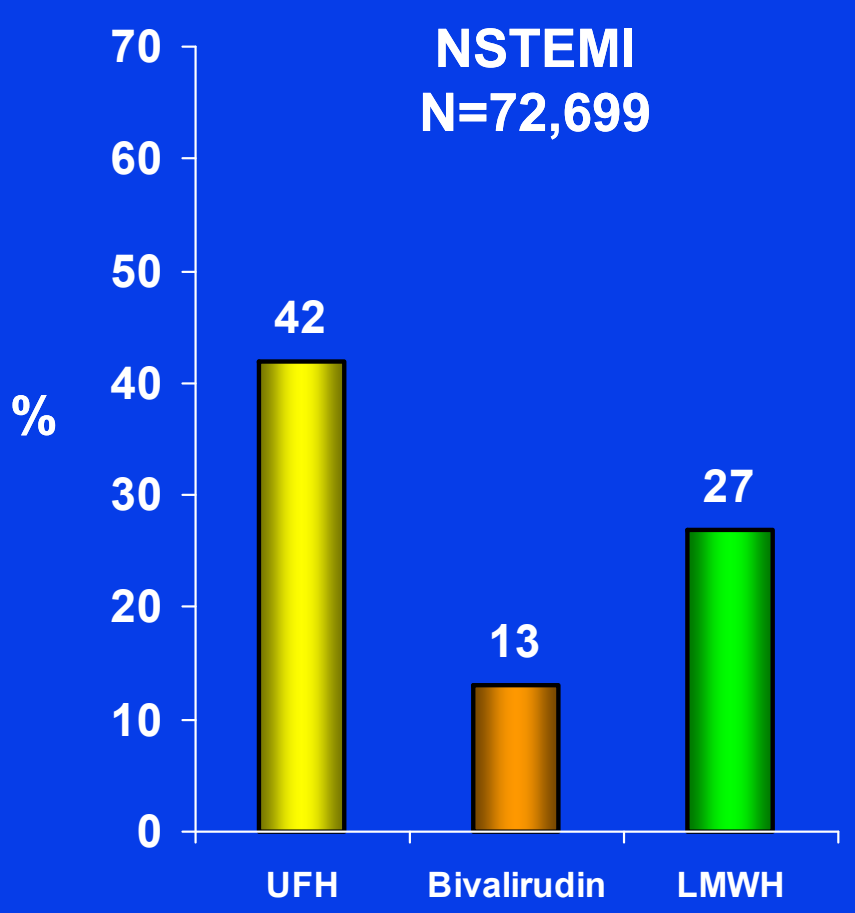
CRUSADE Bleeding Score

- Baseline HCT
- CR clearance
- Heart rate
- Sex
- CHF
- Systemic BP
- Prior vascular disease
- Diabetes

