Management of Patients with Atrial Fibrillation and Stents: Is Three Drugs Too Many?

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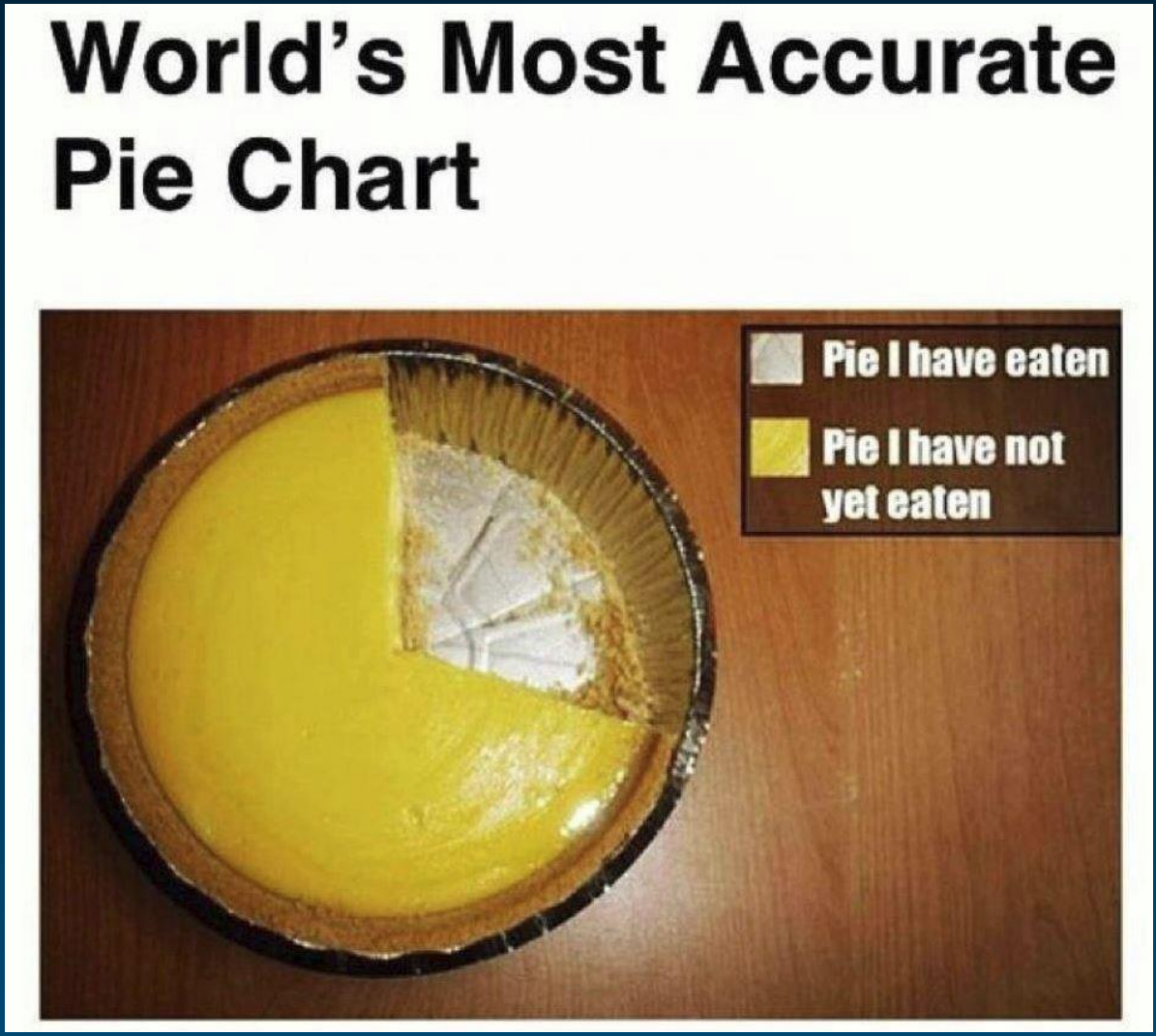
& Vascular Center

Some Things Are Really Clear



Therapeutic Controversies

Aspirin, Clopidogrel, and Warfarin: Is the Combination Appropriate and Effective or Inappropriate and Too Dangerous?

A Janelle Hermosillo and Sarah A Spinler

2013 – 8 Drugs (4 OACs, 3 APs, ASA) = 39 Combinations!

(Before you consider duration of treatment.)

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Management of Antithrombotic Therapy in Atrial Fibrillation Patients Presenting with Acute Coronary Syndrome and/or Undergoing Percutaneous Coronary Intervention/ Stenting

A Consensus Document of the European Society of Cardiology Working Group on

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

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doi:10.1016/j.jacc.2009.03.044

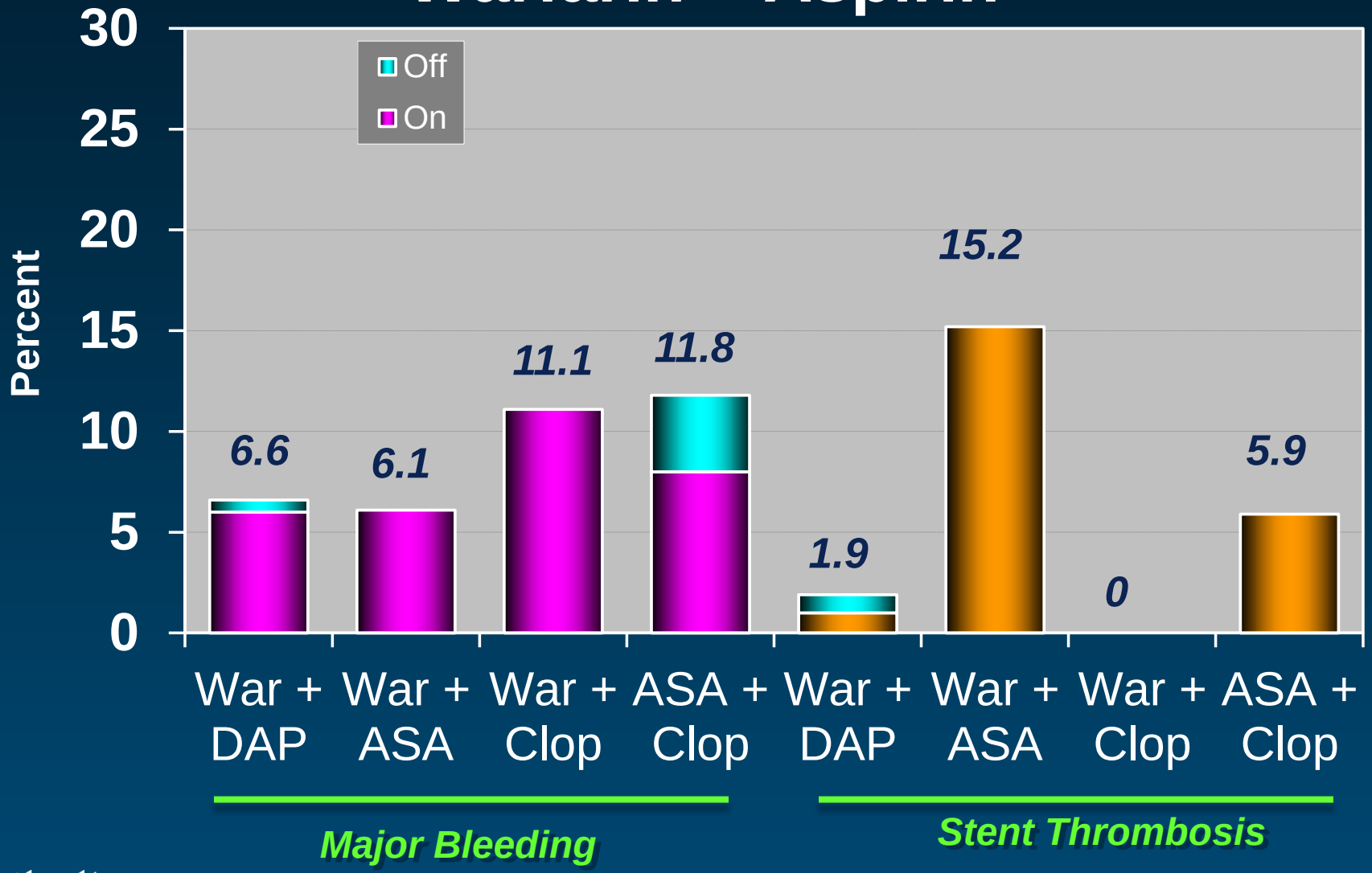
JACC White Paper

Combining Antiplatelet and Anticoagulant Therapies

"The combined use of antiplatelet and anticoagulant drugs…is associated with an increase in bleeding complications. For patients who require triple therapy, careful follow-up is indicated, with low dose (<100 mg) ASA, conventional dose (75 mg) clopidogrel, a lower target INR (approximately 2.0), and consideration of prophylactic proton pump inhibition."

