Antithrombotic therapy in AF patients requiring stent implantation

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Introduction

- The optima regimen for antiplatelet therapy in patients on OAC and undergoing coronary stenting is not clearly defined.

- This clinical dilemma occurs in a significant proportion of patients undergo coronary stenting (5~7%).

  : chronic AF (mc), prosthetic valve, LV thrombus, DVT, pulmonary thromboembolism

Goal of antithrombotic therapy

- Anticoagulant therapy

  reduce risk of stroke/ thrombotic complication

- Antiplatelet therapy

  reduce risk of stent thrombosis/ myocardial infarction

- consider bleeding complication

Procedural management

- In stable pts: discontinue OAC 5~7 days, INR <1.5
- In urgent pts: do not stop OAC

- safety of uninterrupted warfarin

  pacemaker or defibrillator implantation

  Cheng A, et al. Hear Rhythm 2011;8:536-540

  cardiac catheterization and PCI

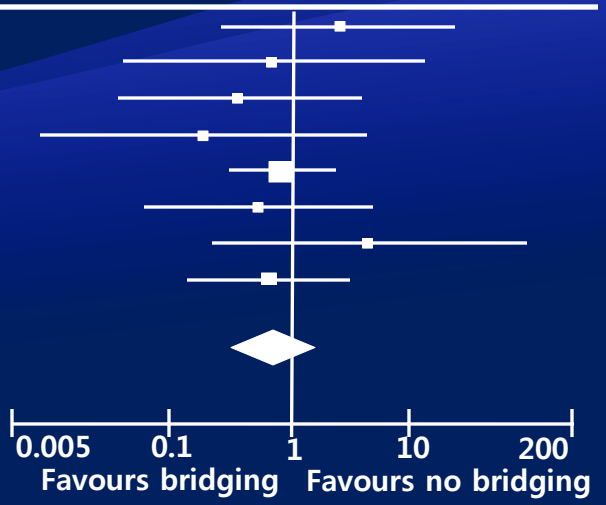
  Lahtela H, et al. Circ J 2012;76:1363-1368

  Kiviniemi T, et al. Am J Cardiol 2012;110:30-35

Heparin bridging in high-risk patients

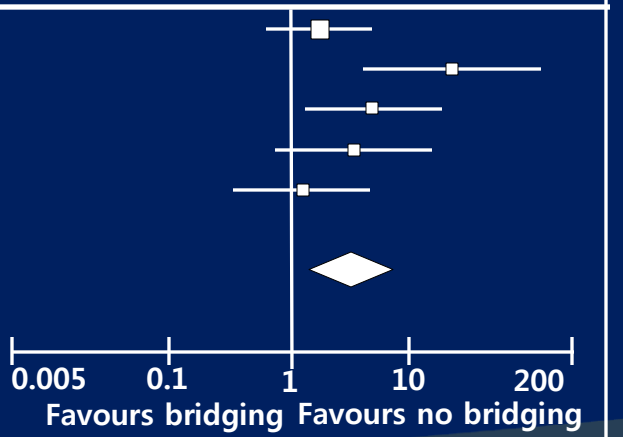
Thromboembolic event

Study or Subgroup	Odds Ratio M-H, Random, 95%CI
Daniels et al. 2009	2.51 (0.28, 22.60)
Garcia et al. 2008	0.72 (0.04, 12.76)
Jaffer et al. 2010	0.38 (0.04,3.68)
Marquie et al. 2006	0.20 (0.01, 4.14)
McBane et al. 2010	0.84 (0.30, 2.35)
Tompkins et al. 2010	0.55 (0.07,4.59)
Varkarakis et al. 2005	4.25 (0.21. 84.56)
Wysokinski et al. 2008	0.66 (0.15, 3.01)
Total (95% CI)	0.80 (0.42, 1.54)



Major bleeding event

Study or Subgroup	Odds Ratio M-H, Random, 95%CI
Daniels et al. 2009	1.91 (0.68, 5.33)
Garcia et al. 2008	22.75 (4.12, 125.68)
Jaffer et al. 2010	5.22 (1.47, 18.54)
McBane et al. 2010	3.63 (0.82, 16.08)
Wysokinski et al. 2008	1.35 (0.37, 4.86)
Total (95% CI)	3.60 (1.52, 8.50)



Siegal D, et al.
Circulation 2012;126:1630-1639

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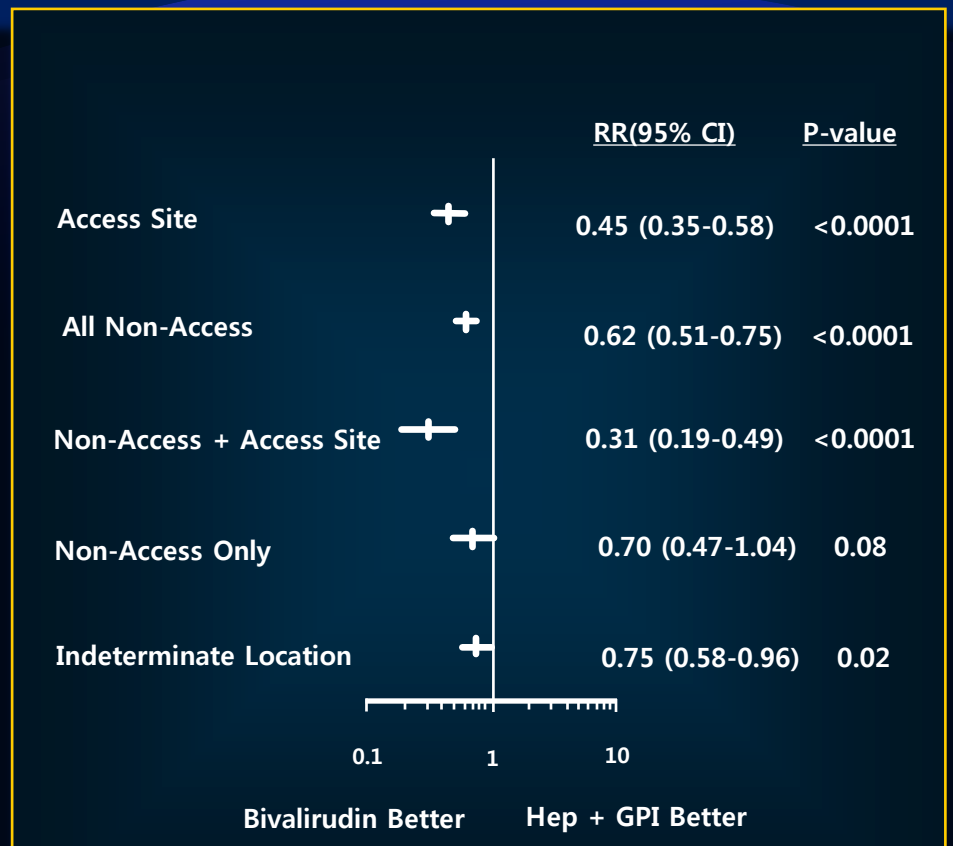
Bleeding is powerful predictor of mortality

1y mortality asso. with 30d bleeding

	1y mortality	p
No bleed	2.54%	-
Access site only	6.16%	<0.001
All non-access site	14.4%	<0.0001
Non-access site only	14.1%	<0.001
Both	14.5%	<0.001



Conclusion: Nonaccess site bleeding after PCI is common, and is associated with a 4-fold increase in 1-year mortality

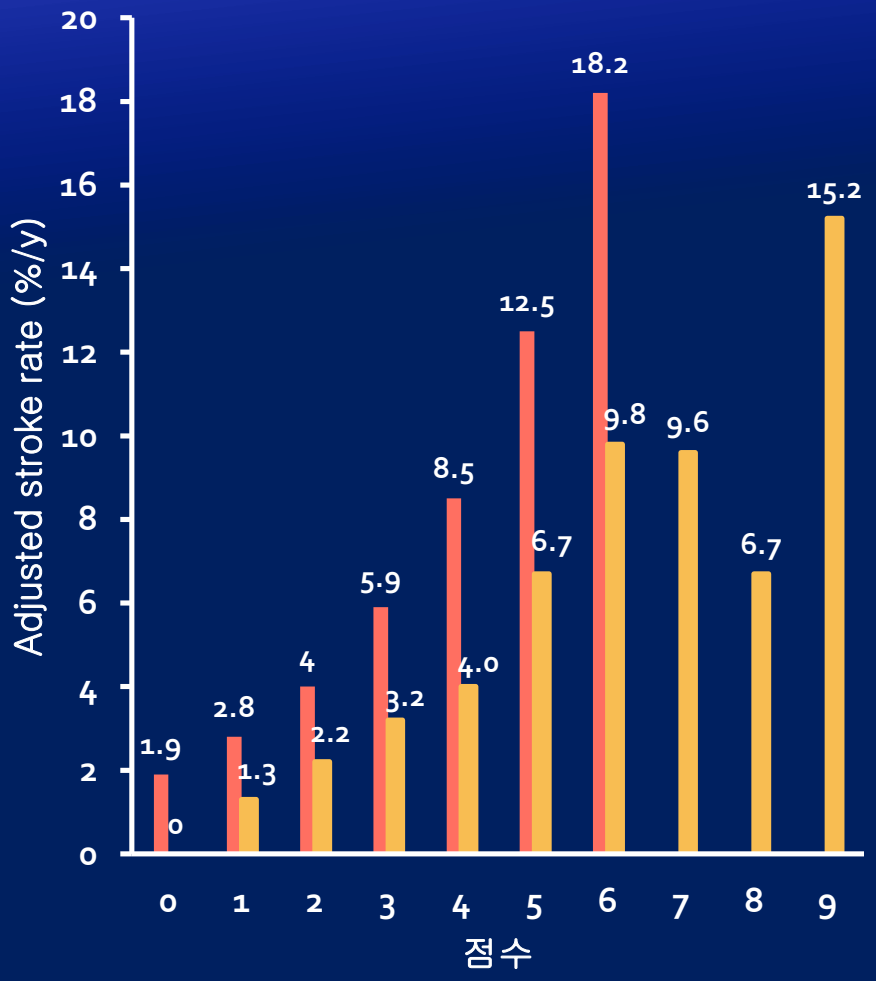
Verheugt FWA, et al.
JACC Interv. 2011;4:191-197.