NCDR Bleeding
NSTEMI and STEMI

Jan. 2007 – June 2009

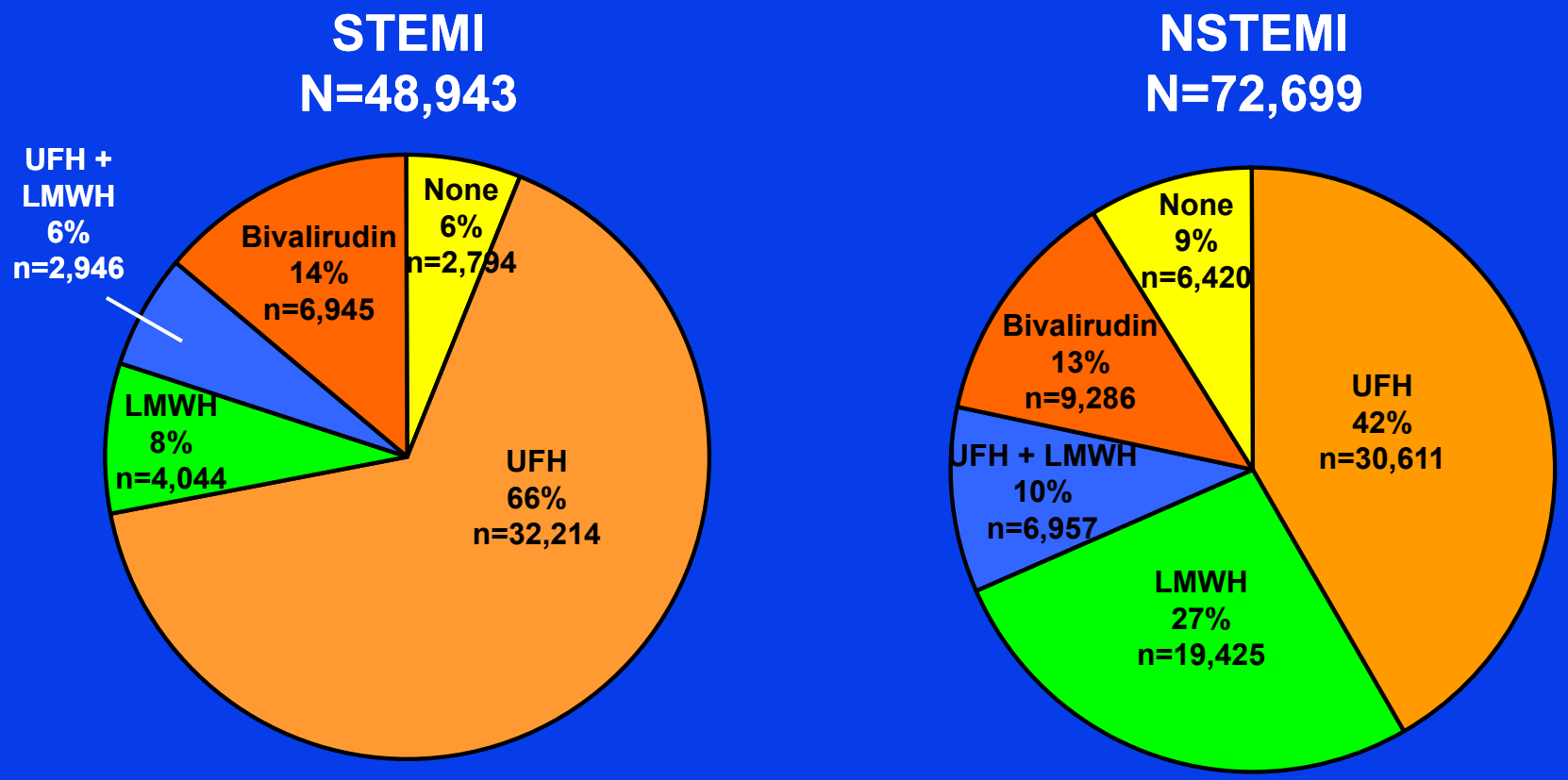




MAYO CLINIC

Kadakia MB et al: J AM Coll Cardiol Intv 3:1166-77, 2010

Usage of Anticoagulant Regimens



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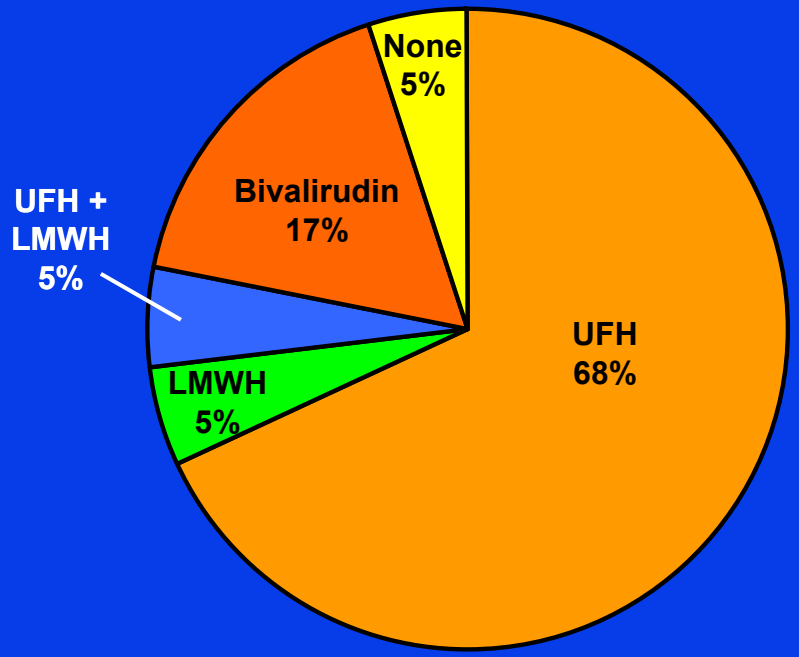
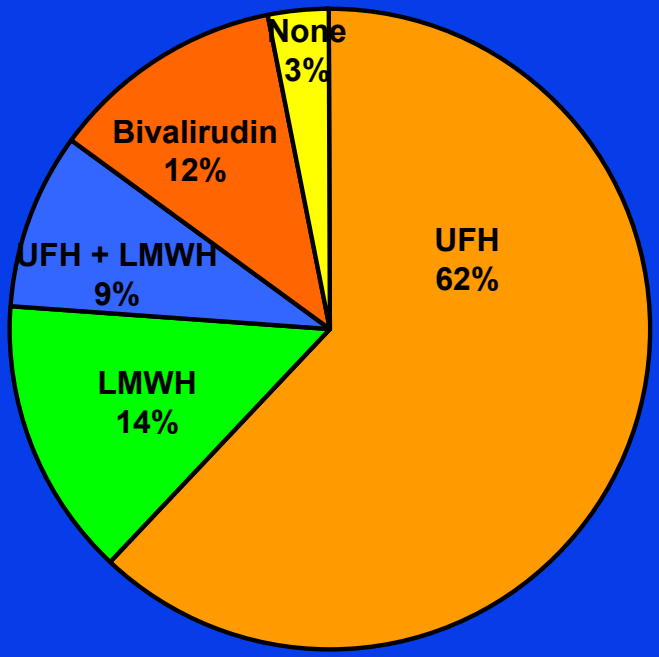
Anticoagulant Use According to Therapeutic Strategy

