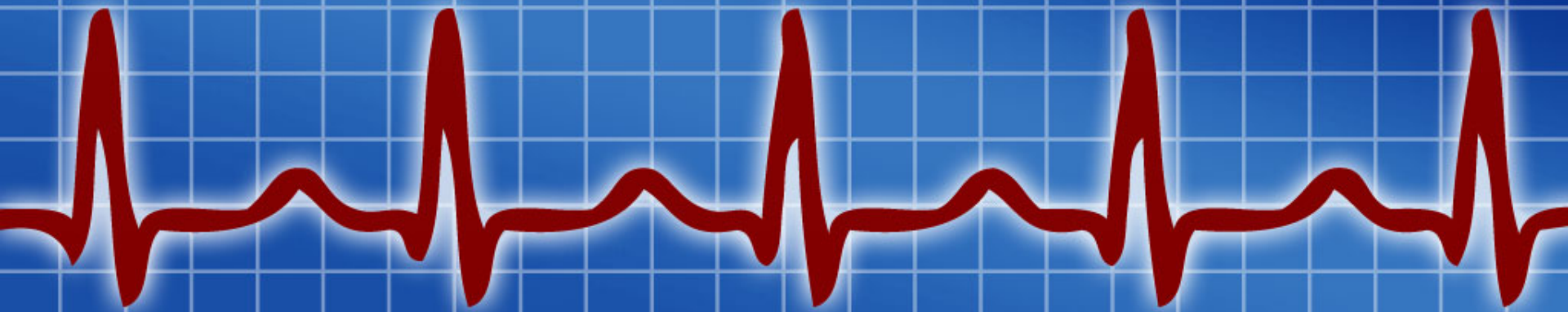
Triple antithrombotic therapy following an acute coronary syndrome

prevalence, outcomes and prognostic utility of the HAS-BLED score



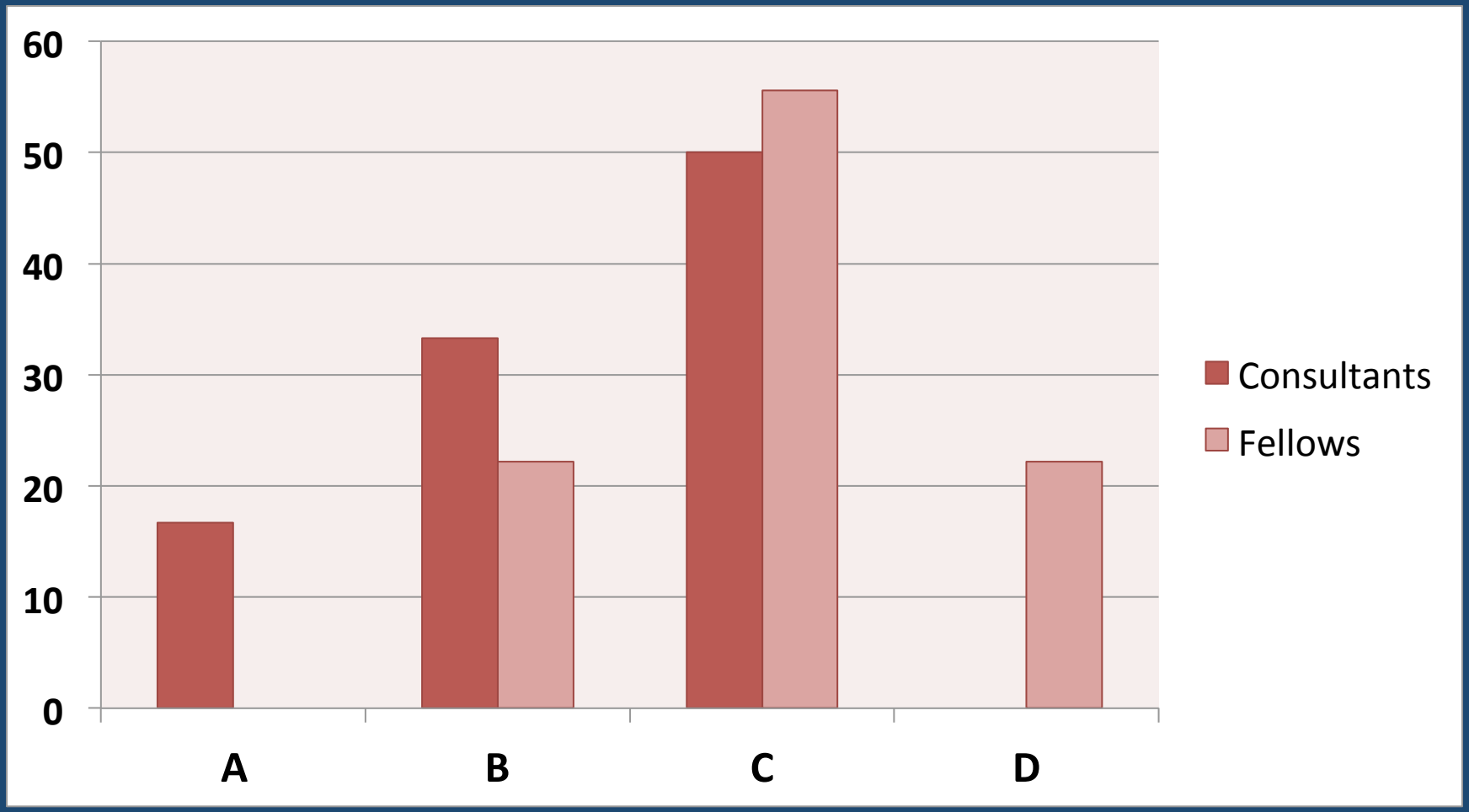
Presented by: Nouf alanazi
Supervised by: Dr.Khalid Alhabib

Scenario 1

- **70 y/o male K/C of AF, DM, HTN, had a small subarachnoid hemorrhage 2 months ago. Presented with NSTEMI and underwent PCI with DES. Your management will be**:

A. Warfarin + plavix + ASA for 1 year, then lifelong warfarin.
B. Plavix + ASA lifelong.
C. Warfarin + plavix for 1 year, then lifelong warfarin.
D. Dabigatran + plavix for 1 year, then lifelong dabigatran.

