Convegno
«Anticoagulazione: attualità cliniche, di laboratorio e aspetti sociali»

Bologna, 21-22 Gennaio 2016

Anticoagulanti e doppia antiaggregazione: la difficile convivenza tra FA, sindrome coronarica acuta e stenting coronarico.

Giuseppe Patti

Università Campus Bio-Medico di Roma

Patients on anticoagulants and PCI

- **Atrial Fibrillation**

5% - 7% of the overall population referred for stenting have atrial fibrillation. Incidence of AF is increasing as the population ages

- **Prosthetic heart valves**
- **Previous systemic or venous thromboembolism**
- **Left ventricular thrombus**

Bernard et al., Thromb Haemost 2013;110;560-568

Number of strategies in ACS pts with Atrial Fibrillation

ASA dose: None High (2)
ASA duration (mo): 1 3 6 12 (4) ASA: 1+8=9

Thienopyridine: None Ticl Clop Prasu Tica (4)

Thienopyridine duration (mo): 1 3 6 12 (4) Thieno 1+16=17
OAC: None Warf Dabi Riva Apix Edox (5)
OAC INR/Dose: Low High (2) OAC: 1+10=11

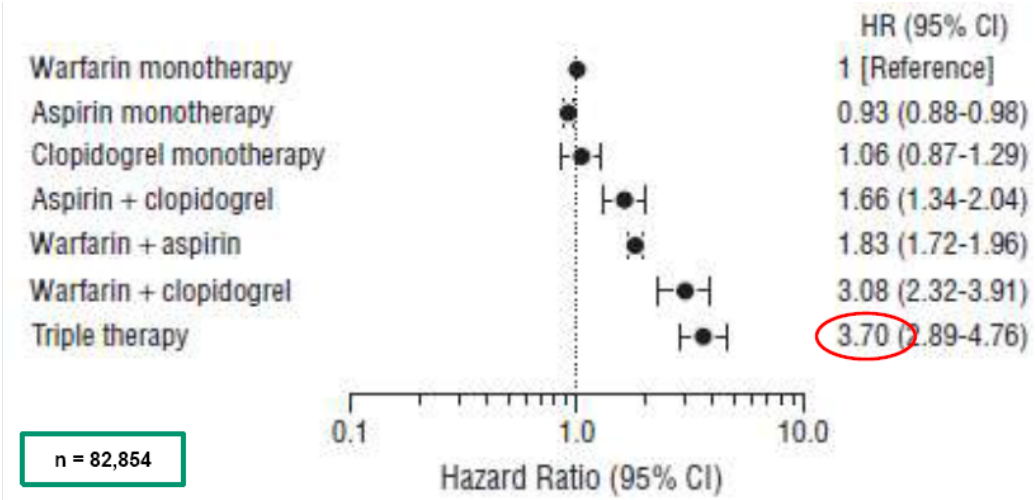
Permutations of single, dual or triple Rx as early initial Rx (0,1,3,6 mo) after ACS: 9 x 17 x 11: 1,683

Permutations of single or dual Rx as early initial Rx (0,1,3,6 mo) during follow-up: 1,683

TOTAL PERMUTATIONS THROUGHOUT ONE YEAR: 2.8 million

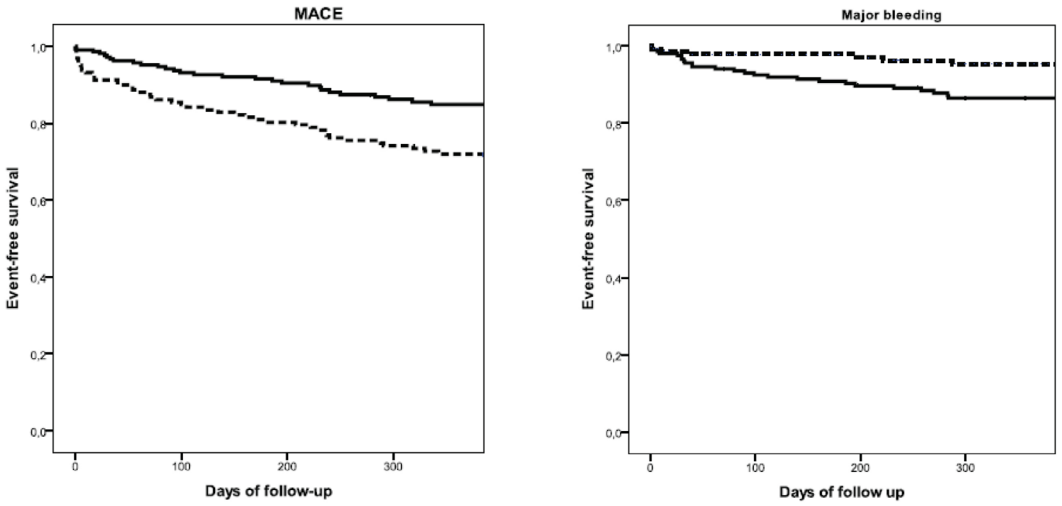
Risk of Bleeding with Single, Dual or Triple Therapy

Non Fatal and Fatal Bleeding



Hansen ML et al. Arch Intern Med 2010

Should We Recommend Oral Anticoagulation Therapy in Patients With Atrial Fibrillation Undergoing Coronary Artery Stenting With a High HAS-BLED Bleeding Risk Score?



——— OAT – – – No OAT

Ruiz-Nodar JM. Circ Cardiovasc Intv 2012

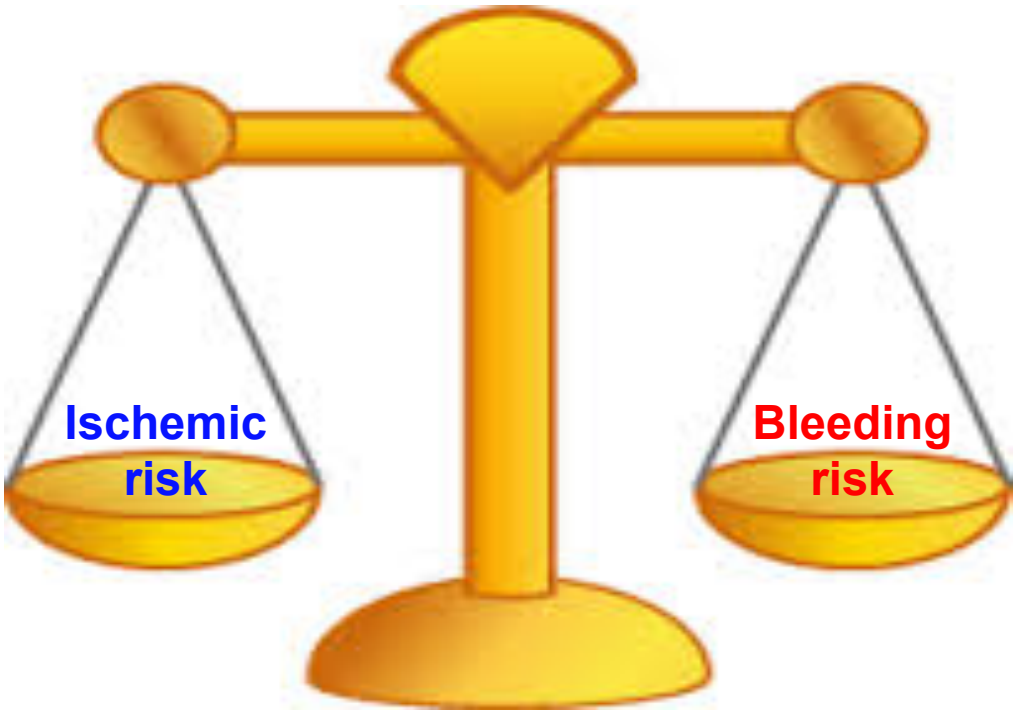
Author (Ref. #)	Outcome With Triple Therapy (vs. Dual Antiplatelet Therapy)			
	Absolute Reduction of Myocardial Infarction	Absolute Reduction of Stroke	Absolute Reduction of Stent Thrombosis	Absolute Increase of Major Bleeding
Khurram et al. (53)	NA	NA	NA	6.6%
DeEugenio et al. (79)	NA	NA	NA	11%*
Karjalainen et al. (57)	−2.6%	6.0%	4.0%	−5.2%
Ruiz-Nodar et al. (59)	3.9%	5.2%*†	0.1%	5.9%
Sarafoff et al. (80)	−1.2%	2.8%	1.2%	−1.7%
Rossini et al. (81)	0%	1%	1%	0.9%

*p < 0.05; †Stroke + any thromboembolism.

