The patient with atrial fibrillation who needs PCI. The anticoagulant/antiplatelet conundrum.

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Who needs anticoagulation for AF? Almost everyone!

- Based on the current guidelines of the ESC the thromboembolic risk stratification is widely based on the the scoring systems like $CHADS_2$ and more recently the CHA_2DS_2-VASc Score.
- If we simply apply the $CHADS_2$ score almost 70-80% of the AF patients will be eligible for oral anticoagulation (OAC). If you apply the CHA_2DS_2-VASc Score – the number could increase to almost 94%.
- On the other hand 20-30% of AF patients have coronary artery disease (CAD) and about 10% of patients with acute coronary syndromes (ACS) have AF.

Ruiz-Nodar, JM et al. Rev Esp Cardiol. 2013; 66(1): 12-16.

We are facing a conundrum!
We have to much variables to balance between.

(a) Risk factors for stroke and thrombo-embolism in non-valvular AF	
'Major' risk factors	**'Clinically relevant non-major' risk factors**
Previous stroke, TIA, or systemic embolism Age ≥75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40%) Hypertension - Diabetes mellitus Female sex - Age 65–74 years Vascular disease[a]

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

- **AF + OAC – Embolism vs bleeding ?**
- **AF – OAC vs novel OAC ?**
- **PCI + DAPT duration – Stent thrombosis vs bleeding ?**
- **PCI - standard vs**

Where to start from?

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

- **First – indication for PCI -** unmodifiable
  - Elective
  - ACS
    - STEMI and PPCI;
    - NSTE-ACS – mid, longterm
  - Type of stent - modifiable
- **Bleeding risk**
  - HAS-BLED Score system: 3+ - High risk

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What the real situation is?

- On one hand in ACS patients DAPT should be continued for 12 months.
- Real life patients are usually much more complex. These AF patients are usually elderly with a high prevalence of diabetes and unfavorable coronary anatomy (multivessel disease; long, calcified small vessel lesions). Ideally, single focal lesions would be found in large vessels, where only a conventional stent would be implanted.
- Guideline recommendations have clear arguments for their strategies, i.e. that ‘‘DES should be avoided’’ and ‘‘DES should be limited to clinical and anatomical situations with high risk of restenosis’’. These 2 contrasting positions must be discussed in each individual case between the clinical and interventional cardiologists, balancing the pros and cons of both strategies.

What to mind during and post PCI?

- First choice - radial approach:
  - The femoral approach is an independent predictor of access site complications in warfarin treated patients (a hazard ratio of 9.9).
- In PPCI for STEMI:
  - Mechanical thrombus removal is encouraged.
  - GPIs or bivalirudin would not be considered if the INR is >2, except in a 'bail-out' option.
- Try to avoid bridging with Heparin.
- DES should be limited to only situations with clear benefit.
- In NSTEMI - Uninterrupted OAC strategy is recommended
- **Target INR – 2,0-2,5**

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What the guidelines actually say?

Haemorrhagic risk	Clinical setting	Stent implanted	Anticoagulation regimen
Low or intermediate (e.g. HAS-BLED score 0–2)	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 2.0–3.0) 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: VKA (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 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
High (e.g. HAS-BLED score ≥3)	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