STEMI - PCI
N=32,455



STEMI – Fibrinolytics only
N=5,123



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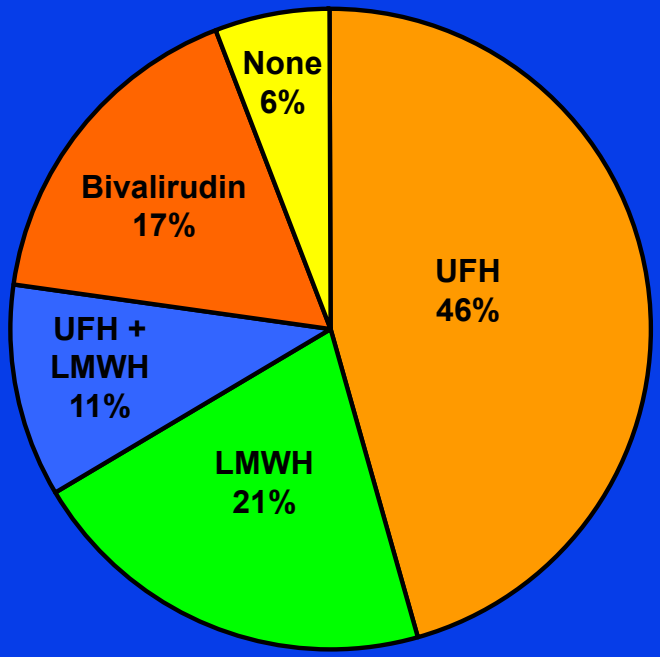
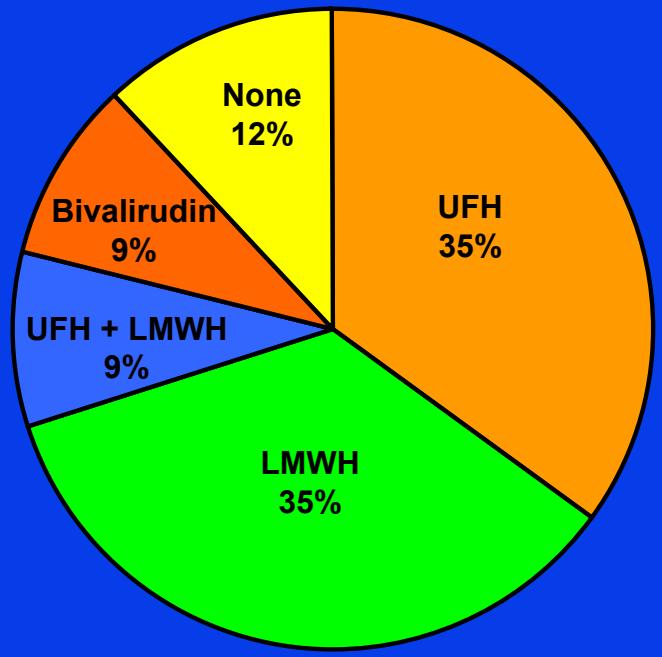
Anticoagulant Use According to Therapeutic Strategy

NSTEMI – Invasive Strategy N=46,012



NSTEMI – Conservative Strategy N=15,631



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Bleeding Risk Scores

STEMI n=42,918	CRUSADE Bleeding Score	N (%)	Major Bleeding Events (%)
	≤20	19,050 (44.4)	1,036 (5.4)
	21-30	9,864 (23.0)	1,002 (10.2)
	31-40	6,565 (15.3)	956 (14.6)
	41-50	4,250 (9.9)	857 (20.2)
	>50	3,189 (7.4)	928 (29.1)

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Bleeding Risk Scores

NSTEMI n=61,540	CRUSADE Bleeding Score	N (%)	Major Bleeding Events (%)
	≤20	19,803 (32.2)	605 (3.1)
	21-30	11,134 (18.1)	670 (6.0)
	31-40	9,831 (16.0)	822 (8.4)
	41-50	8,944 (14.5)	1,099 (12.3)
	>50	11,828 (19.2)	2,314 (19.6)

