Thrombozytenaggregation und DOAKs aus der Sicht der Kardiologie

Kurt Huber, MD, FESC, FACC, FAHA

3rd Medical Department

Cardiology & Emergency Medicine

Wilhelminenhospital

Vienna, Austria

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Disclosures

DISCLOSURE STATEMENT OF FINANCIAL INTEREST
Kurt Huber, MD, FESC, FACC

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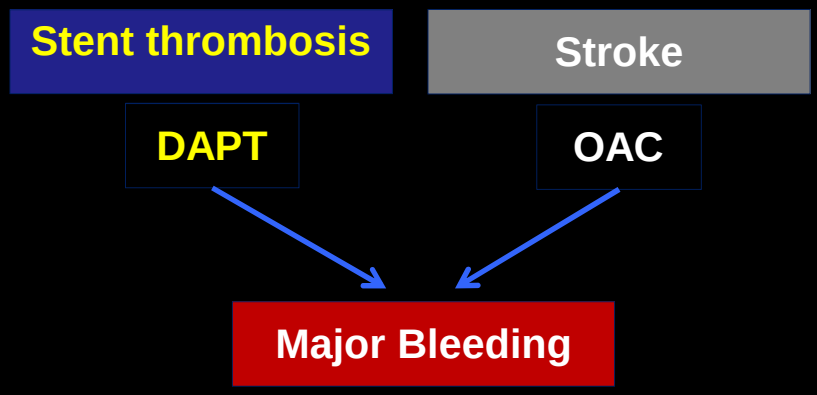
Lecture Fees **from AstraZeneca, Boehringer-Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cordis / Johnson&Johnson, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Pfizer, and Sanofi-Aventis.**

“triple”-Therapy in pts. with Atrial Fibrillation after ACS (or Elective Stent Implantation)

8-10% of Afib patients of cardiology departments develop ACS (or need elective stent implantation)
AND
15-20% of post ACS / electively stented patients develop Afib and are automatocally prone for anticoagulation

Lip, Andreotti, Huber et al. EJ 2010

(The problem: You can not simultaneously prevent all three!)



ORIGINAL INVESTIGATION

LESS IS MORE

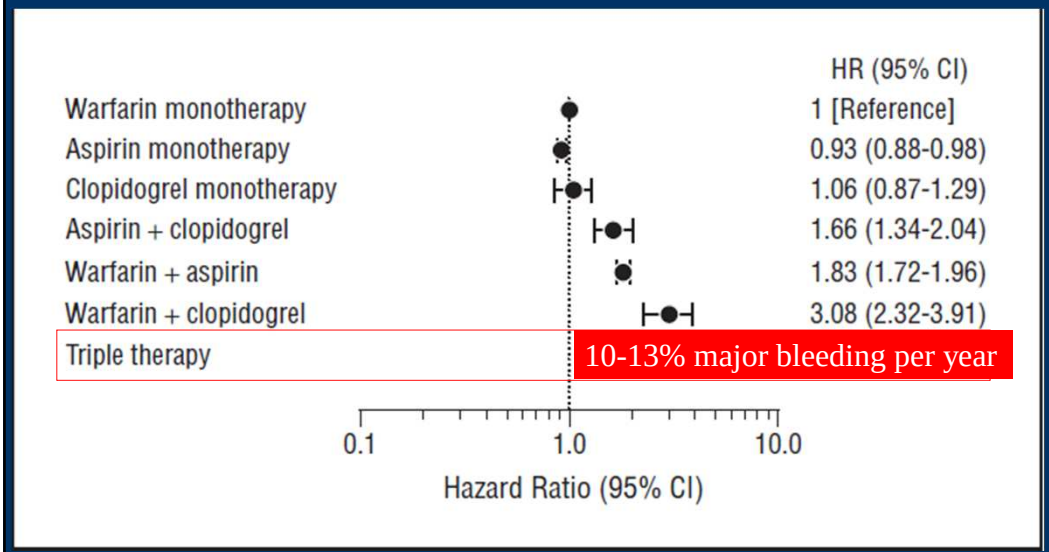
Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

Morten L. Hansen, MD, PhD; Rikke Sørensen, MD; Mette T. Clausen, MSc Pharm; Marie Louise Fog-Petersen, MSc Pharm; Jakob Raunsø, MD; Niels Gadsbøll, MD, DMSc; Gunnar H. Gislason, MD, PhD; Fredrik Folke, MD; Søren S. Andersen, MD; Tina K. Schramm, MD; Steen Z. Abildstrøm, MD, PhD; Henrik E. Poulsen, MD, DMSc; Lars Køber, MD, DMSc; Christian Torp-Pedersen, MD, DMSc

- Over 82,000 Danish Patients with AF
- National Registry
- 1997-2006
- Mean Follow-up: 3.3 Years
- 11.4% developed a non fatal or fatal bleeding

Arch Intern Med. 2010;170(16):1433-41

HR for Risk of Bleeding



Arch Intern Med. 2010;170(16):1433-41

76 year old woman with high-risk NSTEMI

- Elective angiography 2 years after PCI+stenting (LAD) and 12 months after CABG (venous grafts to ACx and RCA)
- Cardiac cath day after admission, patent grafts to RCA and LCX; 75% stenosis in stented segment of LAD, received XienceTM DES
- Creatinine increased to 2.2 mg/dL (195 µmol/L)
- Day 3, developed atrial fibrillation with worsened dyspnea

Duke Clinical Research Institute

Courtesy of Chris Granger

ACS, DES, who develops Afib with CHADS score of 4, CHADS-VASc of 7.

Which treatment?