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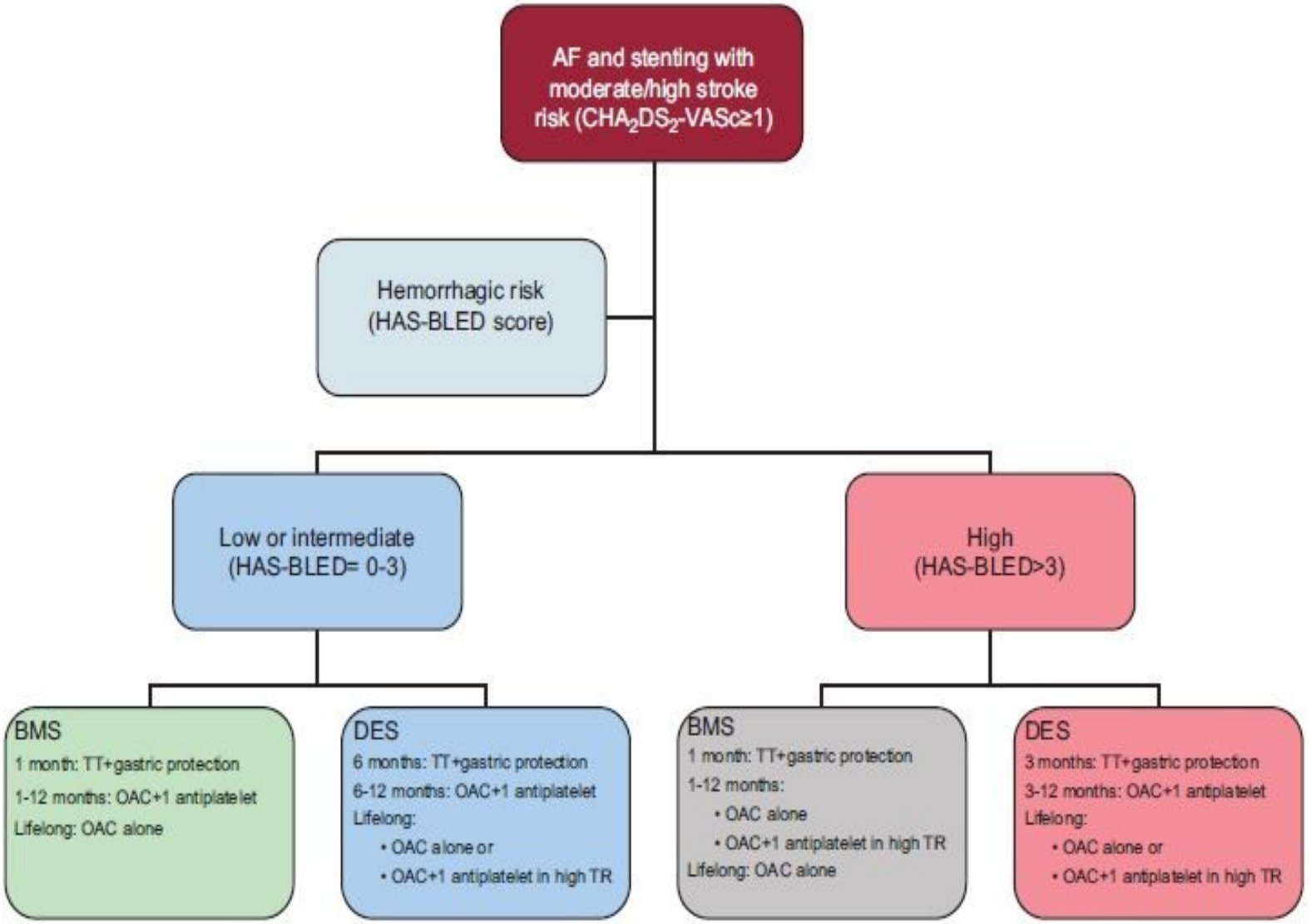
Practically – an easy algorythm



Ruiz-Nodar, JM et al. Rev Esp Cardiol. 2013; 66(1): 13-16

Things could be easier. Try WOEST.

- WOEST - Tests the hypothesis that in patients on OAC undergoing PCI, clopidogrel alone is superior to the combination aspirin and clopidogrel with respect to bleeding but is not increasing thrombotic risk in a multicentre two-country study (BE, NL).

WOEST

Study Design

1:1 Randomisation:

Dual therapy group:	Triple therapy group
OAC + 75mg Clopidogrel qd	OAC + 75mg Clopidogrel qd + 80mg Aspirin qd
1 month minimum after BMS	1 month minimum after BMS
1 year after DES	1 year after DES