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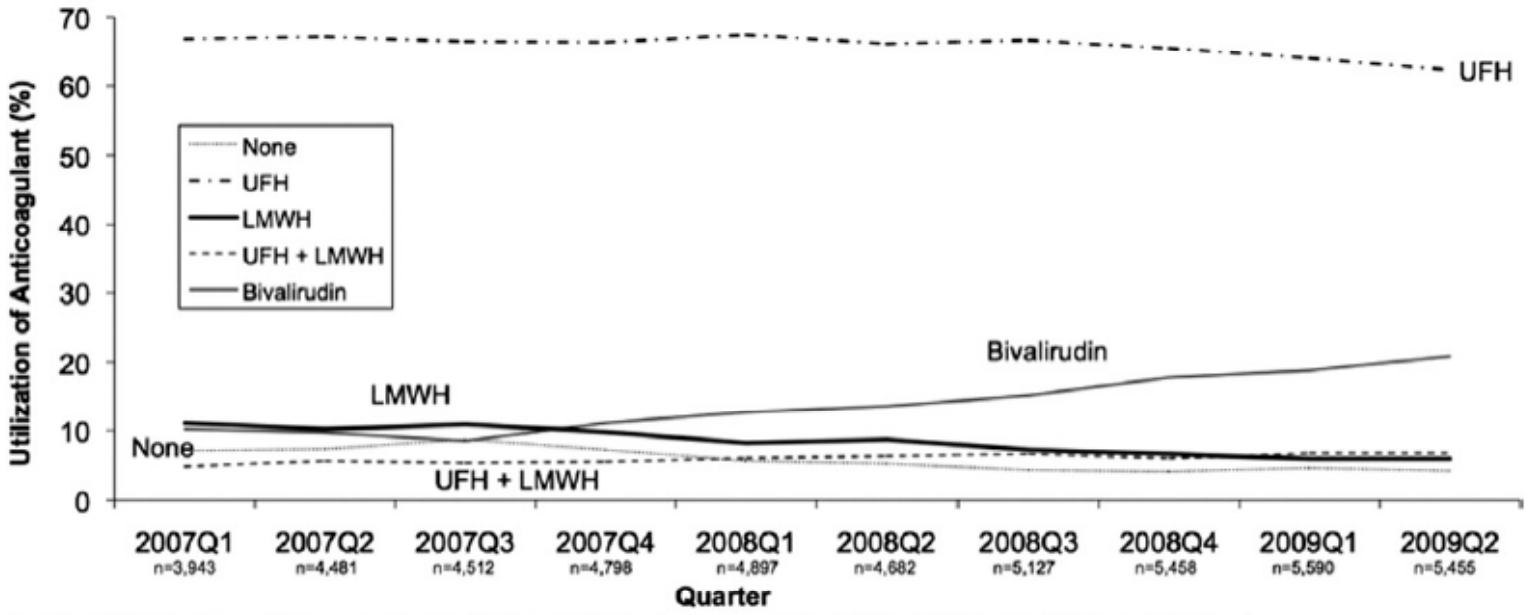
Anticoagulant Regimens in STEMI



Quarter	None	UFH	LMWH	UFH + LMWH	Bivalirudin
2007Q1	7.1	66.9	11.1	4.8	10.2
2007Q2	7.3	67.2	10.2	5.6	9.7
2007Q3	8.7	66.5	10.9	5.3	8.5
2007Q4	7.2	66.4	9.8	5.5	11.1
2008Q1	5.6	67.5	8.2	6	12.7
2008Q2	5.2	66.2	8.7	6.3	13.6
2008Q3	4.3	66.7	7.2	6.6	15.2
2008Q4	4.1	65.5	6.6	6	17.8
2009Q1	4.6	64	5.9	6.7	18.8
2009Q2	4.2	62.3	5.9	6.7	20.9

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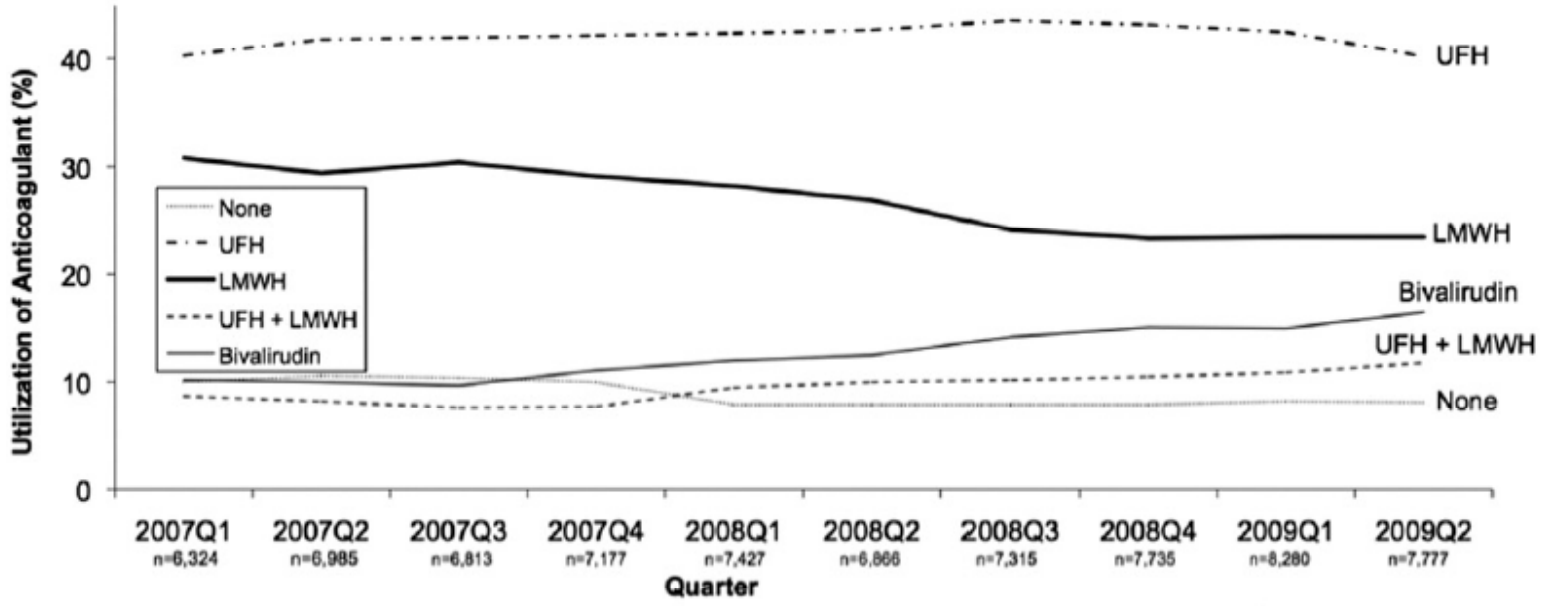
Anticoagulant Regimens in NSTEMI