A. Aspirin, clopidogrel, warfarin for one year

B. Aspirin, clopdiogrel, warfarin; stop clopidogrel after 3 months

C. Aspirin, ticagrelor, warfarin; stop ticagrelor after 3-6 months

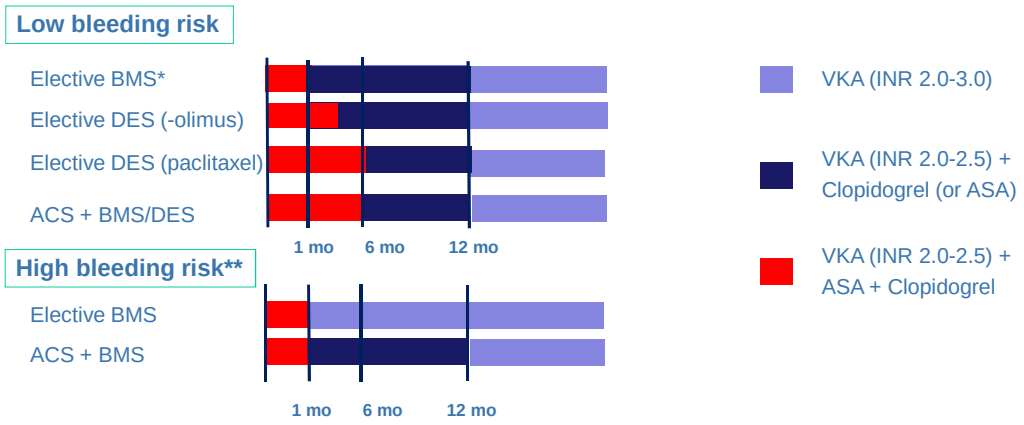
D. Clopidogrel and warfarin (stop aspirin after 0-30 days)

E. Aspirin and clopidogrel alone, due to high risk of bleeding

Duke Clinical Research Institute

Courtesy of Chris Granger

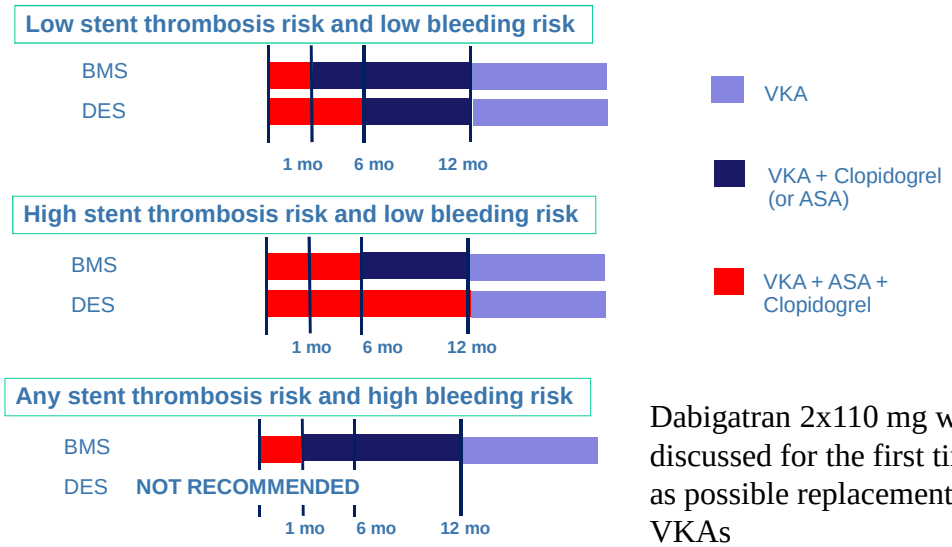
ESC Guidelines in AF patients at moderate to high thromboembolic risk in whom OAC is required



9

Adapted from *Camm J et al. Eur Heart J 2010;31:2369-2429*

A North-American consensus document on antithrombotic therapy in AF patients and a coronary stent with moderate/high stroke risk ($CHADS_2$ ≥2)

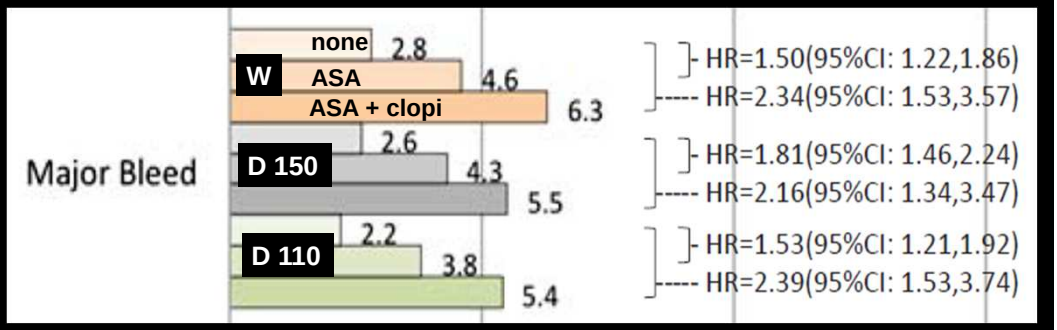


Dabigatran 2x110 mg was discussed for the first time as possible replacement of VKAs

10

Adapted from *Faxon DP. Circ Cardiovasc Interv 2011;4:522-534*

Bleeding According to Antiplatelet Rx



Series of no, single, and dual antiplatelet therapy

HRs adjusted for age, gender, warfarin experience, SBP, CAD, HF, hypertension, diabetes, TIA, CrCl and statin use.

Circulation. published online December 27, 2012

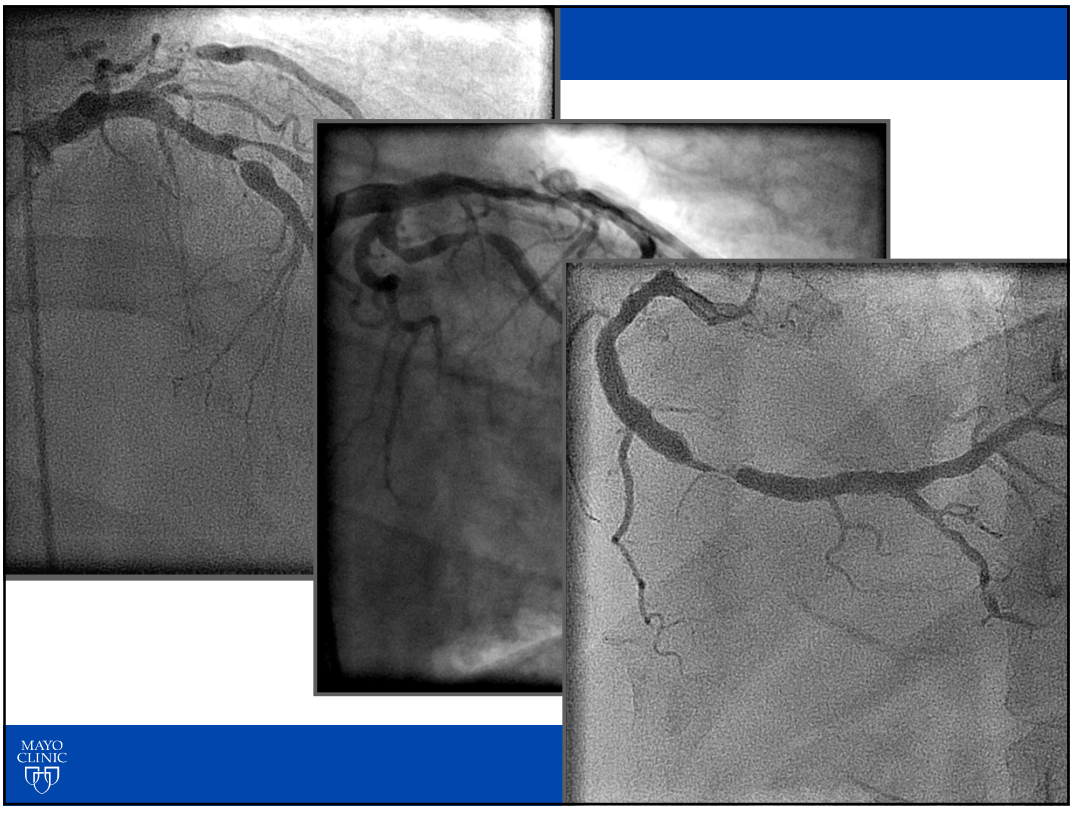
Novel oral anticoagulants in patients with AF and ACS and/or coronary stents