Follow up: 1 year

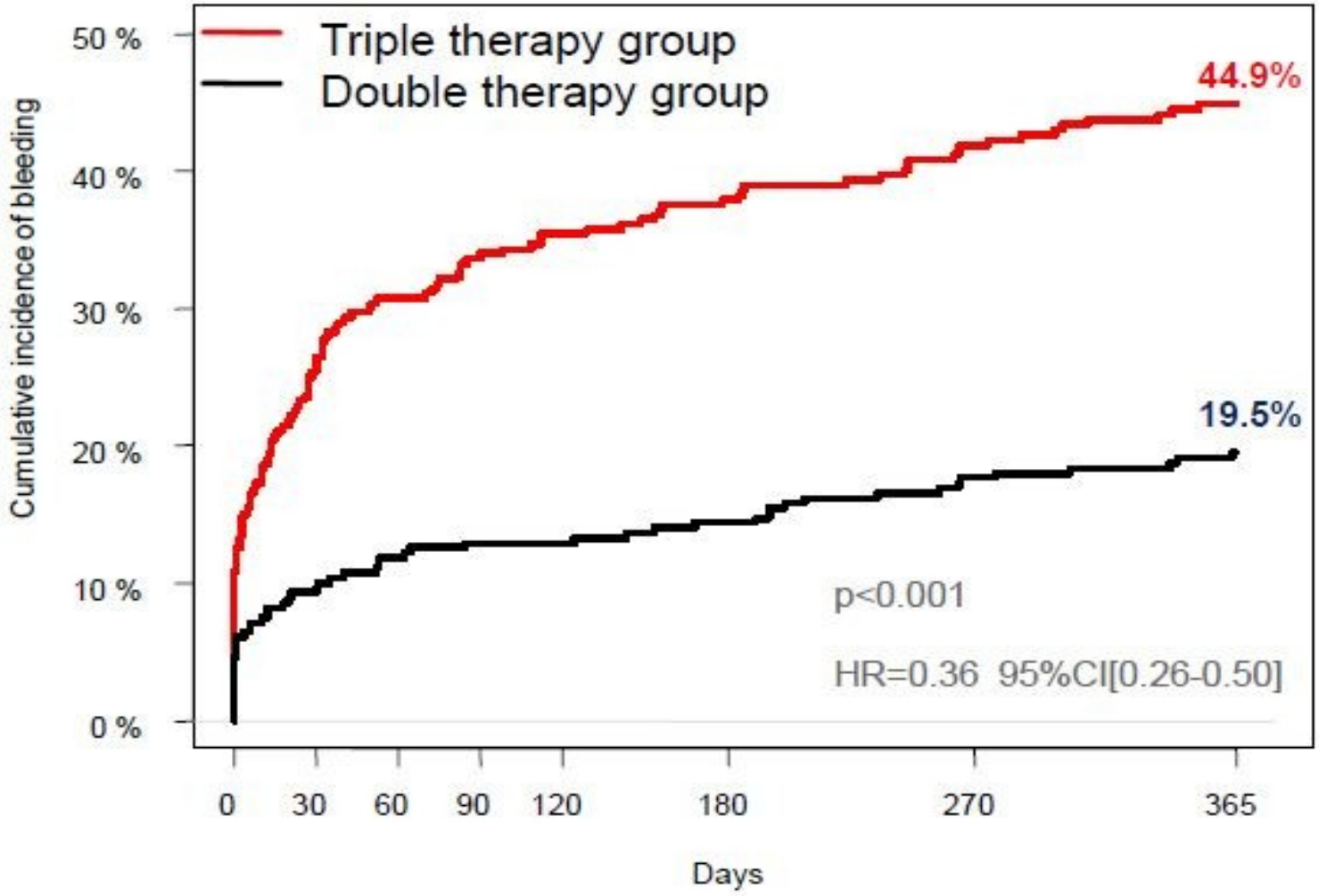
Primary Endpoint: The occurence of all bleeding events (TIMI criteria)

Secondary Endpoints:

