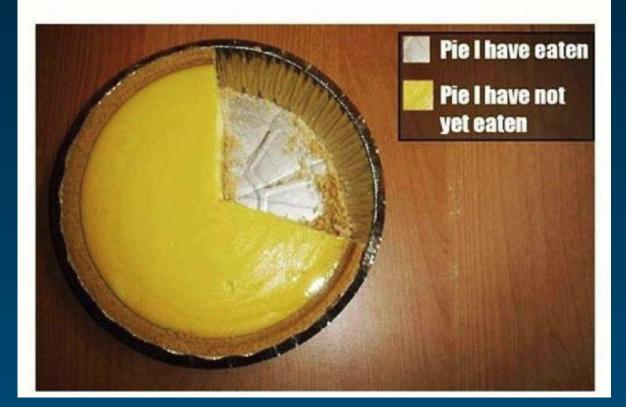
Management of Patients with Atrial Fibrillation and Stents: Is Three Drugs Too Many?

### Neal S. Kleiman, MD Houston Methodist DeBakey Heart and Vascular Center, Houston, TX



### Some Things Are Really Clear

### World's Most Accurate Pie Chart



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Therapeutic Controversies

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

A Janelle Hermosillo and Sarah A Spinler

**790** The Annals of Pharmacotherapy 2008 June, Volume 42

www.theannals.com

### 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

© Schattauer 2011

Consensus Document

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

Journal of the American College of Cardiology © 2009 by the American College of Cardiology Foundation Published by Elsevier Inc. Vol. 54, No. 2, 2009 ISSN 0735-1097/09/\$36.00 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, <u>careful follow-up</u> is indicated, with low dose (<100 mg) ASA, conventional dose (75 mg) clopidogrel, <u>a lower target INR</u> (approximately 2.0), and consideration of prophylactic proton pump inhibition."

Meth DeBakey I & 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.

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### 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<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-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<sub>2</sub>-VASc = 0
- Bleeding risk exceeded stroke risk in only <u>0.4%</u> of the patient population



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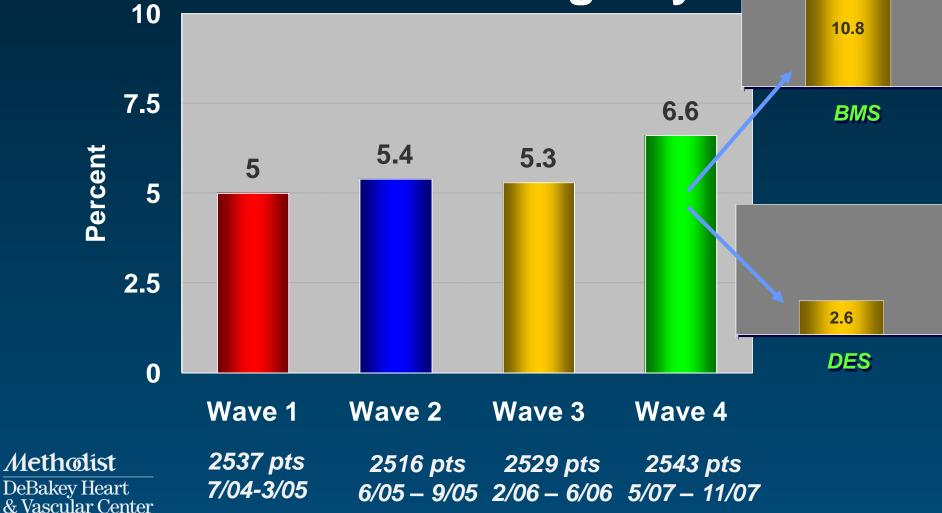
Friberg. Circulation.2012;125:2298

# Considerations for Stenting in Pts with Atrial Fibrillation

- Type of stent (DES vs BMS; 1<sup>st</sup> vs 2<sup>d</sup> gen.)
- Complexity of the stent procedure
- Need for OACs
  - Stroke risk (CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores)
  - Bleeding risk (HAS-BLED score)
- Duration of antiplatelet therapy
- Type of OAC and type of AP drug
- Worsening of AP drug compliance