- Rivaroxaban PIONEER
- Dabigatran RE-DUAL
- Apixaban AAA
- Edoxaban being considered

72 year old male

- Class II Angina Pectoris
- Mild HTN, hyperlipidemia
- Beta-blockade (sotalol), long acting oral nitrate, aspirin
- Paroxysmal atrial fibrillation 1-2 episodes per year. CHADS2 = 1, CHADS2-Vasc-Score = 2
- Normal rest ECG, normal LVEF on echo
- Referred for exercise testing
  - 8.5 minutes Bruce protocol; mild angina at peak
  - 1 mm ST depression at 7.5 minutes; resolves 5 min

MAYO CLINIC



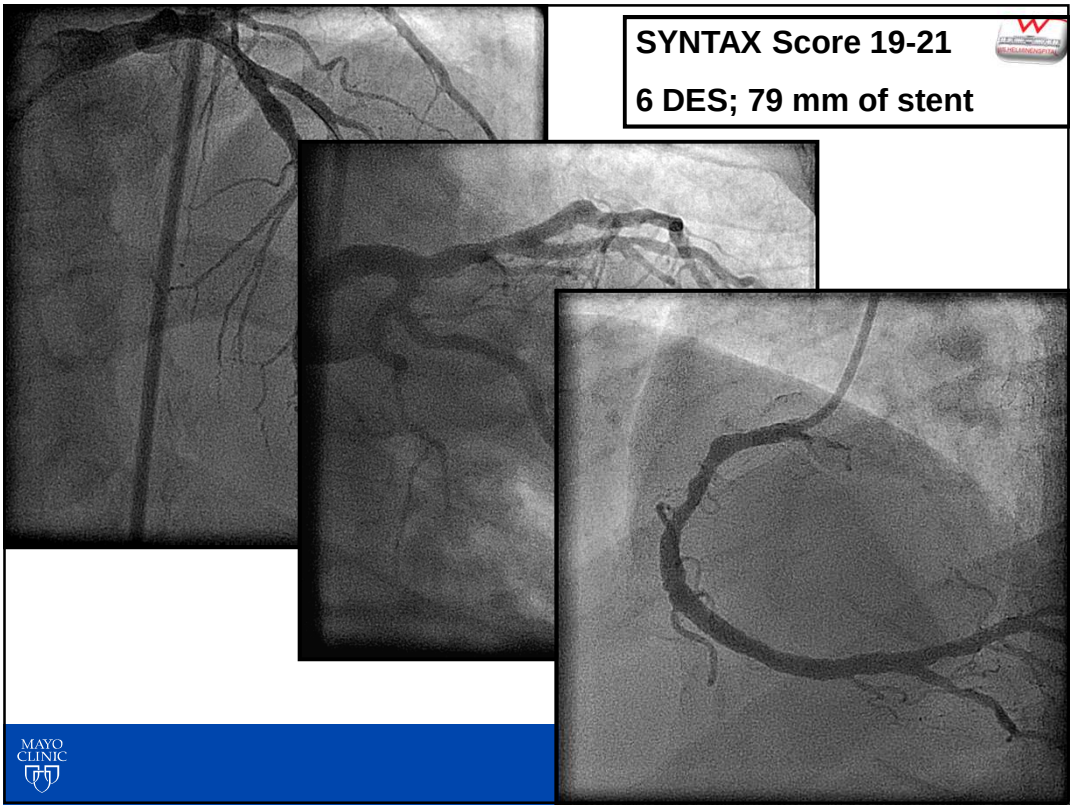
MAYO CLINIC

What to Do?

- Medical therapy
- Medical therapy plus PCI
- Medical therapy plus PCI plus catheter based pulmonary vein isolation
- Medical therapy plus CABG
- Medical therapy plus CABG plus surgical MAZE plus surgical LAA ligation

Decision was …

- Medical therapy
- Medical therapy plus PCI
- Medical therapy plus PCI plus catheter based pulmonary vein isolation
- Medical therapy plus CABG
- Medical therapy plus CABG plus surgical MAZE plus surgical LAA ligation



Which post-PCI pharmacologic strategy should be chosen?