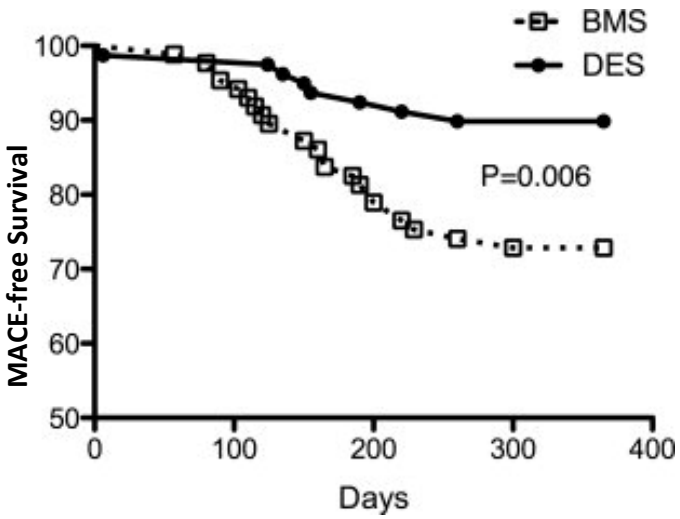
- 3-5 fold increase in major bleeding risk with triple Rx, with consequent increase in MACE rates
- GI bleeding in 60% of cases
- Relationship between bleeding risk and duration of triple Rx (6 vs 1 mo.)
- Pts receiving VKAs have 2-fold lower ischemic stroke rates (vs dual antiPLT)
- High MI rates are paralleled by high stent thrombosis rates (DES)

Patti G. Cathet Cardiovasc Intv 2010

Bleeding events and clinical outcome



One month of triple therapy after PCI: BMS vs. DES

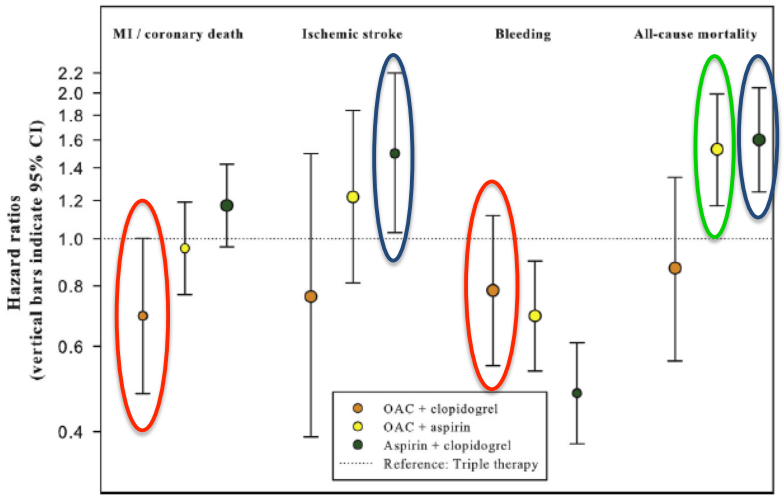


79 pts with BMS and 86 with DES - After one month: OAC + Clop.

Pasceri V, Patti G et al. Cathet Cardiovasc Intv 2010

Different antithrombotic regimen in AF patients following MI and coronary intervention

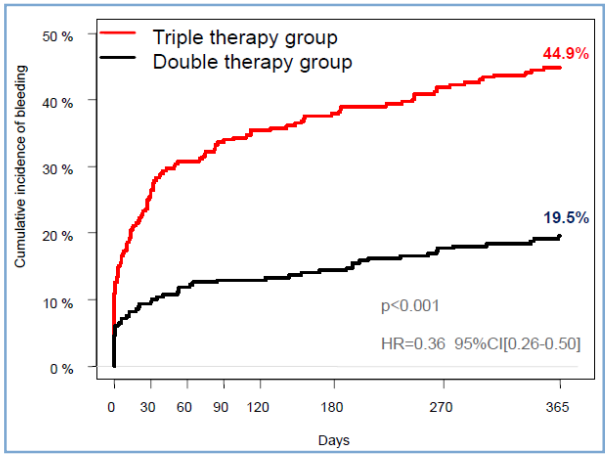
12165 AF patients from Danish registry hospitalized for MI and/or PCI between 2001 and 2009



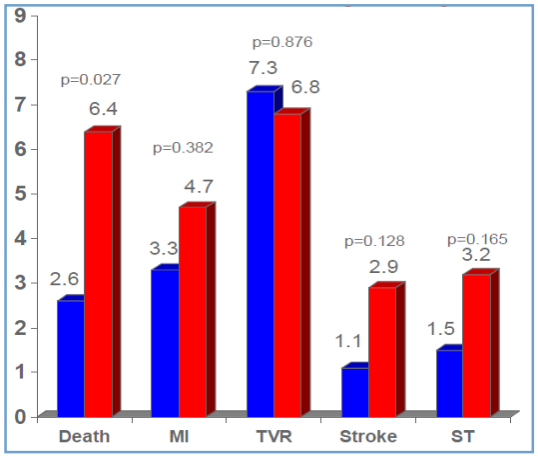
Lamberts M et al., J Am Coll Cardiol 2013

WOEST trial (N=573 pts)

Primary endpoint: bleeding events



Secondary endpoint: ischemic events



Dewilde W et al. ESC Congress 2012, Munchen

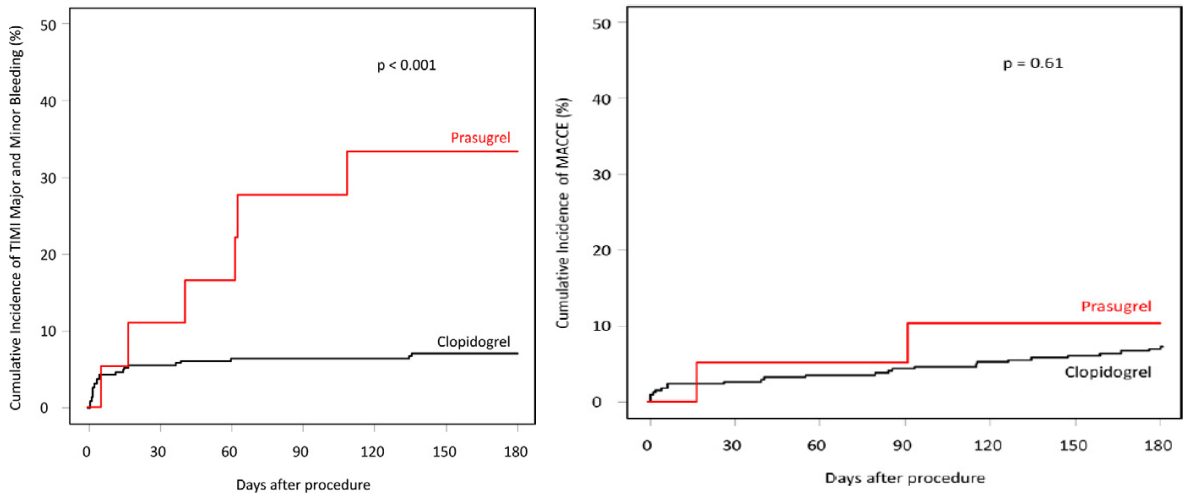
WOEST Limitations

SAFETY
- ❖ Open label study
- ❖ Safety results driven by non-major bleeding
- ❖ Bleeeding excess in the triple Rx arm (vs previous literature data)
- ❖ Femoral approach in 74% of pts
- ❖ PPI in 20% of pts
- ❖ Target INR was 2-3 (and not 2-2.5)
- ❖ TTR in warfarin pts?

EFFICACY
- ❖ Driven by non-cardiac death
- ❖ Underpowered for ST
- ❖ Low clopidogrel response unknown
- ❖ 70% of pts had stable angina

Prasugrel in triple therapy

377 pts who underwent DES implantation and were discharged with a triple therapy recommendation for 6 months or longer: 21 pts received prasugrel and 356 received clopidogrel



Sarafoff N et al., J Am Coll Cardiol 2013

JACC White Paper

Combining Antiplatelet and Anticoagulant Therapies

David R. Holmes, Jr, MD,* Dean J. Kereiakes, MD,† Neal S. Kleiman, MD,§
David J. Moliterno, MD,‖ Giuseppe Patti, MD,¶ Cindy L. Grines, MD‡
Rochester, Minnesota; Cincinnati, Ohio; Royal Oak, Michigan; Houston, Texas; Lexington, Kentucky; and Rome, Italy

J. Am. Coll. Cardiol. 2009;54:95-109

- Careful INR monitoring during VKAs; administer VKAs to achieve a slightly lower target INR of 2 to 2.5 (even between 1.6 and 2 in selected cases)
- Liberal use of gastro-protective agents
- Keep ASA dose as low as possible and use standard clopidogrel maintenance dose
- Limit the duration of dual antiPLT Rx to the time necessary for stent endothelialization
- In case of bleeding:
  - ASA may be discontinued
  - reversal of VKAs or platelet transfusions (severe bleeding)
  - maintain INR as close to 2 as possible (moderate bleeding)
- Second-generation DES. DES with bioabsorbable polymers?
- No extensive data with NOACs, newer antiplatelet agents, PAR-1 antagonists

Individual-based approach

Thrombo-embolic risk

- Atrial fibrillation with recent stroke/TIA
- Atrial fibrillation with risk factors
- Mechanical valve prosthesis
- Recent thrombo-embolism
- Hypercoagulable states

