Perioperative Anticoagulation Management

ACP Delaware Chapter
Scientific Meeting
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DISCLOSURES

- Desai Pharmaceuticals – research funding
- Pfizer / BMS – research funding
- BMS – funding for Afib educational module

Goals

- Describe the major factors when determining whether to bridge patients on anticoagulants undergoing surgery
- Discuss key features in the management of direct oral anticoagulants
- Identify when to continue anti-platelet therapy
- Understand when to use antidotes for patients on anticoagulants undergoing procedures

Case 1

- 80 year-old male with a history of hypertension, DM, and atrial fibrillation. The patient has had no history of TIA/stroke or bleeding. Patient is on warfarin with well controlled INRs.
- The patient will undergo elective major abdominal surgery.
- Does this patient need to be bridged?

To bridge or not to bridge…

- Risk of thromboembolism off anticoagulants
- Risk of postoperative bleeding after being started on full-dose anticoagulation soon after surgery
- Consequences of thromboembolism and bleeding
- Efficacy of anticoagulation
- Cost and inconvenience

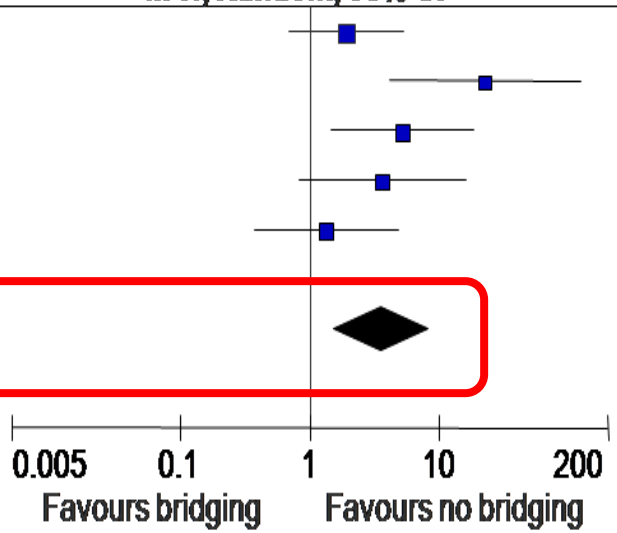
Risk of event off AC

Risk	Atrial Fibrillation
High	$CHADS_2$ score of 5 or 6 Recent (within 3 mo) stroke or transient ischemic attack Rheumatic valvular heart disease
Intermediate	$CHADS_2$ score of 3 or 4
Low	$CHADS_2$ score of 0 to 2 (assuming no prior stroke or transient ischemic attack)

Douketis J, et al. *Chest*. 2012;14 (2 suppl):326-50.

Perioperative Risk for Bleeding

Study or Subgroup	Bridging Events	Bridging Total	No bridging Events	No bridging Total	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	15	342	5	213	1.91 [0.68, 5.33]
Garcia et al., 2008	4	108	2	1185	22.75 [4.12, 125.68]
Jaffer et al., 2010	13	229	3	263	5.22 [1.47, 18.54]
McBane et al., 2010	14	514	2	261	3.63 [0.82, 16.08]
Wysokinski et al., 2008	6	204	4	182	1.35 [0.37, 4.86]
Total (95% CI)		**1397**		**2104**	**3.60 [1.52, 8.50]**
Total events	52		16		
Heterogeneity: $I^2 = 52\%$					



Bridging associated with 3-4-fold increase in *major* bleeding

Siegal D, et al. *Circulation* 2012;126:1630.

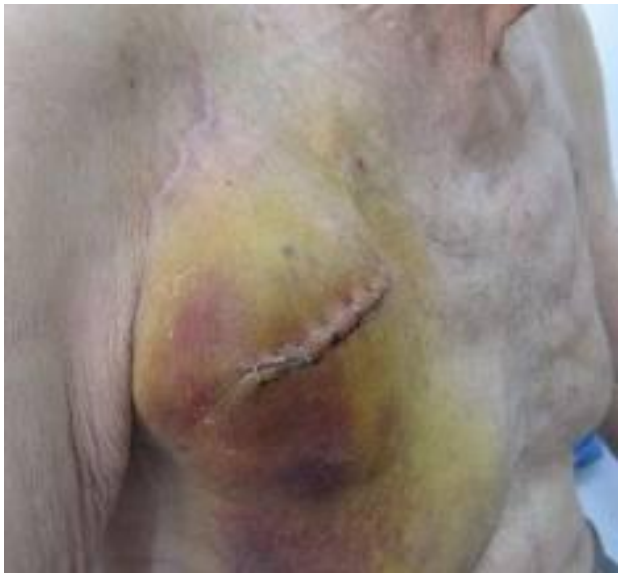
Risk of Post-Op Bleeding

- For certain invasive procedures, major bleeding is rare on OAC
  - Dental extractions (4/2014, 0.2%)
  - Arthrocentesis and joint injection (0/32, 0%)
  - Cataract surgery (0/203, 0%)
  - Upper endoscopy or colonoscopy, with or without biopsy (0/111, 0%). Polypectomy is considered high risk
  - Pacemaker insertion (4%)