Meth
DeBakey
& Vascula

12 –Month Outcomes in Patients on Warfarin + Aspirin



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Karjalainen: Eur Heart J.2007:28 726

So What is Clear?

1. Patients with atrial fibrillation need antithrombotic therapy.
2. Patients with IC stents need dual antiplatelet therapy.
3. The risk of bleeding appears to increase substantially as more antithrombotic drugs are combined.
4. Patients who need OACs represent a higher risk group than those who don't.
5. The clinical decision to use OACs doesn't appear related to the thrombotic risk.

A Tale of Two Trials

Warfarin is Superior to Clopidogrel + ASA

- **ACTIVE W:** 6,706 pts with atrial fibrillation randomized to OAC (INR 2-3) or ASA + Clopidogrel
- Prematurely terminated because of 44% excess in composite EP and 72% excess in stroke for ASA + Clopidogrel

ACTIVE Writing Group.Lancet.2006; 367: 1903

Clopidogrel + ASA is Superior to ASA

- **ACTIVE A:** 7,554 pts with atrial fibrillation deemed **"unsuitable" for warfarin**
- Adding Clopidogrel to ASA → 19% reduction in composite EP, 28% reduction in stroke
- **BUT, 30% of pts who DC'd study medication ended up on warfarin**

ACTIVE A Inv. N Engl J Med 2009;360:2066

The Pendulum is Swinging Toward Aggressive Use of OACs for A Fib: Swedish Registry

- 182,678 pts followed for 1.5 years
- Stratification by $CHADS_2$, CHA_2DS_2-VASc, and HAS BLED risk scores
  - For *a) Death/Ischemic Stroke/Intracranial Hemorrhage* AND *b) Adjusted Net Clinical Benefit* hazard ratios favored warfarin treatment for all categories, regardless of HAS-BLED score, except those with $CHADS_2$-VASc = 0
- Bleeding risk exceeded stroke risk in only 0.4% of the patient population

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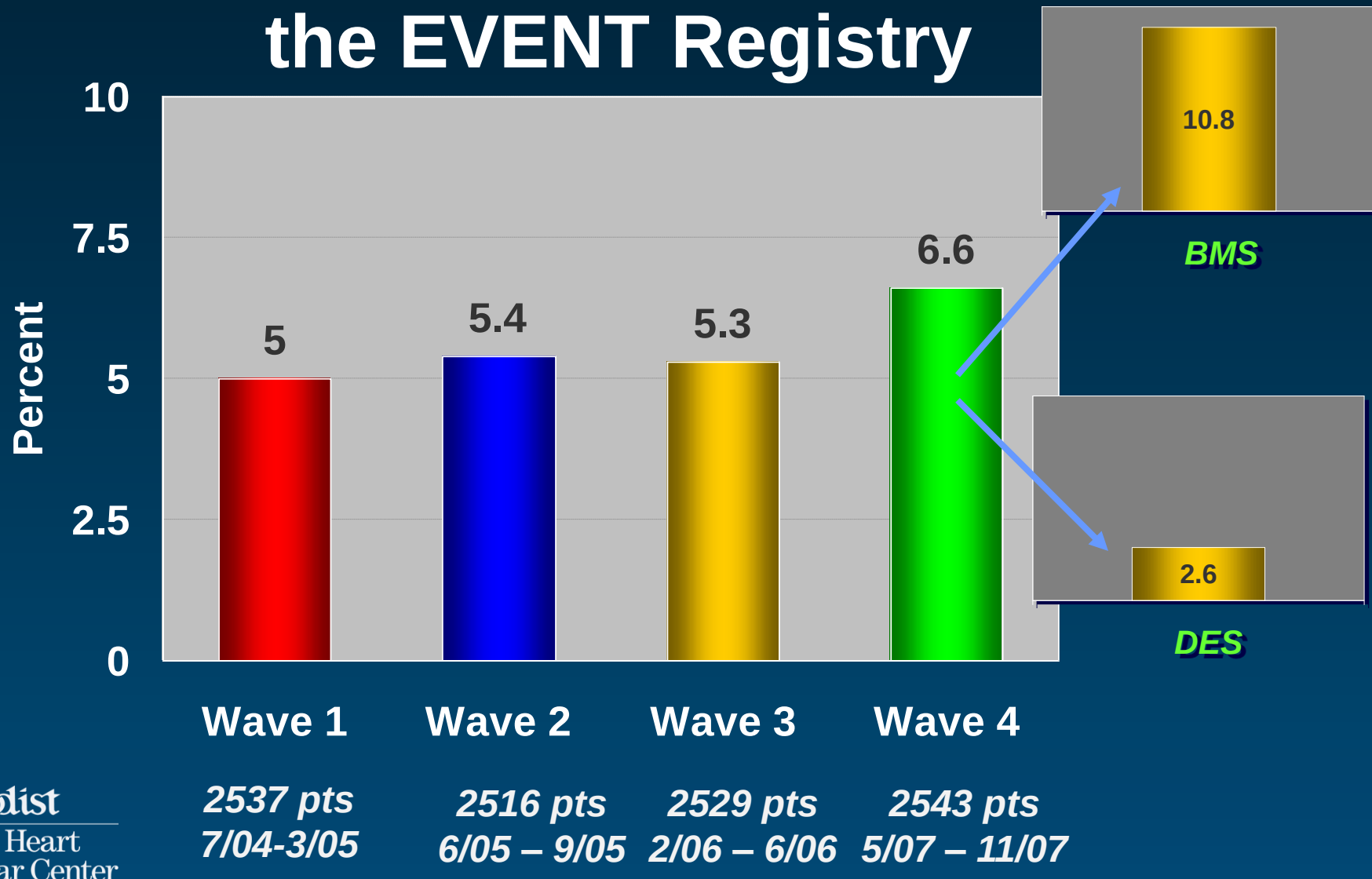
Friberg. Circulation.2012;125:2298

Considerations for Stenting in Pts with Atrial Fibrillation

- Type of stent (DES vs BMS; 1st vs 2d gen.)
- Complexity of the stent procedure
- Need for OACs
  - Stroke risk ($CHADS_2$ and CHA_2DS_2-VASc scores)
  - Bleeding risk (HAS-BLED score)
- Duration of antiplatelet therapy
- Type of OAC and type of AP drug
- Worsening of AP drug compliance

Proportion of Patients Discharged on Warfarin after Stent Implantation in the EVENT Registry



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Serious Events Between Index Procedure and One Year Among Patients Discharged on Warfarin: EVENT Registry

	*Not Discharged on Warfarin (N=9457)	Discharged on Warfarin (N=557)	Hazard Ratio	P
Death	2.7%	5.9%	2.25 (1.56, 3.25)	<0.0001
MI	7.9%	9.5%	1.2 (0.90, 1.59)	0.21
Stent Thrombosis	0.8%	1.5%	1.94 (0.93, 4.04)	0.08
Death/MI/Stent Thrombosis	10.2%	15.5%	1.54 (1.23, 1.92)	0.0001
Target Vessel Revascularization	6.0%	7.3%	1.2 (0.86, 1.67)	0.28