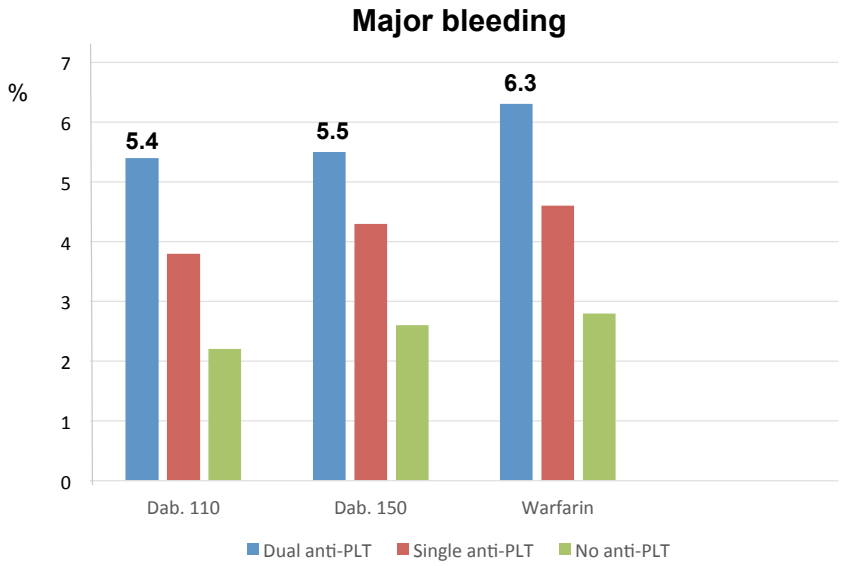
Bleeding risk ⟷ **Ischemic risk**

- Age > 75 yrs, low BMI
- Major bleeding (<6 mo.)
- Bleeding-prone GI or genito-urinary lesions
- Previous haemorragic stroke
- Uncontrolled HT
- Malignancies
- Haematol., renal, liver disorders

- Large area of jeopardized myocardium (also including LM disease and MV disea
- LV dysfunction
- Diabetes
- ACS
- ISR, small or long stents, multiple stents

Patti G. Cathet Cardiovasc Intv 2010

Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the RE-LY trial

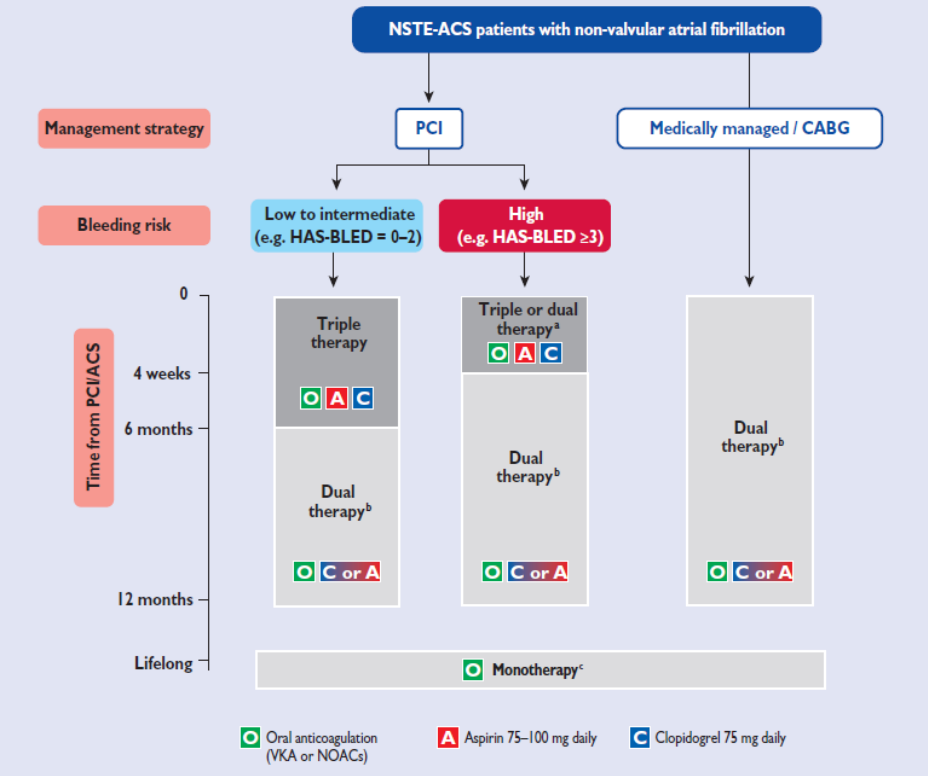


Dans AL et al. Circulation 2013

Comparative bleeding outcomes from ROCKET-AF

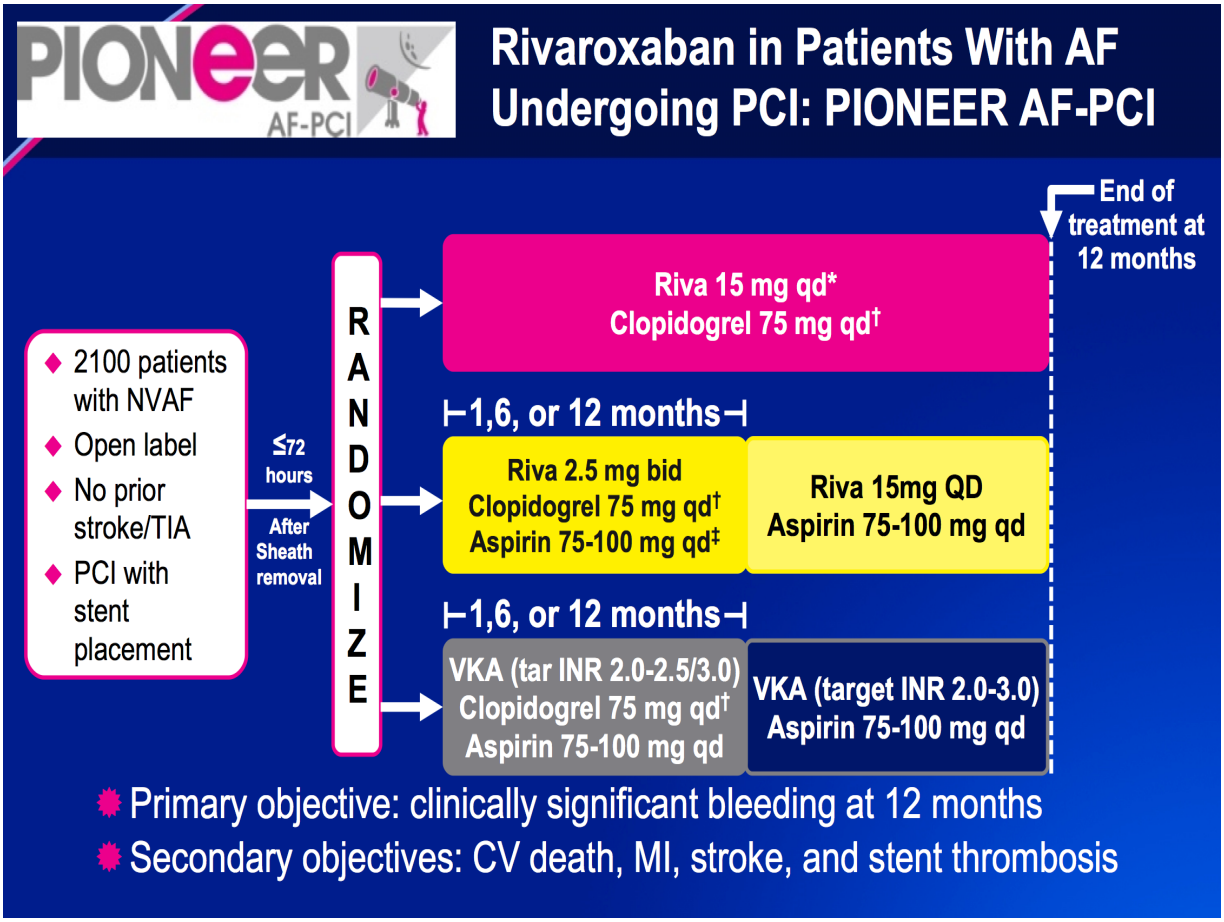
	Rivaroxaban	Warfarin	P
# Pts with bleeds	395	384	NS
# units/person (median)	2	2	
# who received FFP	45	81	<0.0001
# who received PCCs	4	9	
Stroke/embolism	4.7%	5.4%	
All cause death	20.4%	26.1%	

2015 ESC Guidelines on NSTE-ACS



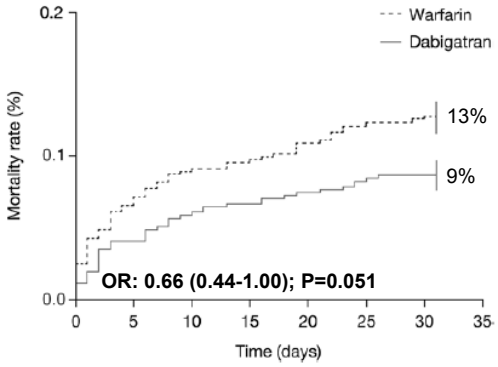
Millions of choices, but a very few data ……

- 2.8 million strategies
- 30 non-randomized, small-sized studies
- 1 undersized CRT
- 0 trials with NOACs and anti-PLT therapy
- Ongoing use of warfarin/full doses NOACs plus ACS doses of DAPT despite known bleeding hazard
- Need CRTs to evaluate combinations that optimize safety and efficacy