- Aspirin, clopidogrel and VKA (INR-goal 2,0-2,5) for 3 (-6) months followed by aspirin or clopidogrel plus VKA up to 12 months
- Aspirin, clopidogrel and VKA (INR-goal 2,0-2,5) for 3 (-6) months followed by aspirin or clopidogrel plus a DOAC up to 12 months
- Aspirin, clopidogrel and a DOAC (reduced dosage) for 3 (-6) months followed by aspirin or clopidogrel plus a DOAC up to 12 months
- Aspirin and clopidogrel for 12 months
- Aspirin and clopidogrel for 3 (-6) months, followed by dual therapy (aspirin or clopidogrel plus an anticoagulatn)
- Clopidogrel and VKA (INR-goal 2,0-2,5) for 12 months

MAYO CLINIC

We decided …

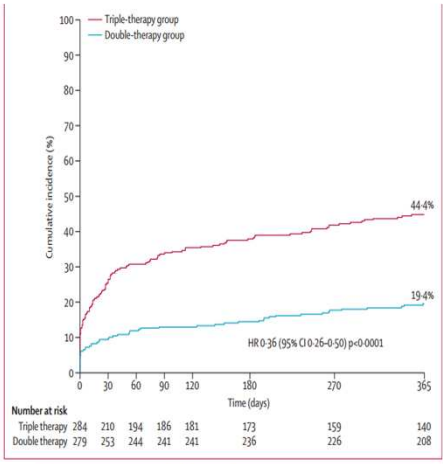
- Aspirin, clopidogrel and VKA (INR-goal 2,0-2,5) for 3 (-6) months followed by aspirin or clopidogrel plus VKA up to 12 months
- Aspirin, clopidogrel and VKA (INR-goal 2,0-2,5) for 3 (-6) months followed by aspirin or clopidogrel plus a DOAC up to 12 months
- Aspirin, clopidogrel and a DOAC (reduced dosage) for 3 (-6) months followed by aspirin or clopidogrel plus a DOAC up to 12 months
- Aspirin and clopidogrel for 12 months
- Aspirin and clopidogrel for 3 (-6) months, followed by dual therapy (aspirin or clopidogrel plus an anticoagulatn)
- Clopidogrel and VKA (INR-goal 2,0-2,5) for 12 months

MAYO CLINIC

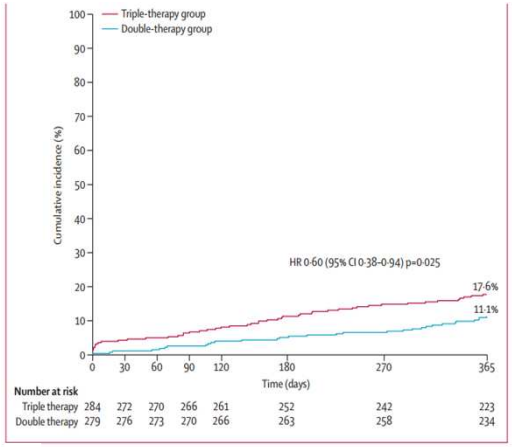
Should we skip aspirin ?

WOEST

Primary endpoint (any bleeding) and secondary endpoint (death, myocardial infarction, stroke, target vessel revascularisation and stent thrombosis)



: Incidence of the primary endpoint (any bleeding)
HR=hazard ratio.



Cumulative incidence of the secondary endpoint (death, myocardial infarction, stroke, target-vessel revascularisation, and stent thrombosis)
HR=hazard ratio.

Trial of NOAC in stented patients with AF

Inclusion
- AF (prior, persistent, and/or >6 hours duration)
- CHADS ≥ 1
- Physician decision that oral anticoag is indicated
- Coronary stent (with (≥1/3) or without ACS)

Randomize
n ≥ 5,000
after successful stenting

Exclusion
- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, moderate/severe MS)

NOAC | **Warfarin**

Triple therapy for all for 2-4 weeks, then randomize. Duration of DAPT depends on ACS and on stent type

ASA | **placebo** | **ASA** | **placebo**

Primary outcome: major/clinically relevant bleeding (through 6-12 months)

Secondary objective: exclude substantial increased in risk of stent and substantial increased risk of stroke

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RE-DUAL PCI

Randomize
Event driven

Dabigatran 110 bid + single APT

Dabigatran 150 bid + single APT

Warfarin + dual APT

Outcomes:
Bleeding, death, MI, and stroke

http://us.boehringer-ingelheim.com/news_events/press_releases/press_release_archive/2013/11-19-2013-boehringer-ingelheim-global-clinical-trials-pradaxa-dabigatran-etexilate-mesylate.html

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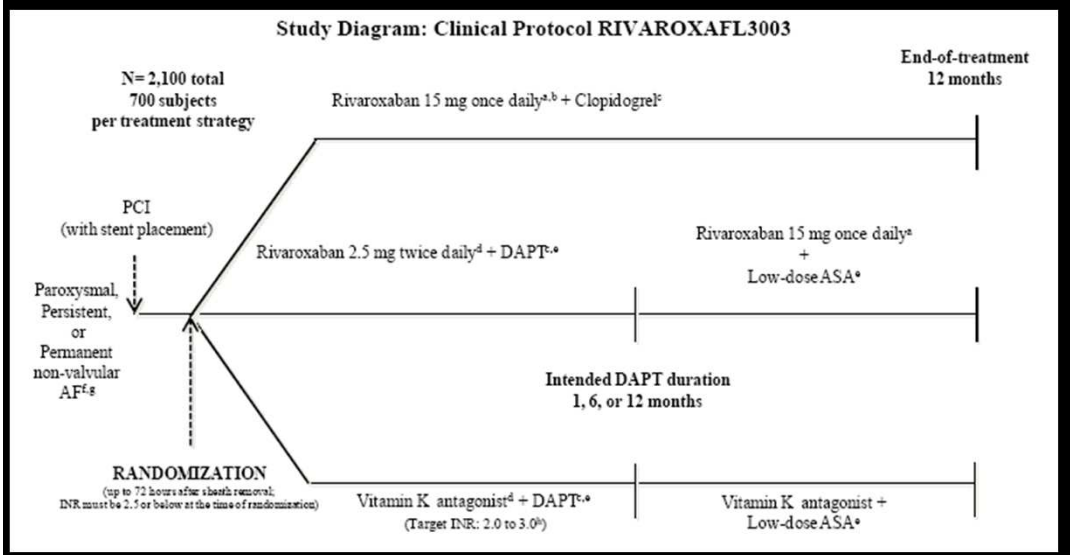
PIONEER AF-PCI