Answers

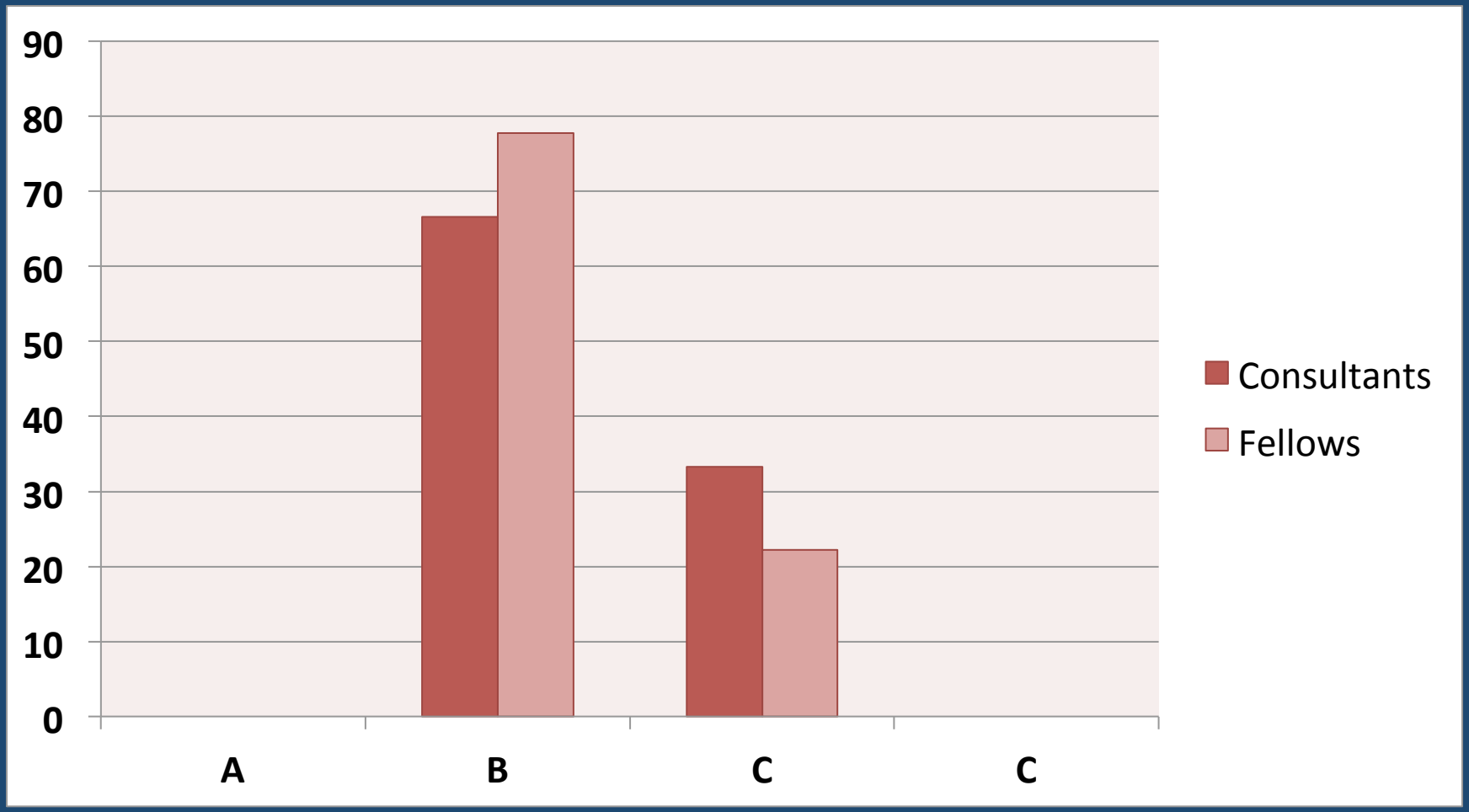


Scenario 2

- **60 y/o female, DM on insulin, K/C of mechanical MVR and AF on warfarin. Presented with ACS & underwent PCI with BMS, how would you manage her:**

A. Warfarin + plavix + ASA for 1 month, then lifelong warfarin.
B. Warfarin + plavix + ASA for 1 month, then lifelong warfarin + ASA.
C. Warfarin + plavix for 1 month, then lifelong warfarin.
D. Dabigatran + plavix for 1 month, then lifelong dabigatran.

Answers

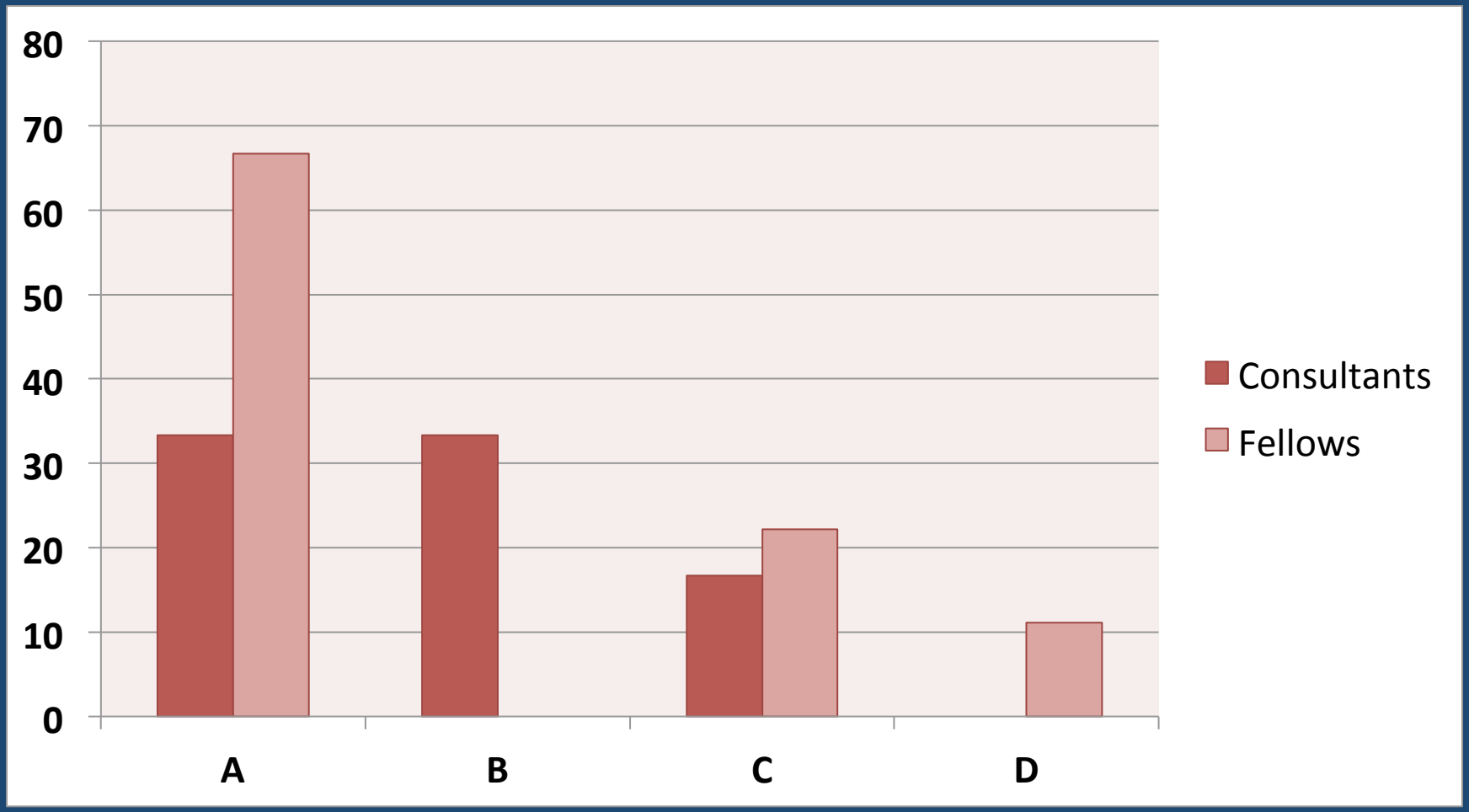


Scenario 3

- **55 y/o male, heavy smoker, uncontrolled DM, non-compliant with medical therapy, presented with STEMI and new AF, thrombolysed, and discovered to have TVD but refused CABG. Underwent PCI with 6 DESs (1 in LM, 2 in LAD, and 3 in RCA). Your management will be:**

A. Warfarin + plavix + ASA for 1 year, then lifelong warfarin + ASA.
B. Plavix + ASA lifelong.
C. Warfarin + plavix for 1 year, then lifelong warfarin + plavix.
D. Dabigatran + ASA for 1 year, then lifelong dabigatran + ASA.

Answers



Background

- Long term anticoagulation is **a *class I indication*** in many clinical situations like mechanical valves, AF or thromboembolic events.