PIONEER AF-PCI
Rivaroxaban in Patients With AF Undergoing PCI: PIONEER AF-PCI
End of treatment at 12 months
2100 patients with NVAF
Open label
No prior stroke/TIA
PCI with stent placement
≤72 hours
After Sheath removal
RANDOMIZE
Riva 15 mg qd*
Clopidogrel 75 mg qd†
1,6, or 12 months
Riva 2.5 mg bid
Clopidogrel 75 mg qd†
Aspirin 75-100 mg qd‡
Riva 15mg QD
Aspirin 75-100 mg qd
1,6, or 12 months
VKA (tar INR 2.0-2.5/3.0)
Clopidogrel 75 mg qd†
Aspirin 75-100 mg qd
VKA (target INR 2.0-3.0)
Aspirin 75-100 mg qd
Primary objective: clinically significant bleeding at 12 months
Secondary objectives: CV death, MI, stroke, and stent thrombosis

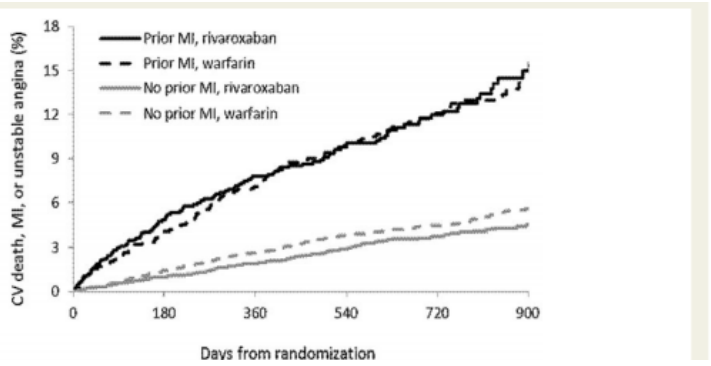
Outcome of patients with major bleeding while on Dabigatran vs Warfarin (5 CRTs; N=1,034)

Dabigatran: more transfusions, less plasma, more PCC/Rec. VII a, shorter ICU stay



Majeed A. Circulation 2013

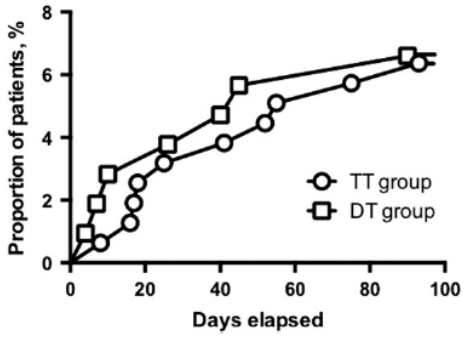
Ischaemic cardiac outcomes in patients with atrial fibrillation treated with vitamin K antagonism or factor Xa inhibition: results from the ROCKET AF trial



Mahaffey KW. Eur Heart J 2014

Retrospective comparison of Triple Rx vs Warf + Ticagrelor on 266 Swedish pts with ACS (52% STEMI)

Major bleeding



MACE

Event, n (%)	TT (n = 157)	DT (n = 106)	p-value
Mortality	5 (3.2)	4 (3.8)	NS
Peripheral embolism	0 (0.0)	1 (0.9)	NS
Stroke/TIA[a]	2 (1.3)	1 (0.9)	NS
ACS[b]	3 (1.9)	3 (2.8)	NS
Stent thrombosis	0 (0.0)	0 (0.0)	NS

Braun OO. Thromb Res 2015

AF Patients Taking NOACs and Undergoing Interventional/Surgical Procedures Is Increasing

- An analysis of the RE-LY trial demonstrated
  - Approximately 25% of RE-LY patients underwent at least 1 invasive procedure during 2 years of follow-up
  - Most common procedures included
    - Pacemaker/defibrillator insertion (10.3%)
    - Dental procedures (10.0%)
    - Diagnostic procedures (10.0%)
    - Cataract removal (9.3%)
    - Colonoscopy (8.6%)
    - Joint replacement (6.2%)

RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy

Arrhythmia & EP

Healey JS, et al. *Circulation*. 2012;126(3):343-348.

Medscape EDUCATION

The NEW ENGLAND JOURNAL of MEDICINE

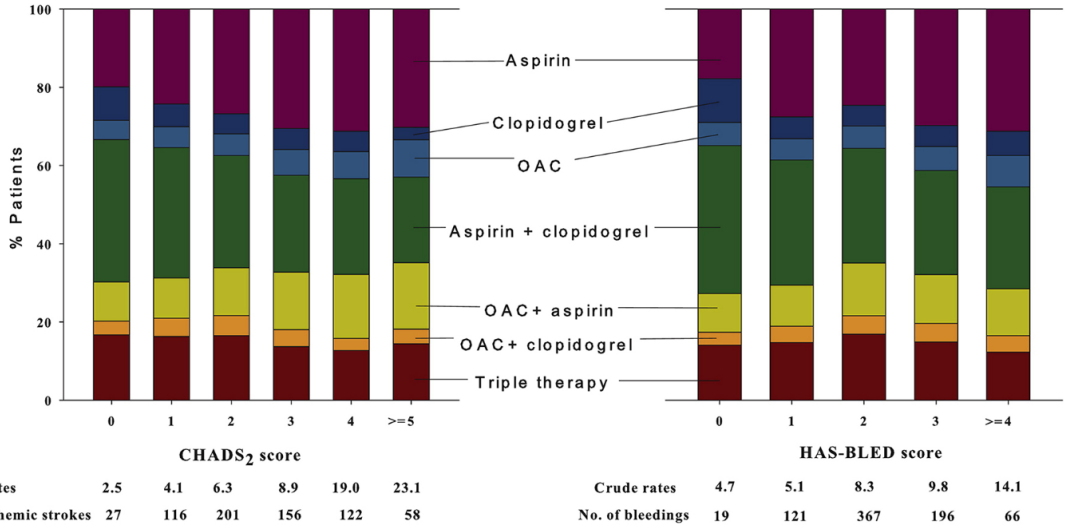
ORIGINAL ARTICLE

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O., Richard C. Becker, M.D., Joseph A. Caprini, M.D., Andrew S. Dunn, M.D., David A. Garcia, M.D., Alan Jacobson, M.D., Amir K. Jaffer, M.D., M.B.A., David F. Kong, M.D., Sam Schulman, M.D., Ph.D., Alexander G.G. Turpie, M.B., Vic Hasselblad, Ph.D., and Thomas L. Ortel, M.D., Ph.D., for the BRIDGE Investigators*

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†

Registro Danese di 12165 pazienti con FA e IMA o PTCA Tipo di Terapia alla Dimissione e Score Clinici



Crude rates	2.5	4.1	6.3	8.9	19.0	23.1
No. of ischemic strokes	27	116	201	156	122	58

Crude rates	4.7	5.1	8.3	9.8	14.1
No. of bleedings	19	121	367	196	66

Lamberts et al. J Am Coll Cardiol 2013

European Heart Journal (2014) 35, 1831–1833
doi:10.1093/eurheartj/ehu034

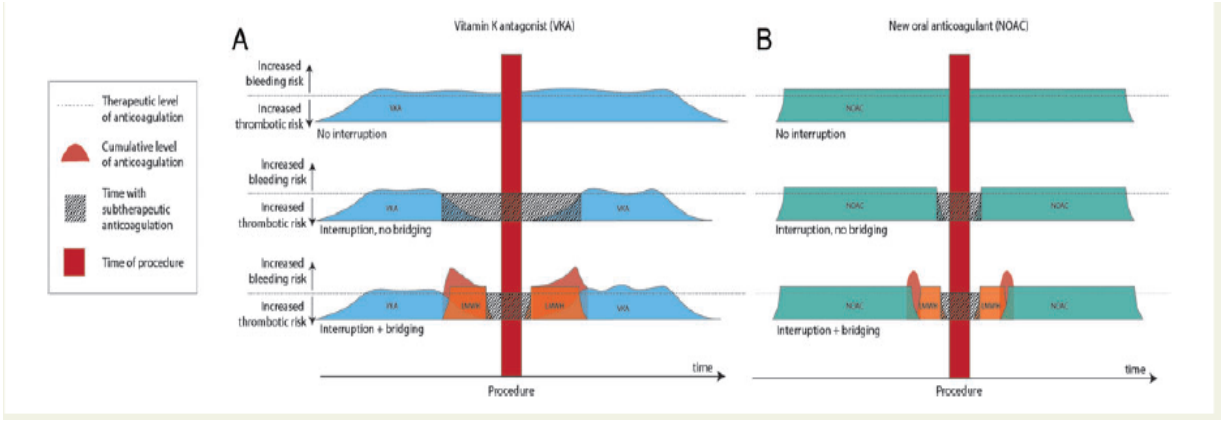
EDITORIAL

Heparin bridging in peri-procedural management of new oral anticoagulant: a bridge too far?