Procedural management; summary

- High INR (therapeutic range of INR) are usually tolerated.
- Current practice is to load dual DAPT prior to PCI, use an parenteral anticoagulant (heparin, LMWH, bivalirudin) during the PCI, and continue triple therapy (DAPT + OAC) thereafter.
- Bleeding is predictor of mortality. Consider radial assess.

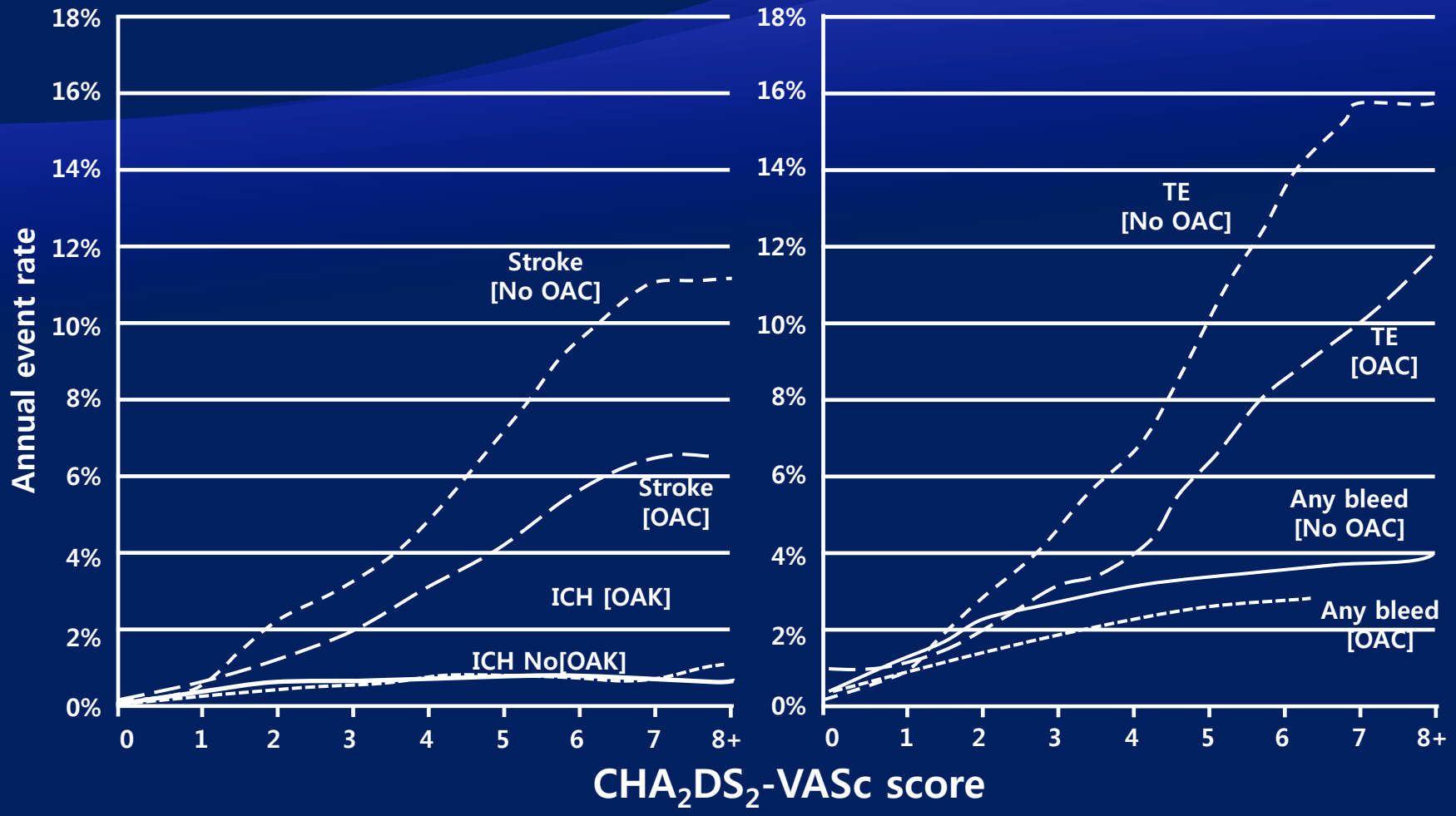
Stroke risk – CHA2DS2-VASc score

CHA_2DS_2-VASc criteria	Score
Congestive heart failure/ left ventricular dysfunction	1
Hypertension	1
Age ≥75 yrs	**2**
Diabetes mellitus	1
Stroke/transient ischaemic attack/TE	**2**
Vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque)	1
Age 65–74 yrs	1
Sex **c**ategory (i.e. female gender)	1



2012 ESC Guidelines

CHA2DS2-VASc score

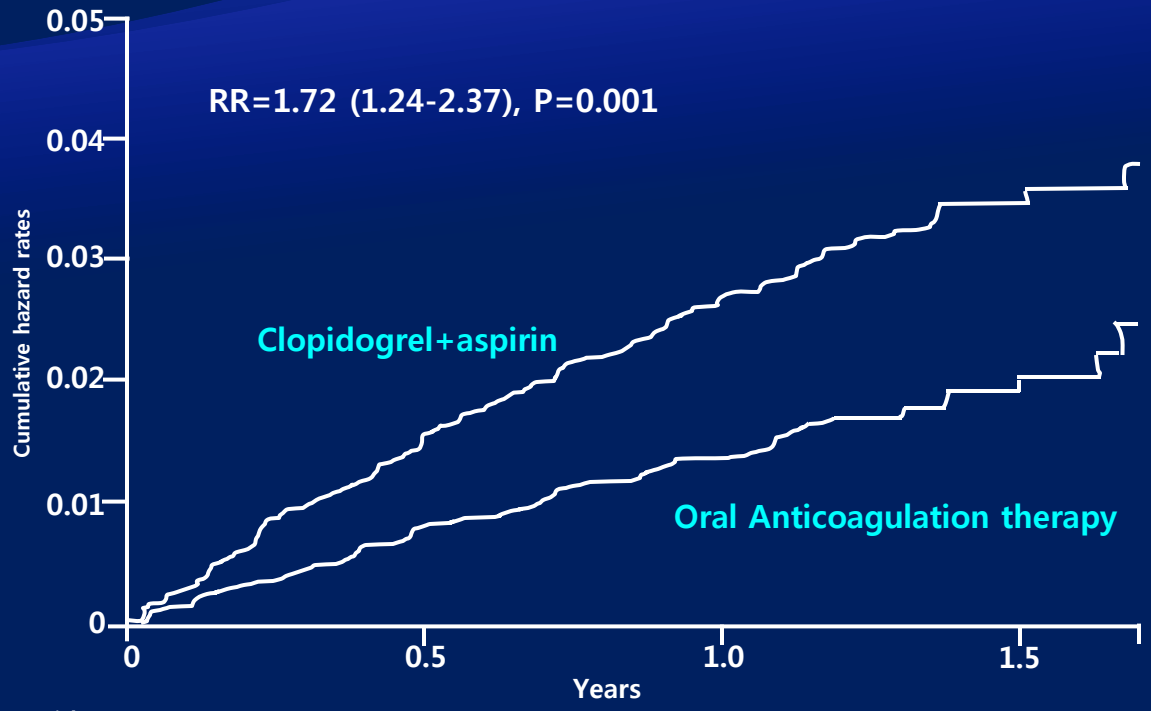


Friberg L, et al.
Eur Heart J 2012;33:1500-1510

DAPT vs. OAC in AF

ACTIVE W trial, 6706 pts with AF and risk of stroke

Stroke risk



Number at risk				
Clopidogrel +aspirin	3335	3168	2419	941
Oral Anticoagulation therapy	3371	3232	2466	930