- It is estimated that 5–7% of patients undergoing PCI have AF or other indications for chronic oral anticoagulant therapy

Am Heart J 2008; 155: 361–368

J Interv Cardiol 2009; 22: 390–397

- The ***American College of Cardiology/ American Heart Association/European Society of Cardiology*** *(ACC/AHA/ESC)* guidelines have classified TT in PCI patients with AF as a class IIb recommendation *(level of evidence C)*

- The recommendations are largely based upon *expert opinion* rather than strong registry and randomized trial data

ACC/AHA/ESC 2006 Guidelines for the management AF

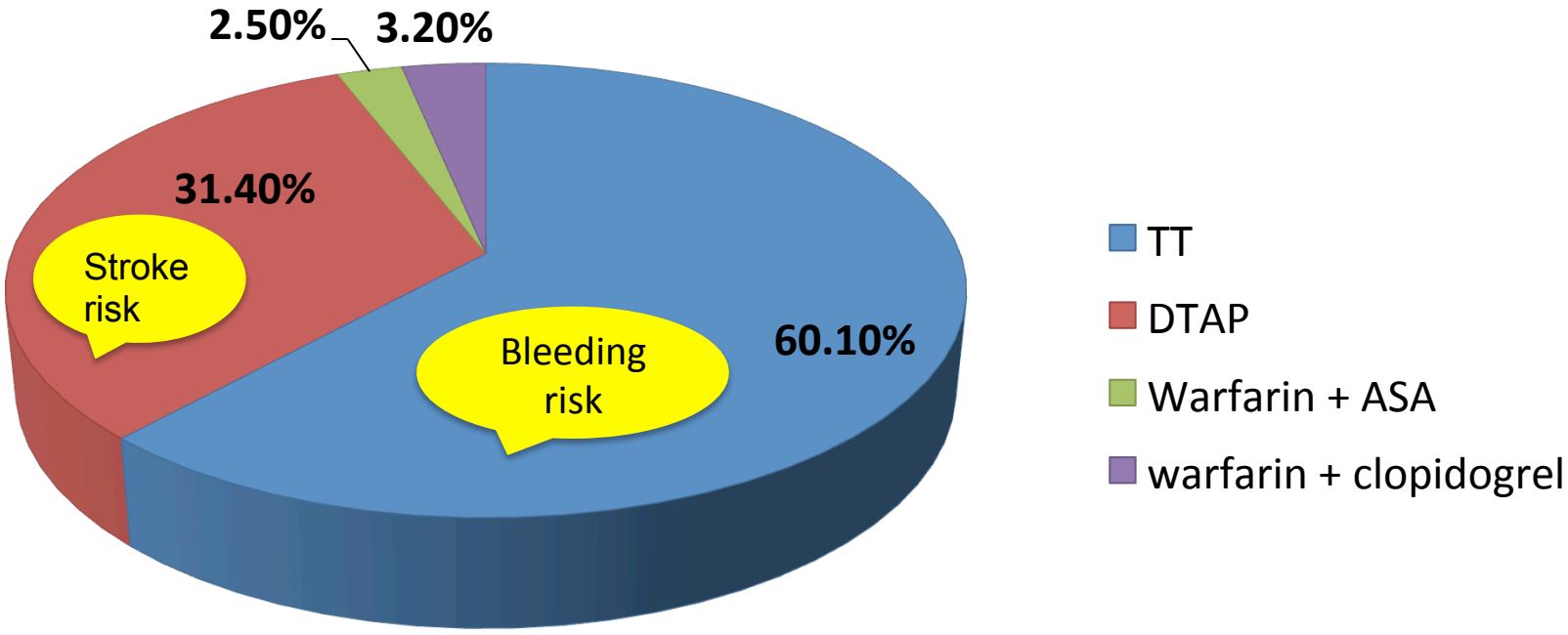
- TT use poses a significant dilemma since it carries high risk of major bleeding, estimated to be around **4.7 %.**

- This remains **a controversial area without strong available prospective data** to help guide clinicians on how to manage such patients.

JACC Cardiovasc Interv 2008; 1: 56–61

Wide variability in practice

Rx at discharge in the CRUSADE registry among 1,470 pts with AF undergoing PCI



Wang TY et al, AM Heart J 08;155:361

- ***Ultimately, 4 things should be balanced:***

  - ✓ Risk of bleeding
  - ✓ Risk of stroke or thromboembolic complications
  - ✓ Risk of recurrent cardiac ischemia with ACS
  - ✓ Risk of stent thrombosis.

EUROPEAN SOCIETY OF CARDIOLOGY®

Europace (2011) **13**, 723–746
doi:10.1093/europace/eur126

EHRA POSITION PAPER

Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis

Gregory Y.H. Lip (Chair)[1*†], Felicita Andreotti[2†‡], Laurent Fauchier[3†], Kurt Huber[4*†], Elaine Hylek[5†], Eve Knight[6†], Deirdre A. Lane[1†], Marcel Levi[7†], Francisco Marin[8†], Gualtiero Palareti[9†], and Paulus Kirchhof (Co-chair)[10†]

Document reviewers: Jean-Philippe Collet[11], Andrea Rubboli[12], Daniela Poli[13], and John Camm[14]

Recommended antithrombotic strategies following PCI in patients with AF at moderate-to-high thrombo-embolic risk

Haemorrhagic risk	Clinical setting	Stent implanted	Anticoagulation regime
Low/intermediate risk	Elective	Bare metal	1 month: triple therapy of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day
			Up to 12th month: combination of VKA (INR 2.0–2.5)+Clopidogrel 75 mg/day[b] (or aspirin ≤100 mg/day)
			Lifelong: VKA (INR 2.0–20) alone
	Elective	Drug eluting	3 (-olimus[a] group) to 6 (paclitaxel) months: triple therapy of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day
			Up to 12th month: combination of VKA (INR 2.0–2.5)+Clopidogrel 75 mg/day[b] (or aspirin ≤100 mg/day)
			Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	Bare metal/drug eluting	6 months: triple therapy of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day
			Up to 12 th month: combination of VKA (INR 2.0–2.5)+Clopidogrel 75 mg/day[b] (or aspirin ≤100 mg/day)
			Lifelong: warfarin (INR 2.0–3.0) alone
High	Elective	Bare metal[c]	2–4 weeks: triple therapy of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day
			Lifelong: VKA (INR 2.0–3.0) alone
	ACS	Bare metal[c]	4 weeks: triple therapy of VKA (INR 2.0–2.5)+aspirin≤100 mg/day+Clopidogrel 75 mg/day
			Up to 12th month: combination of VKA (INR 2.0–2.5)+Clopidogrel 75 mg/day[b] (or aspirin ≤100 mg/day)
			Lifelong: VKA (INR 2.0–3.0) alone

ESC Anticoagulation regimen in patients with low- intermediate bleeding risk after stent implantation

Setting stent	Anticoagulation (HAS-BLED 0–2)
Elective BMS	1 month: VKA + aspirin + clopidogrel Lifelong: VKA
Elective DES	3* months: VKA + aspirin + clopidogrel Up to 12th month: VKA + clopidogrel (or aspirin) Lifelong: VKA
ACS BMS/DES	6 months: VKA + aspirin+clopidogrel Up to 12th month: VKA + clopidogrel (oraspirin) Lifelong: VKA

Thrombosis Volume 2012, Article ID 184573

ESC Anticoagulation regimen in patients with high bleeding risk after stent implantation

Setting stent	Anticoagulation (HAS-BLED ≥ 3)
Elective BMS#	2–4 weeks: VKA + aspirin + clopidogrel Lifelong: VKA
ACS BMS#	4 weeks: VKA + aspirin+ clopidogrel Up to 12th month: VKA + clopidogrel (oraspirin) Lifelong: VKA