Quarter	None	UFH	LMWH	UFH + LMWH	Bivalirudin
2007Q1	10	40.3	30.8	8.7	10.2
2007Q2	10.6	41.8	29.4	8.2	10
2007Q3	10.4	42	30.4	7.6	9.7
2007Q4	10	42.2	29.1	7.7	11.1
2008Q1	7.9	42.4	28.2	9.5	12
2008Q2	7.9	42.7	26.9	10	12.5
2008Q3	7.9	43.6	24.1	10.2	14.2
2008Q4	7.9	43.2	23.3	10.5	15.1
2009Q1	8.2	42.5	23.4	10.9	15
2009Q2	8.1	40.2	23.4	11.8	16.5

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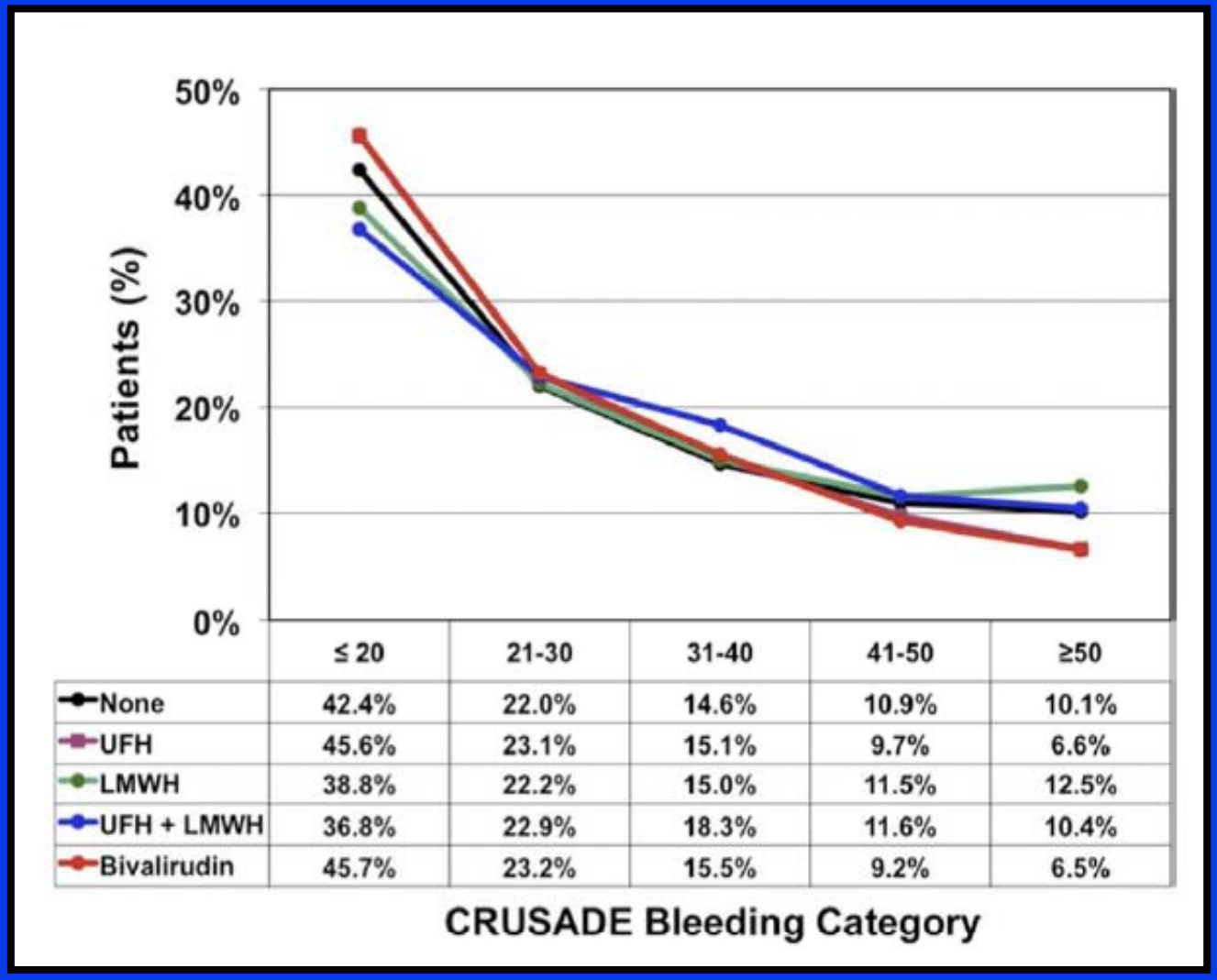
Anticoagulant Strategy in STEMI



	≤ 20	21-30	31-40	41-50	≥50
None	42.4%	22.0%	14.6%	10.9%	10.1%
UFH	45.6%	23.1%	15.1%	9.7%	6.6%
LMWH	38.8%	22.2%	15.0%	11.5%	12.5%
UFH + LMWH	36.8%	22.9%	18.3%	11.6%	10.4%
Bivalirudin	45.7%	23.2%	15.5%	9.2%	6.5%