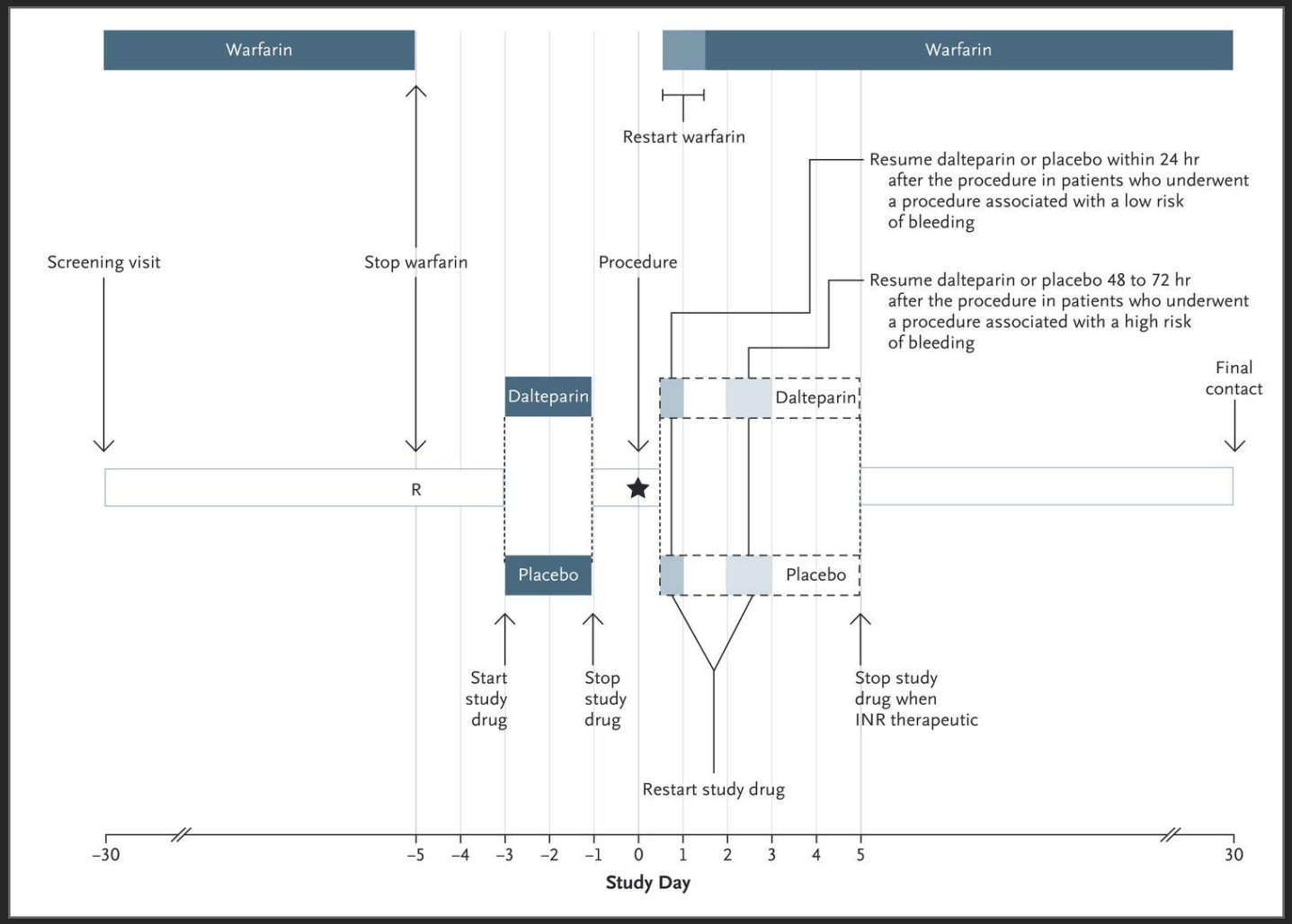
BRUISECONTROL - Results

Pacemaker hematoma

- **continue warfarin** **4%**
- **interrupt warfarin + bridging** **16%**



BRIDGE - Study Design



Douketis JD, et al. N Engl J Med 2015.

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	No Bridging (N=950)	Bridging (N=934)
Age — yr	71.8±8.74	71.6±8.88
Male sex — no. (%)	696 (73.3)	686 (73.4)
Race — no. (%)†		
White	860 (90.5)	849 (90.9)
Nonwhite	88 (9.3)	82 (8.8)
Unknown	2 (0.2)	3 (0.3)
Weight — kg	96.2±24.87	95.4±23.50
$CHADS_2$ score‡		
Mean	2.3±1.03	2.4±1.07
Distribution — no. (%)		
0	1 (0.1)	1 (0.1)
1	216 (22.7)	212 (22.7)
2	382 (40.2)	351 (37.6)
3	229 (24.1)	232 (24.8)
4	96 (10.1)	106 (11.3)
5	23 (2.4)	27 (2.9)
6	3 (0.3)	5 (0.5)
CHF or left ventricular dysfunction — no. (%)	289 (30.4)	310 (33.2)
Hypertension — no. (%)	833 (87.7)	806 (86.3)
Diabetes mellitus — no. (%)	390 (41.1)	382 (40.9)
Stroke — no. (%)	79 (8.3)	99 (10.6)
Transient ischemic attack — no. (%)	79 (8.3)	77 (8.2)
Mitral valve disease — no. (%)	165 (17.4)	142 (15.2)
Stenosis	19 (2.0)	10 (1.1)
Regurgitation	142 (14.9)	133 (14.2)
Prolapse	13 (1.4)	5 (0.5)
Myocardial infarction — no. (%)	138 (14.5)	155 (16.6)
Renal disease — no. (%)	108 (11.4)	92 (9.9)
Solid malignant disease — no. (%)	68 (7.2)	52 (5.6)
Laboratory values		
Hemoglobin — g/dl	13.8±1.67	13.8±1.62
Platelet count — thrombocytes/mm^3	209,300±592,900	209,200±580,500
INR	2.4±0.57	2.4±0.57
Serum creatinine — mg/dl	1.1±0.32	1.1±0.32
Creatinine clearance — ml/min	88.1±39.50	87.6±40.14
Medication use — no. (%)		
Aspirin	324 (34.1)	329 (35.2)
Clopidogrel	30 (3.2)	21 (2.2)
Nonsteroidal antiinflammatory drug	34 (3.6)	25 (2.7)
COX-2 inhibitor	8 (0.8)	13 (1.4)

* Plus–minus values are means ±SD. There were no significant differences between the groups ($P<0.05$). CHF denotes congestive heart failure, COX-2 cyclooxygenase type 2, and INR international normalized ratio.
† Race was self-reported. The patients for whom data were unknown are those who chose not to provide information.
‡ $CHADS_2$ is a score used to estimate the risk of stroke in patients with atrial fibrillation. The score ranges from 1 to 6; 1 point each is assigned for congestive heart failure, hypertension, age of 75 years or older, and diabetes mellitus, and 2 points are assigned for stroke or transient ischemic attack.

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Patient Characteristics

Douketis JD, et al. N Engl J Med 2015.

OUTCOMES

Table 3. Study Outcomes.

Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

* P value for noninferiority.
† P value for superiority.

Douketis JD, et al. N Engl J Med 2015.

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Case 1

80 year-old male with HTN, DM, afib. No history of TIA/stroke or bleeding.

CHADS score?

- ✓ 3

Guideline?

- ✓ Intermediate risk of event – bridging can be considered but no certain benefit

Risk of bleeding?

- ✓ Moderate

Plan:

- ✓ No bridging. Stop warfarin 5 days prior to OR and restart the evening of surgery

Case 2

- 45 year-old female with a history of Crohn's Disease.
- Subtotal colectomy 2 years ago, which was complicated by a PE in the post-operative period. The patient was treated with warfarin uneventfully for 6 months.
- The patient subsequently developed a spontaneous DVT 4 months ago and has been on warfarin since that time.
- The patient is now scheduled for major abdominal surgery.

What next?

- Does this patient need to be bridged?
  - What is her risk of recurrent DVT/PE?
  - What is her risk of major post-op bleeding?

Risk of event off AC

Risk	VTE
High	Recent (within 3 mo) VTE Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Intermediate	VTE within the past 3-12 mo Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) Recurrent VTE Active cancer (treated within 6 mo or palliative)
Low	VTE >12 mo previous and no other risk factors

Douketis J, et al. *Chest*. 2012;14 (2 suppl):326-50.

Efficacy of AC for VTE patients

- Treatment dose
  - 80-90%
- Prophylaxis dose
  - 66-75%

Case 2

45 year-old female Crohn's Disease, h/o VTE x2, most recently 8 months ago, now on warfarin.

Risk of VTE?

- Intermediate risk

Bridge?

- Consider bridging

Plan: Bridge preop, use prophylaxis dose post-op

Case 3

- 68M with PMH DM, HTN, AS status post mechanical AV replacement 2 years ago taking warfarin.
- Patient planned for nephrectomy for newly diagnosed renal cell carcinoma.
  - What is his risk of an event off AC?
  - Does he need to be bridged?

Table 7. Major Factors Affecting Risk of ATE in Mechanical Valve Patients

Type of prosthetic valve	Bileaflet valves	0.5%/y on AC
	Tilting disk valves	0.7%/y on AC
	Caged-ball valves	2.5%/y on AC
Position of the valve	Mitral valve	22%/y off AC
	Aortic valve	12%/y off AC
Duration of time since valve placement	<3 mo	Higher risk
	<1 y	Moderately increased risk
	>1 y	Usual risk
Other factors	Concomitant AF	
	Older age	
	Previous episode of ATE	
	Left ventricular dysfunction	
	Left atrial enlargement	
	Hypercoagulable disorder	
	Pregnancy	

AC = anticoagulation; AF = atrial fibrillation; ATE = arterial thromboembolism.

Risk of event off AC

Risk	Mechanical Heart Valves
High	Any mitral valve prosthesis Any caged-ball or tilting disc aortic valve prosthesis Recent (within 6 mo) stroke or transient ischemic attack
Intermediate	Bileaflet aortic valve prosthesis and one or more of the of following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age > 75 y
Low	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke

Douketis J, et al. *Chest*. 2012;14 (2 suppl):326-50.

Case 3

68M DM, HTN, mechanical AV replacement for nephrectomy

Risk of TE event?