ACTIVE investigators.
Lancet 2006;367:1903-1912

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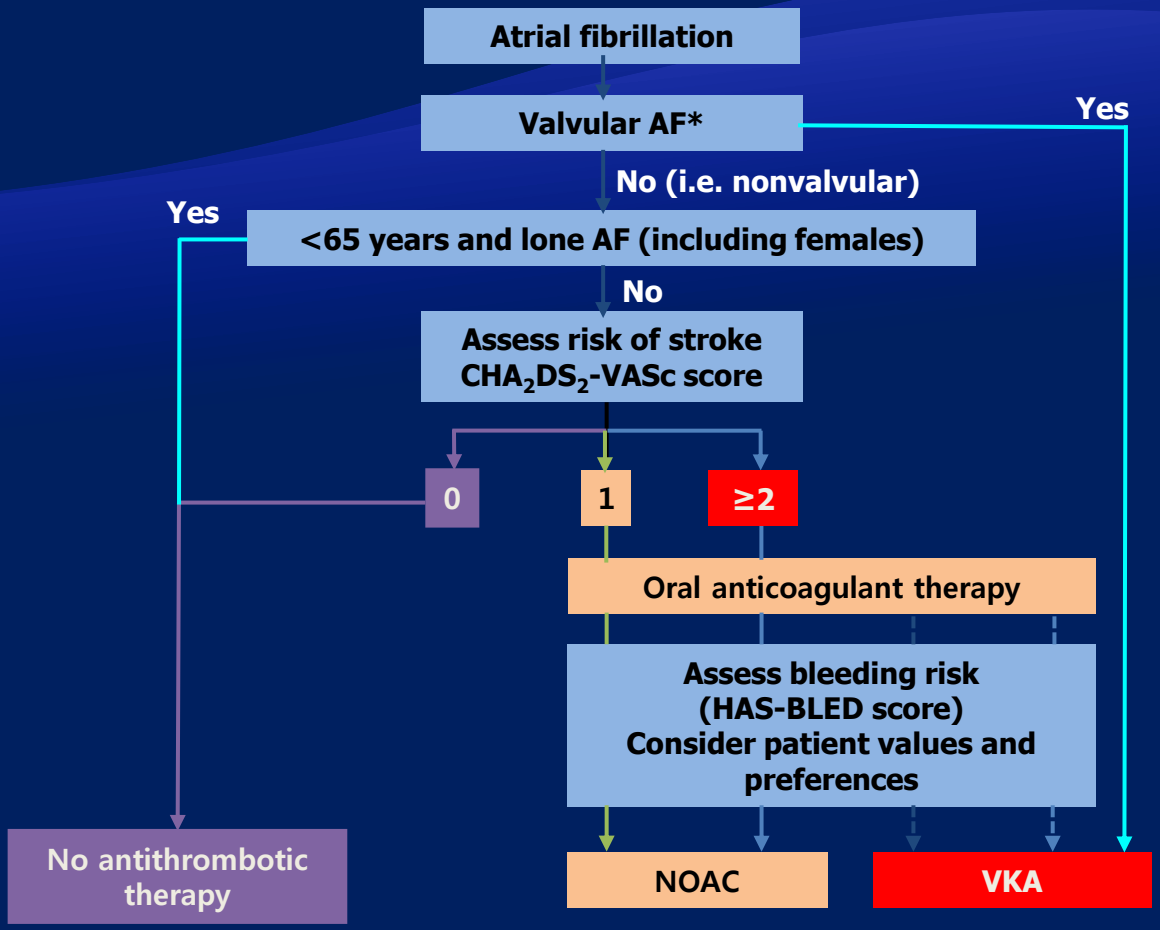
2012 ESC Guidelines

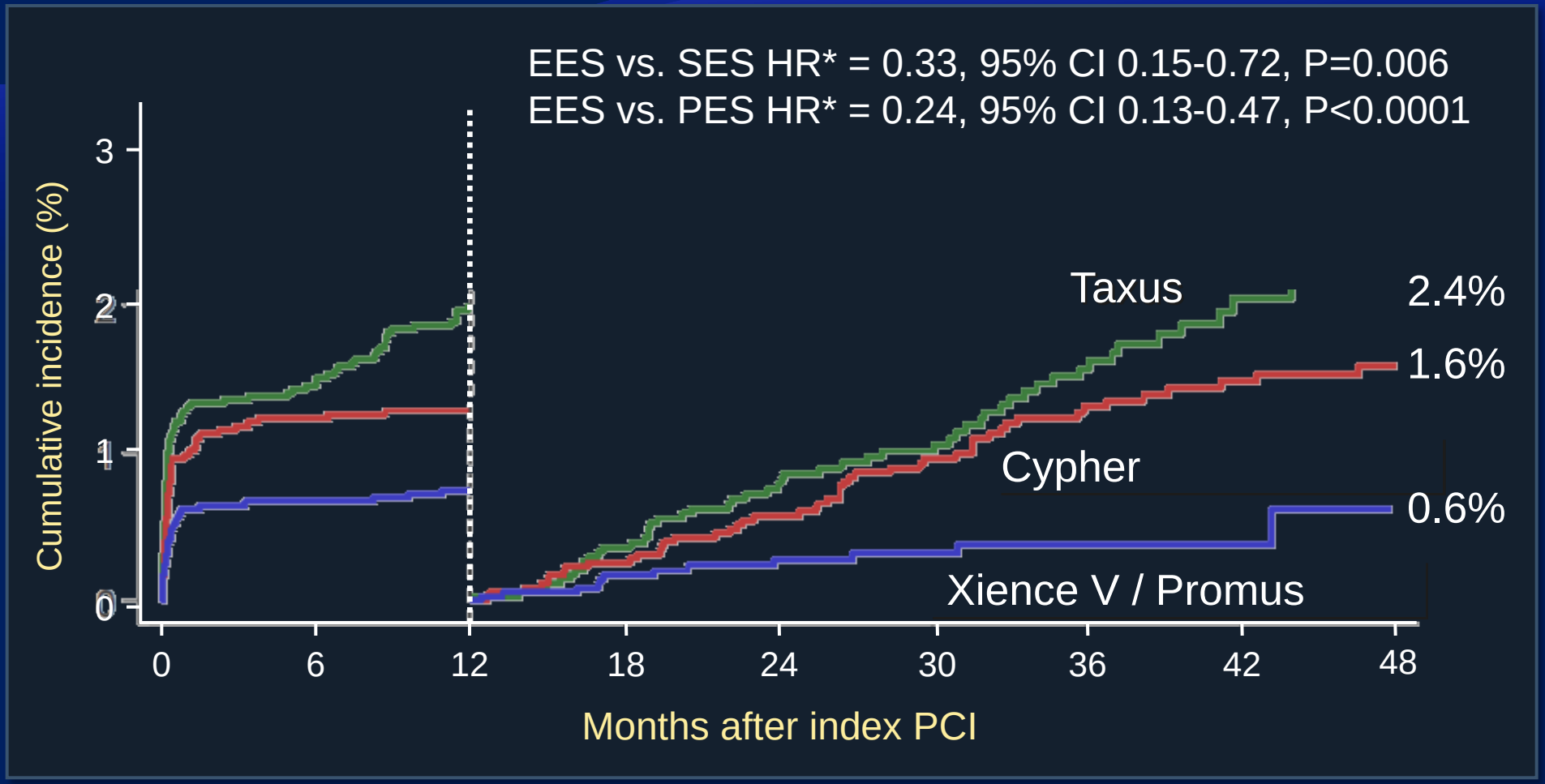


Antiplatelet therapy with aspirin plus clopidogrel, or – less effectively – aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage closure or excision may be considered.