Thrombosis Volume 2012, Article ID 184573

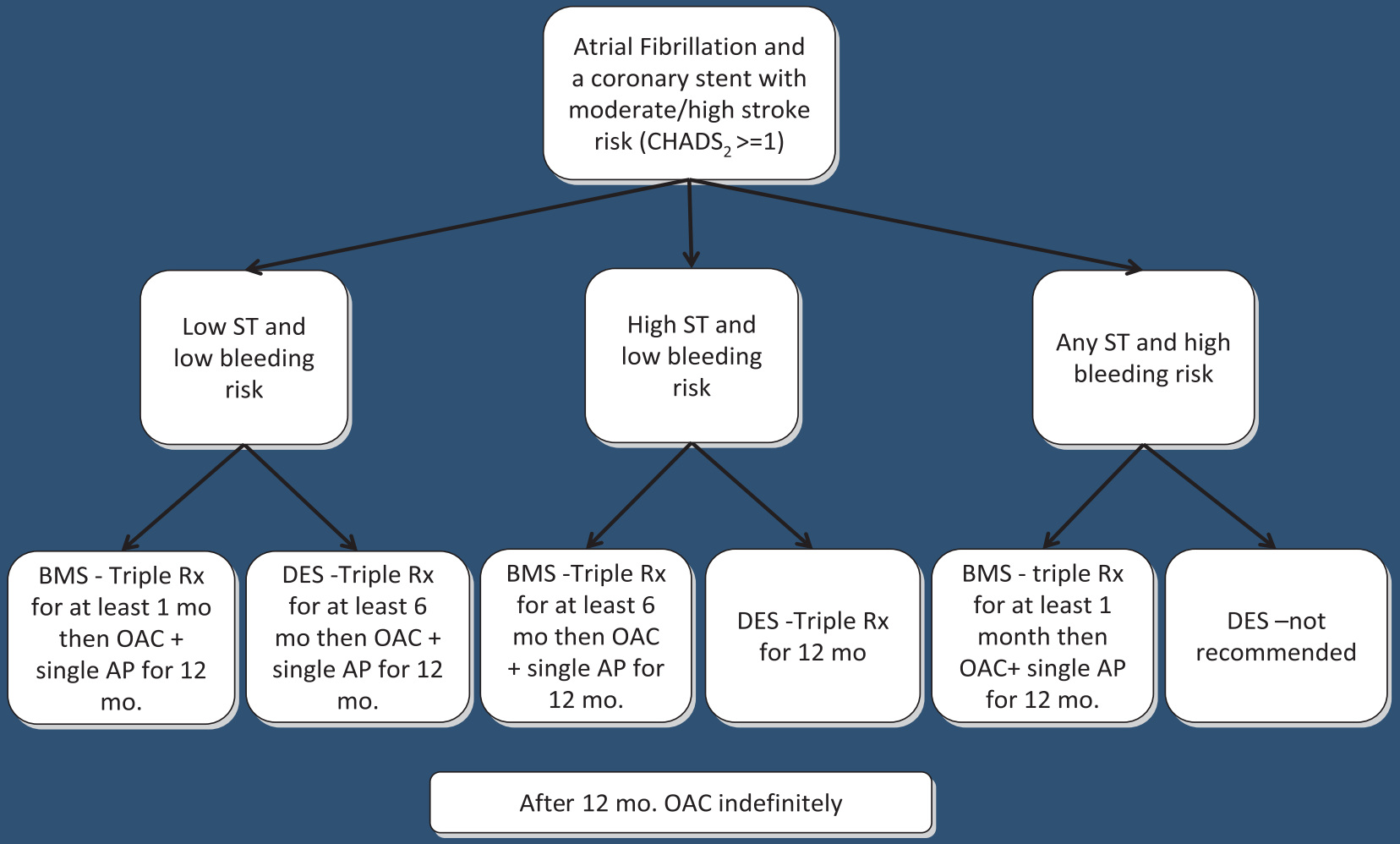
Consensus Document: Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting*

A North-American perspective

David P. Faxon[1]; John W. Eikelboom[2]; Peter B. Berger[3]; David R. Holmes[4]; Deepak L. Bhatt[5]; David J. Moliterno[6]; Richard C. Becker[7]; Dominick J. Angiolillo[8]

[1]Division of Cardiology, Brigham and Women's Hospital, Boston, Massachusetts, USA; [2]Department of Medicine, Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada; [3]Geisinger Clinic, Danville, Pennsylvania, USA; [4]Mayo Clinic, Rochester, Minnesota, USA; [5]Division of Cardiology, VA Boston Health System, Boston, Massachusetts, USA; [6]Gill Heart Institute and Division of Cardiovascular Medicine, University of Kentucky, Lexington, Kentucky, USA; [7]Divisions of Cardiology and Hematology, Duke University School of Medicine, Durham, North Carolina, USA; [8]Division of Cardiology, University of Florida College of Medicine-Jacksonville, Jacksonville, Florida, USA

Recommendations for the duration of TT in patients with AF & PCI (BMS or DES) with moderate/high stroke risk (CHADS2 ≥1)



EuroIntervention 2012;8:672-678

Triple antithrombotic therapy following an acute coronary syndrome: prevalence, outcomes and prognostic utility of the HAS-BLED score

J. Gustav Smith[1], MD, PhD; Mattias Wieloch[1], MD, PhD; Sasha Koul[1], MD; Oscar Ö. Braun[1], MD, PhD; Jonathan Lumsden[1], MSc; Emil Rydell[1], MSc; Jenny Öhman[1], MD, PhD; Fredrik Scherstén[1], MD, PhD; Peter J. Svensson[2], MD, PhD; Jesper van der Pals[1]*, MD, PhD

1. Department of Cardiology, Skane University Hospital, Lund University, Lund and Malmö, Sweden; 2. Department for Coagulation Disorders, Skane University Hospital, Lund University, Lund and Malmö, Sweden

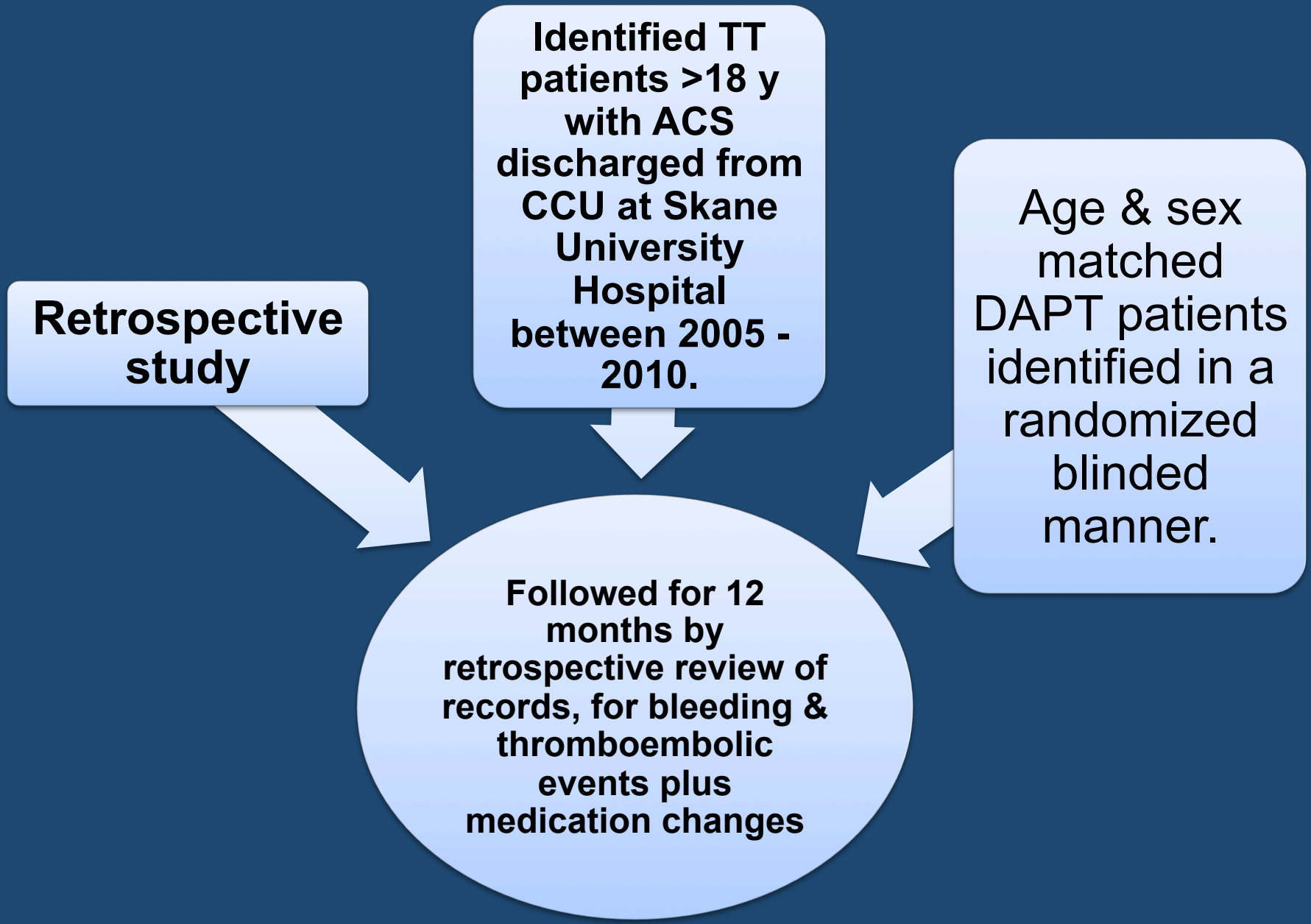
Aim of the study

Evaluate the prevalence of TT in patients following ACS

Evaluate the bleeding risk compared to double antiplatelet therapy (DAPT) (aspirin and clopidogrel)

Evaluate the accuracy of the HAS-BLED risk score in predicting serious bleeding events in TT patients.