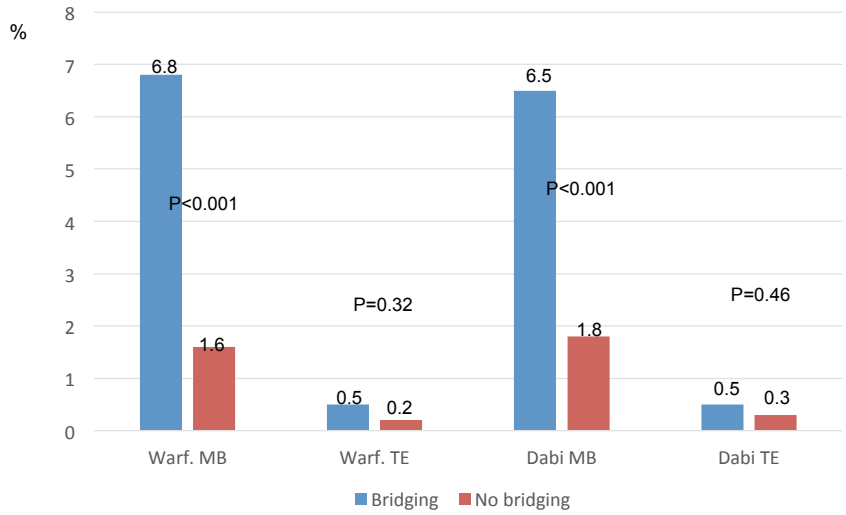
Thomas Vanassche[1,2†], Mandy N. Lauw[1,3†], Stuart J. Connolly[1], and John W. Eikelboom[1*]

[1]Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [2]Department of Cardiovascular Sciences, University of Leuven, Belgium; and [3]Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Online publish-ahead-of-print 18 February 2014



Data from the RELY trial in pts undergoing elective surgery



Douketis JD et al. Throm Haemost 2015

Type of surgery

Interventions not necessarily requiring discontinuation of anticoagulation
- Dental interventions
  - Extraction of 1 to 3 teeth
  - Paradontal surgery
  - Incision of abscess
  - Implant positioning
- Ophthalmology
  - Cataract or glaucoma intervention
- Endoscopy without surgery
- Superficial surgery (e.g. abscess incision; small dermatologic excisions; . . .)

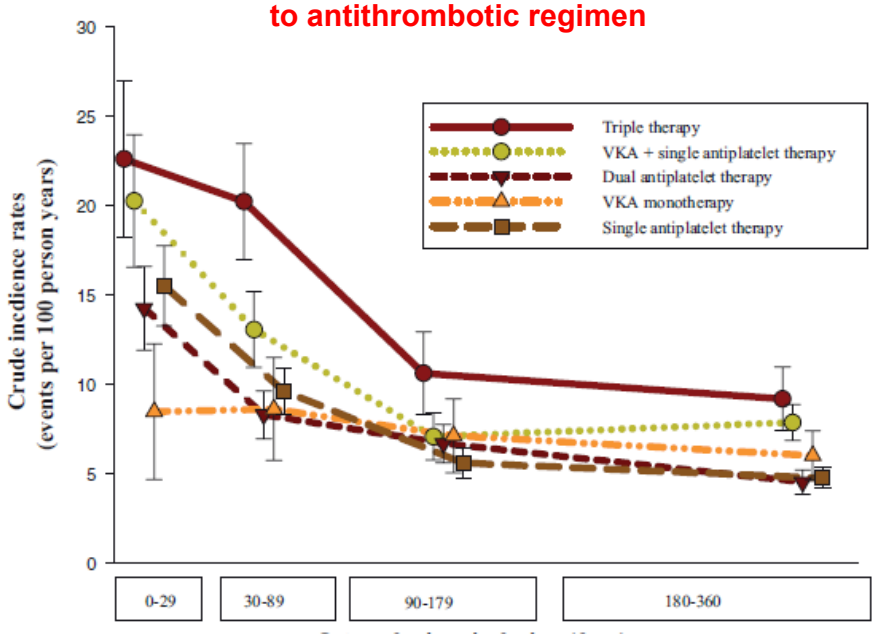
Interventions with low bleeding risk
- Endoscopy with biopsy
- Prostate or bladder biopsy
- Electrophysiological study or radiofrequency catheter ablation for supraventricular tachycardia (including left-sided ablation via single transseptal puncture)
- Angiography
- Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)

Interventions with high bleeding risk
- Complex left-sided ablation (pulmonary vein isolation; VT ablation)
- Spinal or epidural anaesthesia; lumbar diagnostic puncture
- Thoracic surgery
- Abdominal surgery
- Major orthopedic surgery
- Liver biopsy
- Transurethral prostate resection
- Kidney biopsy

Trough concentrations
(skip one BID dose, 18-24 hrs for OD;
restart 6-8 hrs after, even for spinal anest. Or spinal puncture)

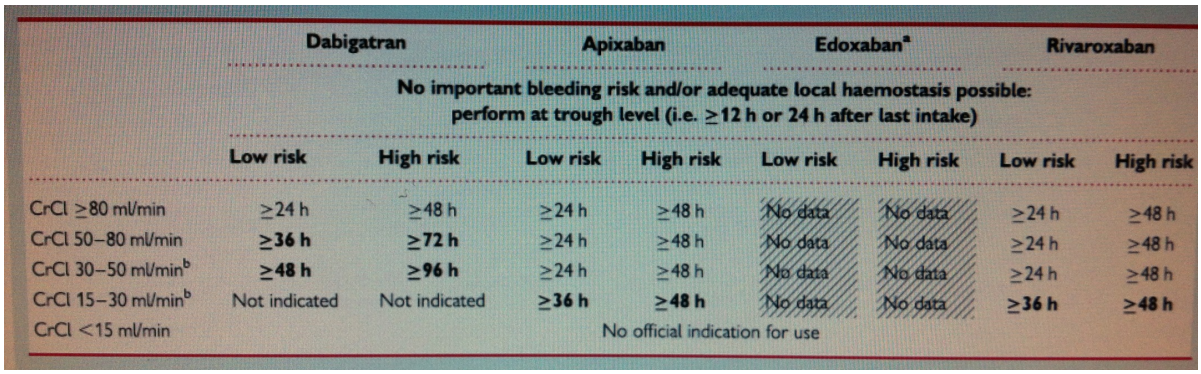
Bleeding events among different antithrombotic regimen

Crude incidence rates of fatal and nonfatal bleeding according to antithrombotic regimen



Lamberts M et al., Circulation 2012:126;1185.1193

NOAC
Last drug intake before elective surgery



	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 h or 24 h after last intake)							
	Low risk	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 ml/min	≥24 h	≥48 h	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 50–80 ml/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 30–50 ml/min[b]	**≥48 h**	**≥96 h**	≥24 h	≥48 h	No data	No data	≥24 h	≥48 h
CrCl 15–30 ml/min[b]	Not indicated	Not indicated	**≥36 h**	**≥48 h**	No data	No data	**≥36 h**	**≥48 h**
CrCl <15 ml/min	No official indication for use							

Caution with regard to time of interruption:
- Liver impairment
- Older age
- Co-medications
- History of bleeding

….. Laboratory tests/serum concentrations
….. Reversal agents

Heidbuchel et al. Europace 2013

NOAC
Restoration after surgery

Low bleeding risk and high thromboembolic risk
- 24 hours

Low bleeding risk and low thromboembolic risk
- 48 hours

High bleeding risk and high thromboembolic risk
- 48 to 72 hours on an individual basis

High bleeding risk and low thromboembolic risk
- 72 hours

Background slides

NOACs vs Warfarin in Patients Undergoing Interventional Procedures

- Onset of action
  - NOACs have a faster onset of action
- NOACs have more predictable pharmacodynamic/pharmacokinetic properties compared with warfarin
  - Wider therapeutic window vs warfarin

Arrhythmia & EP

Bauer KA. *Hematology Am Soc Hematol Educ Program*. 2013;2013:464-70.

Medscape EDUCATION

Conclusions

- **Patients on anticoagulant therapy undergoing PCI represent a high-risk population**
- **Treatment options offer great benefit but also pose potential harm**
- **Patient-specific risk assessment is advised**
- **"Ad hoc" prospective large studies with NOAC are needed, but encouraging data are expected**

SAFE SURGERY: Choosing the Best Approach

Must Answer three basic questions

1- What is the risk of bleeding with AC based upon the type of procedure and patient's history?

2- What is the risk of thrombosis if AC reduced or stopped?

3- Other issues: time of OAC interruption/restoration; rebound effect?