Stent thrombosis risk

- Risk factors
  - **Premature discontinuation of DAPT**
  - Stent mal-apposition
  - Acute coronary syndrome
  - Bifurcation disease
  - Chronic kidney disease, DM
  - Stent length

ARC Definite ST: Landmark analysis
Bern Rotterdam (n=12,339 pts)



Räber et al, Circulation 2012

RESOLUTE Pooled DAPT Interruption Analysis

Timing of First DAPT Interruption and ST Through 1 Year

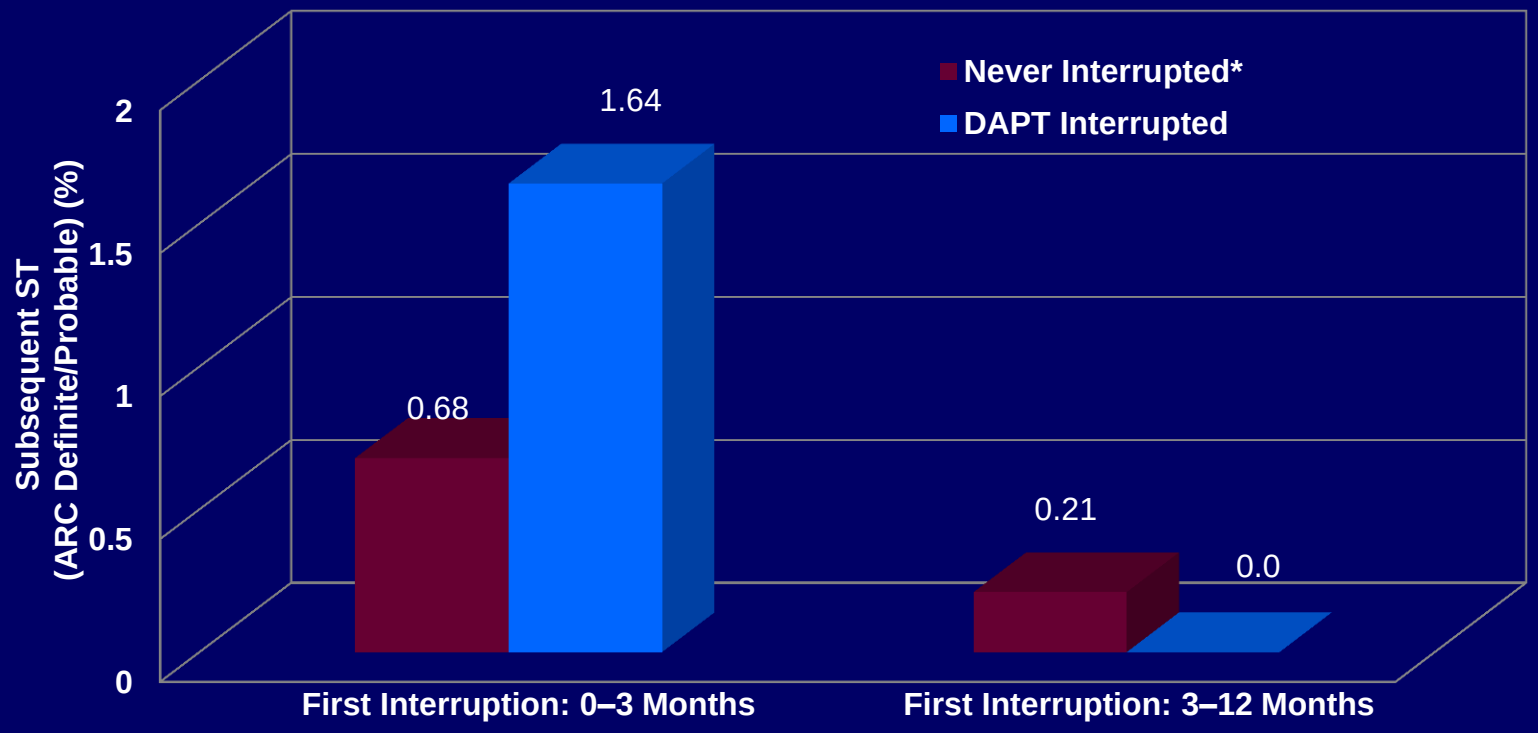
3 Months

# of pts at risk at baseline	3,858	260	3,858	816‡
# of events	30	5†	4	0
# of days to interruption (median)	NA	14	NA	275
95% CI	[0.53%, 1.11%]	[0.63%, 4.43%]	[0.03%, 0.27%]	[0.00%, 0.37%]
	First Interruption 0-3 Months		First Interruption 3-12 Months	

TCT 2012

DAPT interruption on Xience V

Timing of First DAPT Interruption and ST Through 1 Year



No. of pts. at risk at baseline	8,996	700	8,996	919
No. of events	60	11	18	0
No. of days to interruption (median)	NA	0	NA	277
95% CI	[0.58%, 0.98%]	[0.95%, 3.36%]	[0.14%, 0.36%]	[0.00%, 0.44%]

PCR 2012

Bleeding risk – HAS-BLED score

HAS-BLED	Score
Hypertension (SBP > 160 mmHg)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile INRs (if taking VKA)	1
Elderly (e.g., > 65, frail condition)	1
Drugs (concomitant aspirin, NSAID) or alcohol (1 point each)	1 or 2
	Maximum 9 points

Hypertension is defined as uncontrolled blood pressure e.g., systolic blood pressure > 160mmHg. **Abnormal kidney** is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 umol/L. **Abnormal liver function** is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin >2x upper limit of normal, in association with AST/ALT/ALP >3x upper limit of normal, etc). **Bleeding** refers to previous bleeding history and/or predisposition to bleeding, e.g., bleeding diathesis, anemia, etc. **Labile INRs** refers to unstable/high INRs or poor time in therapeutic range (e.g., <60%). **Drugs or alcohol** refers to concomitant use of drugs such as antiplatelet agents, NSAID, etc., or alcohol abuse.

2012 ESC Guidelines

HAS-BLED score

Major bleeding rate by HAS-BLED scores in SPORTIVE cohort (n=7329)

Has-Bled Score	Whole Cohort *N*(%)	Major Bleeding Events *N*(%)	Patients taking Warfarin Only *N* (%)	Major Bleeding Events *N* (%)
0	1,767 (24.0)	21 (1.2)	746 (20)	7 (0.9)
1	2,717 (37.1)	76 (2.8)	1,283(35)	44 (3.4)
2	1,752(23.9)	63 (3.6)	950 (25)	39 (4.1)
3	836 (11.4)	50 (6.0)	483 (13.2)	28 (6.8)
4	241 (3.3)	23 (9.5)	180 (4.9)	16 (8.9)
5	27 (0.4)	2 (7.2)	22 (0.6)	2 (9.1)
6	1 (0.0)	0	1 (0)	0