- Intermediate

Bridge?

- Yes

Plan: Bridge with LMWH

Summary – AF / MVR / VTE

Risk	Example	Strategy
High	VTE within 3 months VTE with severe thrombophilia Afib with CHADS 5-6 or CVA Mechanical mitral valve Older type of AVR	Bridge - monitor closely for post-op bleeding
Moderate	VTE 3-12 months ago Recurrent VTE Bileaflet AVR + risk factor Afib with 3-4 stroke risk factors	Bridging can be considered but unproven benefit and possible increased risk
Low	1 prior VTE >12 months ago Afib with 0-2 stroke risk factors Mechanical bileaflet AVR	No bridging

THE MECHANICS

- Hold warfarin at least 5 days prior to procedure
- Start LMWH 3 days prior to procedure
- Hold LMWH 24 hours prior to procedure
  - Hold IV heparin 4-6 hours prior to procedure
- Resume warfarin 12-24 hours post-op when there is adequate hemostasis
- Resume heparin post-op depending on risk of bleeding and risk of thrombosis
  - 12-24 hours after surgery for low bleeding risk surgery
  - 48-72 hours after surgery for high bleeding risk surgery
  - Consider initially using prophylaxis dose for VTE patients

Anti-Platelet Agents

- 60M with PMH DM, HTN, CAD s/p STEMI with LCx DES placed 8 months ago. Patient now found to have colon cancer on routine colonoscopy and planned for right hemicolectomy.
  - Reports excellent exercise tolerance without CP or DOE.
  - Patient takes ASA and Clopidogrel

  - Should we hold?
    - ASA
    - Clopidogrel
    - Both
    - Neither

Risk Stratification

- Primary prevention
  - no known CAD
- Secondary prevention
  - CAD, MI, PCI, CABG, CVA
- Stent
  - BMS / DES

Primary Prevention

- Low risk of event
- Hold 7 days prior to surgery

Secondary Prevention

Moderate to high risk of event

POISE 2 - APRIL 2014

- Randomized 10,010 patients to asa or placebo
  - Patients were “at risk” for vascular complications
  - At risk defined as:
  - Stratified to whether previously on asa (5600 patients) or were asa naïve (4400 patients)
  - 200mg just before surgery then 100mg daily
  - Primary outcome: Death or nonfatal MI at 30 days

Devereaux PJ. *NEJM.* 2014;370:1494-53.

Inclusion criteria

Age >45 years and 1 or more of the following:

1. CAD

2. PAD

3. CVA

4. Major vascular surgery

5. Any 3 of the following
    - A. Age ≥70 years
    - B. Major surgery (intraperitoneal, intrathoracic, retroperitoneal, major ortho)
    - C. CHF
    - D. TIA
    - E. DM
    - F. Hypertension
    - G. CKD (creatinine >2.0 mg/dl)
    - H. Smoking (within 2 years)
    - I. Emergent/urgent surgery

Outcome	Aspirin (N=4998)	Placebo (N=5012)	Hazard Ratio (95% CI)†	P Value
	no. (%)			
Primary composite outcome: death or nonfatal myocardial infarction	351 (7.0)	355 (7.1)	0.99 (0.86–1.15)	0.92
Secondary outcomes				
Death, nonfatal myocardial infarction, or nonfatal stroke	362 (7.2)	370 (7.4)	0.98 (0.85–1.13)	0.80
Death, nonfatal myocardial infarction, cardiac revascularization, nonfatal pulmonary embolism, or nonfatal deep venous thrombosis	402 (8.0)	407 (8.1)	0.99 (0.86–1.14)	0.90
Tertiary outcomes — no. (%)				
Death from any cause	65 (1.3)	62 (1.2)	1.05 (0.74–1.49)	0.78
Death from cardiovascular cause	35 (0.7)	35 (0.7)	1.00 (0.63–1.60)	0.99
Myocardial infarction	309 (6.2)	315 (6.3)	0.98 (0.84–1.15)	0.85
Nonfatal cardiac arrest	9 (0.2)	12 (0.2)	0.75 (0.32–1.79)	0.52
Cardiac revascularization	13 (0.3)	17 (0.3)	0.77 (0.37–1.58)	0.47
Pulmonary embolism	33 (0.7)	31 (0.6)	1.07 (0.65–1.74)	0.79
Deep-vein thrombosis	25 (0.5)	35 (0.7)	0.72 (0.43–1.20)	0.20
New clinically important atrial fibrillation	109 (2.2)	94 (1.9)	1.16 (0.88–1.53)	0.28
Peripheral arterial thrombosis	13 (0.3)	15 (0.3)	0.87 (0.41–1.83)	0.71
Amputation	10 (0.2)	13 (0.3)	0.77 (0.34–1.76)	0.54
Rehospitalization for cardiovascular reasons	70 (1.4)	54 (1.1)	1.30 (0.91–1.86)	0.15
Acute kidney injury with receipt of dialysis‡	33 (0.7)	19 (0.4)	1.75 (1.00–3.09)	0.05
Safety outcomes				
Life-threatening bleeding	87 (1.7)	73 (1.5)	1.19 (0.88–1.63)	0.26
Major bleeding	230 (4.6)	188 (3.8)	1.23 (1.01–1.49)	0.04
Clinically important hypotension	2143 (42.9)	2096 (41.8)	1.03 (0.97–1.09)	0.37
Stroke	16 (0.3)	19 (0.4)	0.84 (0.43–1.64)	0.62
Congestive heart failure	44 (0.9)	38 (0.8)	1.16 (0.75–1.79)	0.50

Secondary Prevention - Guidelines

- ACC / AHA cites POISE-2 and PEP as negative trials. States only 23% POISE-2 patients had CAD – 2,300 subjects!
- Cites meta-analysis purporting to show increased MI when asa discontinued; actually found no studies comparing rates
- Gives 2 conflicting recommendations:
  - *May be reasonable to continue asa when the risk of potential increased cardiac events outweighs the risk of increased bleeding.*
  - *Initiation or continuation of asa is not beneficial in patients undergoing elective surgery who have not had previous coronary stenting, unless the risk of ischemic events outweighs the risk of surgical bleeding.*
- Bottom Line: Data supports holding

Secondary Prevention – What to Do

- Minor surgery / procedures: Doubtful any benefit but can continue given lack of harm
- Major surgery: Preferably hold anti-platelet agent; Clinician flexibility given need to work with other disciplines (Anesthesia)

Intracoronary Stents

- Patients are on DAPT for variable duration
- RCT in peri-op period – none
- Safety of holding thienopyridine – uncertain
- Determine risk off DAPT

DAPT Trial

12 vs 30 months DAPT after DES

- All receive 12 months thienopyridine (clopidogrel or prasugrel) and asa
- All patients cont asa
- Randomized to continue thienopyridine or placebo for 18 months

Primary efficacy end points:

- Stent thrombosis
- Major adverse cardiovascular and cerebrovascular events (death, MI, or CVA)

Mauri L et al. *N Engl J Med.* 2014;371:2155-2166.