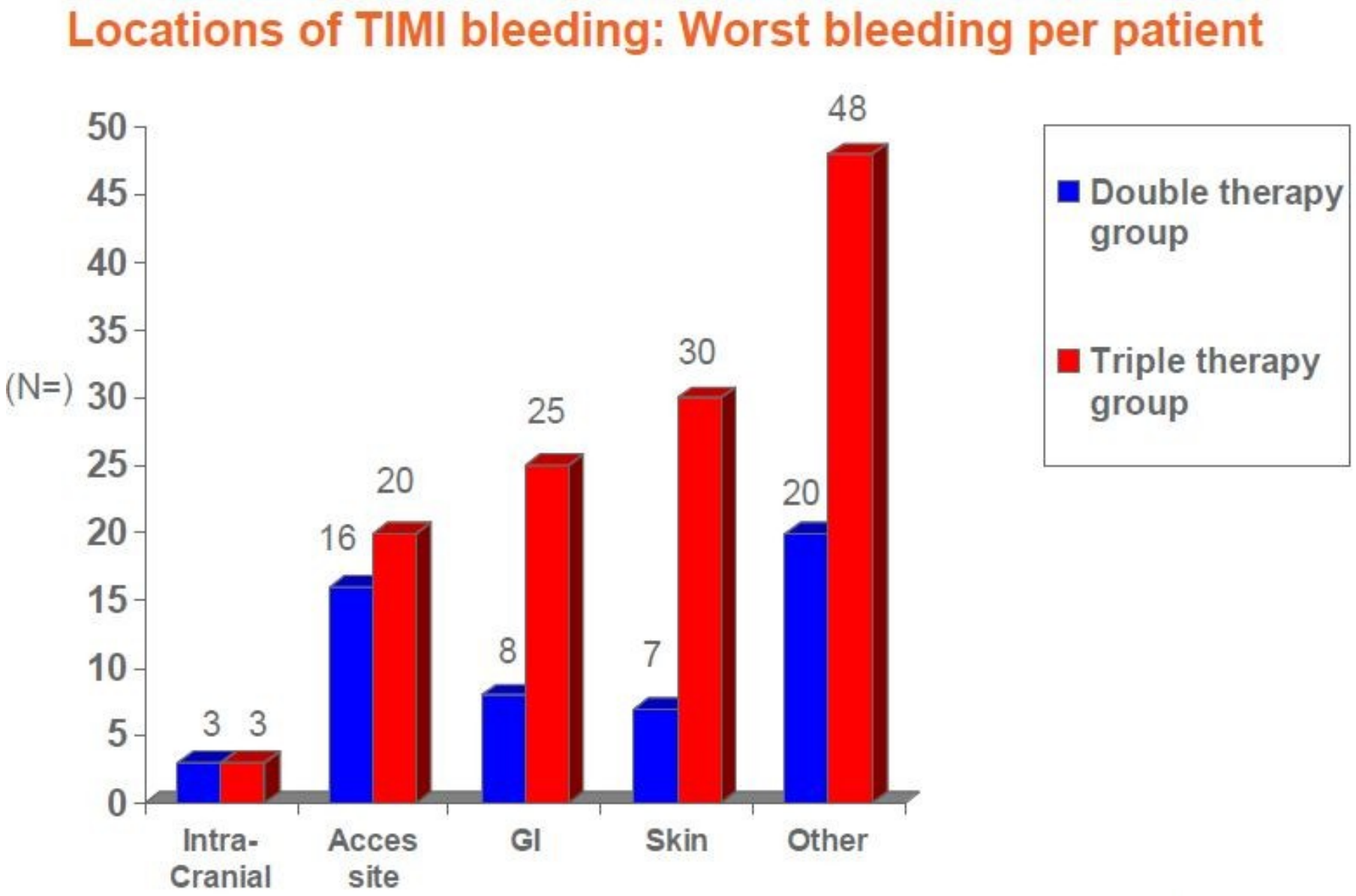
- Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation

WOEST

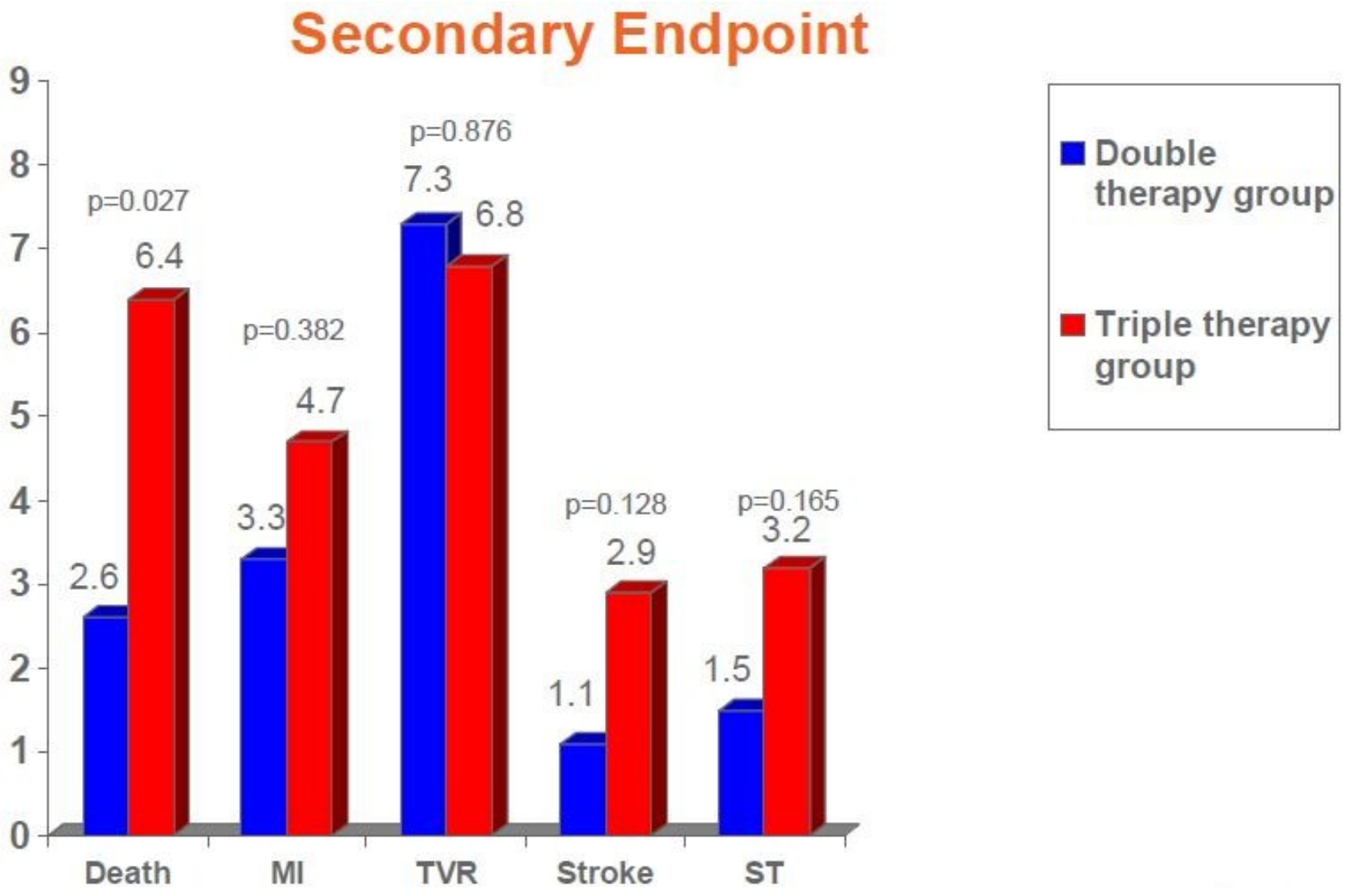
Primary Endpoint: Total number of bleeding events



WOEST


Locations of TIMI bleeding: Worst bleeding per patient
(N=)
50
45
40
35
30
25
20
15
10
5
0
3
3
16
20
8
25
7
30
20
48
Intra-Cranial
Acces site
GI
Skin
Other
Double therapy group
Triple therapy group

WOEST


Secondary Endpoint
9
8
7
6
5
4
3
2
1
0
p=0.027
6.4
2.6
p=0.382
4.7
3.3
p=0.876
7.3
6.8
p=0.128
2.9
1.1
p=0.165
3.2
1.5
Death
MI
TVR
Stroke
ST
Double therapy group
Triple therapy group

WOEST - Conclusions

- First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting.
- Primary endpoint was met: as expected, OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy, but now shown in a randomized way
- Secondary endpoint was met: with dual therapy there is no excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death
- Less all-cause mortality with dual therapy.

What about novel anticoagulant (NOAC) regimens in AF and PCI?