* c-statistic= 0.654; *p* for trend<0.001

Lip GY, et al.
JACC 2011;57:173-180

Bleeding risk

- High bleeding risk

  ≥ 3 HAS-BLED score

- Expert consensus

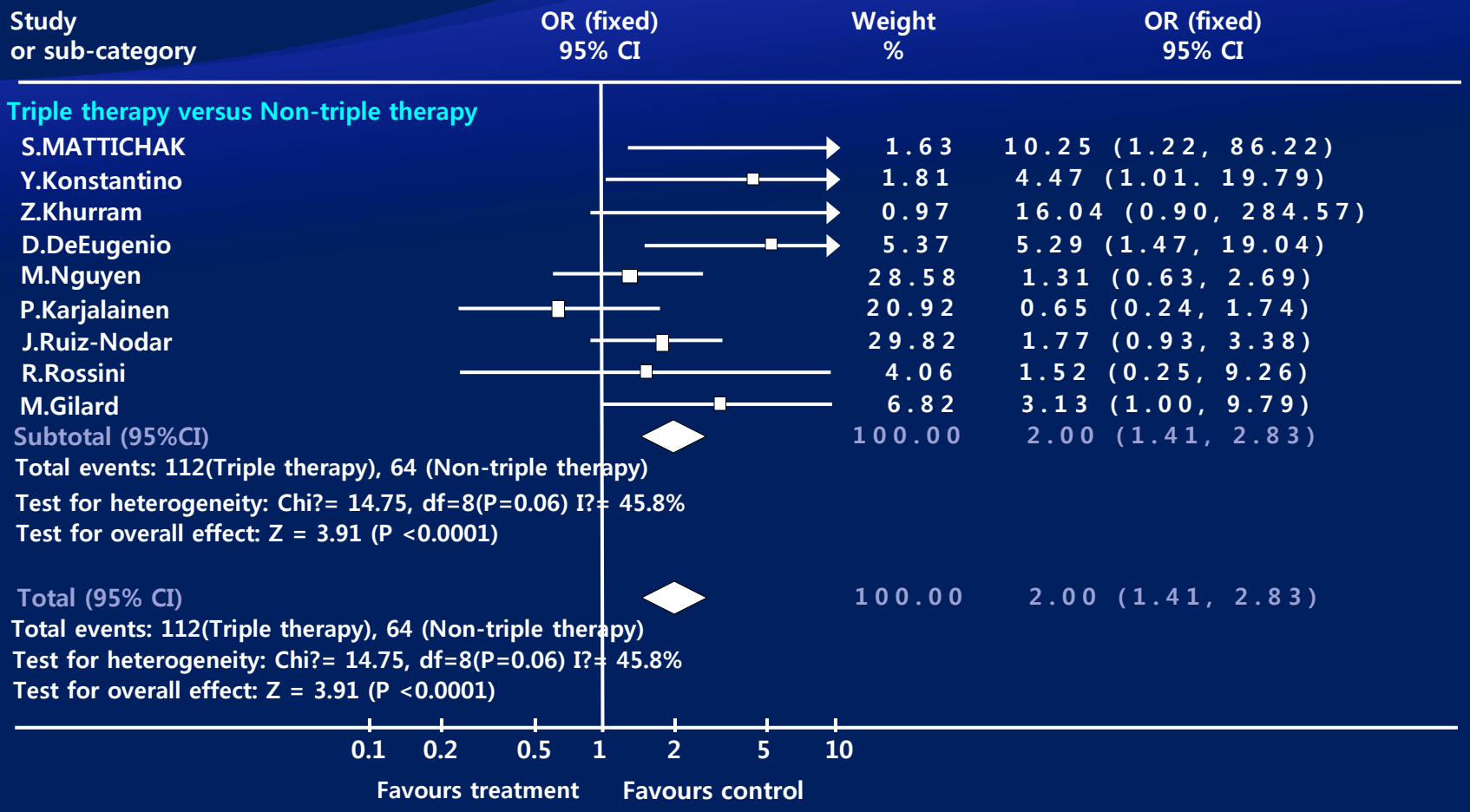
  bare metal stent

  triple therapy for 1 mo, followed by SAPT + OAC

Faxon DP, et al. Circ Cardiovasc Interv 2011;4:522-534

Balancing risks and benefits

meta-analysis, n=5181, stenting in pts with OAC



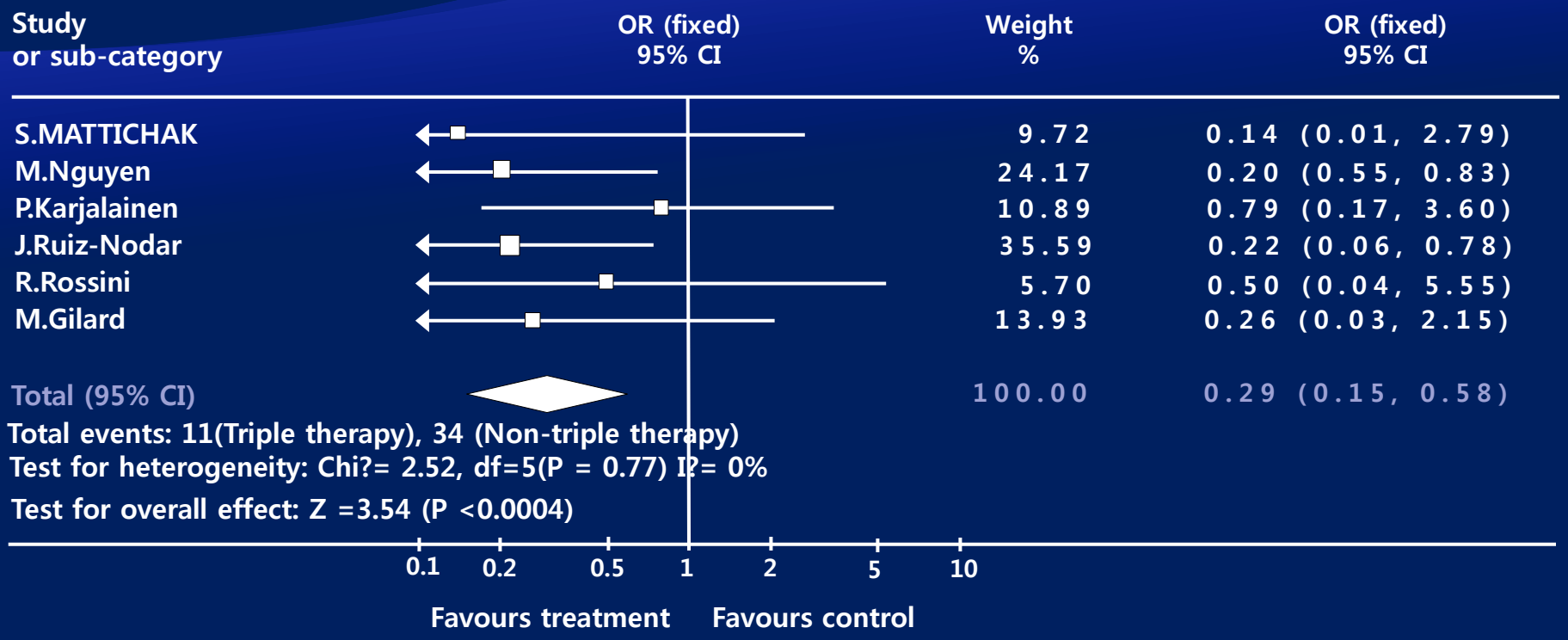
Risk of bleeding

Gao F, et al.

Int J Cardiol 2011;148:96-101

Balancing risks and benefits

meta-analysis, n=5181, stenting in pts with OAC

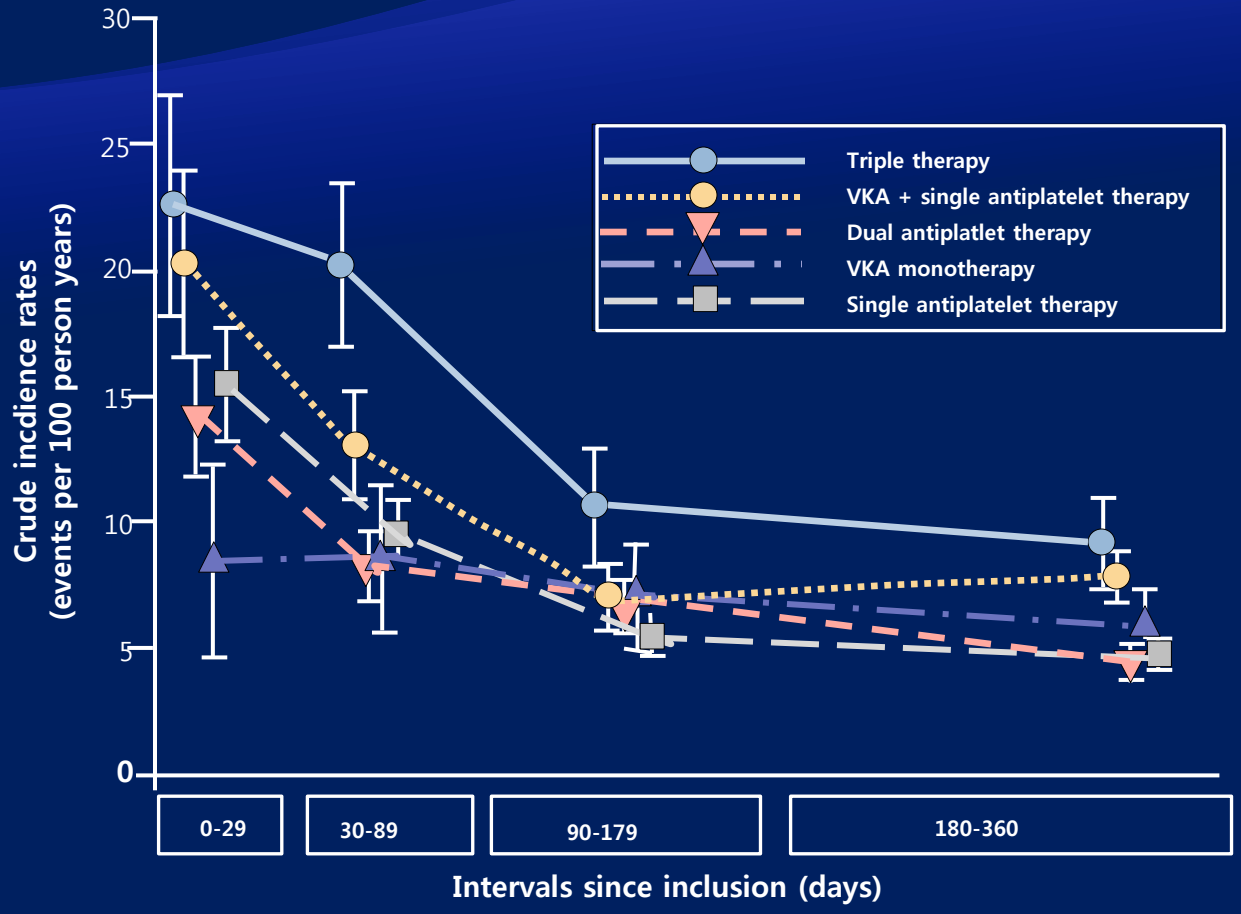


Risk of stroke

Gao F, et al.
Int J Cardiol 2011;148:96-101

Triple therapy has greatest risk

Denmark nationwide registry, n=11,480, AF and MI or PCI (stent 19%)