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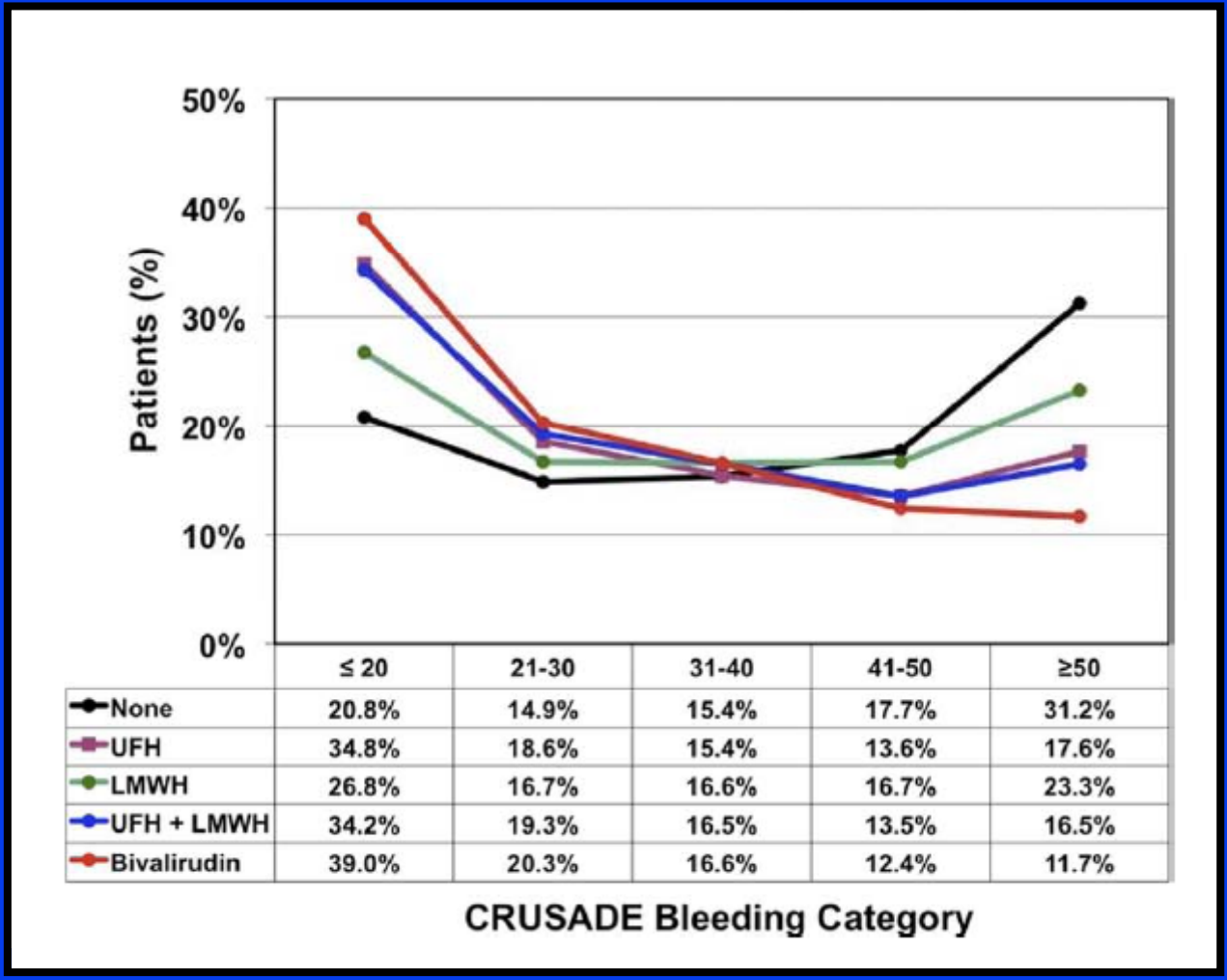
Anticoagulant Strategy in NSTEMI



	≤ 20	21-30	31-40	41-50	≥50
None	20.8%	14.9%	15.4%	17.7%	31.2%
UFH	34.8%	18.6%	15.4%	13.6%	17.6%
LMWH	26.8%	16.7%	16.6%	16.7%	23.3%
UFH + LMWH	34.2%	19.3%	16.5%	13.5%	16.5%
Bivalirudin	39.0%	20.3%	16.6%	12.4%	11.7%