DAPT OUTCOMES

Table 2. Stent Thrombosis and Major Adverse Cardiovascular and Cerebrovascular Events.*

Outcome	Continued Thienopyridine (N=5020)	Placebo (N=4941)	Hazard Ratio, Thienopyridine vs. Placebo (95% CI)†	P Value†
	no. of patients (%)			
Stent thrombosis‡	19 (0.4)	65 (1.4)	0.29 (0.17–0.48)	<0.001
Definite	15 (0.3)	58 (1.2)	0.26 (0.14–0.45)	<0.001
Probable	5 (0.1)	7 (0.1)	0.71 (0.22–2.23)	0.55
Major adverse cardiovascular and cerebrovascular events§	211 (4.3)	285 (5.9)	0.71 (0.59–0.85)	<0.001
Death	98 (2.0)	74 (1.5)	1.36 (1.00–1.85)	0.05
Cardiac	45 (0.9)	47 (1.0)	1.00 (0.66–1.52)	0.98
Vascular	5 (0.1)	5 (0.1)	0.98 (0.28–3.39)	0.98
Noncardiovascular	48 (1.0)	22 (0.5)	2.23 (1.32–3.78)	0.002
Myocardial infarction	99 (2.1)	198 (4.1)	0.47 (0.37–0.61)	<0.001
Stroke	37 (0.8)	43 (0.9)	0.80 (0.51–1.25)	0.32
Ischemic	24 (0.5)	34 (0.7)	0.68 (0.40–1.17)	0.16
Hemorrhagic	13 (0.3)	9 (0.2)	1.20 (0.50–2.91)	0.68
Type uncertain	0	1 (<0.1)	—	0.32

* At 12 months after placement of a drug-eluting stent, patients were randomly assigned to receive either continued thienopyridine therapy plus aspirin or placebo plus aspirin for 18 months. Data are presented for the intention-to-treat population. The primary analysis was performed on data from the period of 12 to 30 months after enrollment, and the study coprimary efficacy end points were stent thrombosis and major adverse cardiovascular and cerebrovascular events. Percentages are Kaplan–Meier estimates.

† The hazard ratios and P values were stratified according to geographic region (North America, Europe, or Australia and New Zealand), thienopyridine drug received at the time of randomization, and presence or absence of risk factors for stent thrombosis. P values were calculated with the use of a log-rank test.

‡ Definite and probable stent thrombosis were determined according to the criteria of the Academic Research Consortium.

§ The end point of major adverse cardiovascular and cerebrovascular events was a composite of death, myocardial infarction, or stroke.

Mauri L et al. *N Engl J Med.* 2014;371:2155-2166.

DAPT – Longer vs Shorter Duration

Impact on Mortality

Meta-analysis of longer- versus shorter-duration DAPT (aspirin plus a P2Y12 inhibitor) after DES

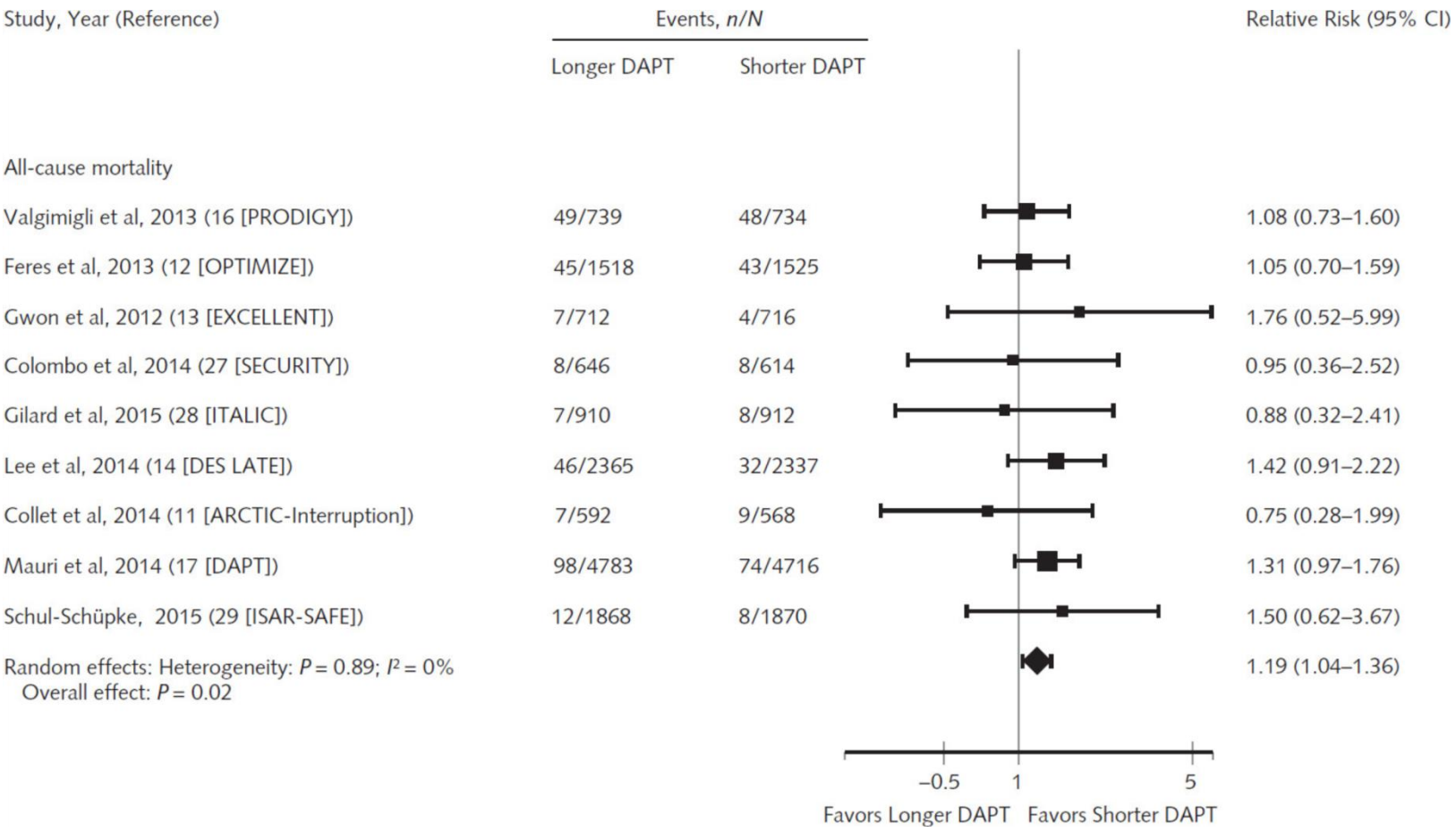
Main outcomes - Mortality, MI, Major bleeding.

Spencer FA, et al. *Ann Int Med.* 2015.

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

Longer Versus Shorter Duration Dual-Antiplatelet Therapy After Drug-Eluting Stent Placement: A Systematic Review and Meta-analysis