Bleeding risk

Lamberts M, et al.
Circulation 2012;126:1185-1193

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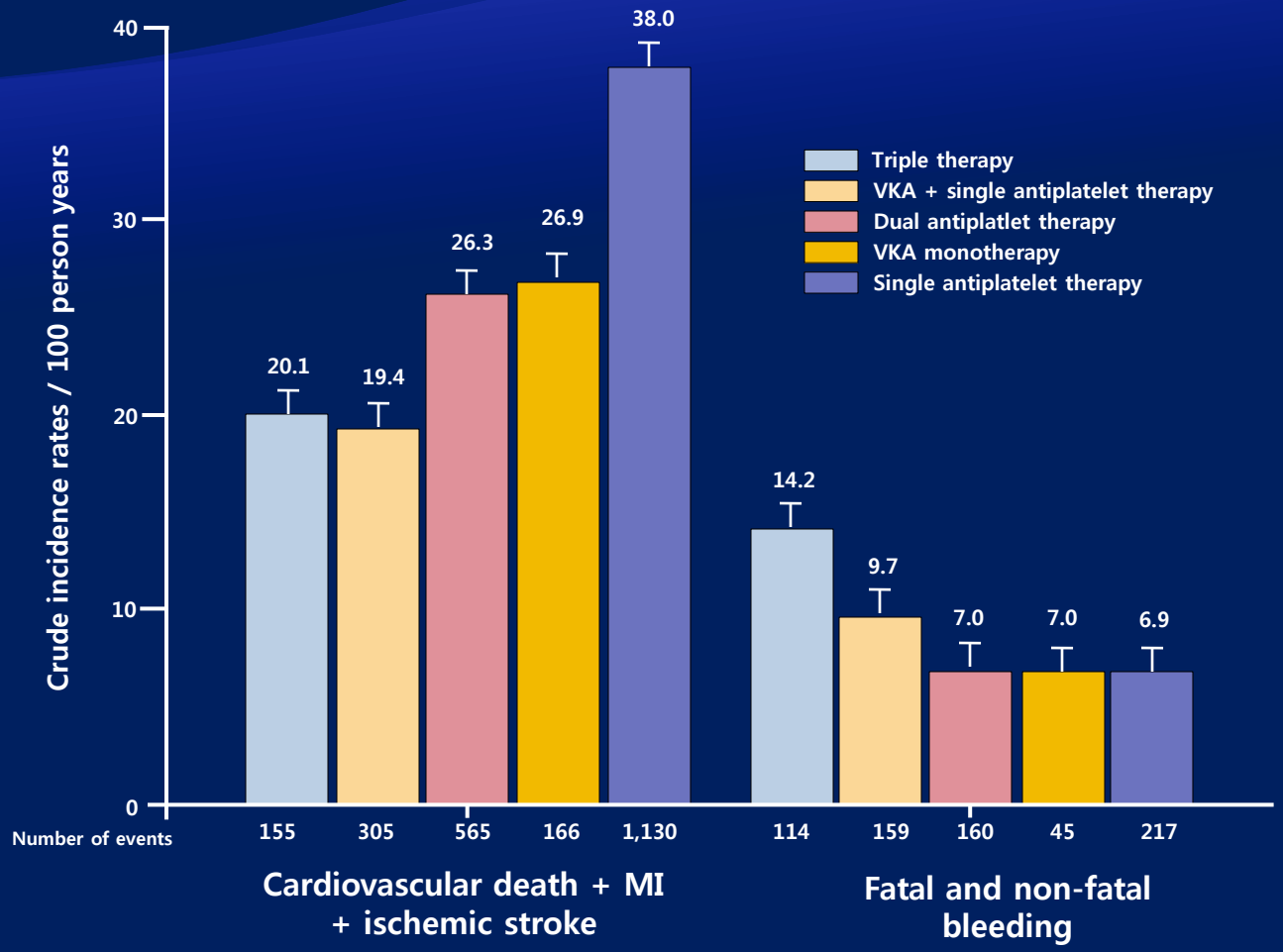
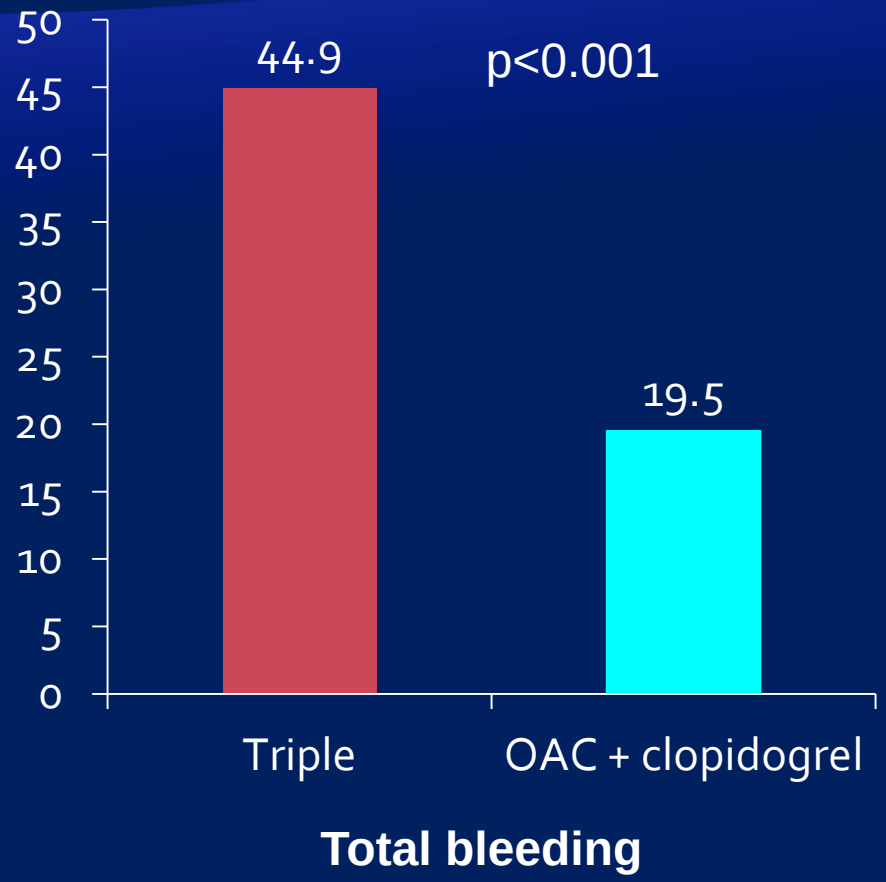
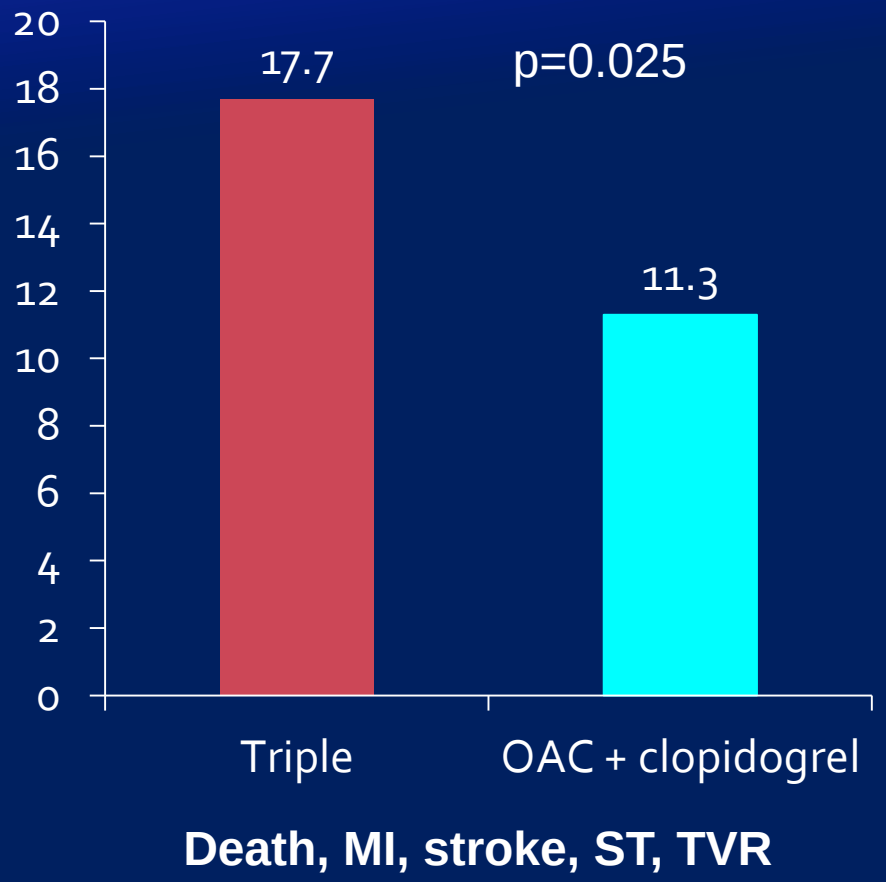


Lamberts M, et al.
Circulation 2012;126:1185-1193

What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting (WOEST trial)



Total bleeding



Death, MI, stroke, ST, TVR

ESC 2012

Ongoing trial (AF + PCI)