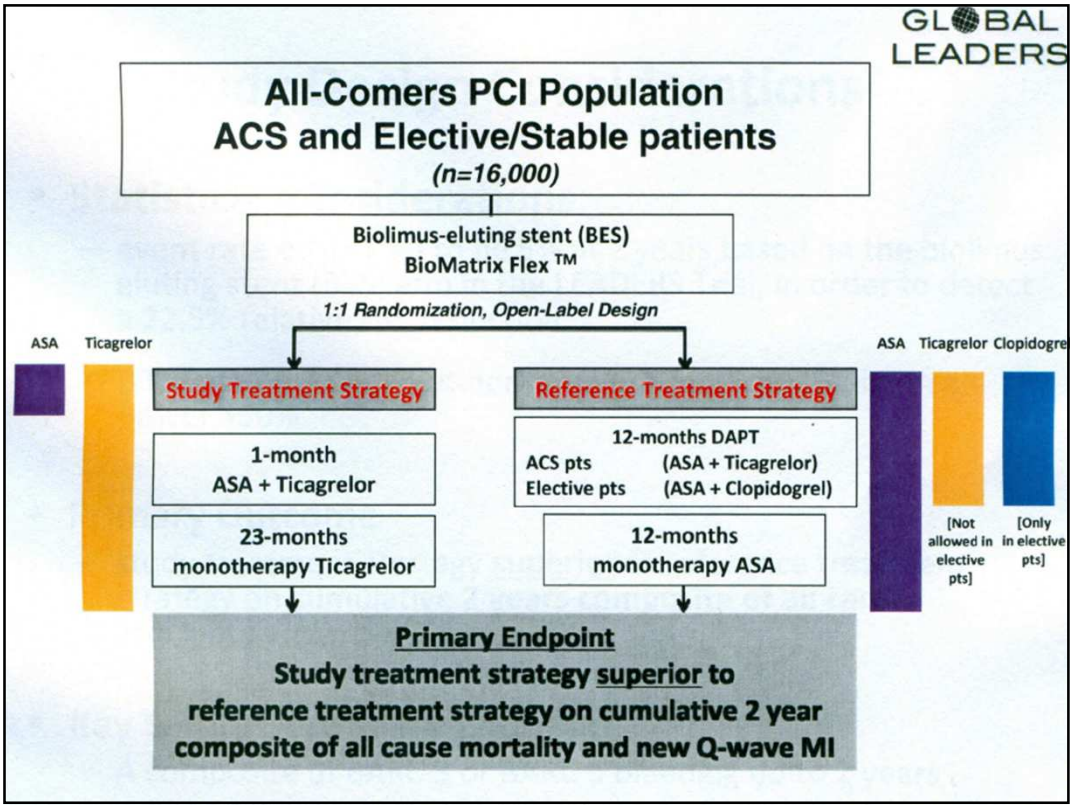
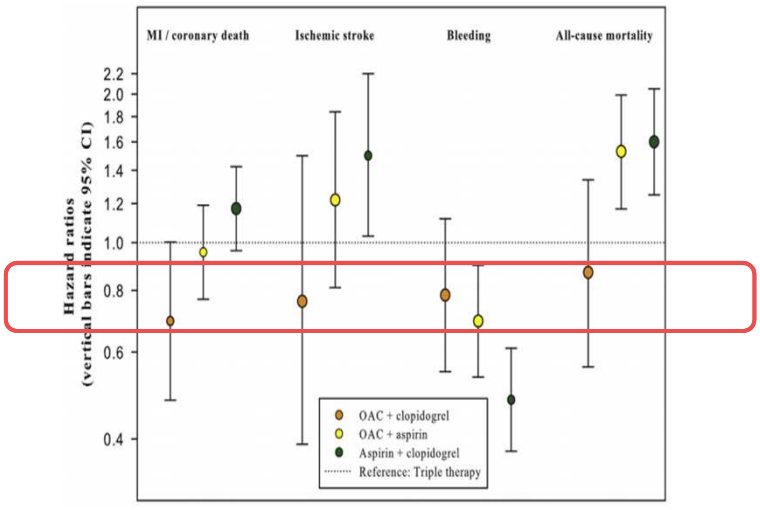


Figure 1

Benefit and Safety With Triple Therapy Versus Dual Therapies in AF Patients After Myocardial Infarction and Coronary Intervention

Triple therapy (oral anticoagulant [OAC] plus aspirin plus clopidogrel [dotted line]) is used as reference (hazard ratio 1.00).



Conclusions

- Multiple antithrombotics clearly increase bleeding
  - Benefits on ischemic events less clear
- "Triple Therapy" has to be redefined
  - New P2Y12 inhibitors: prasugrel, ticagrelor
  - DOACs
- Results of ongoing trials are essential for future recommendations
  - Does aspirin add benefit or just risk?
- Right patient, right drugs, right dosage, right duration

Future Recommendations for combination therapy

- All oral anticaogulants will be allowed (VKA, DOACs)
  - If VKA: INR 2,0-2,5
  - If DOAC: lower dose (2x110 mg dabigatran, 1x15 mg rivaroxaban, 2x2,5 mg apixaban)
- DAPT (ASA+Clopi) or dual therapy (DOAC or VKA+Clopi) may be used in patients with low ischemic risk (CHADs-VASc =1)
  - Do not switch from DOACs to a VKA if patients are already on treatment
  - Start with a VKA OR a DOAC if patients are not pre-treated

Thank you

Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data

Rikke Sørensen, Morten L Hansen, Steen Z Abildstrom, Anders Hvelplund, Charlotte Andersson, Casper Jørgensen, Jan K Madsen, Peter R Hansen, Lars Køber, Christian Torp-Pedersen, Gunnar H Gislason

- Over 40,000 patients
- Registries from Denmark
- 2000-2005
- Mean Follow-up 476 days
- 4.6% of patients were admitted to hospital with bleeding