MORTALITY



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Annals of Internal Medicine
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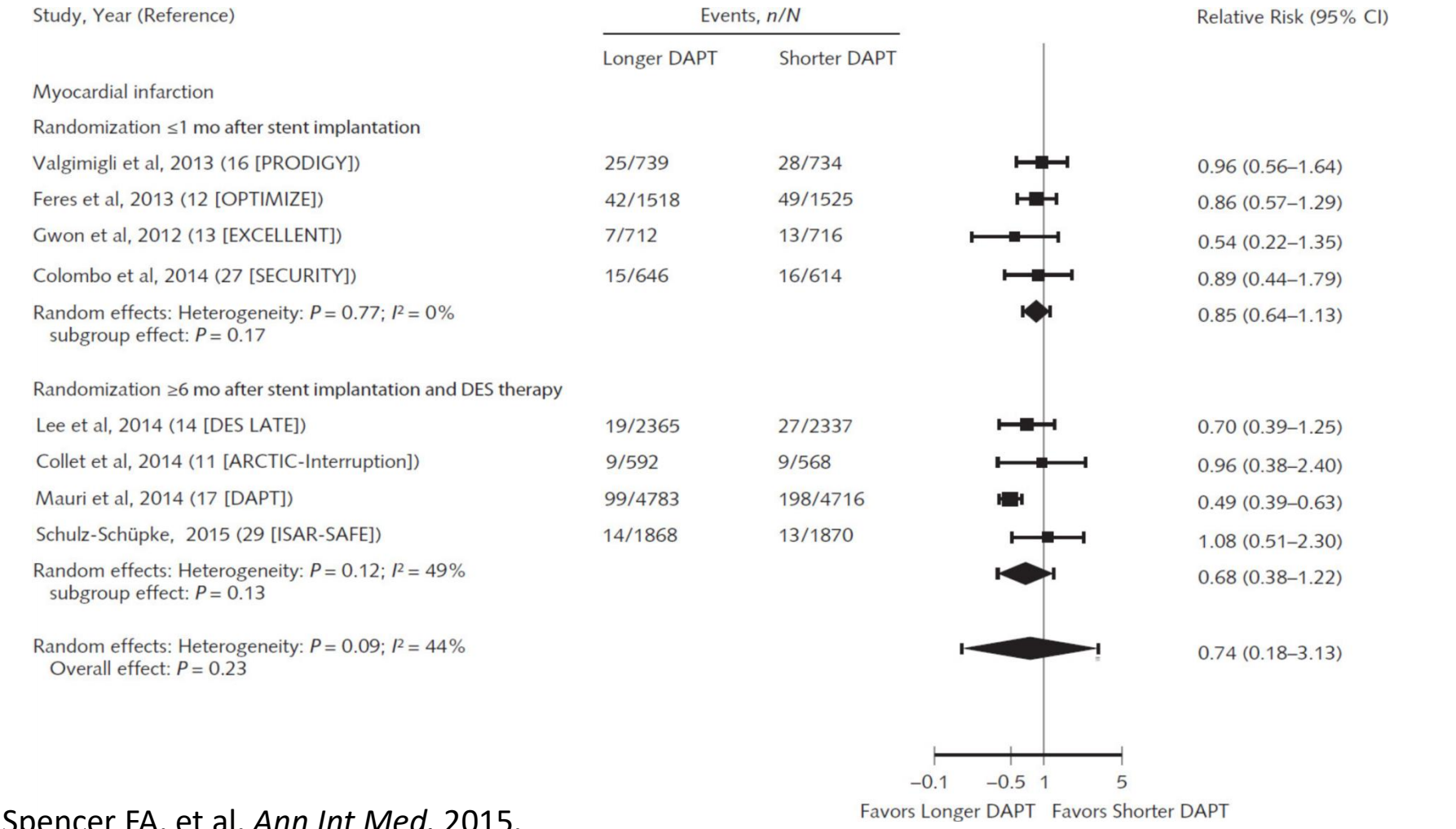
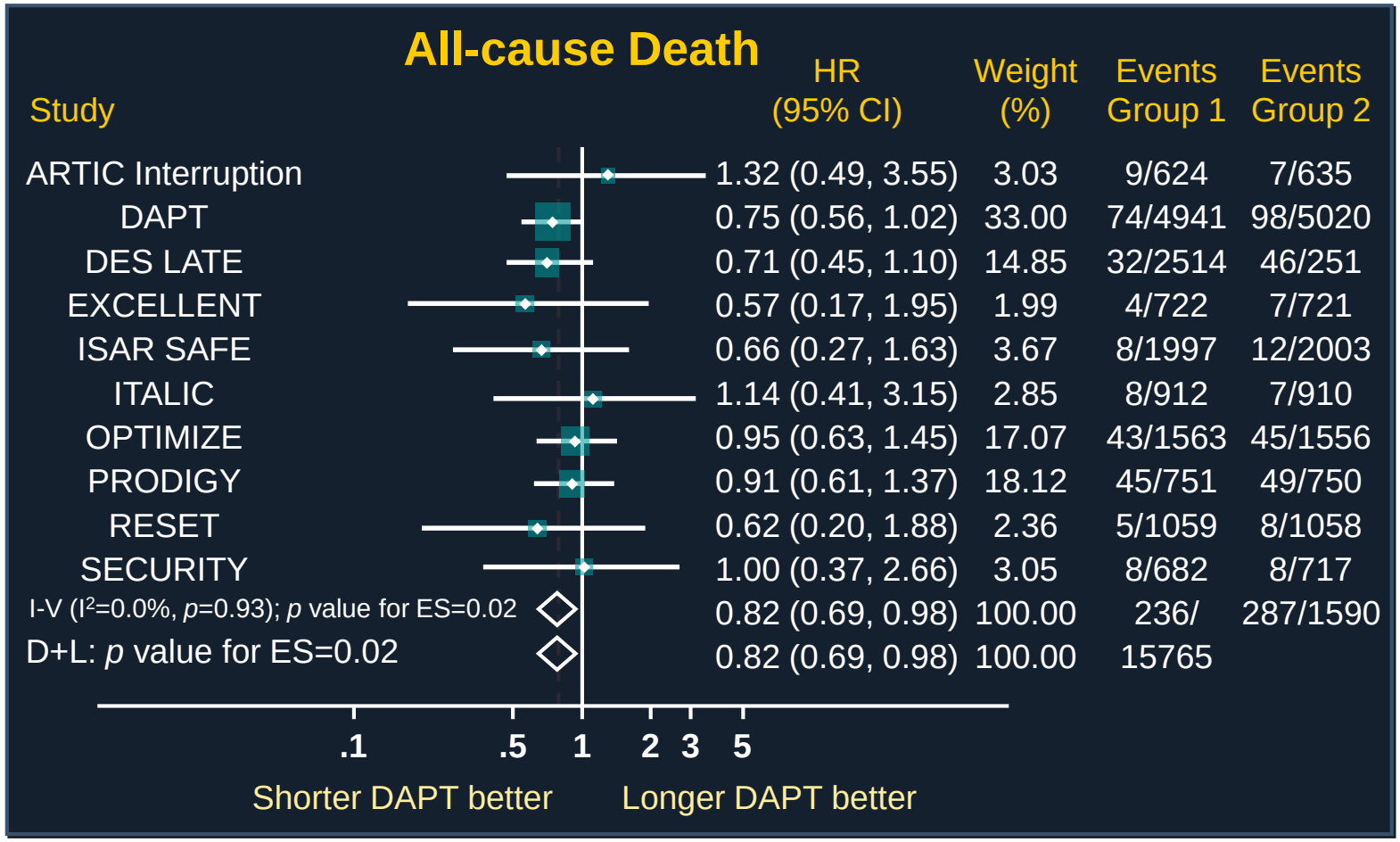
Longer Versus Shorter Duration Dual-Antiplatelet Therapy After Drug-Eluting Stent Placement: A Systematic Review and Meta-analysis

MI



Spencer FA, et al. *Ann Int Med.* 2015.

Mortality with Extended Duration DAPT After DES: Meta-Analysis of 10 RCTs and 31,666 Pts



MI: No diff

Palmerini T, et al. *JACC.* 2015;65:1092-1102.