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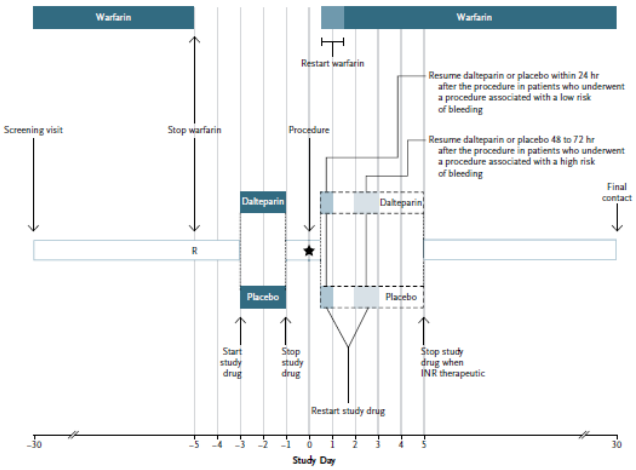
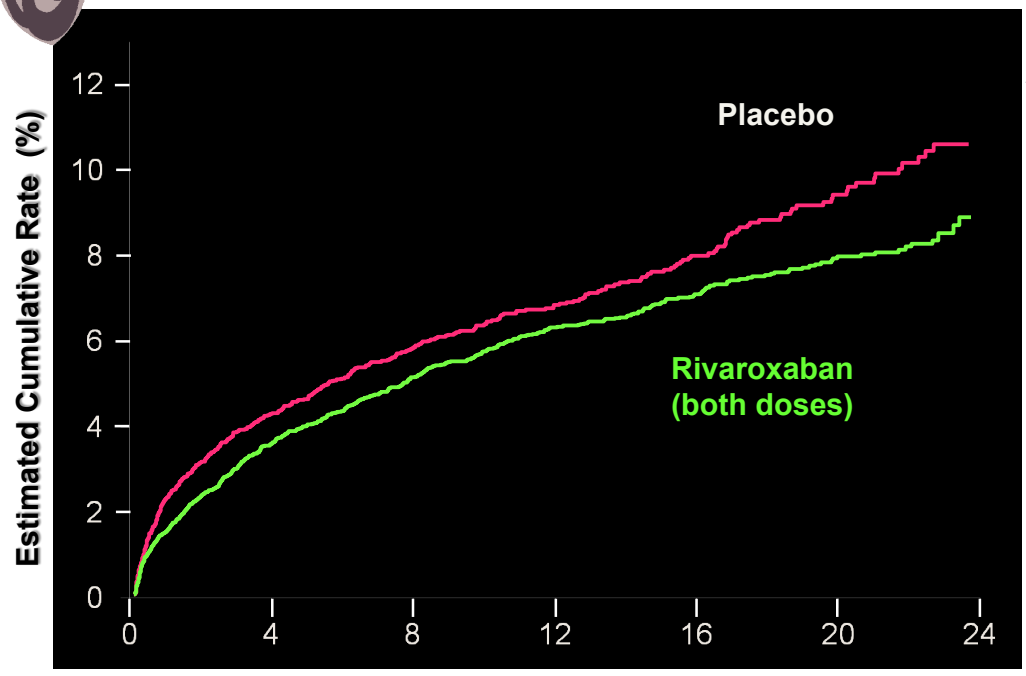


ATLAS ACS 2

Primary Efficacy End-point: CV Death / MI / Stroke (Ischemic + Hemorr.)



2 Yr KM Estimate

10.7%

8.9%

HR 0.84 (0.74-0.96)
ARR 1.8%

P = 0.002

NNT = 59

Mega JL et al. N Engl J Med 2012

The SAMe – TT_2R_2 score

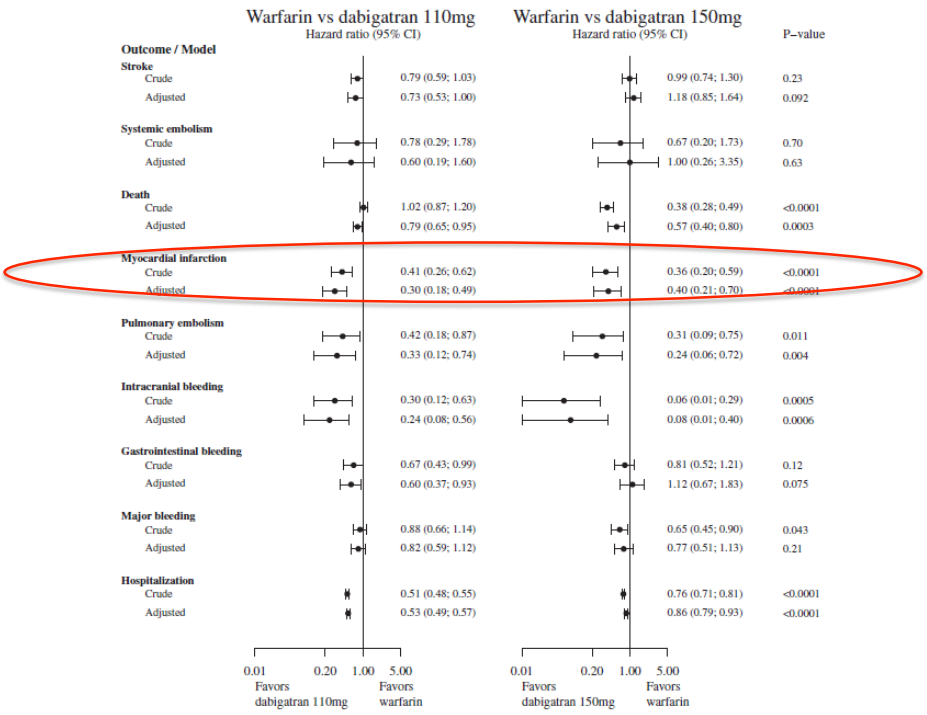
Acronym	Definitions	Points
S	Sex (female)	1
A	Age (< 60 y)	1
M	Medical history[a]	1
e		
T	Treatment (interacting drugs, eg, amiodarone for rhythm control)	1
T	Tobacco use (within 2 y)	2
R	Race (nonwhite)	2
Maximum points		8

[a]Defined as more than two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease. SAMe-TT_2R_2 = sex female, age < 60 years, medical history (more than two comorbidities), treatment (interacting drugs, eg, amiodarone for rhythm control), tobacco use (doubled), race (doubled).

A score 0-1 predicted a TTR ≥65%

Apostolakis S. Chest 2013

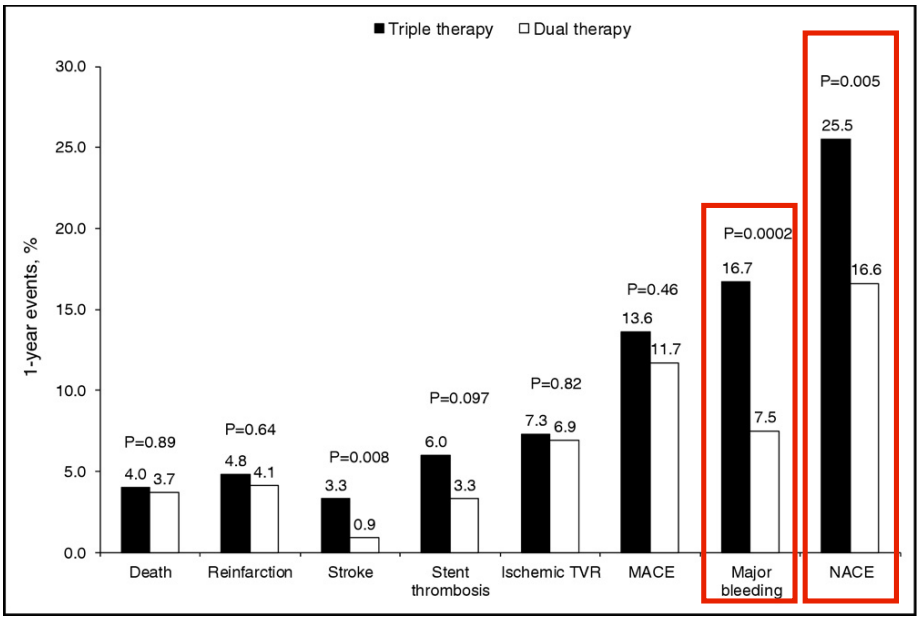
Dabigatran vs warfarin in a real-world registry (N=13,914)



Larsen TB. J Am Coll Cardiol 2013

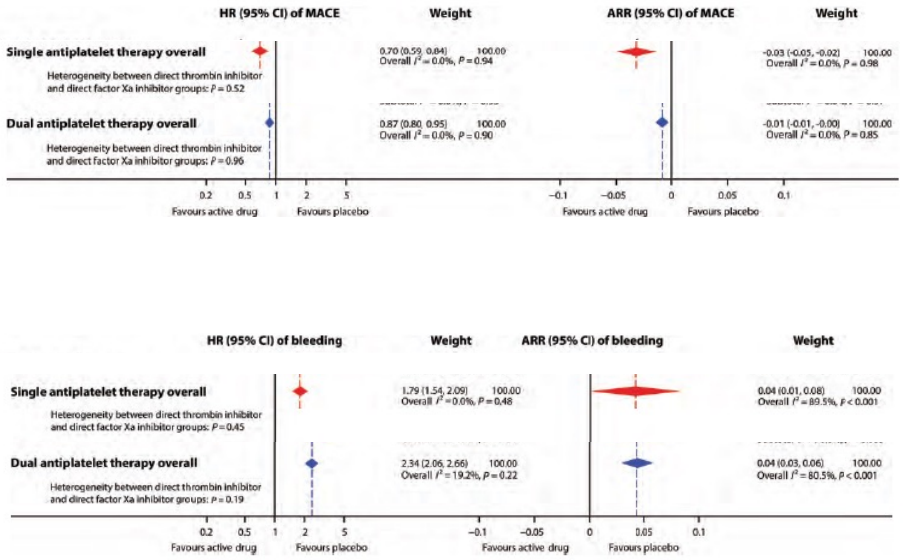
Triple therapy in STEMI: results from HORIZON-AMI

3.8% of patients with STEMI undergoing primary PCI had an indication for oral anticoagulation with VKA