- Patients taking the NOACs may present with an acute coronary syndrome (ACS) and/or undergo percutaneous coronary intervention (PCI). **Concomitant use of antiplatelet therapy with the NOACs significantly increases bleeding risk, as is the case with combining any OAC with antiplatelet therapy. In AF patients at risk of stroke, and irrespective of HAS-BLED score, OAC still confers benefit (reduced mortality and major adverse cardiac events) but with more bleeds.**
- In the absence of robust data, in AF patients with an ACS or PCI/stenting, recommendations based on expert consensus on the management of such patients should

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What about NOAC regimens in AF and PCI? (2)

- Thus, a period of triple therapy is needed (OAC plus aspirin plus clopidogrel), followed by the combination OAC plus single antiplatelet drug and, after one year, management can be with OAC alone in stable patients, where OAC can be adjusted-dose VKA therapy or probably a NOAC.
- Notably, the only trial where clopidogrel use was not contraindicated was RE-LY, so the data on triple therapy with a NOAC (when given at stroke prevention doses in AF patients) are limited.

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Dabigatran and ACS
The **RE-DEEM** Phase II Trial

- 1878 pts at very high risk randomized
- Up to 14 days of STEMI or NSTEMI
- All on dual antiplatelet therapy
- 6 arms – placebo/DGT 50/75/110/150 mg;
- At week 28 – still 79.6% were taking DAPT