**** Includes patients with an indication for OAC and also patients without indication for OAC***

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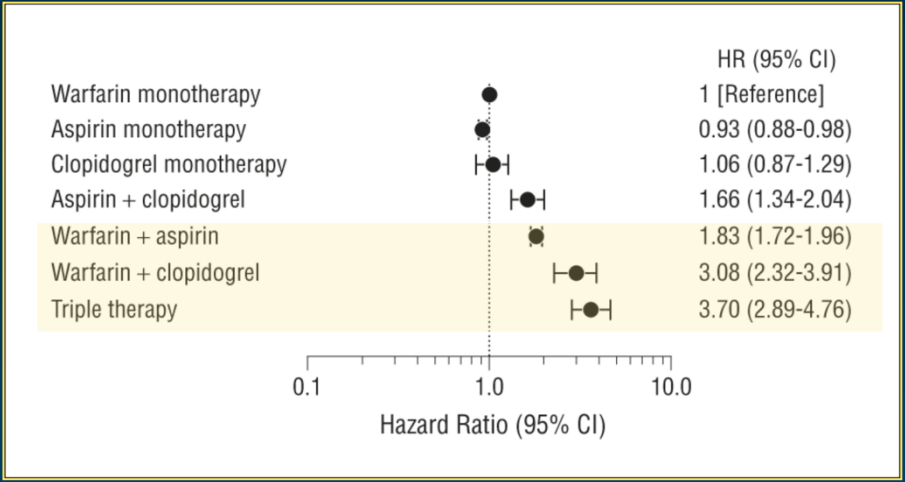
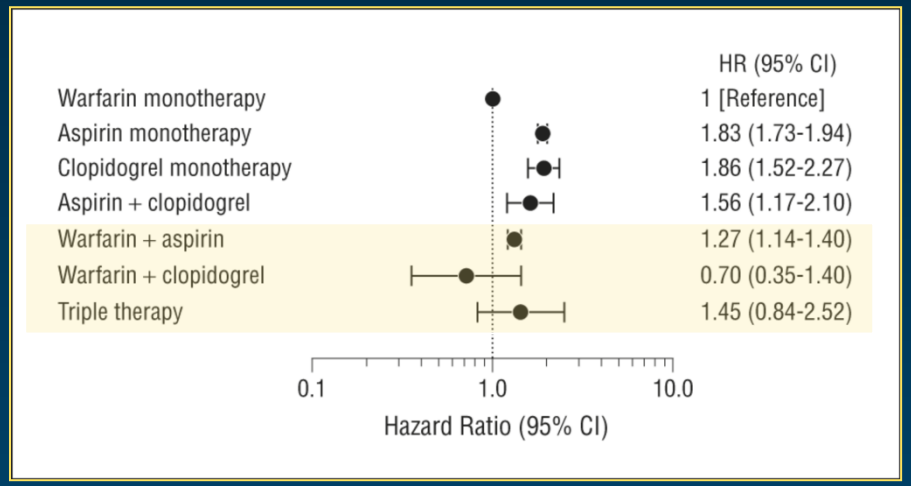
Combination Antithrombotic Therapy in Pts with Atrial Fibrillation (Danish Registry)

21,036 of 118,606 (17.8%) pts discharged with atrial fibrillation received at least one AP drug (25.3% of pts receiving antithrombotic drugs)

Risk of Bleeding



Risk of Ischemic Stroke



Modeled risk of mortality at 3 y was 2.45 (2.37-2.57) for pts with non-fatal bleeding

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Hansen. Arch Int Med. 2010;170:1433

Predictive Value of OAC Use Among Stented Patients with Atrial Fibrillation

8,962 Unselected Patients with Atrial Fibrillation
Median 650 Day Follow-up

↓

2,709 (30%) had Coronary Artery Disease

↓

417 (15%) received stents
AND
Had CHA_2DS_2-VASC $\geq$ 2

→ *97 (23%) Received OAC*

→ *OAC use was not associated w/ perceived bleeding risk*

Lack of an Oral Anticoagulant Independently Predicted Death/Stroke/Systemic Embolism
RR = 2.18 (1.02 – 4.67)

Bernard. Thrombosis and Hemostasis. 2013;110;560

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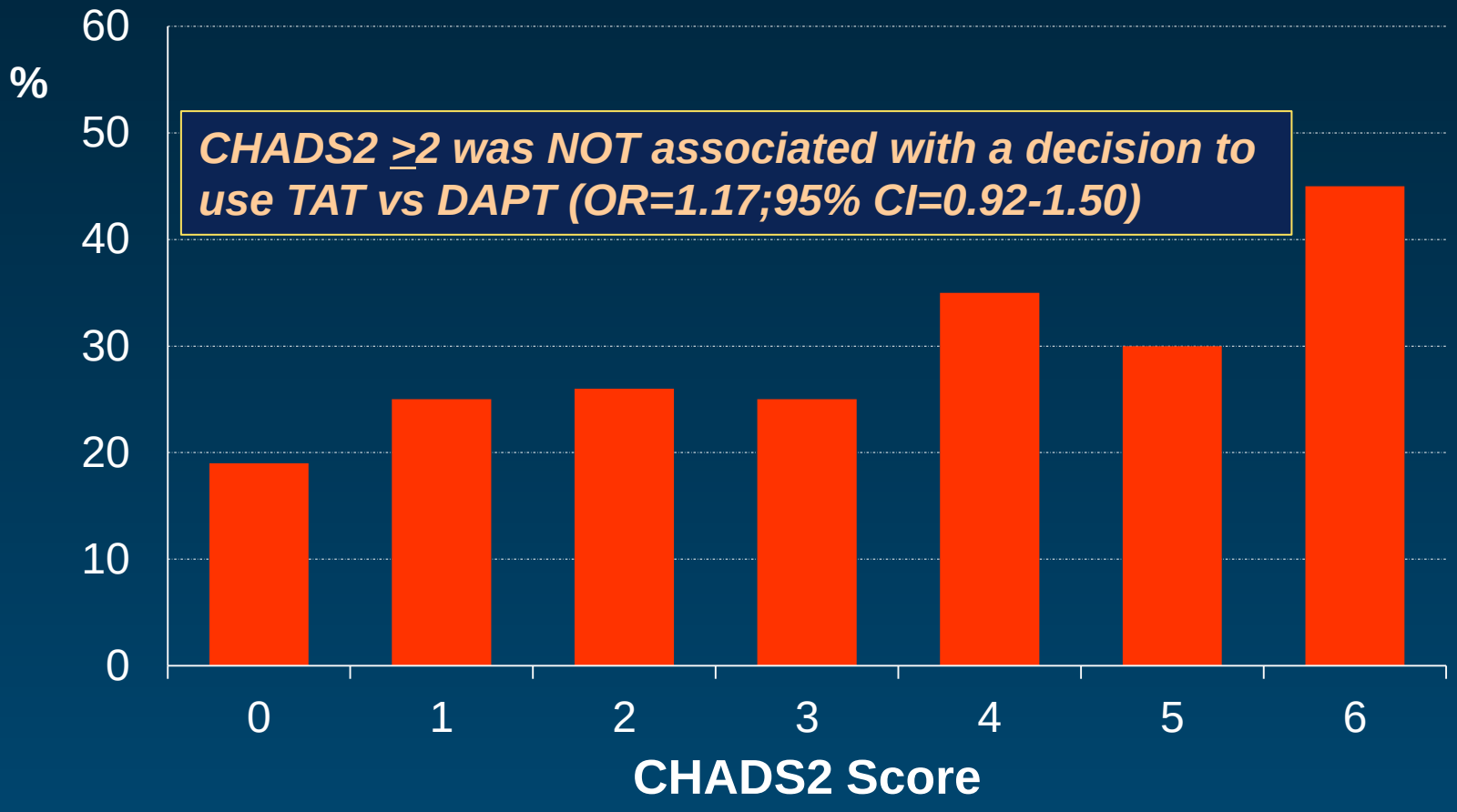
Use of Triple Antithrombotic Therapy According to Bleeding Risk in Patients with NSTEMI + IC Stent and Atrial Fibrillation