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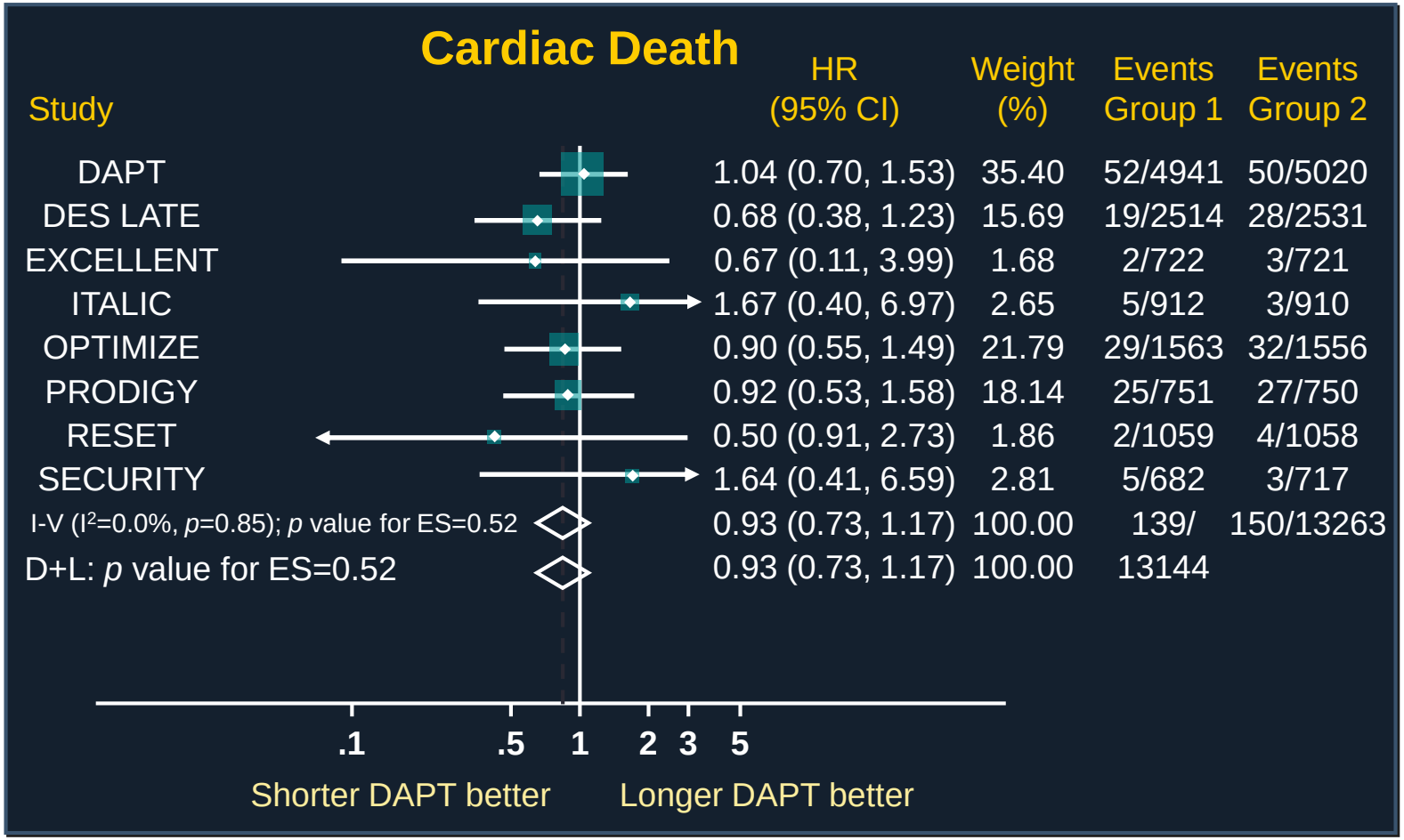

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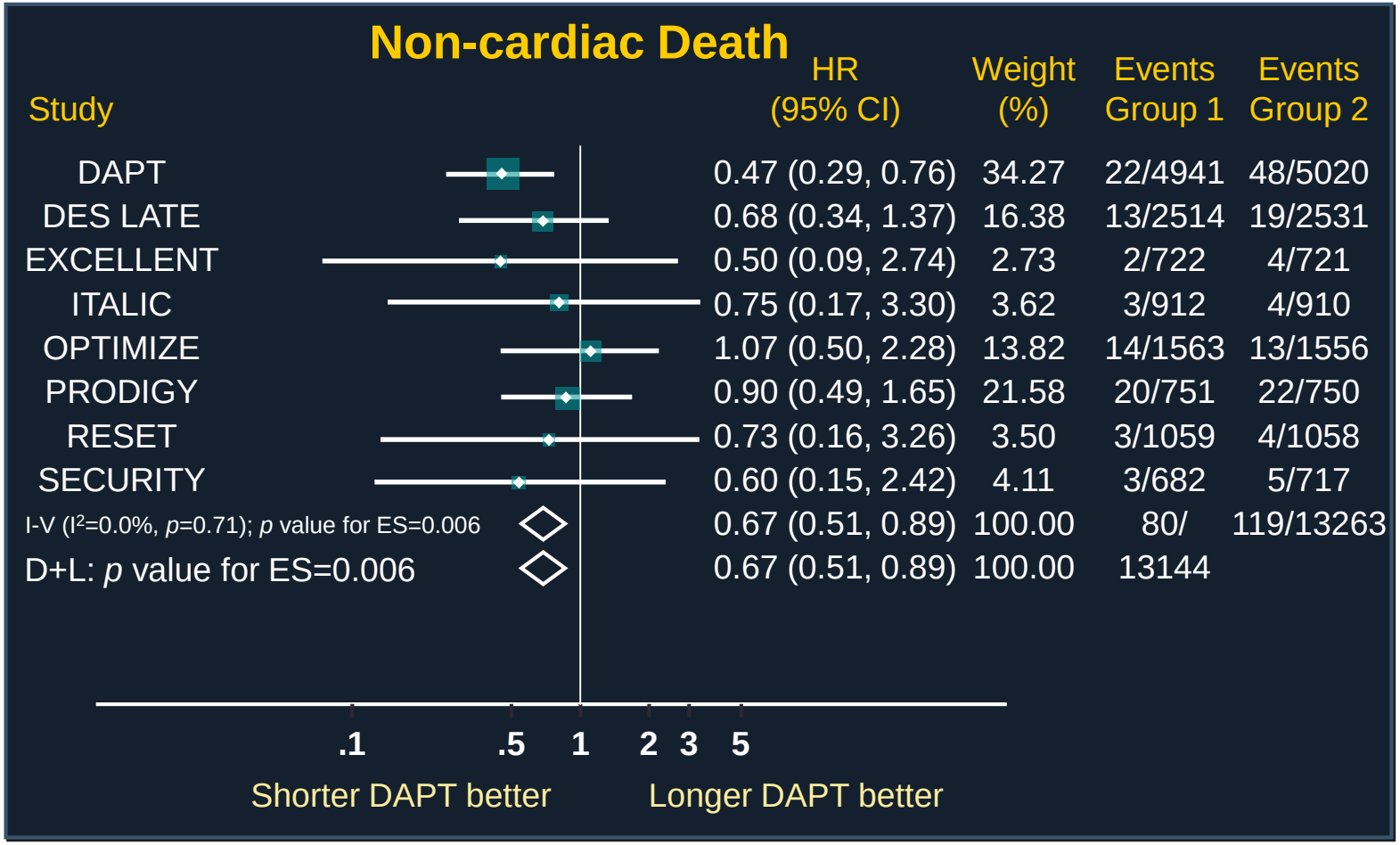

Palmerini T, et al. *JACC.* 2015;65:1092-1102.

Intracoronary Stents – *BOTTOM LINE*

- Complex and mixed results

- 6 months DAPT likely offers equal protection against MI compared to 12 months, and ≥12 months DAPT decreases MI and stent thrombosis but increases mortality and major bleeding.

ACC/AHA Guideline Update on Duration of Dual Antiplatelet Therapy in CAD

- In patients with CAD treated with a DES, clopidogrel should be given for at least 6 months (Class I)
- In patients with CAD treated with a BMS, clopidogrel should be given for at least 1 month (Class I)

Levine GN. *J Am Coll Cardiol*. 2016.