Nikolsky E et al. Am J Cardiol 2012

Pts with ACS while on anticoagulant therapy: addition of antiplatelet therapy

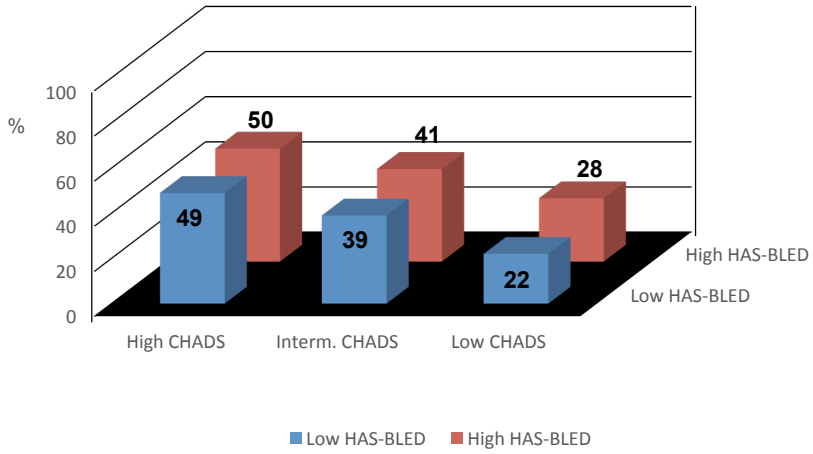


Oldgren J. Eur Heart J 2013

Comparative bleeding outcomes from ROCKET-AF

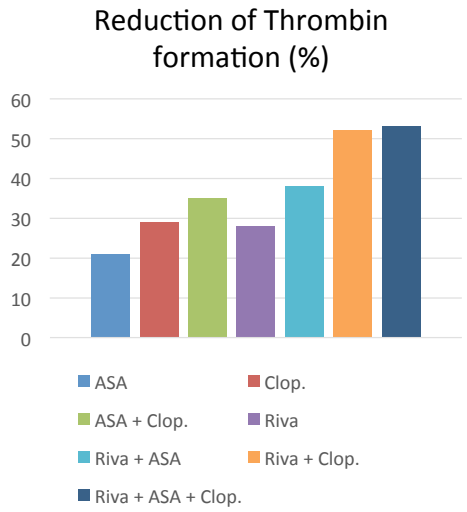
	Rivaroxaban	Warfarin	P
# Pts with bleeds	395	384	NS
# units/person (median)	2	2	
# who received FFP	45	81	<0.0001
# who received PCCs	4	9	
Stroke/embolism	4.7%	5.4%	
All cause death	20.4%	26.1%	

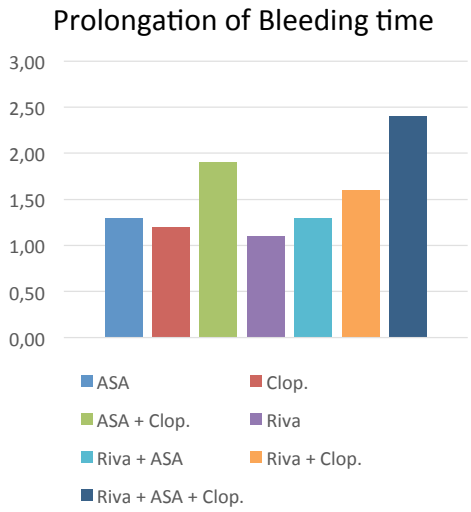
AVIATOR-1: Triple therapy prevalence at discharge among different risk strata



Mannuni M. AHA 2013

Addition of Rivaroxaban to anti-PLT therapy in rats





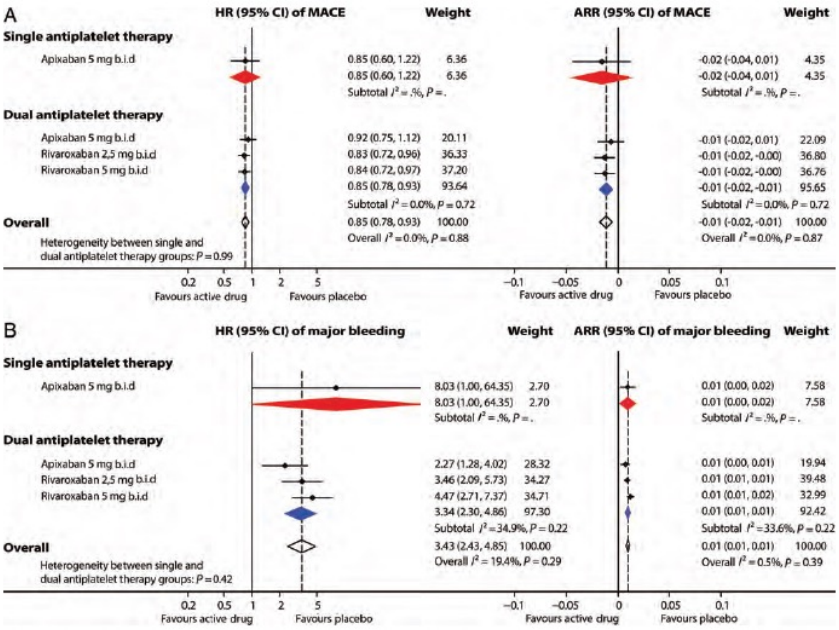
Perzborn. ESC 2010

2014 ESC Guidelines on Myocardial revascularization

Recommendations for antithrombotic treatment in patients undergoing PCI who require oral anticoagulation

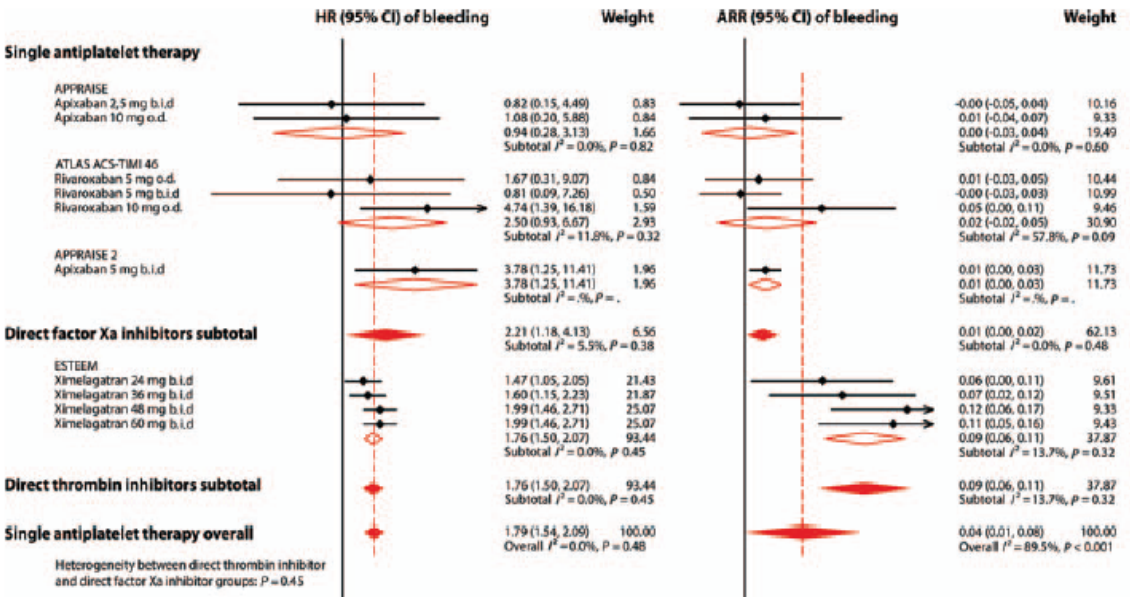
Recommendations	Class[a]	Level[b]	Ref[c]
In patients with a firm indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc score ≥2, venous thromboembolism, LV thrombus, or mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy.	I	C	
New-generation DES are preferred over BMS among patients requiring oral anticoagulation if bleeding risk is low (HAS-BLED ≤2).	IIa	C	
In patients with SCAD and atrial fibrillation with CHA_2DS_2-VASc score ≥2 at low bleeding risk (HAS-BLED ≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of at least one month after BMS or new-generation DES followed by dual therapy with (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
DAPT should be considered as alternative to initial triple therapy for patients with SCAD and atrial fibrillation with a CHA_2DS_2-VASc score ≤1.	IIa	C	
In patients with ACS and atrial fibrillation at low bleeding risk (HAS-BLED≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 6 months irrespective of stent type followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C	
In patients requiring oral anticoagulation at high bleeding risk (HAS BLED ≥3), triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of one month followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) irrespective of clinical setting (SCAD or ACS) and stent type (BMS or new-generation DES).	IIa	C	
Dual therapy of (N)OAC and clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients.	IIb	B	865,870
The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended	III	C	
Anticoagulation therapy after PCI in ACS patient			
In selected patients who receive ASA and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered in the setting of PCI for ACS if the patient is at low bleeding risk.	IIb	B	855
Anticoagulation during PCI in patients on oral anticoagulation			
It is recommended to use additional parenteral anticoagulation, regardless of the timing of the last dose of (N)OAC.	I	C	
Periprocedural parenteral anticoagulants (bivalirudin, enoxaparin or UFH) should be discontinued immediately after primary PCI.	IIa	C	