- WOEST trial

  n = 573, triple vs. OAC + clopidogrel

- MUSICA-2 trial

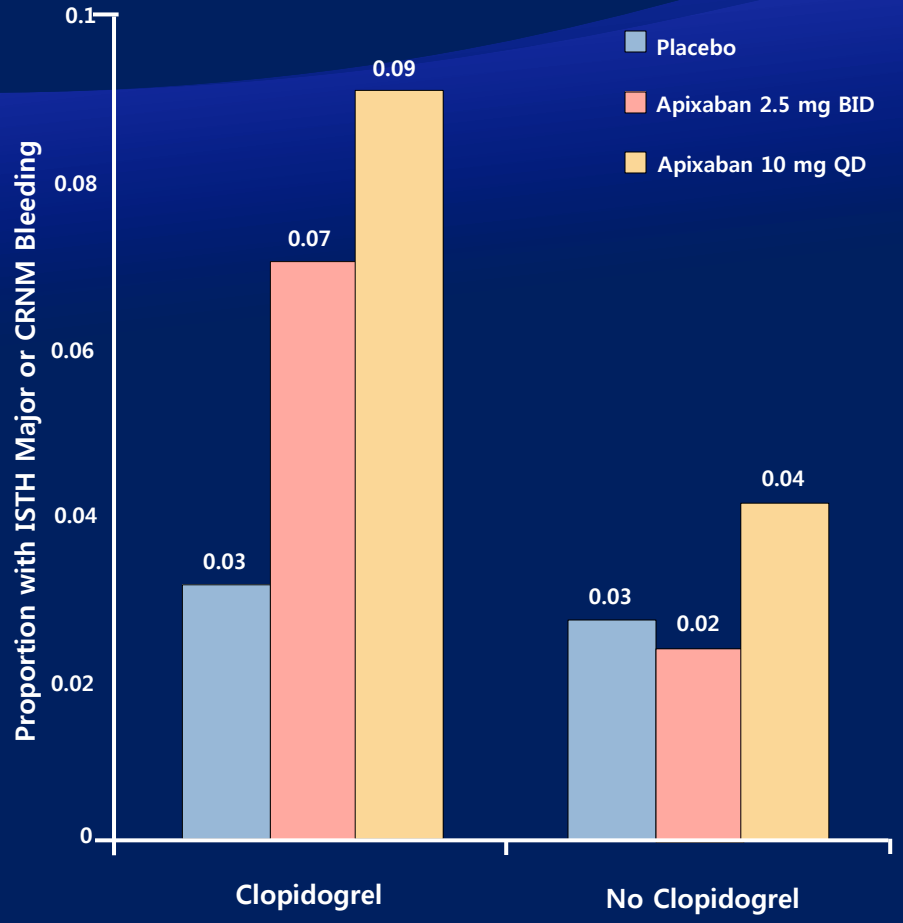
  n = 300, AF with $CHADS_2$ ≤2, triple vs. DAPT