Study design



Study definitions

Major bleeding:

Any bleeding requiring hospital care and/or causing a decrease in Hb level of > 20 g/L and/or requiring blood transfusion and/or with intracranial location.

Thromboembolic events:

Physician's diagnosis of stroke, TIA , ACS or peripheral arterial embolism

HAS-BLED score

Letter	Clinical characteristic	Score	HAS-BLED Score	Bleeds/100 patient-years
H	Hypertension	1	0	1.13
A	Abnormal renal and liver function (1 point each)	1 or 2	1	1.02
S	Stroke	1	2	1.88
B	Bleeding	1	3	3.74
L	Labile INRs	1	4	8.70
E	Elderly	1		
D	Drugs or alcohol (1 each)	1 or 2		
		9 max		

a score of ≥3 indicates high risk

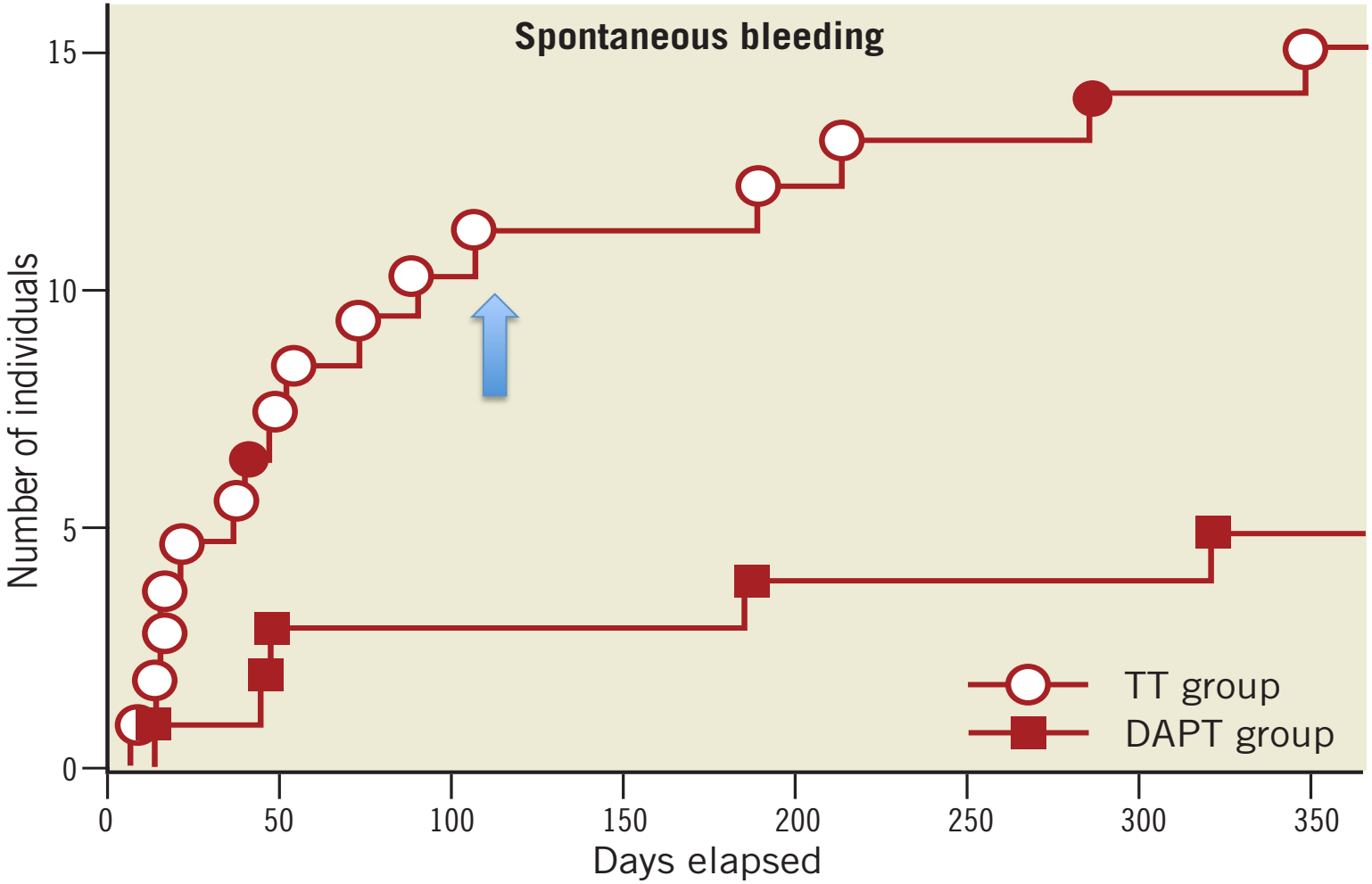
Baseline characteristics

Characteristics	TT (n=159)	DAPT (n=159)	*p*-value
Mean age, years (SEM)	67.2 (±0.9)	67.2 (±0.9)	NS
Female sex	35 (22.0)	35 (22.0)	NS
STEMI[1]	83 (52.2)	55 (34.6)	0.001
Drug-eluting stent implanted	34 (21.4)	23 (14.6)	NS
Medical history, n (%)			
Heart failure	119 (75.8)	53 (33.8)	<0.0001
Mean EF[2], % (SEM)	35 (±1)	39 (±1)	0.001
Stroke/TIA[3]	25 (15.7)	21 (13.2)	NS
Diabetes mellitus	29 (18.2)	28 (17.6)	NS
Hypertension	67 (42.1)	82 (51.6)	NS
Abnormal renal function[4]	3 (1.9)	7 (4.4)	NS
Valvular disease	12 (7.5)	10 (6.3)	NS
COPD[5]	12 (7.5)	10 (6.3)	NS
Thyroid disease	10 (6.3)	12 (7.5)	NS
Malignancy[6]	19 (11.9)	20 (12.6)	NS
Pharmacological treatment, n (%)			
Prior warfarin	53 (33.3)	1 (0.6)	<0.0001
Reduced INR[7]	76 (47.8)	n/a	n/a
Concomitant PPI[8]	49 (30.8)	44 (27.7)	NS