Dabigatran and ACS. The **RE-DEEM** Phase II Trial

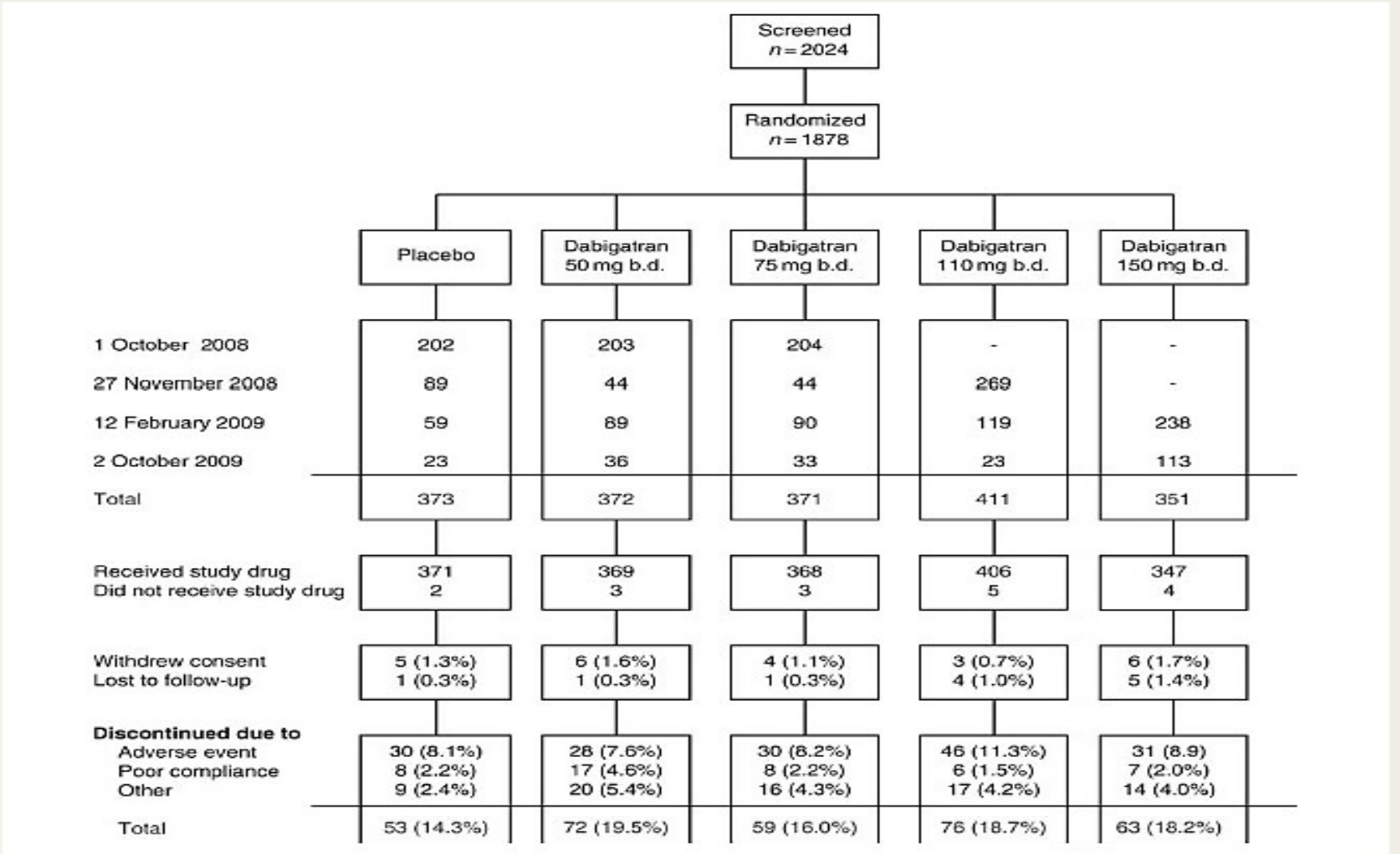
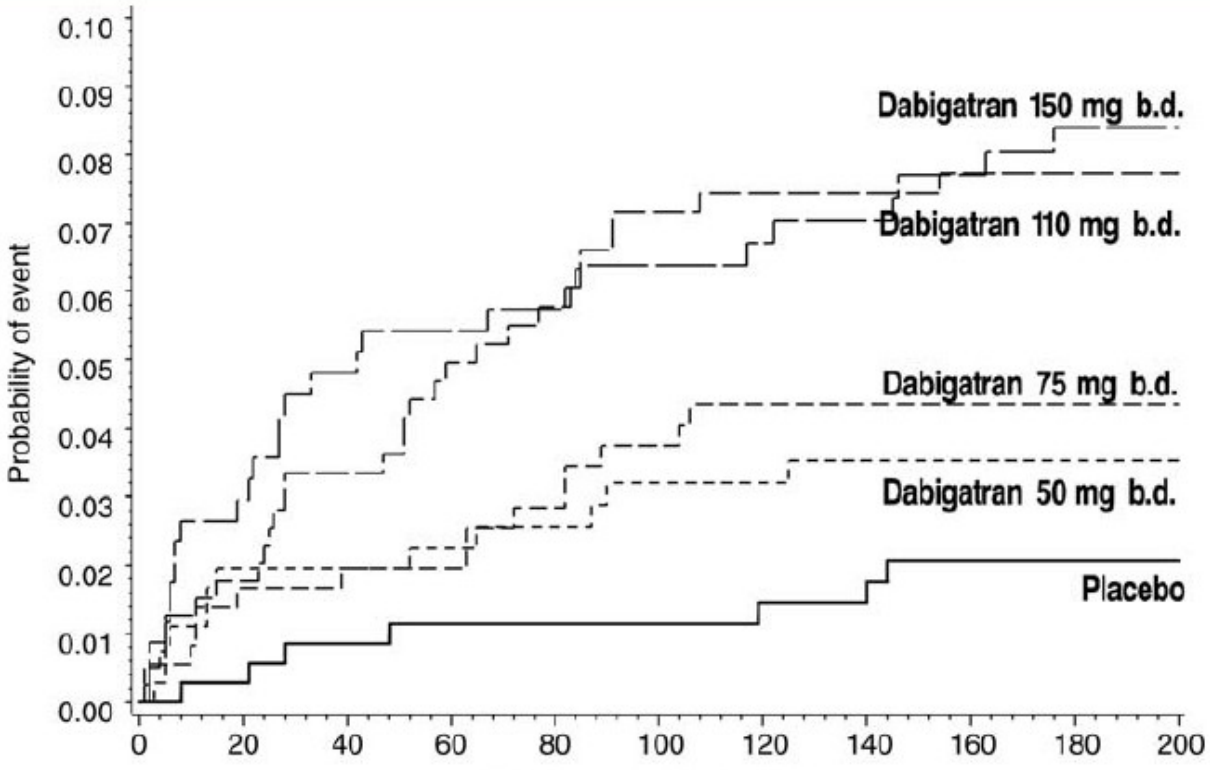


Figure 1 Study design (adaptive dose-escalation) and patient flow.