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



### 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	Р
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)

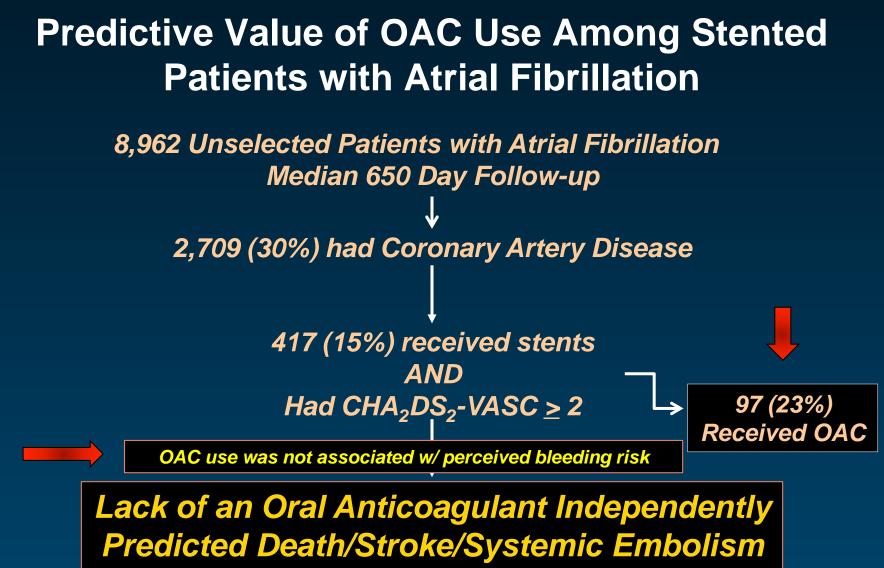
21,036 of 118,606 (17.8%) pts discharged with atrial fibrillation received at least one AP drug (25.3% of pts receiving antithrombotic drugs)

#### Risk of Ischemic Stroke Risk of Bleeding HR (95% CI) HR (95% CI) Warfarin monotherapy 1 [Reference] 1 [Reference] Warfarin monotherapy Aspirin monotherapy 0.93 (0.88-0.98) Aspirin monotherapy 1.83 (1.73-1.94) Clopidogrel monotherapy 1.06 (0.87-1.29) Clopidogrel monotherapy 1.86 (1.52-2.27) ----Aspirin + clopidogrel 1.66 (1.34-2.04) Aspirin + clopidogrel 1.56 (1.17-2.10) Warfarin + aspirin Warfarin + aspirin 1.83 (1.72-1.96) 1.27 (1.14-1.40) 3.08 (2.32-3.91) Warfarin + clopidogrel Warfarin + clopidogrel 0.70 (0.35-1.40) 3.70 (2.89-4.76) 1.45 (0.84-2.52) Triple therapy Triple therapy 0.1 1.0 10.0 0.1 1.0 10.0 Hazard Ratio (95% CI) Hazard Ratio (95% CI)

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

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DeBakey Heart & Vascular Center Hansen. Arch Int Med. 2010;170:1433

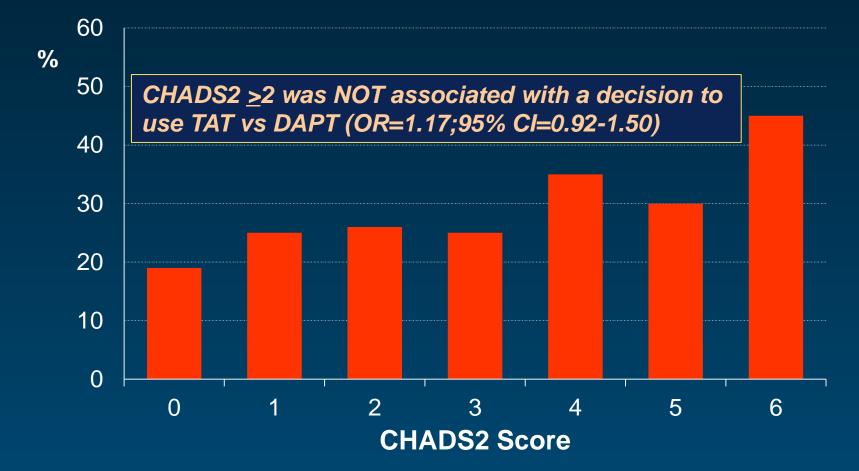


*RR* = 2.18 (1.02 – 4.67)

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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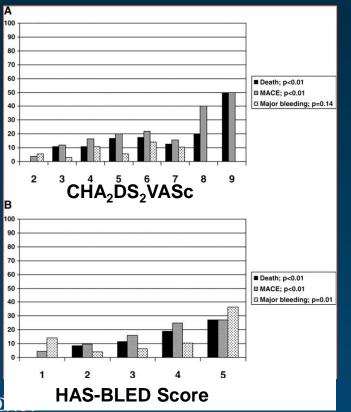
DeBakey Heart & Vascular Center Fosbol. Am Heart J. 2013;166: 864