Outcomes

Event, n (%)	TT (n=157)	DAPT (n=158)	*p*-value
Mortality	7 (4.5)	4 (2.5)	NS
Peripheral embolism	0 (0.0)	0 (0.0)	NS
Stroke/TIA[1]	3 (1.9)	3 (1.9)	NS
ACS[2]	6 (3.8)	2 (1.3)	NS
Major bleeding[3]			
All	21 (13.4)	6 (3.8)	0.002
Surgical/trauma	5 (3.2)	1 (0.6)	NS
Spontaneous	16 (10.2)	5 (3.2)	0.01
Fatal	1 (0.6)	0 (0.0)	NS
Intracranial	2 (1.3)	0 (0.0)	NS
Gastrointestinal	12 (7.6)	3 (1.9)	0.02
Other	2 (1.3)	2 (1.3)	NS
Mean duration of treatment, months (SEM)	3.7±0.3	11.8±0.1	n/a
Drug discontinued			
Warfarin	82 (52.2)	n/a	n/a
Clopidogrel	57 (36.3)	4 (2.5)	<0.0001
Aspirin	3 (1.9)	2 (1.3)	NS
Warfarin+clopidogrel	2 (1.3)	n/a	n/a
Aspirin+clopidogrel	1 (0.6)	0 (0.0)	NS
None	12 (7.6)	152 (96.2)	<0.0001

Spontaneous bleeding



Characteristic, n (%)	Bleed (n=14)	No bleed (n=136)	*p*-value
Mean age, years (SEM)	71.3 (±2.5)	66.6 (±1.0)	NS
Female sex	4 (28.6)	29 (21.3)	NS
STEMI[1]	7 (50.0)	74 (54.4)	NS
Drug-eluting stent implanted	4 (28.6)	28 (20.6)	NS
Medical history, n (%)			
Heart failure	11 (78.6)	103 (76.3)	NS
Mean EF[2], % (SEM)	33 (±2)	35 (±1)	NS
Stroke/TIA[3]	2 (14.3)	21 (15.4)	NS
Diabetes mellitus	4 (28.6)	25 (18.4)	NS
Hypertension	6 (42.9)	60 (44.1)	NS
Abnormal renal function[4]	0 (0.0)	3 (2.2)	NS
Valvular disease	0 (0.0)	11 (8.1)	NS
COPD[5]	1 (7.1)	11 (8.1)	NS
Thyroid disease	0 (0.0)	10 (7.4)	NS
Malignancy[6]	3 (21.4)	16 (11.8)	NS
HAS-BLED, mean (SEM)	2.71 (±0.24)	2.15 (±0.08)	0.04
Indications for warfarin, n (%)			
Atrial fibrillation	9 (64.3)	49 (36.0)	0.04
Mean $CHADS_2$-VA_2Sc[7], (SEM)	3.8 (±0.4)	4.6 (±0.2)	NS
Mean HAS-BLED[8], (SEM)	2.6 (±0.2)	2.8 (±0.1)	NS
Apical akinesia	6 (42.9)	76 (55.9)	NS
Left ventricular thrombus	2 (14.3)	15 (11.0)	NS
Mechanical valve	0 (0.0)	4 (2.9)	NS
Venous thromboembolism	0 (0.0)	10 (7.4)	NS
Other	0 (0.0)	2 (1.5)	NS
Pharmacological treatment, n (%)			
Duration of TT, months (SEM)	4.0 (±0.9)	3.8 (±0.3)	NS
Reduced INR[9]	8 (57.1)	62 (45.6)	NS
Concomitant PPI[10]	5 (35.7)	39 (28.7)	NS
Outcomes at one year			
Mortality	3 (21.4)	4 (2.9)	0.002
Stroke/TIA[11]	0 (0.0)	2 (1.5)	NS
ACS[12]	0 (0.0)	6 (4.4)	NS

Limitations

Retrospective

Monocentric

Medical record-based analysis

Conclusion of this study

- TT was relatively common following an ACS & associated with a **3 fold increase in the incidence of spontaneous major bleeding** at 1 year compared to DAPT.

- **The HAS-BLED score** predicted bleeding events with moderate accuracy, similarly to other settings with warfarin.

- Careful patient selection, potentially supported by HAS-BLED, and short treatment duration appears warranted.

What if we dropped ASA and started on clopidogrel & warfarine only ??!

The WOEST Trial

The WOEST Trial= **W**hat is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing

First randomised trial comparing two regimens with and without ASA in patients on oral anticoagulant therapy undergoing PCI

Presented in **ESC Congress 2012**
(Munich – Germany)

Study design

Double therapy group

OAC + 75mg clopidogrel

(284 patient)

1 month minimum after BMS

1 year after DES

Triple therapy group

OAC + 75mg Clopidogrel + 80mg ASA

(289 patient)

1 month minimum after BMS

1 year after DES

Endpoints

- Specifically designed to detect bleeding events.
- **Primary endpoint:**

✓ The occurrence of all bleeding events (TIMI criteria)

- **Secondary endpoint:**

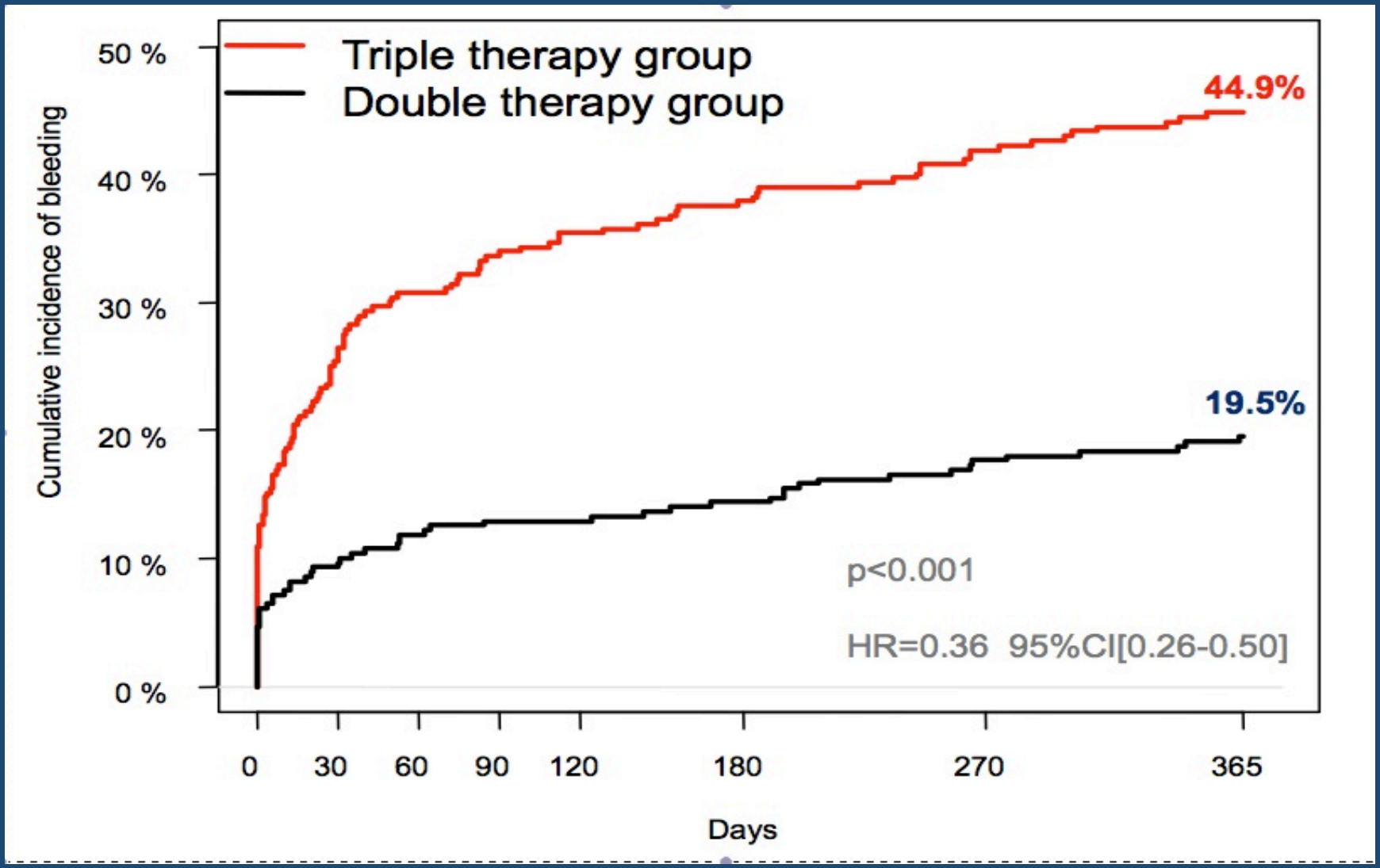
✓ Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation

TIMI bleeding classification

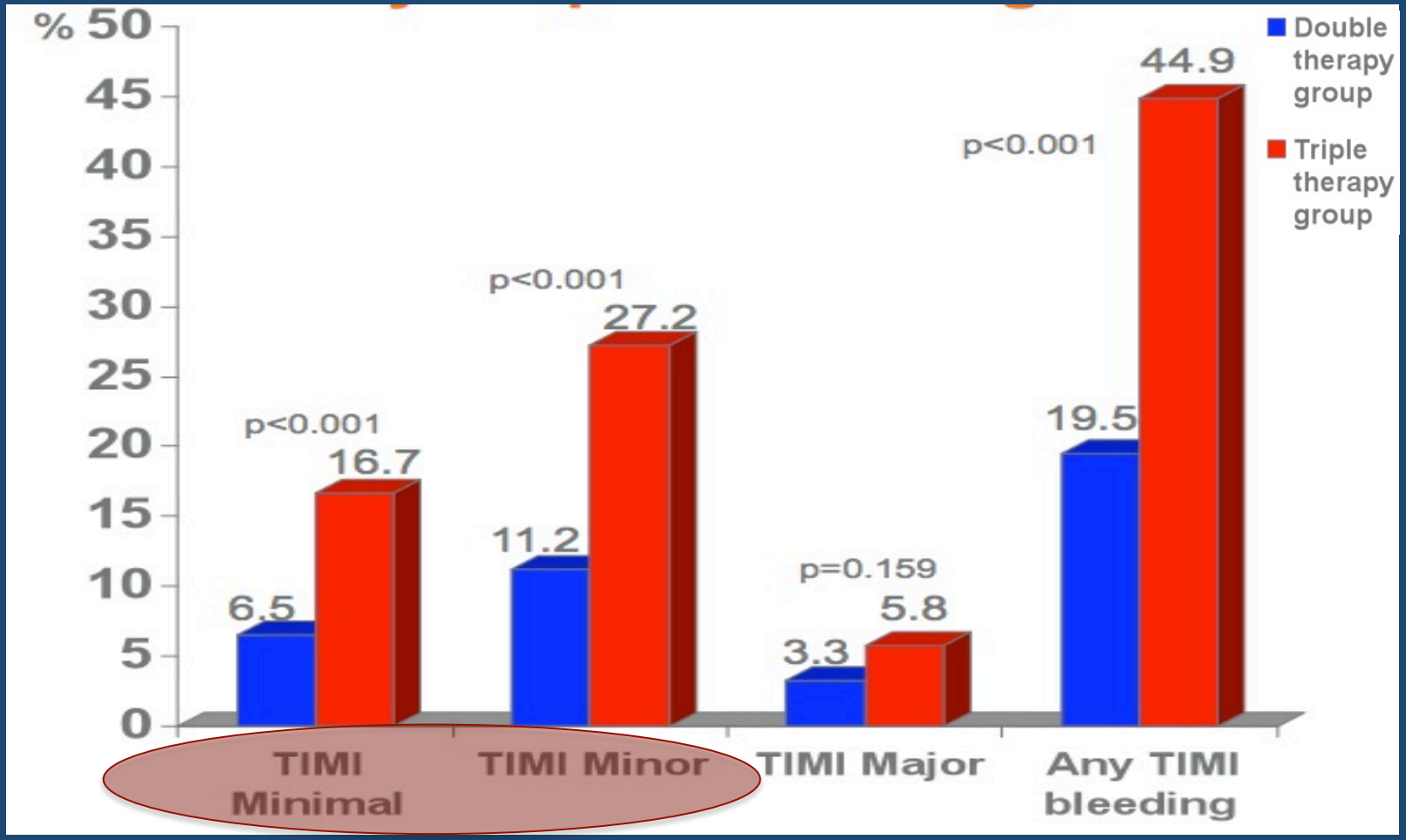
TIMI bleeding classification[10a]

Major	Intracranial haemorrhage or a ≥5 g/dL decrease in haemoglobin concentration or a ≥15% absolute decrease in haematocrit
Minor	Observed blood loss: ≥3 g/dL decrease in haemoglobin concentration or ≥10% decrease in haematocrit. No observed blood loss: ≥4 g/dL decrease in the haemoglobin concentration or ≥12% decrease in haematocrit
Minimal	Any clinically overt sign of haemorrhage (including imaging) associated with a <3 g/dL decrease in haemoglobin concentration or <9% decrease in haematocrit

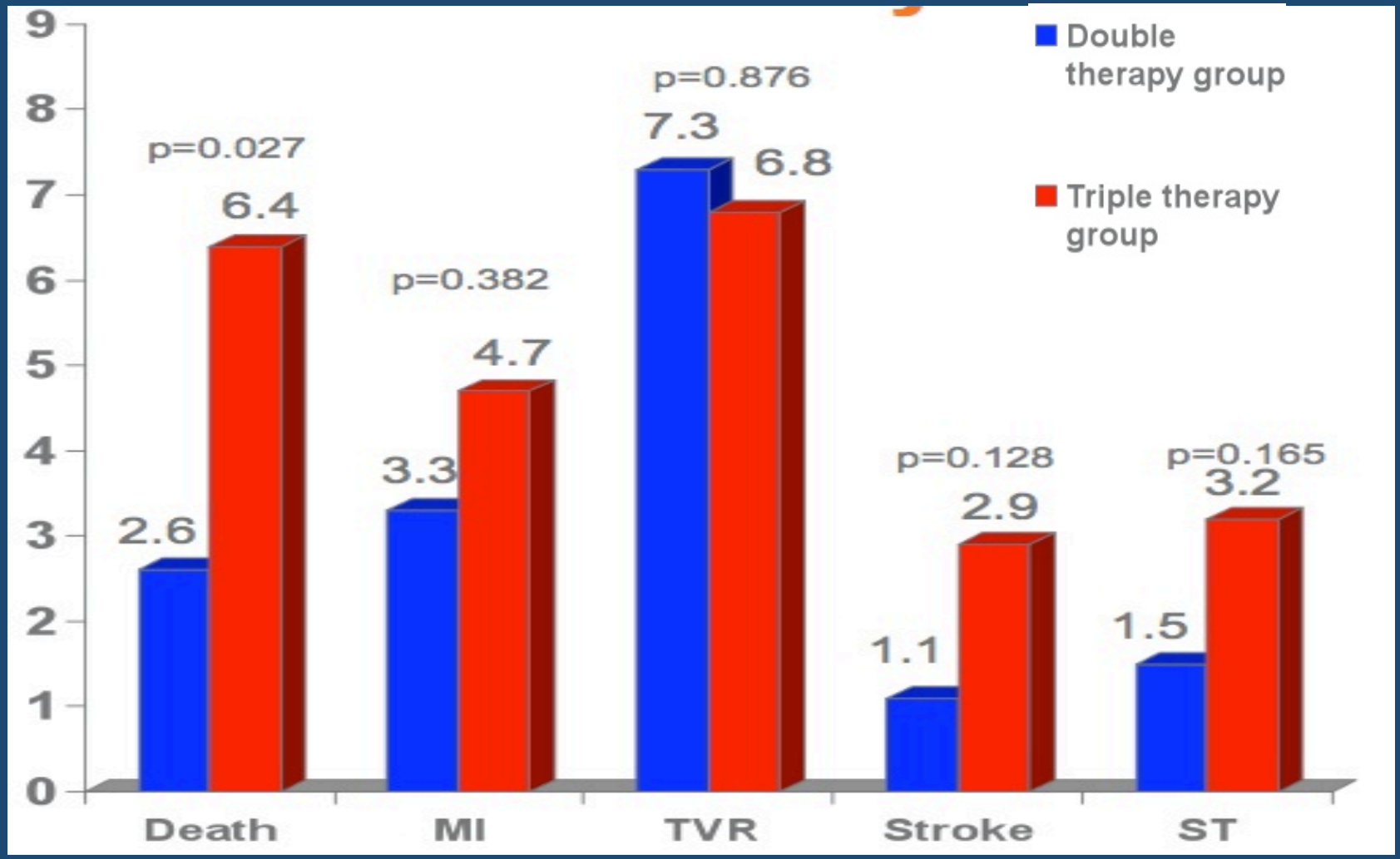
Primary Endpoint: Total number of bleeding events (TIMI criteria)