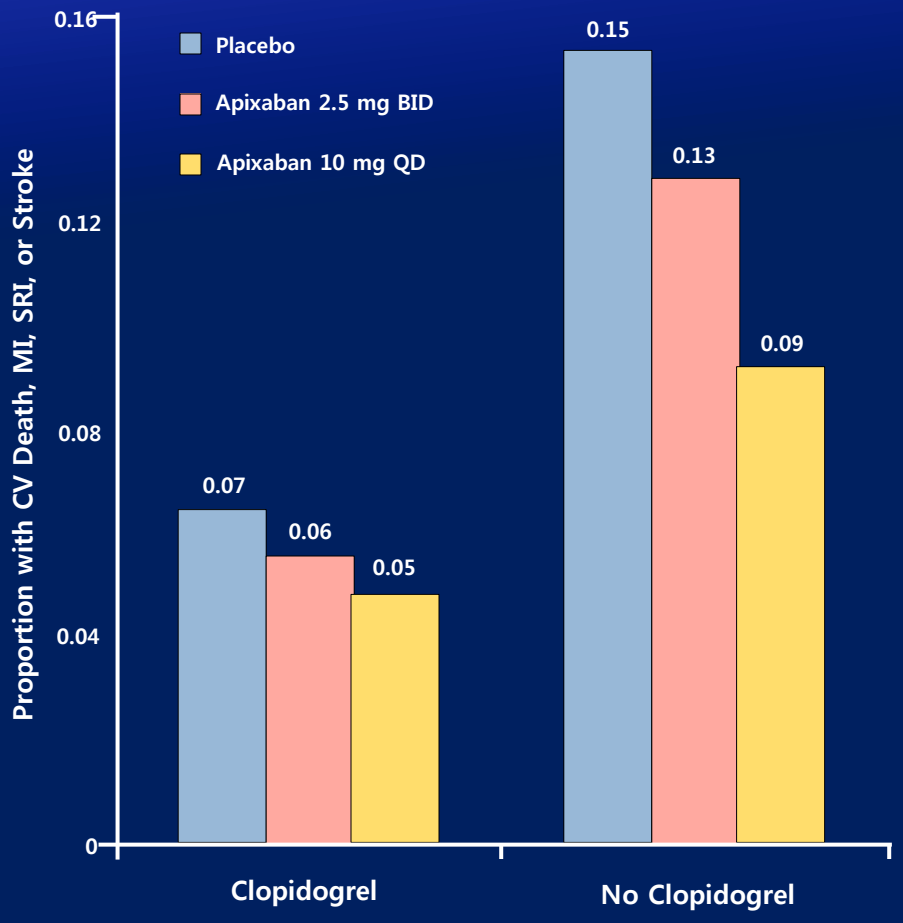
- ISAR-Triple trial

  n = 600, triple 6 weeks vs. 6 months

NOAC: apixaban

1715 ACS pts, PCI 65%

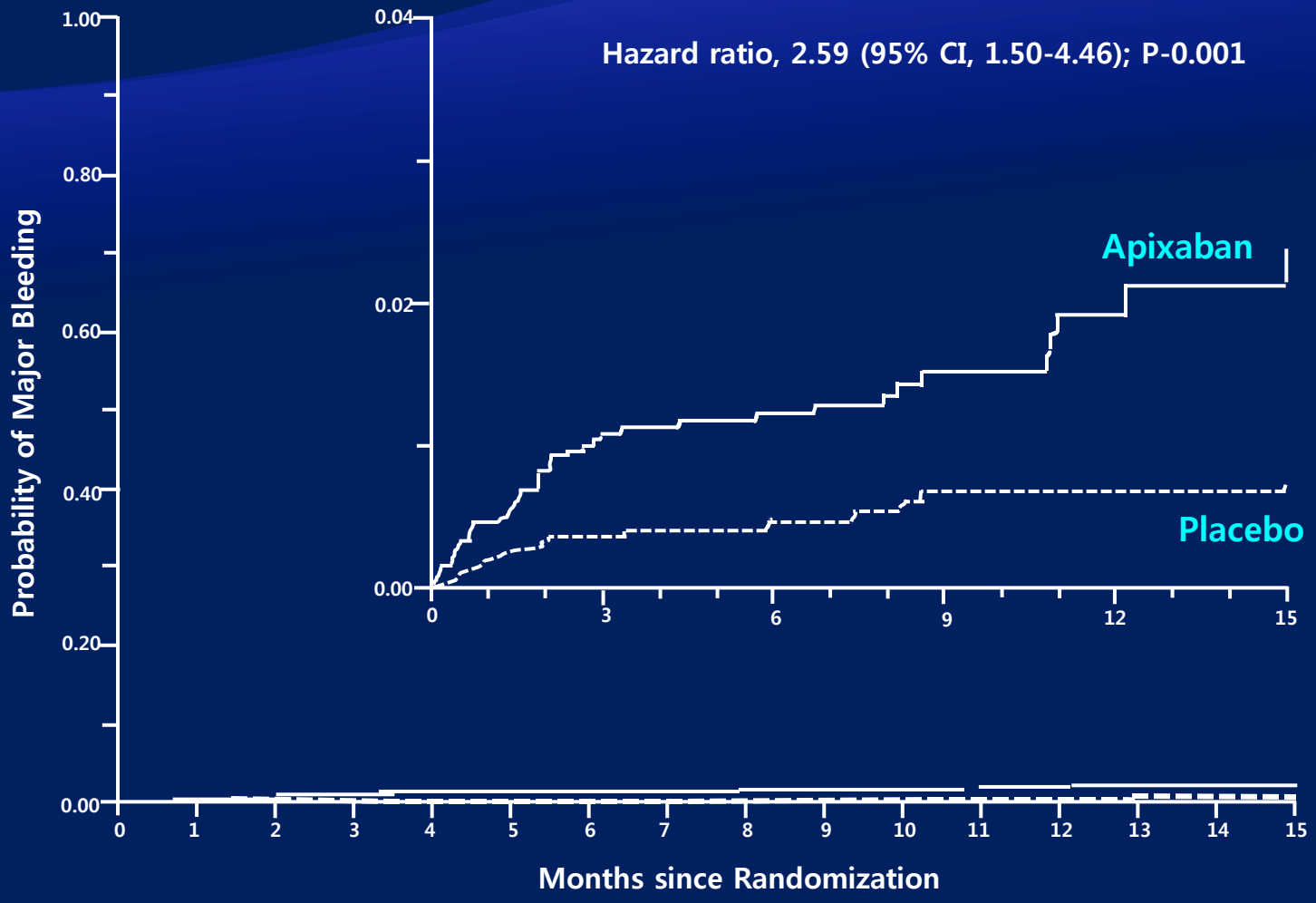




APPRAISE investigators.
Circulation 2009;119:2877-2885

NOAC: apixaban

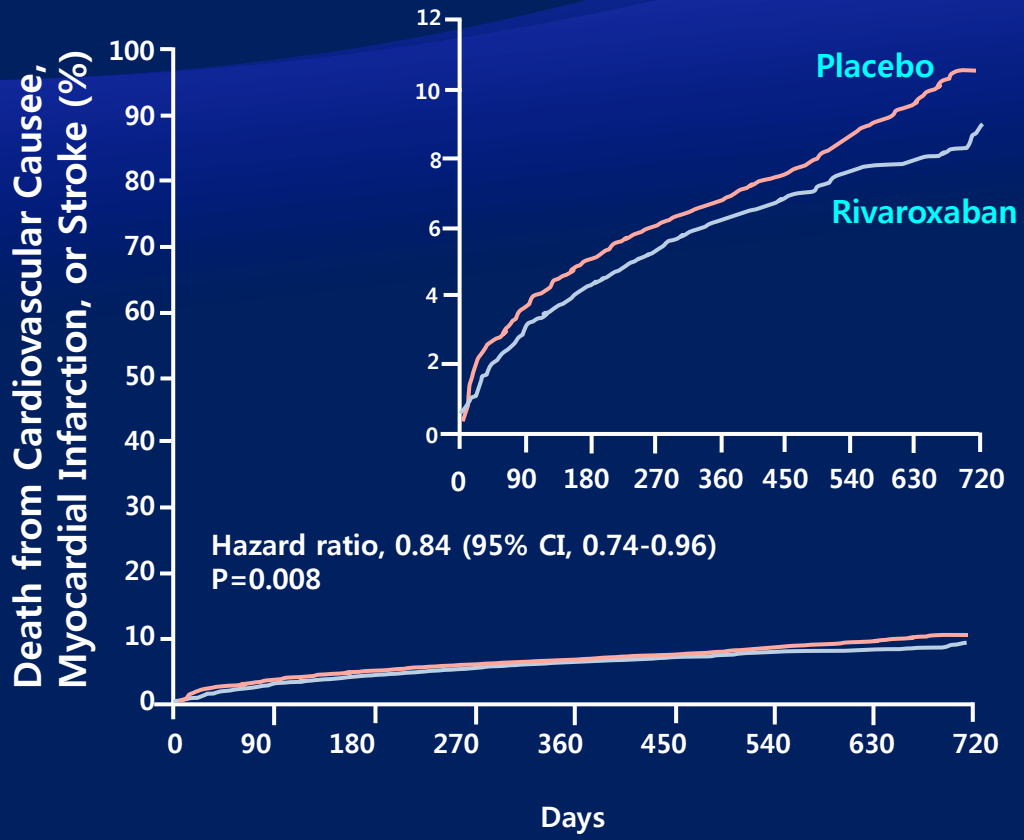
7392 ACS pts with high risk ischemic events, PCI 44%



Alexander JH, et al.
NEJM 2011;365:699-708

NOAC: Rivaroxaban

15,526 ACS pts, PCI 60%



Increase rate of

. major bleeding

(2.1% vs. 0.6%, p<0.001)

. intracranial hemorrhage

(0.6% vs. 0.2%, p=0.009)

Mega JL, et al.
NEJM 2012;366:9-19

Recommendations

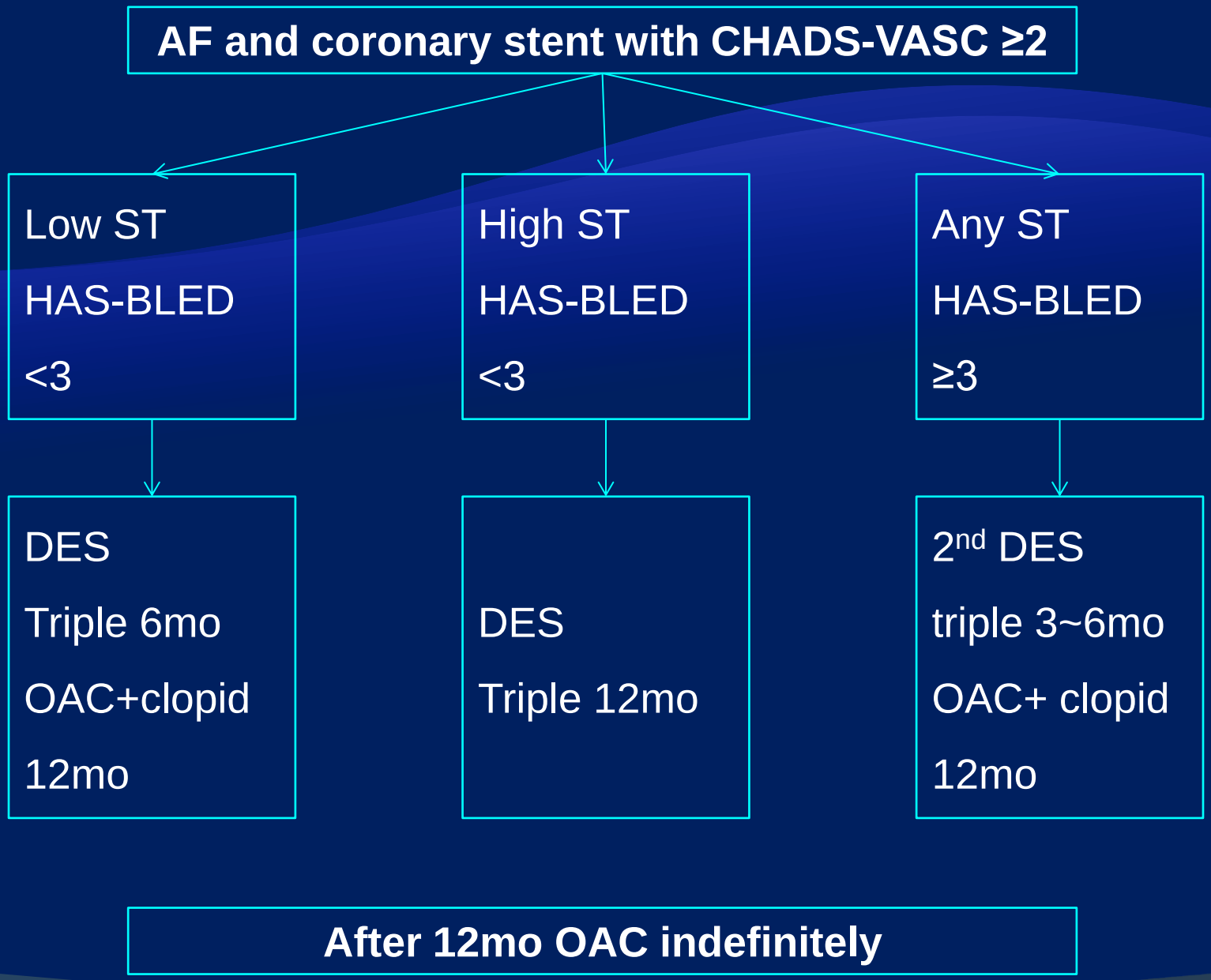
- Assess risk and benefits of triple therapy (VKA + DAPT)
- PPI for GI bleeding complication
- Preference for radial access
- Newer antiplatelet agents (ticagrelor, prasugrel) have not been studied, and are associated with increase risk of bleeding. – should not be used.

Faxon DP, et al.
Circ Cardiovasc Interv 2011;4:522-534

Recommendations

- NOACs have potential advantages over warfarin. However, they have not been studied in this setting.
- VKA with optimal control of INR (2.0~2.5) should be attempted.
- OAC + clopidogrel is attractive.

Faxon DP, et al.
Circ Cardiovasc Interv 2011;4:522-534
Curr Treat Options Cardiovasc Med 2013;15:11-20


AF and coronary stent with CHADS-VASC ≥2
Low ST
HAS-BLED
<3
High ST
HAS-BLED
<3
Any ST
HAS-BLED
≥3
DES
Triple 6mo
OAC+clopid
12mo
DES
Triple 12mo
2nd DES
triple 3~6mo
OAC+ clopid
12mo
After 12mo OAC indefinitely