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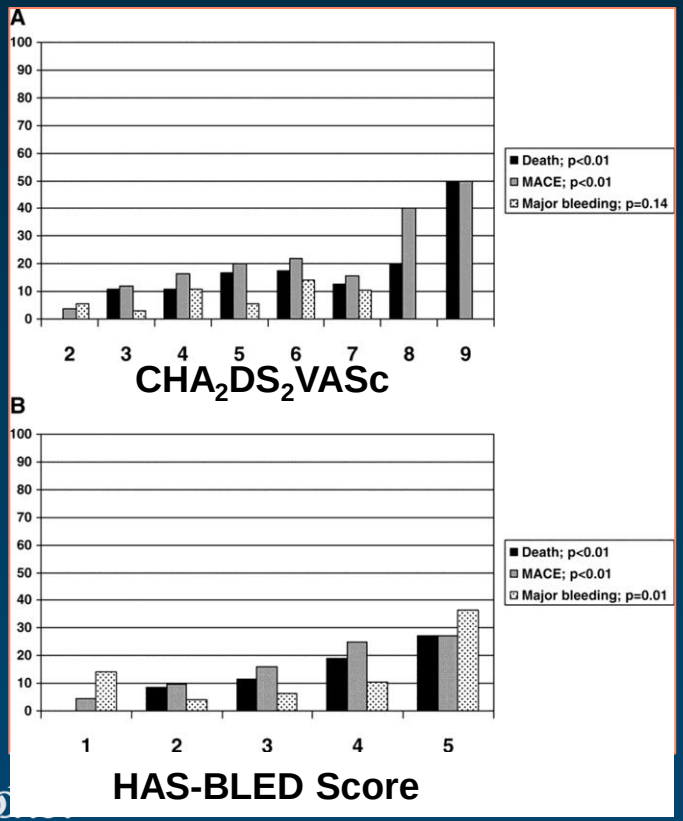
Fosbol. Am Heart J. 2013;166: 864

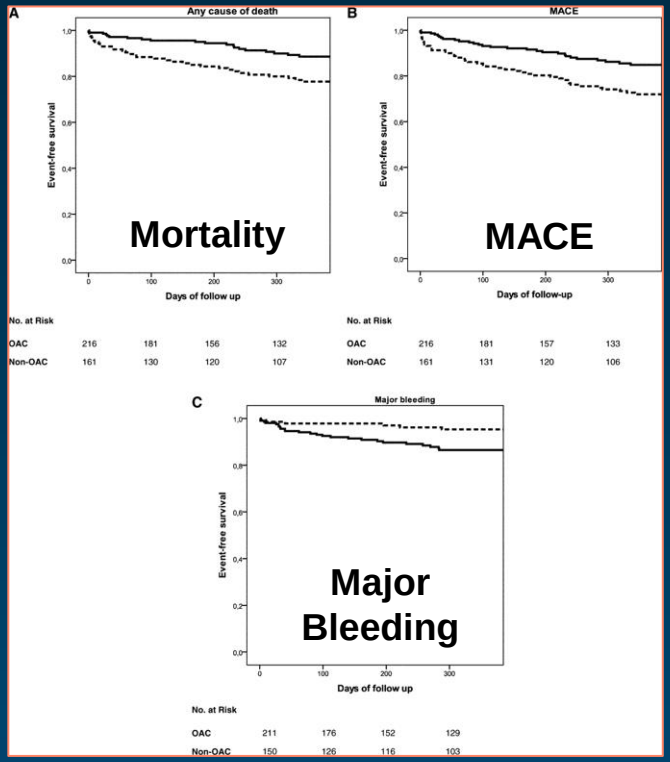
Atrial Fibrillation and PCI Stratified by Bleeding Risk: More Bleeding AND More Benefit

- 590 Patients with AF undergoing PCI and CHA_2DS_2-VASc score >1
- 420 (71%) had HAS-BLED score ≥3
  - OACs were used in **54%** of Low Bldg Risk and **57%** of High Risk Pts