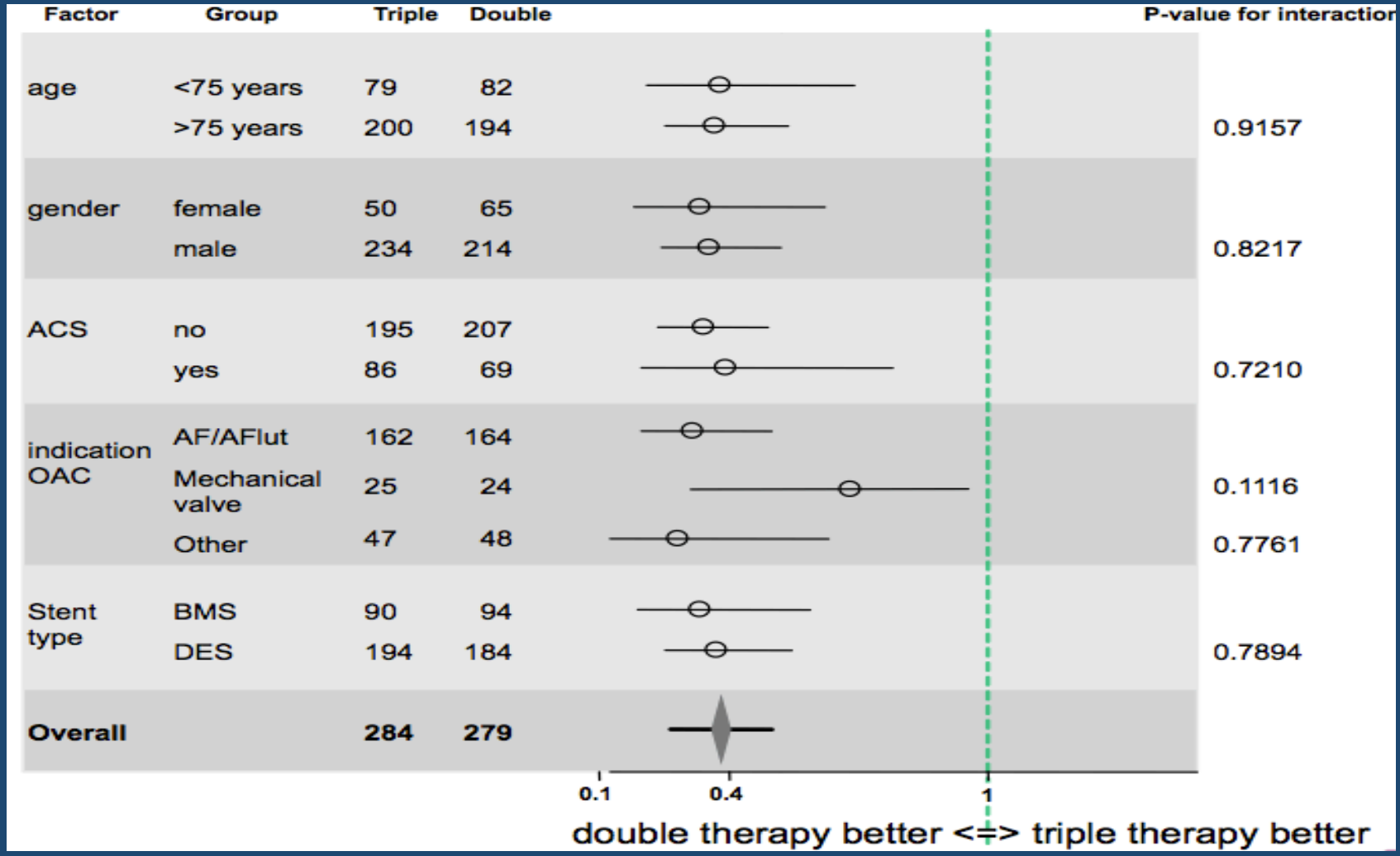
Primary Endpoint: Bleeding events TIMI classification



Secondary Endpoint



Forest plot of primary endpoint Hazard Ratios



Endpoints

- **Primary endpoint:**
  - ✓ OAC plus clopidogrel causes < bleeding than TT
- **Secondary endpoint:**
  - ✓ With double therapy there is no excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, MI or death
  - ✓ Less all-cause mortality with double therapy

Limitations of WOEST trial

- Too small for conclusion to be withdrawn
- 2/3 of patients had DES, so longer-term follow-up is needed
- Minimal-minor bleeds involving the skin drove the results.
- Didn’t study the new anticoagulants.

- Powered to show superiority on the primary bleeding endpoint, but not to show non-inferiority on the secondary .
- Open label trial design with its inherent bias
- Classification of smaller bleeding, although well defined, may be subjective

Let me congratulate the investigators for multiple achievements:

- Completion of a multicenter international purely investigator driven study (no industry funding)
- Very important demonstration (yes…another one !) that we have hit the wall with respect to intensity, variety and duration of anti-thrombotic therapy
- Double Therapy with clopidogrel and Warfarin seems a very reasonable therapy based on the WOEST especially in DES treated patients
- The Taboo of discontinuing/omitting aspirin in contemporary environment has been broken !!

Global LEADERS study will specifically address the outstanding role of aspirin in the context of adequate P2Y12 Inhibition in an all comer 16,000 patient population.

Ongoing trials

- **The MUSICA- 2 trial:**

✓ Compares dual antiplatelet with TT in AF & a low-to-moderate risk of stroke (CHADS ≤ 2) undergoing PCI.

✓ The study is estimated to be completed in December 2012 with about 300 patients.

- **The ISAR Triple trial:**

✓ Examines 600 patients on oral anticoagulation who undergo PCI (DES) with concomitant ASA & clopidogrel medication for either a short duration of 6 weeks or a longer duration of 6 months.

Take home message

- An individualized approach taking into account the individual risk of stroke, bleeding, MI & stent type is needed to assess the best treatment option.

- Dropping ASA significantly decreases the risk of bleeding without jeopardizing the risk of stent thrombosis, MI, or stroke. however keep in mind that WOEST trial has a lot of limitations.

- Apply measures that may minimize bleeding like:
  - ✓Careful assessment of patient before proceeding with angiography
  - ✓DES vs BMS
  - ✓Short TT treatment duration
  - ✓Low dose ASA
  - ✓Lower INR therapeutic target
  - ✓PPI
  - ✓Avoid concomitant NSAID use

Can we apply those results on our patients ?

- Less DES
- Lower number of diabetic patients
- Anticoagulation in apical akinesia

Would you now change your practice ?

References

- Bleeding risk assessment and management

in atrial fibrillation patients: a position document

from the European Heart Rhythm Association,

endorsed by the European Society of Cardiology

Working Group on Thrombosis*, Europace (2011) 13, 723–746*

- Consensus Document: Antithrombotic therapy in patients with atrial

fibrillation undergoing coronary stenting* A North-American perspective. *Thrombosis and Haemostasis 106.4/2011*

- Anticoagulant and Antiplatelet Therapy in Patients with Atrial Fibrillation and Coronary Artery Disease. KarlMischke, Christian Knackstedt, and NikolausMarx. *Thrombosis volume 2012.*
- *www.theheart.org*

Thank you