Dabigatran and ACS - The **RE-DEEM** Phase II Trial



No. at risk											
Placebo	371	351	341	338	330	326	322	319	314	246	0
DE 50 mg b.i.d	369	339	330	322	314	305	300	296	290	239	0
DE 75 mg b.i.d	368	348	338	334	327	320	316	313	309	251	0
DE 110 mg b.i.d	406	380	362	352	344	336	330	324	319	261	0
DE 150 mg b.i.d	347	318	305	301	295	287	285	282	278	200	0

Figure 2 Kaplan–Meier curve depicting the primary endpoint, i.e. the composite of major and clinically relevant minor bleeding. Compared with placebo, primary outcomes differed significantly ($P < 0.001$) for the 110 and 150 mg dabigatran doses using Cox proportional hazards regression models. Number of subjects at risk are given below the *x*-axis.

Dabigatran and ACS - The **RE-DEEM** Phase II Trial Conclusion

- 6 months treatment with Dabigatran 50-150 mg in post-MI pts, receiving DAPT was associated with <u>two to four times dose-related increase in bleeding</u>
- The study had no power to detect the net clinical benefit

What about NOAC regimens in AF and PCI? (3)

- A patient taking Dabigatran may present with an ACS and, given the non-significant but small numerical increase in MI events with dabigatran compared with warfarin, the concerned clinician may consider the use of a VKA or an alternative NOAC (e.g. rivaroxaban or apixaban). There is little evidence to support this, as the relative effects of dabigatran vs. warfarin on myocardial ischaemic events were consistent in patients with or without a baseline history of MI or coronary artery disease.

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Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials.

Table 2. Risk of MI/ACS Across 7 Studies, Including Original RE-LY Results

Measure of Association	Method	Association (95% CI)	*P* Value for Effect	Degree of Heterogeneity (I^2)	*P* Value for Heterogeneity
Odds ratio	M-H	1.33 (1.03 to 1.71)	.03	0% for all	.80
	Peto	1.29 (1.03 to 1.62)	.03		.80
	IV	1.30 (1.02 to 1.65)	.04		.80
	RE	1.32 (1.03 to 1.70)	.03		.80
Relative risk	M-H	1.33 (1.03 to 1.70)	.03	0% for all	.80
	IV	1.31 (1.02 to 1.69)	.03		.80
	RE	1.32 (1.02 to 1.69)	.03		.80
Risk difference	M-H	0.27% (0.04% to 0.50%)	.02	0% for all	.30
	IV	0.14% (−0.03% to 0.31%)	.10		.40
	RE	0.14% (−0.03% to 0.32%)	.10		.40

Conclusions: Dabigatran is associated with an increased risk of MI or ACS in a broad spectrum of patients when tested against different controls. Clinicians should consider the potential of these serious harmful cardiovascular effects with use of dabigatran.

Uchino K, Hernandez AV, Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012 Mar 12;172(5):397-402

What about NOAC regimens in AF and PCI? (4)

- Although twice-daily low-dose Rivaroxaban (2.5 mg or 5 mg b.i.d.) has been used with some benefit in ACS, there are no data on ACS relating to the dose of rivaroxaban used for anticoagulation in AF (20 mg o.d.).
- Apixaban, used in the stroke prevention dose (5 mg b.i.d.) in the ACS setting in combination with aspirin plus clopidogrel, was associated with no reduction in cardiovascular events but an excess of major bleeding.

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Take-home messages

- In AF patients, presenting for PCI always pay attention to clinical characteristics, especially bleeding risk.
- Use the most straightforward PCI technique and stent type, minding the coronary anatomy and risk for restenosis / stent thrombosis.
- Do not underestimate the strict targets of INR (2,0-2,5) in patients on OAC+DAPT/APT.
- Mind the timelines for DAPT discontinuation / reduction.
- There is no hard data to support use of NOAC with DAPT in AF patients.

Aknowledgements

I thank Dr. Christo Dimitrov for the support in developing the presentation.

Thank you for your attention