The Lancet. 2009;374(9706):1967-74

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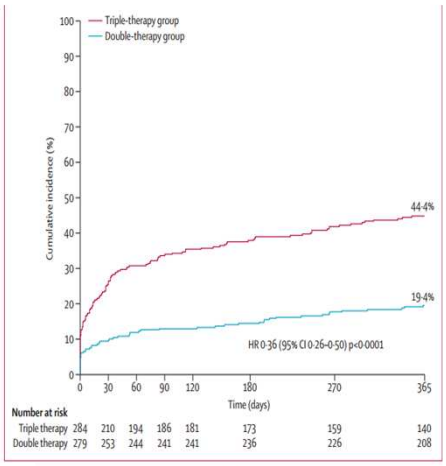
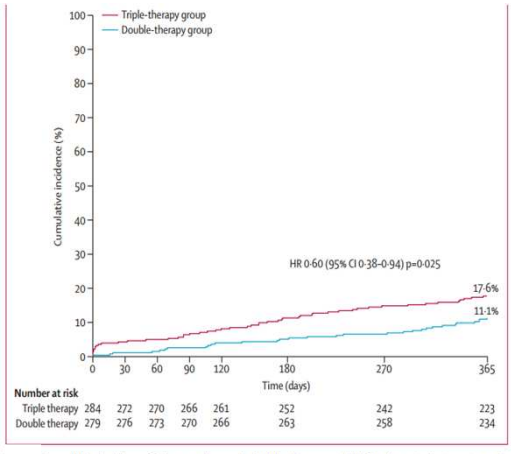
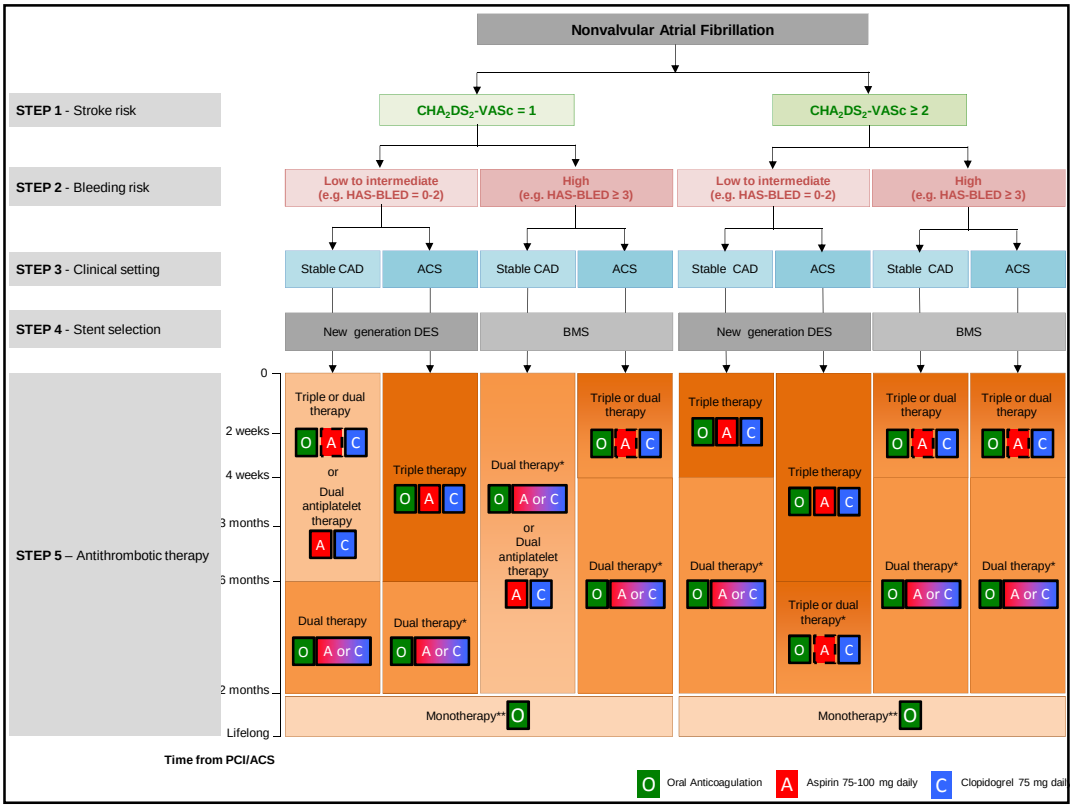
Figure 2
WOEST trial: Primary endpoint (any bleeding) and secondary endpoint (death, myocardial infarction, stroke, target vessel revascularisation and stent thrombosis)

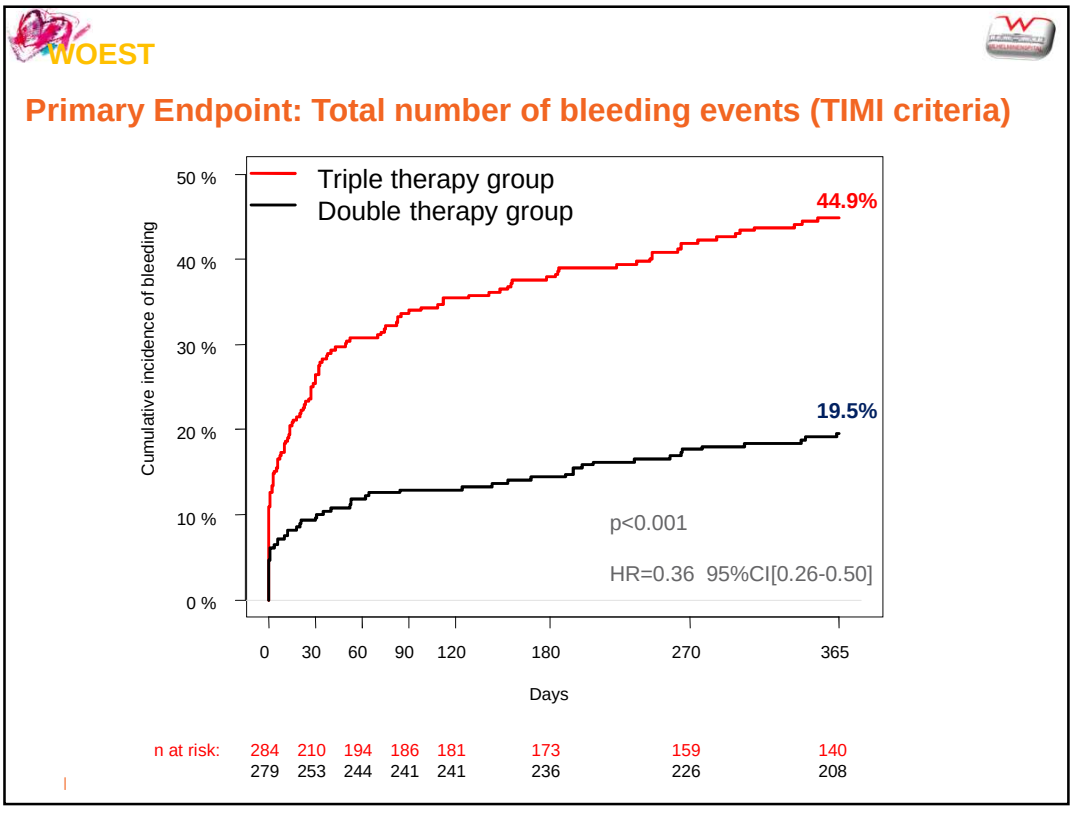


: Incidence of the primary endpoint (any bleeding)
HR=hazard ratio.