Relationship of Risk Scores to Outcomes

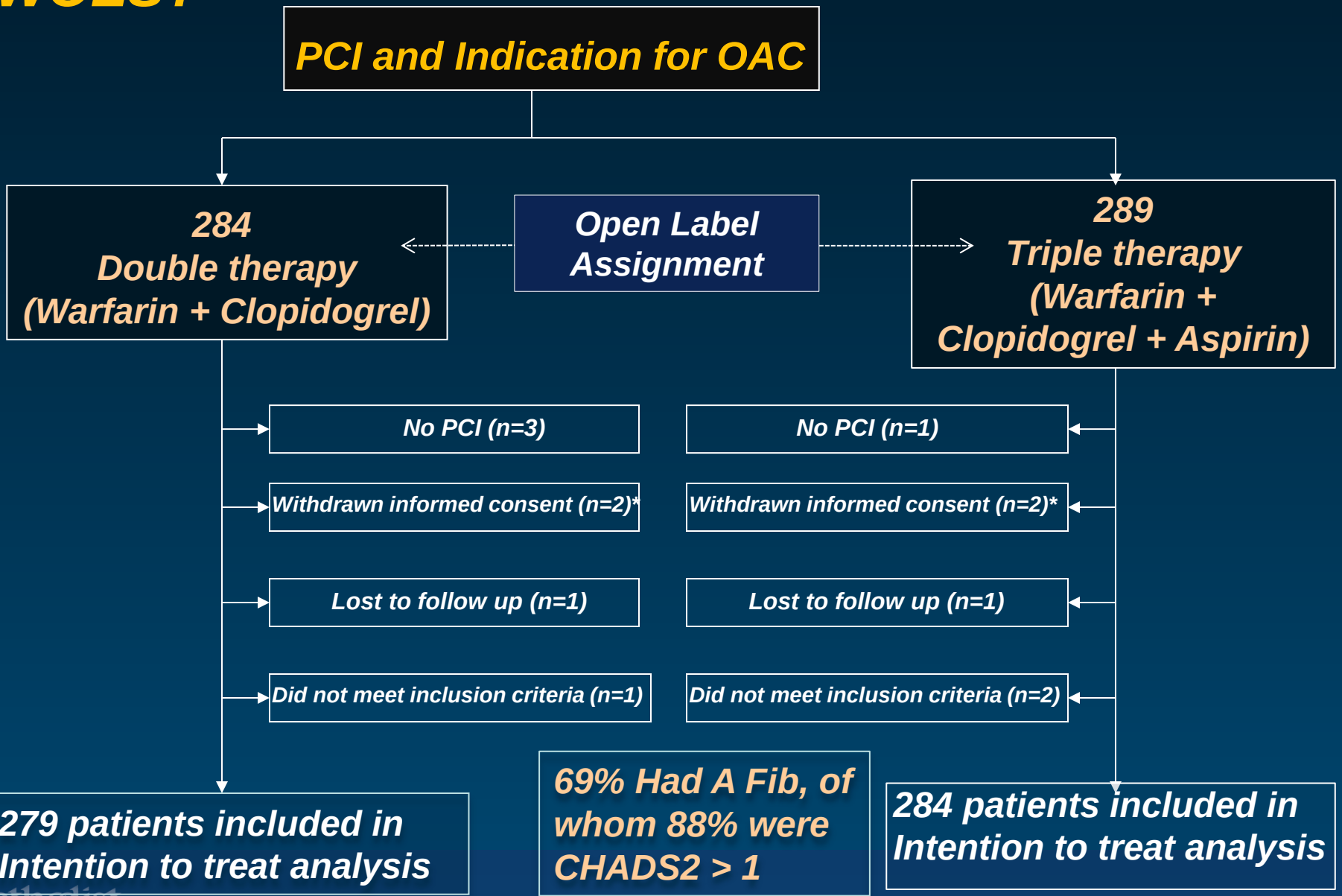


Pts with HB Score ≥ 3



Ruiz-Nodar J M et al. Circ Cardiovasc Interv 2012;5:459-466

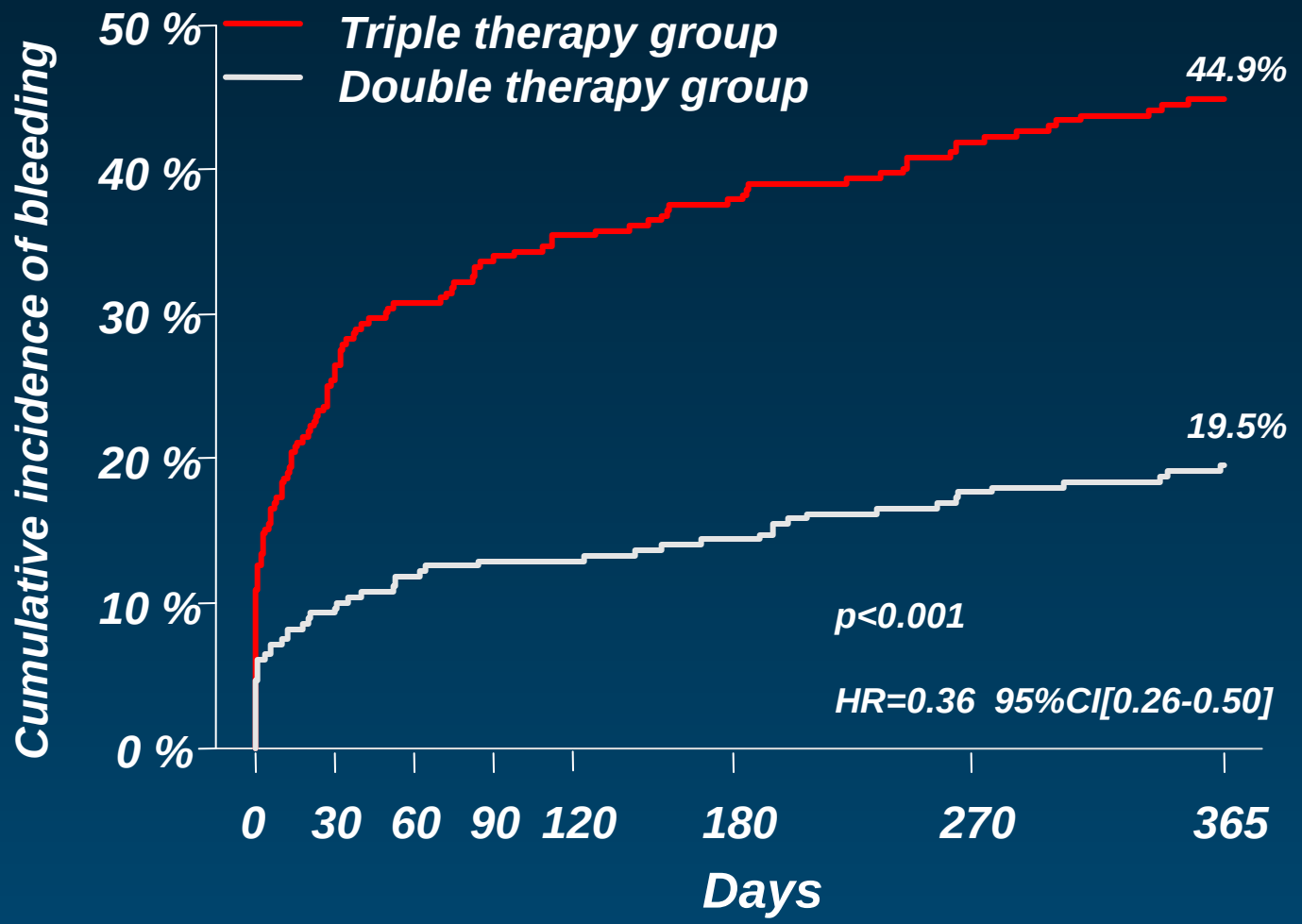
WOEST



** withdrawn informed consent; in double group 2 patients and triple group 1 patient were included in intention to treat analysis until the day of withdrawal*

WOEST

Primary Endpoint: Total number of Bleeding Events (TIMI)



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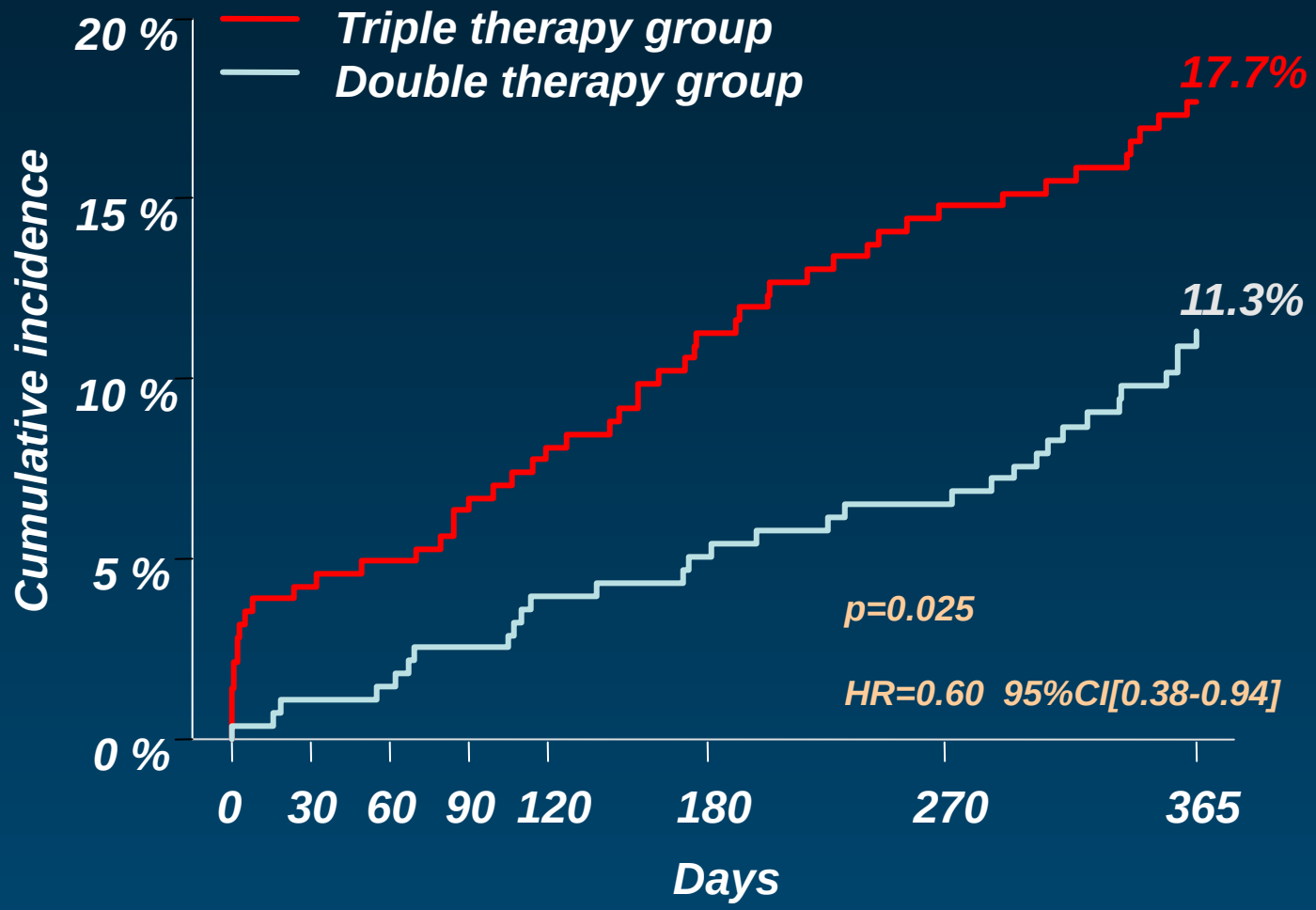
WOEST

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



N at risk:							
Triple therapy group	284	272	270	266	261	252	242	223
Double therapy group	279	276	273	270	266	263	258	234

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WOEST- Secondary Endpoints

	Double	Triple	HR	P
Death				
All Cause	7 (2.5)	18 (6.3)	0.39 (.10-.93)	0.27
Cardiac	3 (1.1)	7 (2.5)	0.43 (.11-1.66)	0.21
Non-Cardiac	4 (1.4)	11 (3.9)	0.36 (.11-1.13)	.069
Stroke				
Any	3 (1.1)	8 (2.8)	0.37 (.10-.40)	1.28
Ischemic	2 (0.7)	8 (2.8)	0.25 (0.05-1.17)	.056
Hemorrhagic	1	0	--	--
St. Thrombosis				
Definite	1 (.4)	3 (1.1)	.44 (.14-1.44)	0.165
Probable	0	2 (0.7)	--	--
Possible	3 (1.1)	4 (1.4)	.75 (.17-3.3)	0.71

(MI not shown)