Intracoronary Stents

- Delay surgery for at least 1 month after BMS and 6 months after DES.
- When outside this window, cont ASA and hold Clopidogrel
- If unable to delay, discuss continuing dual antiplatelet therapy with Surgery
- If <1 month for BMS or <6 months for DES (<12 months if placed in setting of ACS) and unable to delay or to continue DAPT, consider bridging with IV cangrelor

Direct Oral Anticoagulants

- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

Peri-operative benefits:

- Short half life
- No monitoring

Drawbacks:

- Not short enough
- No monitoring

CASE 4

78-yr female with AF on dabigatran, 150 mg BID, scheduled for elective hip replacement

CHADS score = 4 (prior TIA, age >75, htn)

CrCl = 45 mL/min (moderate CKD)

DOAC Management Peri-Op

Depends on renal function and type of surgery

	Low Bleed Risk Surgery	High Bleed Risk Surgery
GFR >50	Pre-op: Hold 1 day prior to OR Post-op: Resume 1 day after OR	Pre-op: Hold 2 days prior to OR Post-op: Resume 2-3 days after OR
GFR <50	Pre-op: Hold 2 days prior to OR Post-op: Resume 1 day after OR	Pre-op: Hold 3-4 days prior to OR Post-op: Resume 2-3 days after OR

* Neuraxial anesthesia – Timing varies by agent and dose.

DOACs:
Implications of Irreversibility

ATRIAL FIBRILLATION			
	VKA	DOAC	NNT
Fatal Bleeding	0.51%	0.27%	419
Case Fatality Rate	8.3%	5.8%	39
VENOUS THROMBOEMBOLISM			
	VKA	DOAC	NNT
Fatal Bleeding	0.16%	0.06%	978
Case Fatality Rate	9.3%	5.2%	NS

11 trials
N = 100,324

Caldeira D, et al. *Heart*. 2015;101:1204-11.

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ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

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ABSTRACT

BACKGROUND

Specific reversal agents for non–vitamin K antagonist oral anticoagulants are lacking. Idarucizumab, an antibody fragment, was developed to reverse the anticoagulant effects of dabigatran.

METHODS

We undertook this prospective cohort study to determine the safety of 5 g of intravenous idarucizumab and its capacity to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding (group A) or required an urgent procedure (group B). The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration

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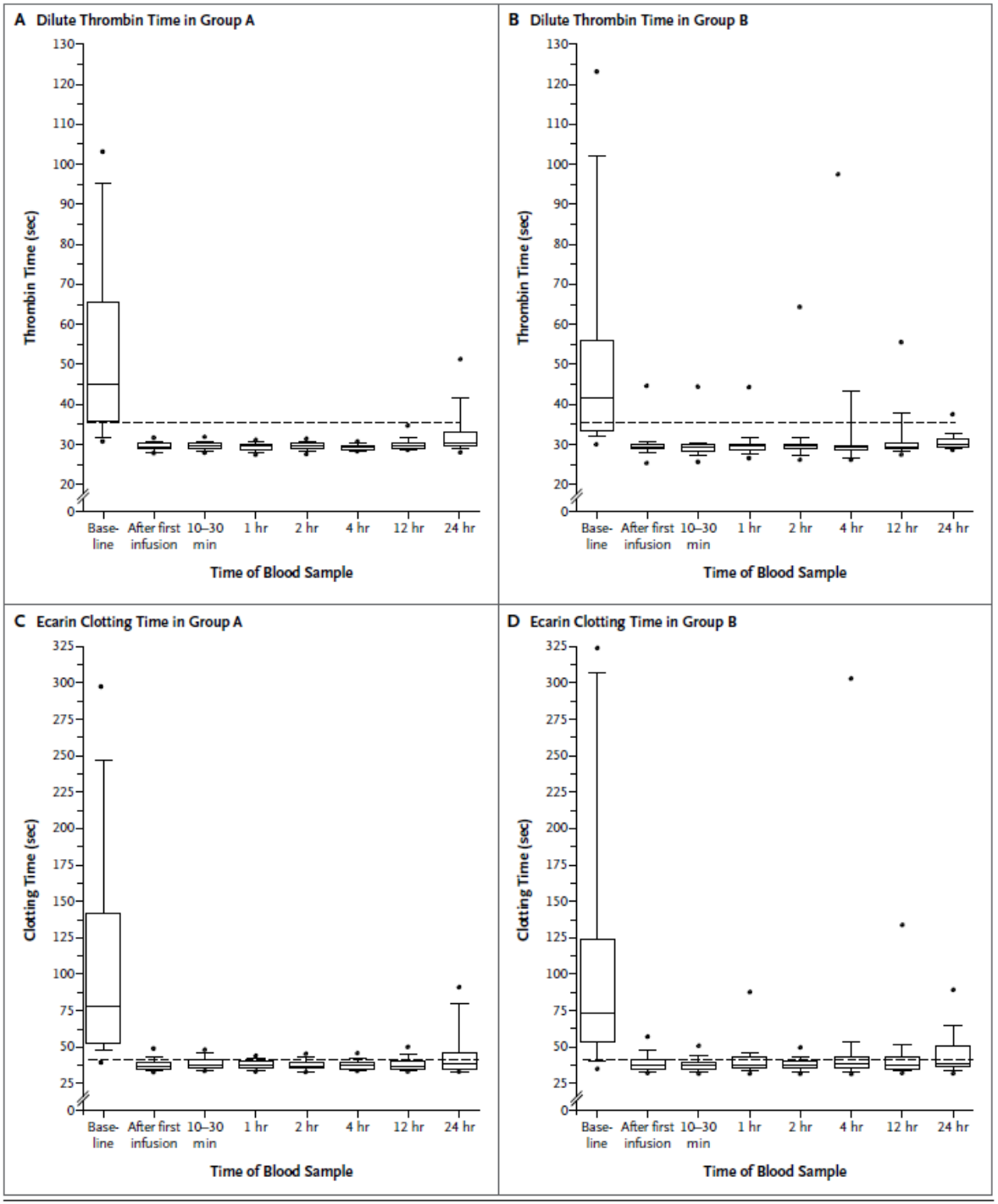
GROUP A: Serious bleeding (n=51)

GROUP B: Urgent procedure (n=39)

Pollack CV. *New Engl J Med.* 2015;373;511-20.



Normalized clotting time

88% to 98% patients;

Onset within minutes.

Group A

Hemostasis restored:

median of 11.4 hours.

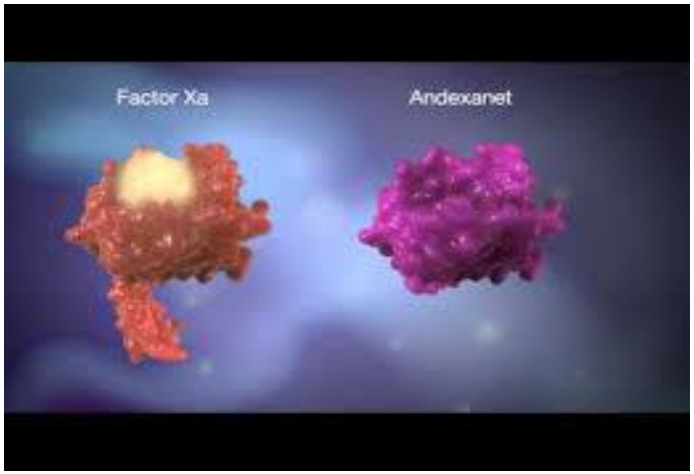
Group B

Normal intra-operative hemostasis: 33/36

Reversal Agents
Factor Xa Inhibitors

Andexanet alfa: F-Xa Inhibitor Antidote

- Factor Xa decoy - Targets and sequesters Factor Xa inhibitors
- Once bound, Factor Xa inhibitors unable to bind native Factor Xa
- Demonstrated reversal of Factor Xa inhibitors by biomarkers