CRUSADE Bleeding Category

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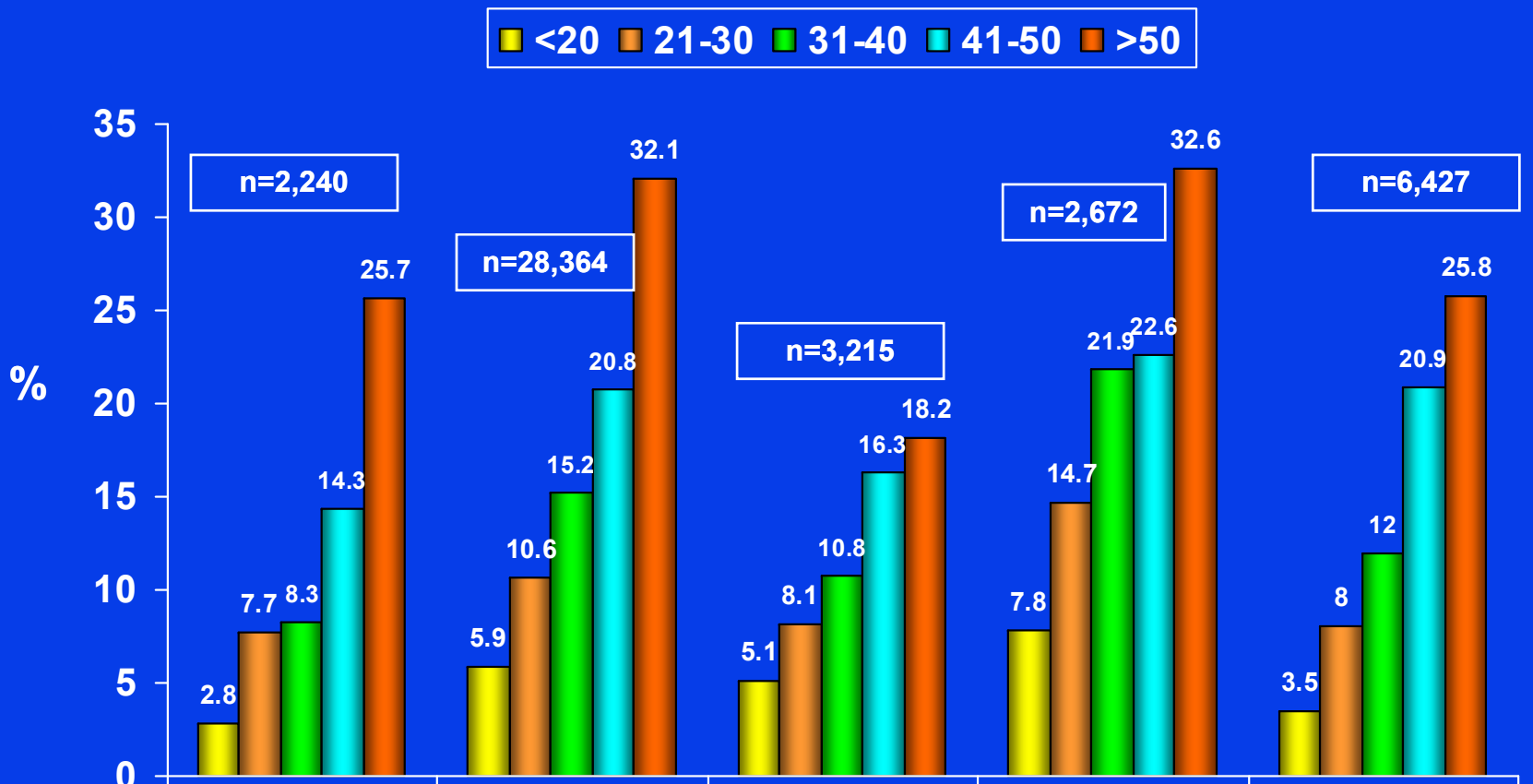
Rate of Major Bleeding by CRUSADE Bleeding Score – STEMI



	None	UFH	LMWH	UFH + LMWH	Bivalirudin
Overall Bleeding Rate	8.3%	11.6%	9.6%	16.3%	8.9%