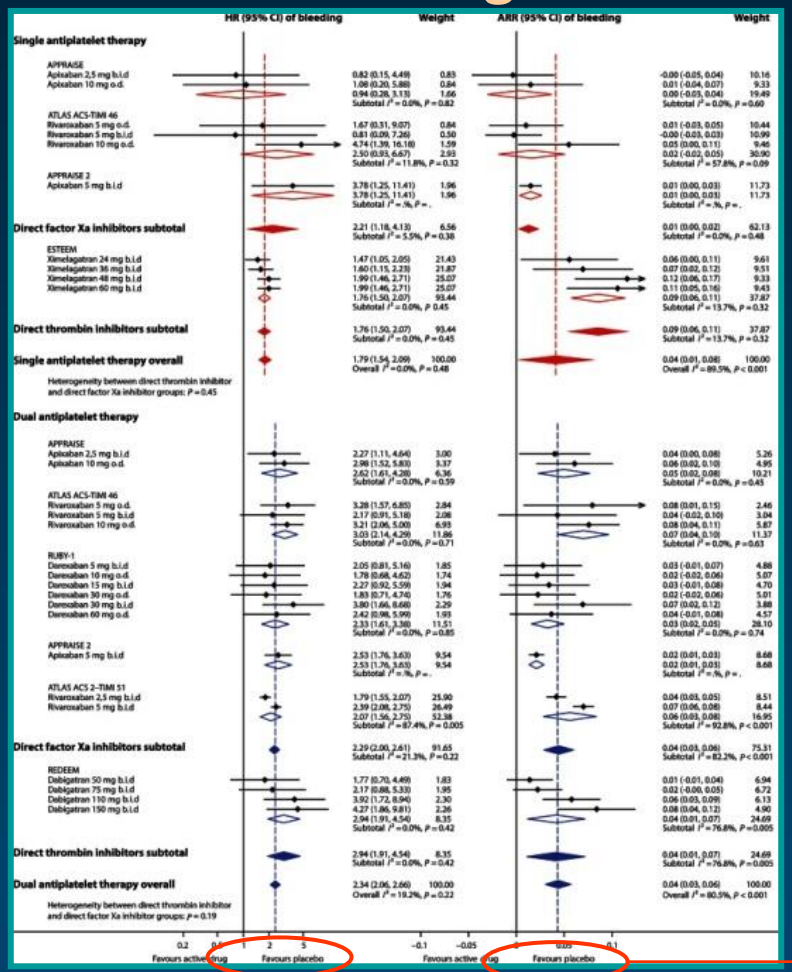
DeWilde. Lancet. 2013; 381:1107

New Trials of Antithrombotic Rx in AF after Stenting

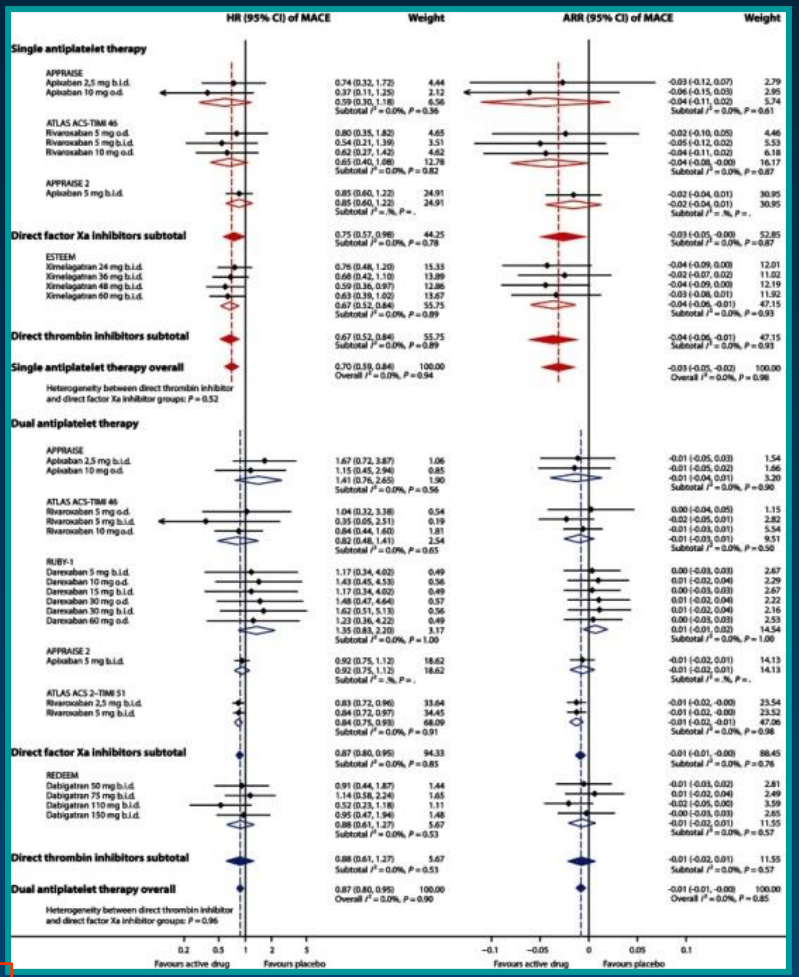
- **ISAR TRIPLE**
  - A Fib with indication for OAC after DES
  - Short (6 wk) vs Long (6 months) course of triple antithrombotic therapy
- **MUSICA – 2**
  - A Fib with low stroke risk (CHADS 2 ≤ 2)
  - Triple antithrombotic therapy vs dual antiplatelet therapy
  - 6 weeks for BMS; 12 months for DES

Meta-Analysis of New OACs and Antiplatelet Therapy

Bleeding



MACE



Oldgren. Eur Heart J. 2013;34:1670

"Favors Placebo"

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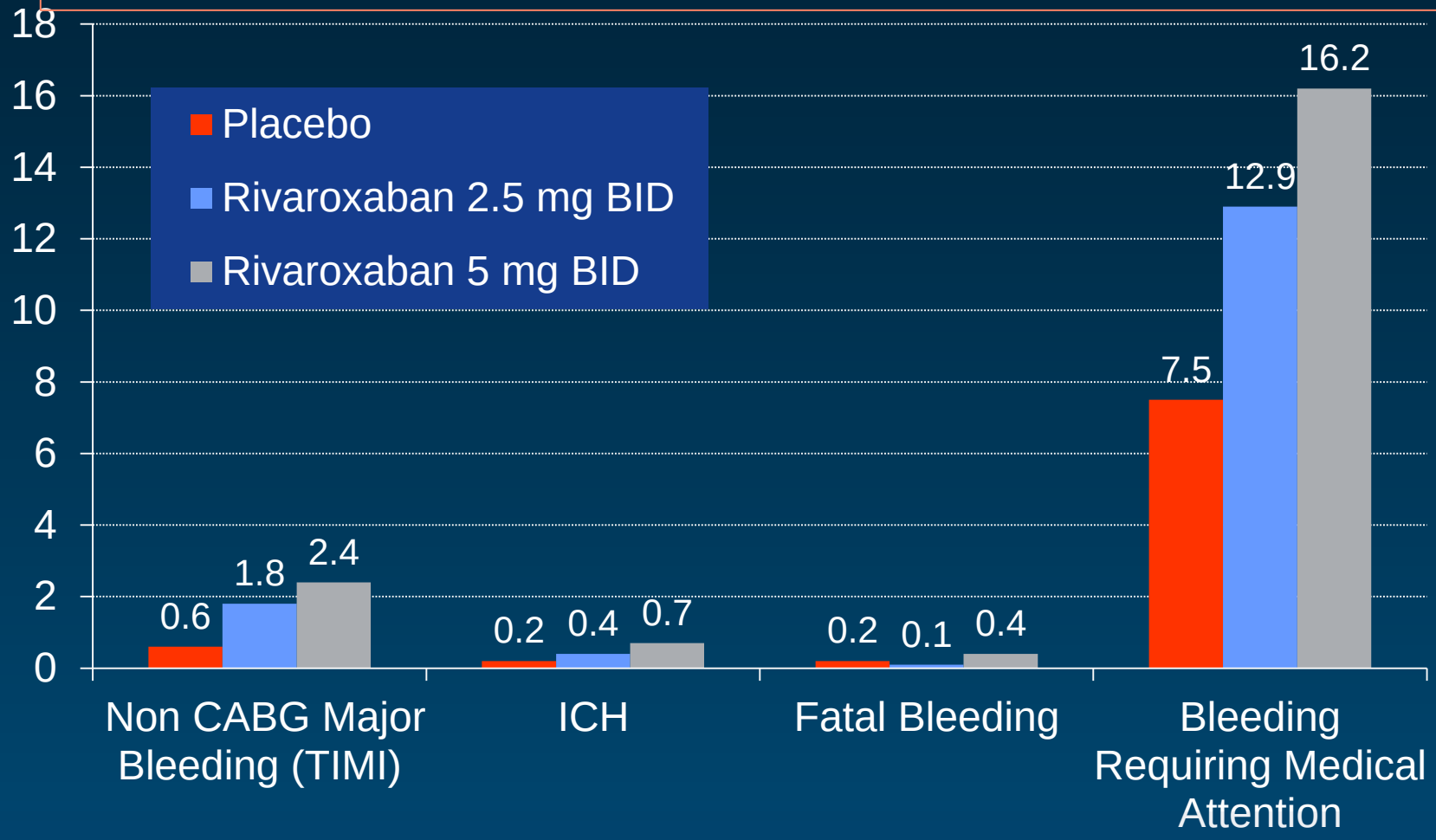
ATLAS ACS 2 Trial of Rivaroxiban and DAPT