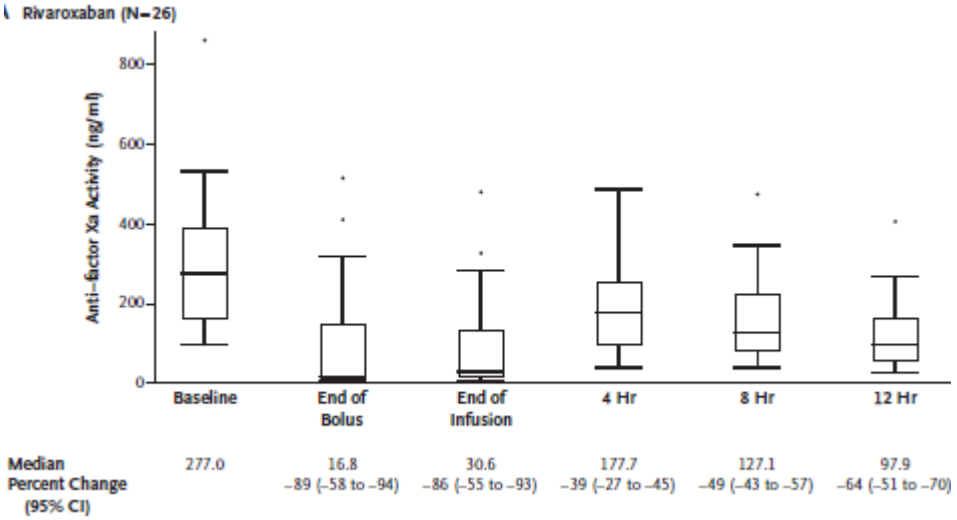
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

Acute major bleeding
N = 67
Bolus plus 2 hour infusion



Connolly SJ. *New Engl J Med.* 2015;375;1131-41.

4-Factor PCC in Patients on VKA with Major Bleeding

Randomized to 4F-PCC or FFP

Primary analyses:
- 24-hour hemostatic efficacy
- INR correction (≤1.3) at 30 minutes

N = 202 patients

Median INR: 3.9 PCC group and 3.6 FFP group

Sarode R. *Circulation.* 2013;128:1234-43.

4-Factor PCC in Patients on VKA with Major Bleeding

RESULTS

- Effective hemostasis achieved in 72% and 65% of patients, non-inferior (CI, –5.8 to 19.9)
- Rapid INR reduction: 62% of patients receiving 4F-PCC versus 9% receiving FFP (P<.05)
- Coagulation factors higher in the PCC group from 0.5 to 3 hours after infusion start (*P*<0.02)
- Adverse events, thromboembolic events, and deaths - No diff

Sarode R. *Circulation.* 2013;128:1234-43.

Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial

Thorsten Steiner, Sven Poli*, Martin Griebe, Johannes Hüsing, Jacek Hajda, Anja Freiberger, Martin Bendszus, Julian Bösel, Hanne Christensen, Christian Dohmen, Michael Hennerici, Jennifer Kollmer, Henning Stetefeld, Katja E Wartenberg, Christian Weimar, Werner Hacke, Roland Veltkamp*

Lancet Neurol 2016; 15: 566–73

See Comment page 535

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Summary

Background Haematoma expansion is a major cause of mortality in intracranial haemorrhage related to vitamin K antagonists (VKA-ICH). Normalisation of the international normalised ratio (INR) is recommended, but optimum haemostatic management is controversial. We assessed the safety and efficacy of fresh frozen plasma (FFP) versus prothrombin complex concentrate (PCC) in patients with VKA-ICH.

Methods We did an investigator-initiated, multicentre, prospective, randomised, open-label, blinded-endpoint trial. Patients aged at least 18 years with VKA-ICH who presented within 12 h after symptom onset with an INR of at least 2·0 were randomly assigned (1:1) by numbered sealed envelopes to 20 mL/kg of intravenous FFP or 30 IU/kg of intravenous four-factor PCC within 1 h after initial cerebral CT scan. The primary endpoint was the proportion of patients with INR 1·2 or lower within 3 h of treatment initiation. Masking of treatment was not possible, but the primary analysis was observer masked. Analyses were done using a treated-as-randomised approach. This trial is registered with EudraCT, number 2008-005653-37, and ClinicalTrials.gov, number NCT00928915.

Findings Between Aug 7, 2009, and Jan 9, 2015, 54 patients were randomly assigned (26 to FFP and 28 to PCC) and 50 received study drug (23 FFP and 27 PCC). The trial was terminated on Feb 6, 2015, after inclusion of 50 patients after a safety analysis because of safety concerns. Two (9%) of 23 patients in the FFP group versus 18 (67%) of 27 in the PCC group reached the primary endpoint (adjusted odds ratio 30·6, 95% CI 4·7–197·9; p=0·0003). 13 patients died: eight (35%) of 23 in the FFP group (five from haematoma expansion, all occurring within 48 h after symptom onset) and five (19%) of 27 in the PCC group (none from haematoma expansion), the first of which occurred on day 5 after start of treatment. Three thromboembolic events occurred within 3 days (one in the FFP group and two in the PCC group), and six after day 12 (one and five). 43 serious adverse events (20 in the FFP group and 23 in the PCC group) occurred in 26 patients. Six serious adverse events were judged to be FFP related (four cases of haematoma expansion, one anaphylactic reaction, and one ischaemic stroke) and two PCC related (ischaemic stroke and pulmonary embolism).

Steiner T. Lancet Neurol. 2016;15:566-73.

Chest Guidelines
Anticoagulation & Thrombosis 9th Edition (AT9)

9.3. For patients with VKA-associated major bleeding, we suggest rapid reversal of anticoagulation with 4-factor prothrombin complex concentrate rather than with plasma (2C).

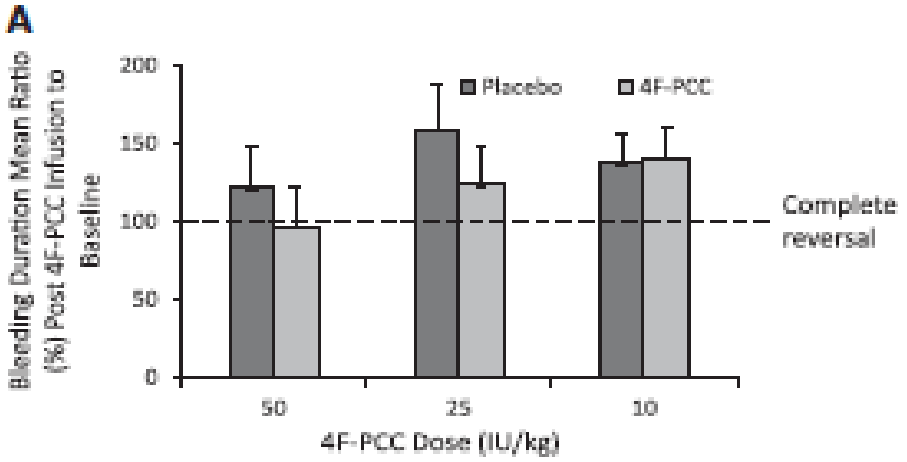
Holbrook A, et al. *Chest.* 2012;e152S-e184S.

4-Factor PCC for DOAC Bleeding

4F-PCC vs placebo in volunteers given anti-FXa inhibitor

Edoxaban 60mg vs Placebo, N=93

Punch biopsy - Bleeding duration fully corrected with the highest dose of 4F-PCC evaluated (50 U/kg)



Zahir H. *Circulation*. 2015;131:82-90.

TAKE HOME POINTS

- AFIB - Don’t bridge (most patients)
- Mech valves – Bridge (except lone A-valve)
- VTE – Bridge high risk patients and consider post-op proph dose after major surgery
- Antiplatelets: Primary prevention hold 7 days; secondary prevention hold for most patients
- DAPT DES – Wait 6-12 months then hold thienopyridine
- DOAC – Bridging rarely indicated; Restart post-op as for LMWH

Questions?