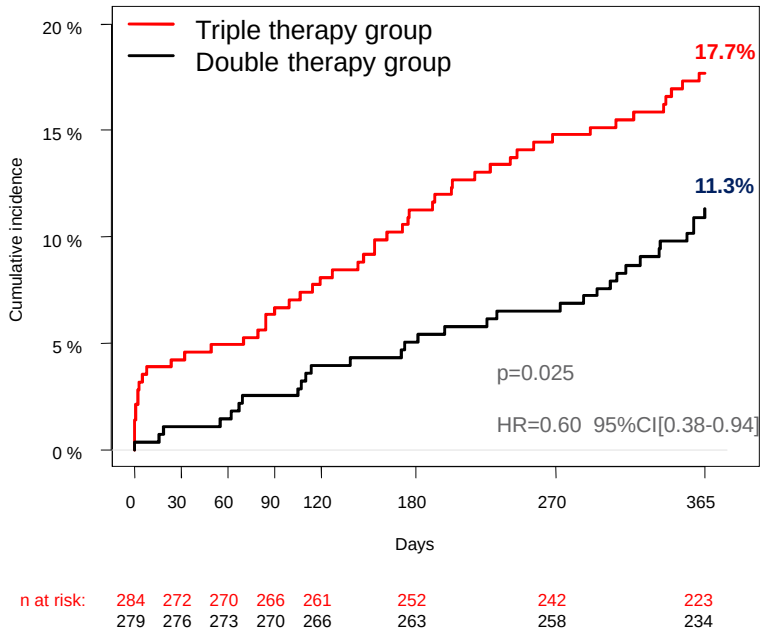
Cumulative incidence of the secondary endpoint (death, myocardial infarction, stroke, target-vessel revascularisation, and stent thrombosis)
HR=hazard ratio.


Nonvalvular Atrial Fibrillation
STEP 1 - Stroke risk
CHA2DS2-VASc = 1
CHA2DS2-VASc ≥ 2
STEP 2 - Bleeding risk
Low to intermediate (e.g. HAS-BLED = 0-2)
High (e.g. HAS-BLED ≥ 3)
STEP 3 - Clinical setting
Stable CAD
ACS
STEP 4 - Stent selection
New generation DES
BMS
STEP 5 – Antithrombotic therapy
0
2 weeks
4 weeks
3 months
6 months
12 months
Lifelong
Triple or dual therapy
Triple therapy
Dual therapy*
Dual therapy
Dual therapy*
Monotherapy**
Time from PCI/ACS
Oral Anticoagulation
Aspirin 75-100 mg daily
Clopidogrel 75 mg daily

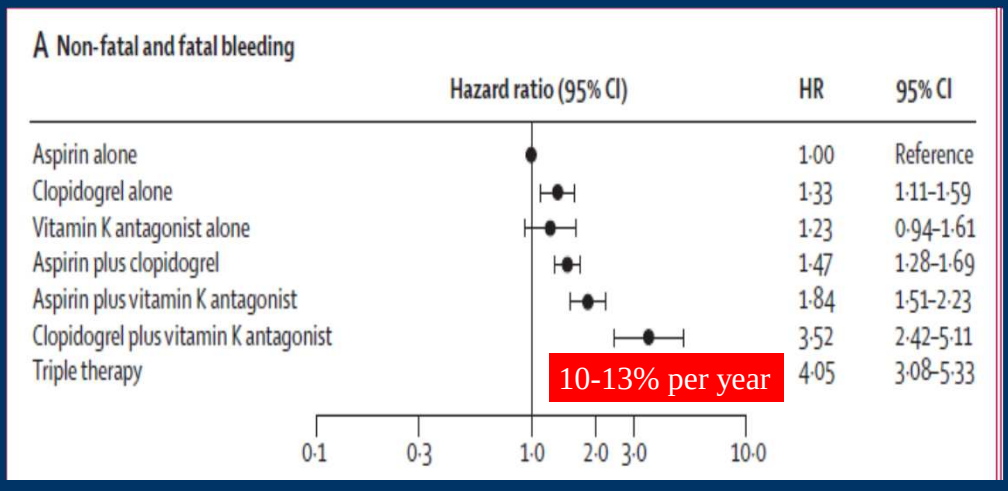

WOEST
Primary Endpoint: Total number of bleeding events (TIMI criteria)
Triple therapy group
Double therapy group
44.9%
19.5%
p<0.001
HR=0.36 95%CI[0.26-0.50]
Cumulative incidence of bleeding
50 %
40 %
30 %
20 %
10 %
0 %
0
30
60
90
120
180
270
365
Days
n at risk:
284 210 194 186 181 173 159 140
279 253 244 241 241 236 226 208

WOEST

Secondary Endpoint (Death, MI,TVR, Stroke, ST)



Hazard Ratios for Bleeding



The Lancet. 2009;374(9706):1967-74

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CHA_2DS_2-VASc
Assessment of Thromboembolic Risk

CHF/ LV dysfunction	1
Hypertension	1
Ag	
Dia	
Stroke/TIA/TE	2
~~Vascular disease~~	~~1~~
Age 65-74	1
Sex category (female)	1

10-20% annual risk of stroke

Score 0 – 9

Validated in 1084 NVAF patients not on OAC with known TE status at 1 year in Euro Heart Survey

Score	Annual stroke rate, %	
n	1084	73 538
		0.78
1	1.3	2.01
2	2.2	3.71
3	3.2	5.92
4	4.0	9.27
5	6.7	15.26
6	9.8	19.78
7	9.6	21.50
8	6.7	22.38
9	15.2	23.64
	Lip GYH, et al. Chest 2009	*Olesen JB et al. BMJ 2011;342:124*

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Yearly Incidence of Bleeding

- Aspirin 2.6%
- Clopidogrel 4.6%
- Warfarin 4.3%
- Aspirin plus clopidogrel 3.7%
- Aspirin plus Warfarin 5.1%
- Warfarin plus clopidogrel 12.3%
- Triple Therapy 12.0%