- *98% on ASA, 93% on Thienopyridine*
- *16% Reduction in Primary EP; 35% Reduction in Stent Thrombosis*



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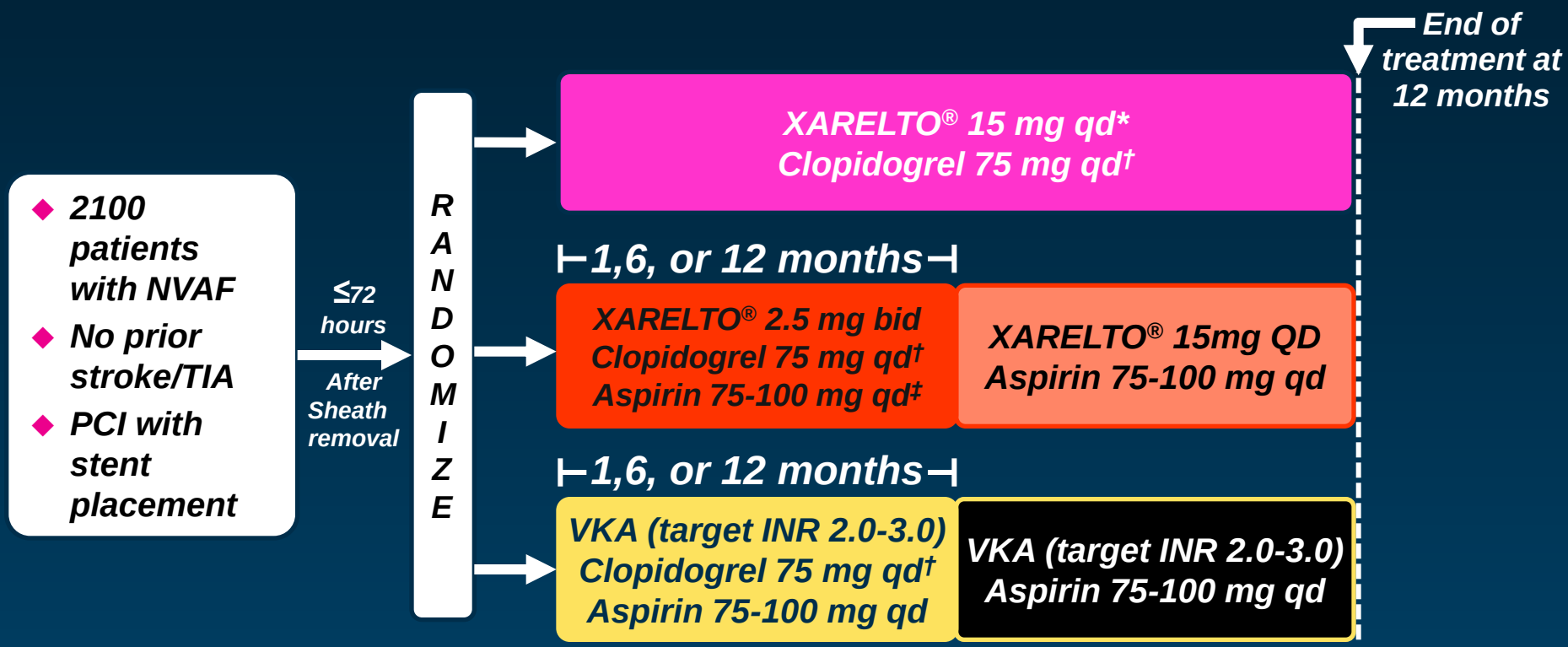
XARELTO® (rivaroxaban) Use in Patients With AF Undergoing PCI: PIONEER AF-PCI



- Primary endpoint: TIMI major, minor, and bleeding requiring medical attention
- Secondary endpoint: CV death, MI, stroke, and stent thrombosis

**XARELTO® dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.*

†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.

‡Low-dose aspirin (75-100 mg/d).

Data on File. Janssen Pharmaceuticals, Inc.

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Alternative Modifications to Pharmacologic Therapy that Might be (Re) Explored

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

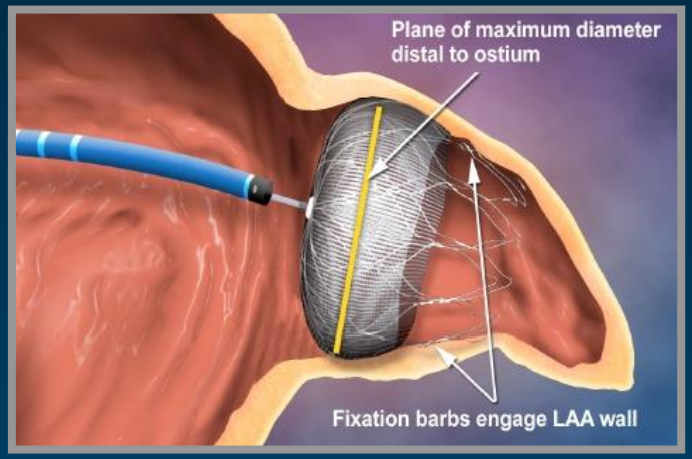
Safety and Efficacy of Ticlopidine for Only 2 Weeks After Successful Intracoronary Stent Placement

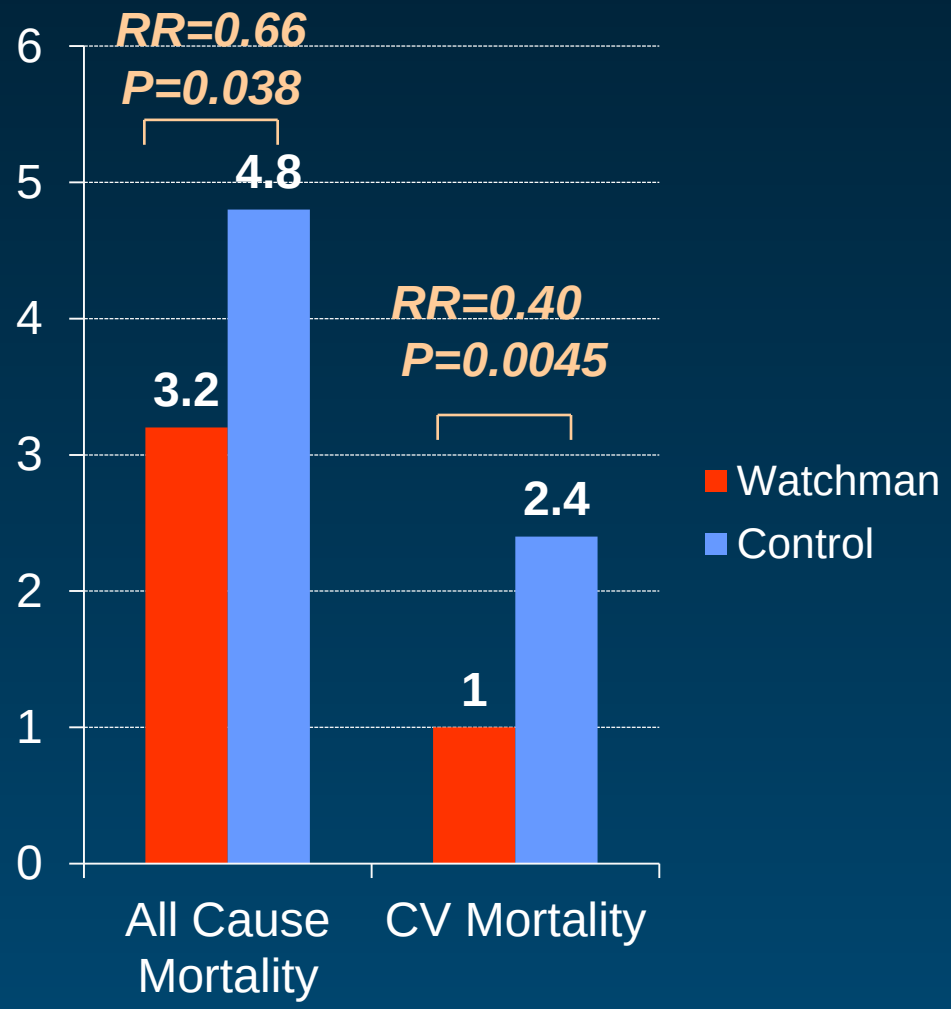
Peter B. Berger, Malcolm R. Bell, David Hasdai, Diane E. Grill, Steve Melby and David R. Holmes, Jr