Pts on antiplatelet therapy after ACS: addition of anticoagulant



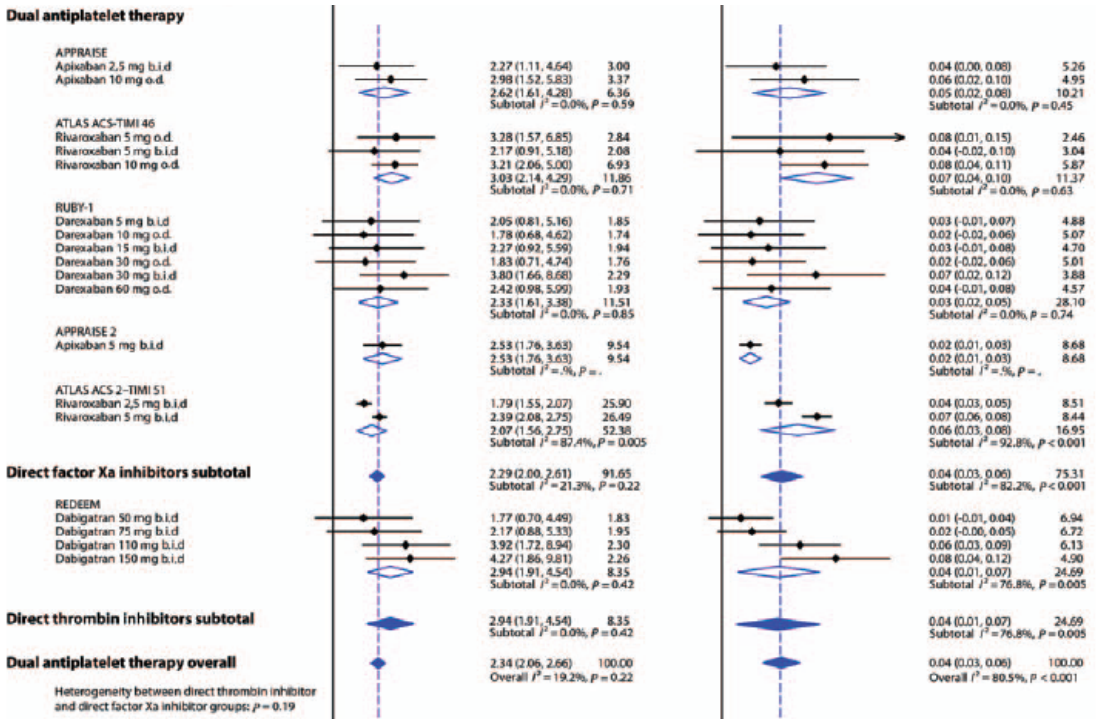
Oldgren J. Eur Heart J 2013

New oral anticoagulants in addition to single or dual antiplatelet therapy after ACS



Oldgren M et al., Eur Heart J 2013

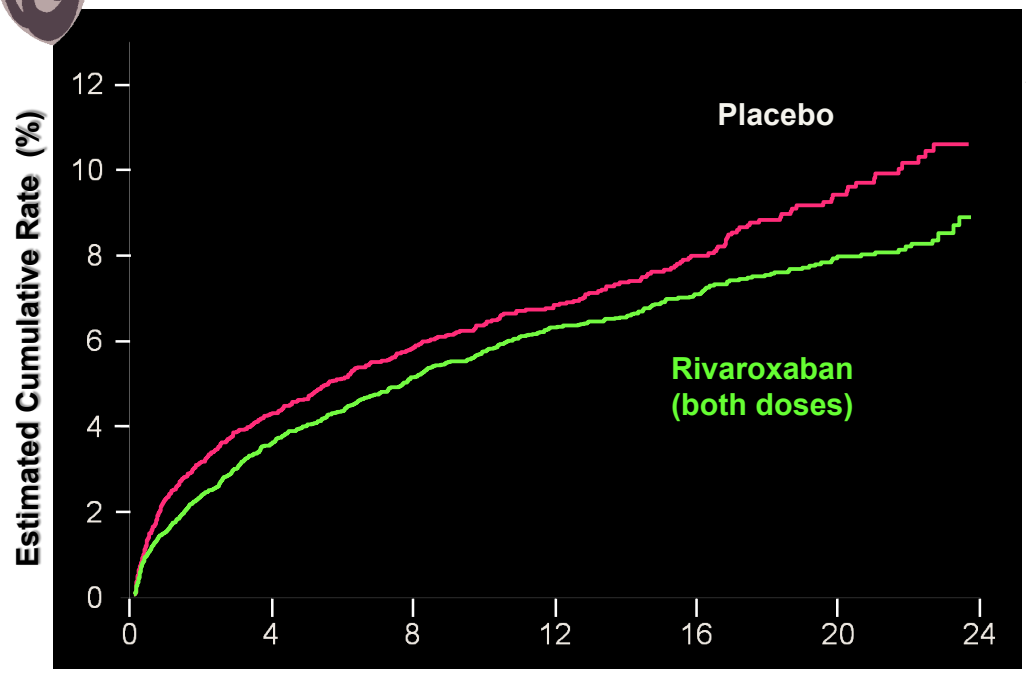
New oral anticoagulants in addition to single or dual antiplatelet therapy after ACS



Oldgren M et al., Eur Heart J 2013

ATLAS ACS 2

Primary Efficacy End-point: CV Death / MI / Stroke (Ischemic + Hemorr.)



2 Yr KM Estimate

10.7%

8.9%

HR 0.84
(0.74-0.96)
ARR 1.8%

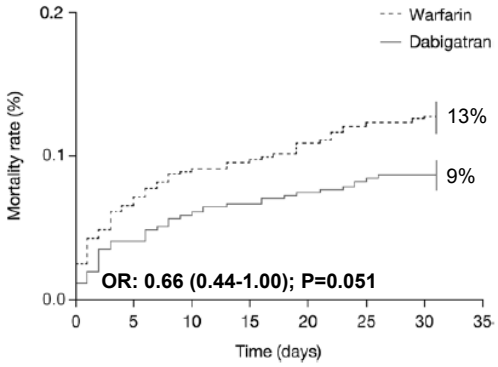
P = 0.002

NNT = 59

Mega JL et al. N Engl J Med 2012

Outcome of patients with major bleeding while on Dabigatran vs Warfarin (5 CRTs; N=1,034)

Dabigatran: more transfusions, less plasma, more PCC/Rec. VII a, shorter ICU stay

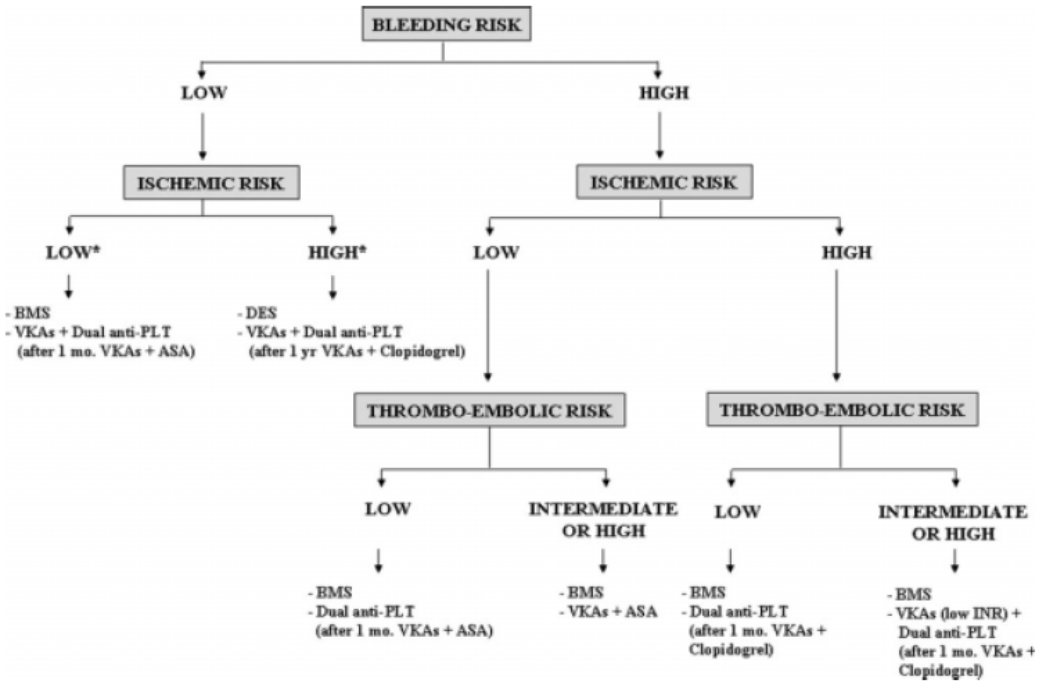


Majeed A. Circulation 2013

Which therapy?

- **Stratification of patients according their risk profile**
- **Risk score (HAS-BLED, CHADS2-VASC2, GRACE, CRUSADE)**

Antithrombotic algorithm in patients with indication for oral anticoagulant therapy undergoing PCI



Patti G. Cathet Cardiovasc Intv 2010

Consensus document EHRA-EAPCI

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

Lip G et al, Eur Heart J 2010;31:1311-1318

Multiple therapeutic options

- ❑Dual Antiplatelet therapy with ASA and clopidogrel
- ❑Triple therapy (VKA, ASA, clopidogrel)
- ❑VKA with ASA
- ❑VKA with clopidogrel
- ❑Single antiplatelet therapy
- ❑New anticoagulants
- ❑More potent P2Y12 inhibitors (prasugrel, ticagrelor)

Lack of data from large randomized clinical trials

Effects of Apixaban vs Warfarin Among Patients Using and Not Using Aspirin in ARISTOTLE

	HR ASA	HR No ASA
Stroke or embolism	0.55	0.80
Major bleeding	0.77	0.65
Hemorrhagic stroke	0.40	0.51

Granger CB et al. N Engl J Med 2011