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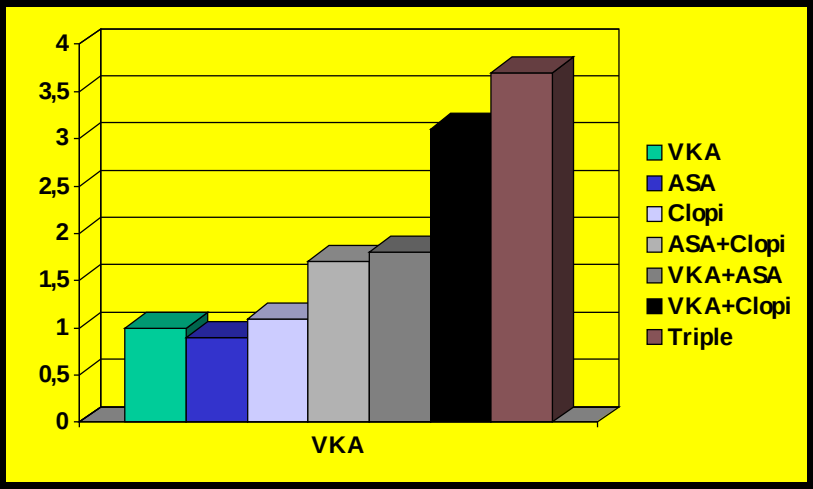
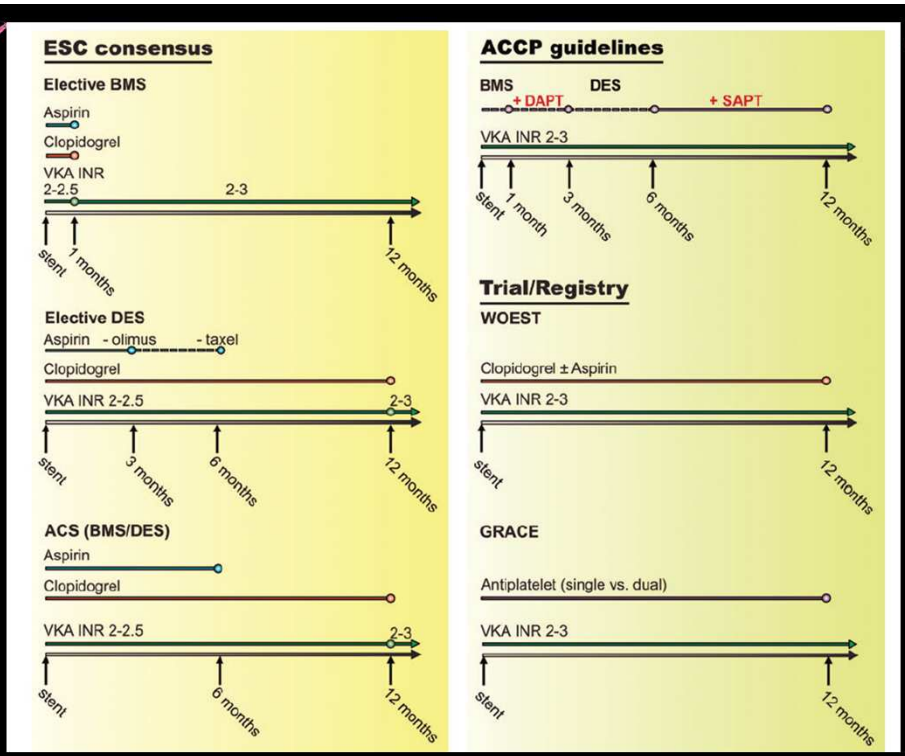
Major Bleeding* per Year

Odds Ratios



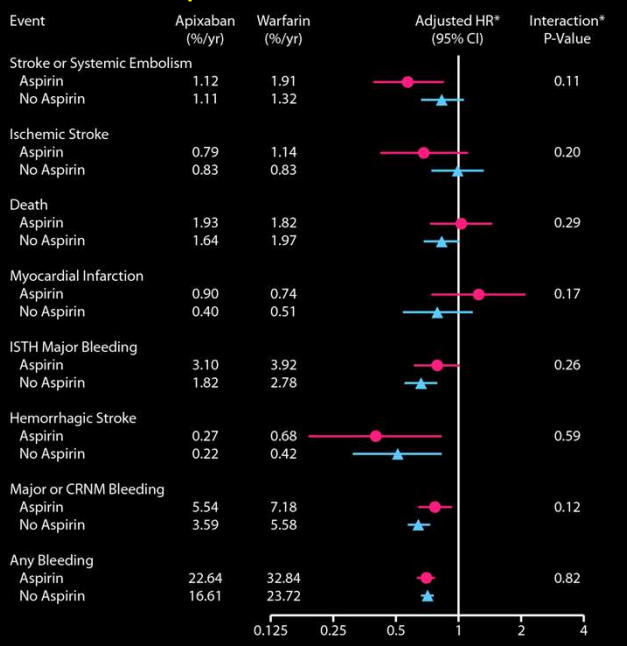
* non-fatal and fatal

Hansen et al. Arch Intern Med 2010;170:1433-1441



ARISTOTLE

Effects of apixaban vs. warfarin with and without aspirin



Alexander JH. Eur Heart J 2014

What we know

Atrial fibrillation and coronary artery disease frequently occur in the same patients

Patients with AF have worse outcomes

What we don't know

- How should we use aspirin, clopidogrel, and warfarin, given the high risk of both thrombotic and bleeding outcomes?
  - Even less known about new P2Y12 inhibitors
  - Even less known about NOACs

What to Do?

- Medical therapy
- Medical therapy plus warfarin or other antithrombin/Factor Xa inhibitor
- Medical therapy plus stress test with imaging
- Medical therapy and proceed with coronary angiography
- Something else

Decision was …

- Medical therapy
- Medical therapy plus warfarin or other antithrombin/Factor Xa inhibitor
- Medical therapy plus stress test with imaging
- **Medical therapy and proceed with coronary angiography**
- Something else

WOEST

WOEST Trial - Study Design

1:1 Randomisation:

Double 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**
- **All individual components of primary and secondary endpoints**

COMPASS

(n = 19,500)

CAD without indication for DAPT*,or PAD

Riva 5 mg bid	Riva 2.5 mg bid + ASA 100 mg qd	ASA 100 mg qd
PPI / no PPI	PPI / no PPI	PPI / no PPI

*previous MI , or
*CAG > 1vd, or
*PCI > 1 vessel, or
*CABG > 1 vessel > 4yr

- primary efficacy endpoint: CV death/MI/ischemic stroke
- safety endpoint: ISTH major bleeding

olvg

Onze Lieve Vrouwe Gasthuis, Amsterdam