Circulation. 1999;99:248-253
doi: 10.1161/01.CIR.99.2.248
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Avoiding Triple Antithrombotic Therapy: Four Year Mortality in the PROTECT Trial





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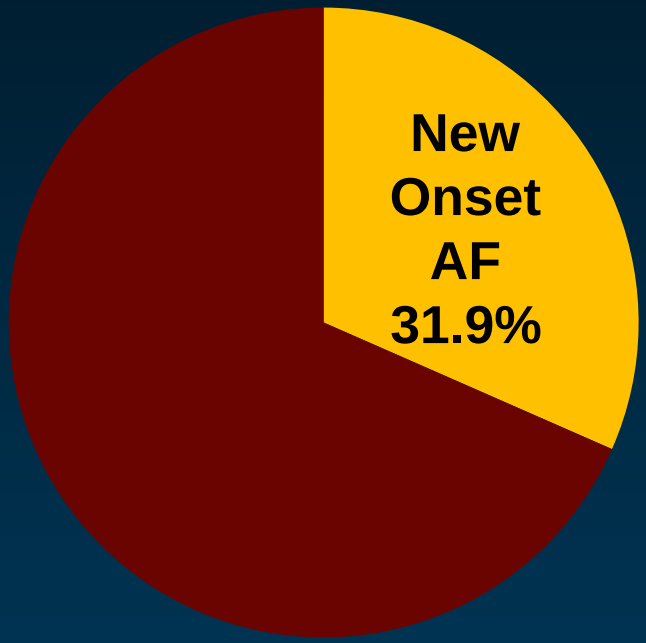
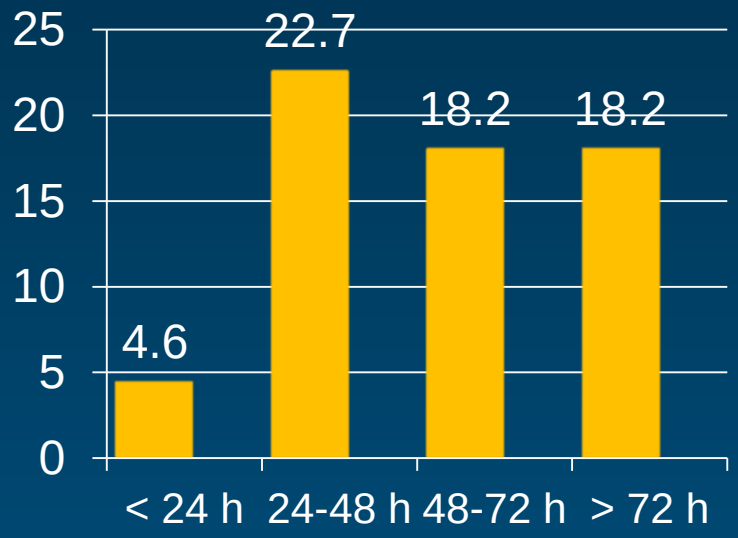
Stent Patients with the Highest Risk of Stroke and of Bleeding





Amat Santos. JACC. 2012;50:178

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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

118,606 pts discharged with atrial fibrillation; 21,036 (17.8%) received at least one prescription for warfarin and an AP drug (25.3% of pts receiving antithrombotic drugs)

Relative Risks for bleeding compared to warfarin alone ranged from 1.75 for warfarin + ASA to 4.03 for warfarin + DAPT ; while the incidence rate jumped from 3.9%/y to 15.7%/y

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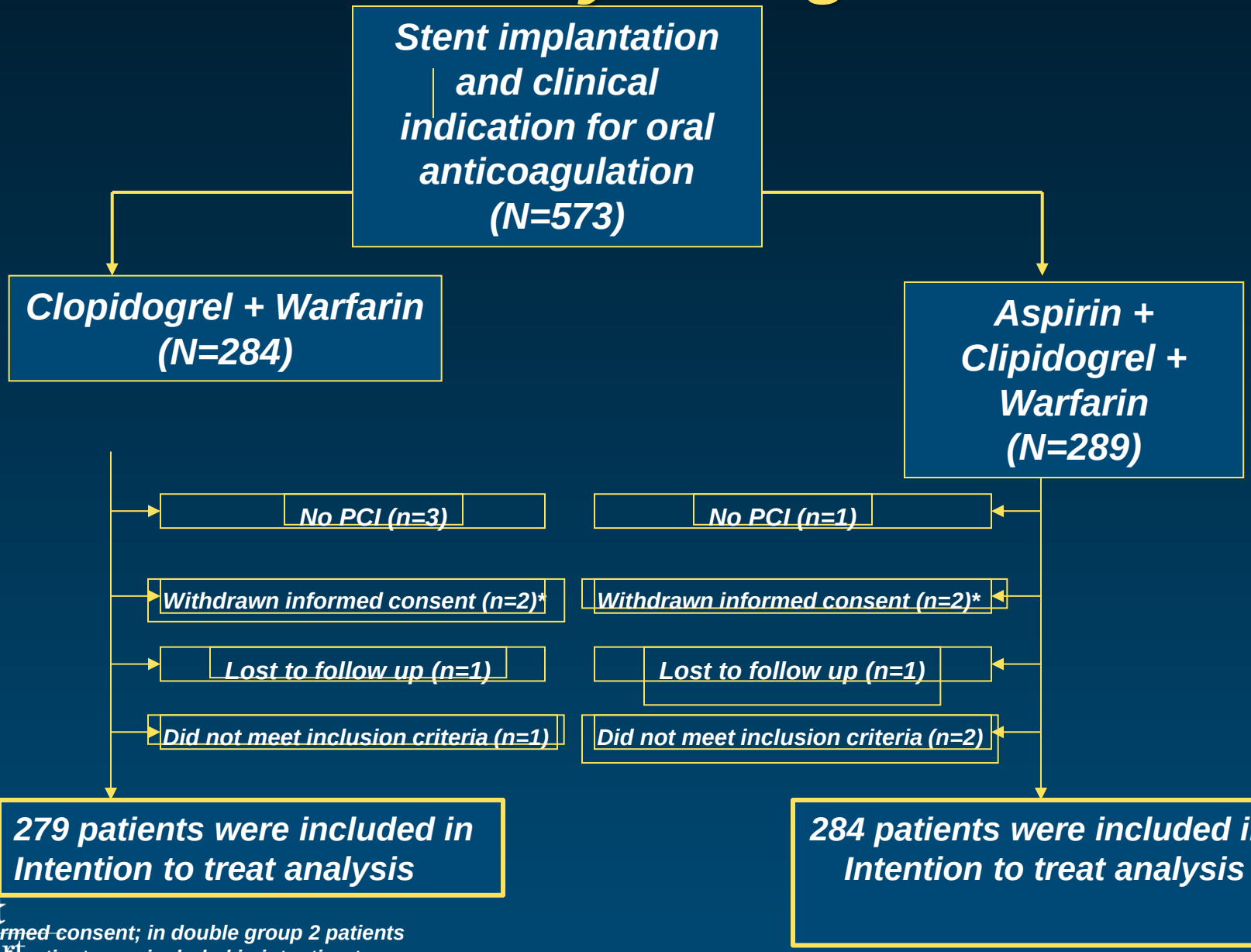
Hansen. Arch Int Med. 2010;170:1433

WOEST Trial: Study Design



* withdrawn informed consent; in double group 2 patients and triple group 1 patient were included in intention to treat analysis until the day of withdrawal

Pioneer Trial

- **Atrial Fibrillation with PCI**
  - **Rivaroxaban 2.5 mg + DAPT x 12 months**

    Or
  - **Rivaroxaban 2.5 mg + DAPT x 12 months followed by rivaroxaban + aspirin to 12 months**
- **Primary outcome is safety (bleeding on TIMI scale)**