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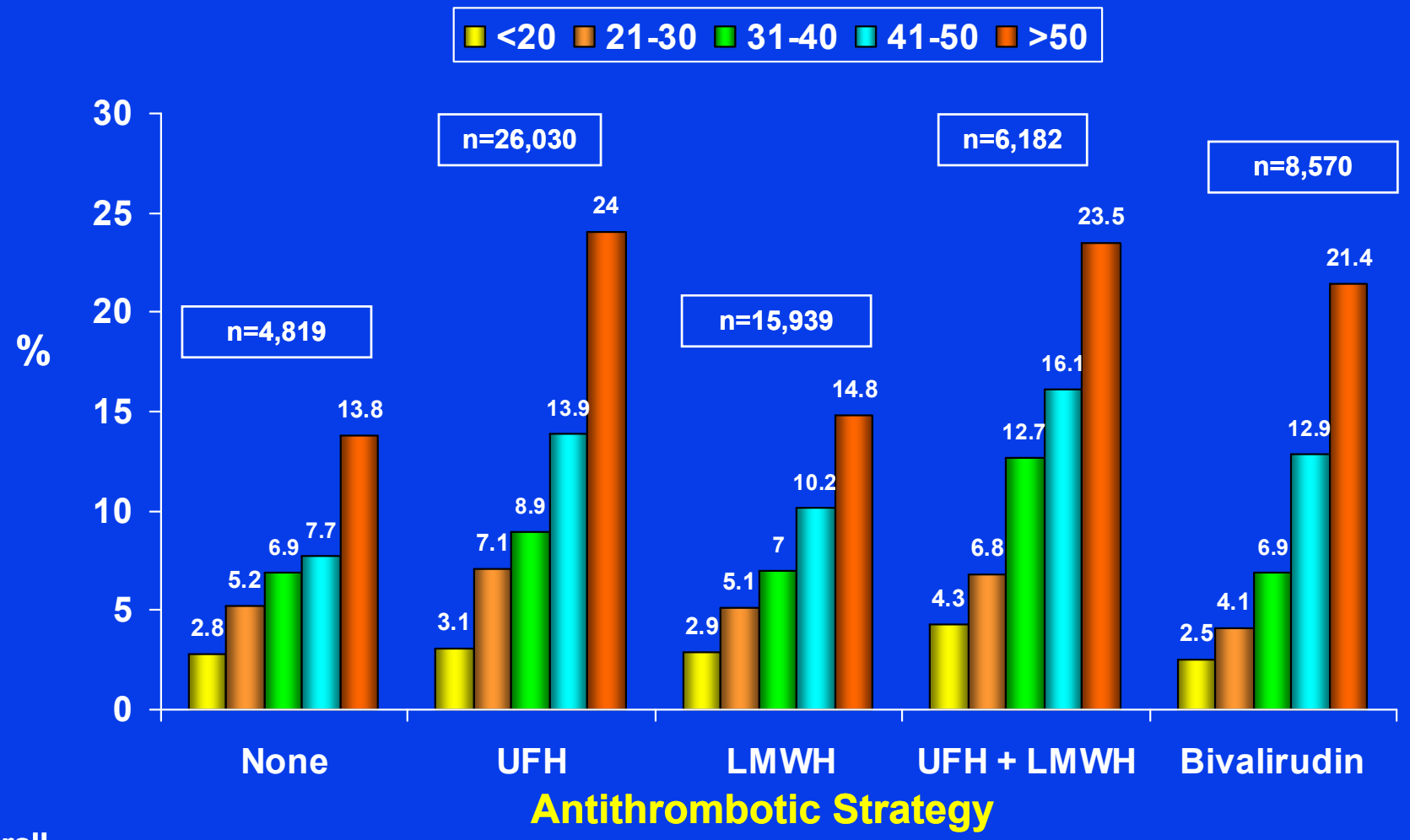
Rate of Major Bleeding by CRUSADE Bleeding Score – NSTEMI



Overall Bleeding Rate	None	UFH	LMWH	UFH + LMWH	Bivalirudin
	8.1%	9.9%	7.9%	10.9%	7.1%

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Cost-Effectiveness of Targeting Patients Undergoing Percutaneous Coronary Intervention for Therapy With

This decision-analytic modeling study demonstrates that for patients undergoing PCI, substitution of bivalirudin for unfractionated heparin monotherapy is projected to increase costs for virtually all patients and would be considered cost-effective for only a minority of patients with a high bleeding risk. From a policy standpoint, studies such as this, aimed at identifying the appropriate risk threshold for initiating treatment, may help in the development of informed guidelines for the use of expensive therapies.

expectancy associated with a major bleed. Major bleeding was predicted to occur in 2.2% of patients. Bivalirudin for all patients was estimated to increase costs by $571 per patient, yielding cost-effectiveness ratios of $287 473 per bleeding event averted and $1 173 360 per quality-adjusted life-year gained. Bivalirudin was cost saving for patients with a predicted bleeding risk >20% (0.16% of CathPCI population). At willingness-to-pay thresholds of $50K and $100K per quality-adjusted life-year gained, bivalirudin was cost-effective for patients with a bleeding risk ≥8% (2.5% patients) and ≥5% (7.9% patients), respectively.

Conclusions—This decision-analytic modeling study demonstrates that for patients undergoing PCI, substitution of bivalirudin for unfractionated heparin monotherapy is projected to increase costs for virtually all patients and would be considered cost-effective for only a minority of patients with a high bleeding risk. From a policy standpoint, studies such as this, aimed at identifying the appropriate risk threshold for initiating treatment, may help in the development of informed guidelines for the use of expensive therapies. (***Circ Cardiovasc Qual Outcomes*. 2010;3:358-365.)**

Key Words: cost-effectiveness analysis ■ bivalirudin ■ unfractionated heparin ■ percutaneous coronary intervention ■ bleeding ■ Markov model

Major bleeding occurs in 0% to 10% of patients undergoing percutaneous coronary intervention (PCI) and is associated with increased morbidity, mortality, prolonged hospital stay, and increased costs.[1–3] Bivalirudin, a direct thrombin inhibitor, reduces major bleeding in patients undergoing PCI.[4–7] Although bivalirudin has been shown to be a safe and effective adjunctive antithrombin during PCI, its high cost may prevent its use in all eligible patients. Nevertheless, use of bivalirudin has been reported by Blue Cross/Blue Shield to be as high as 50% of all PCI procedures.[8] There are limited cost-effectiveness data to guide the optimal use of bivalirudin versus other available antithrombotic therapies in patients undergoing PCI.[9,10]

Editorial see p 335

Although bivalirudin compared with unfractionated heparin (UFH)+glycoprotein IIb/IIIa inhibitor therapy is associated with reduced bleeding and lower costs in patients undergoing PCI,[9,10] little is known about the economic attractiveness of bivalirudin versus UFH alone—a more clinically