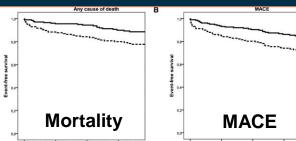
#### Atrial Fibrillation and PCI Stratified by Bleeding Risk: More Bleeding AND More Benefit

- 590 Patients with AF undergoing PCI and CHA<sub>2</sub>DS<sub>2</sub>-VASc score >1
- 420 (71%) had HAS-BLED score <u>></u>3

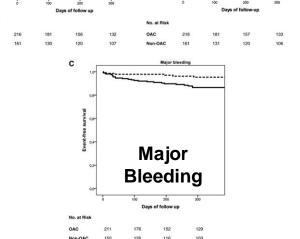
> OACs were used in **54%** of Low Bldg Risk and **57%** of High Risk Pts

#### Relationship of Risk Scores to Outcomes





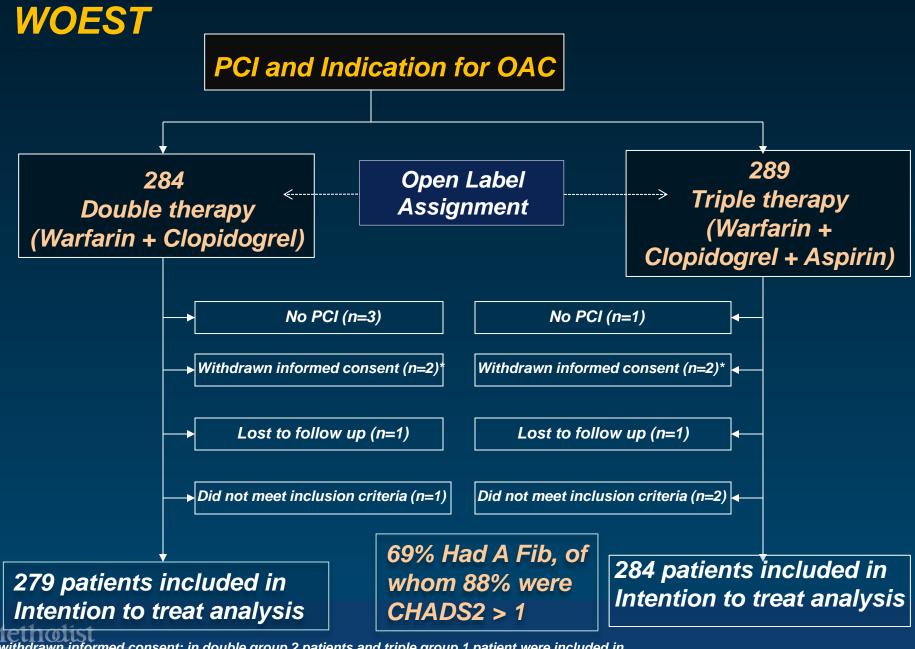
#### Pts with HB Score > 3



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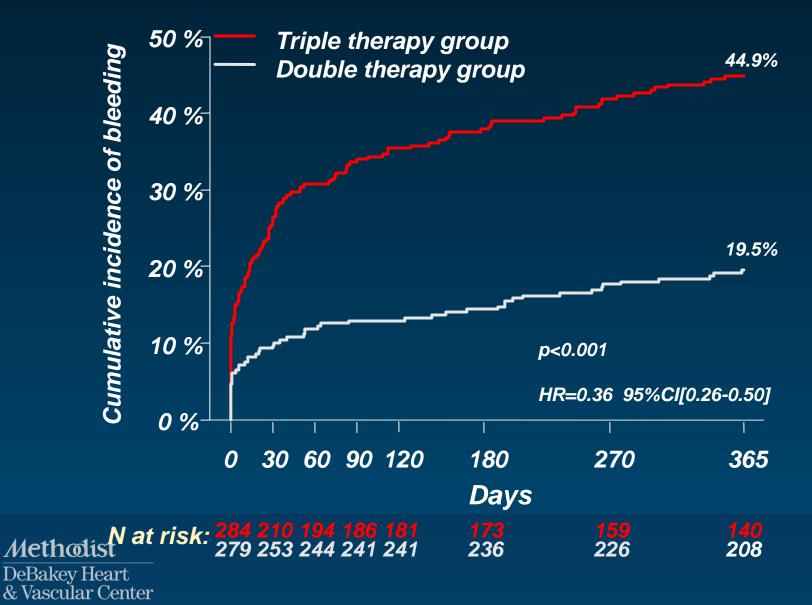
& Vascular Center

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



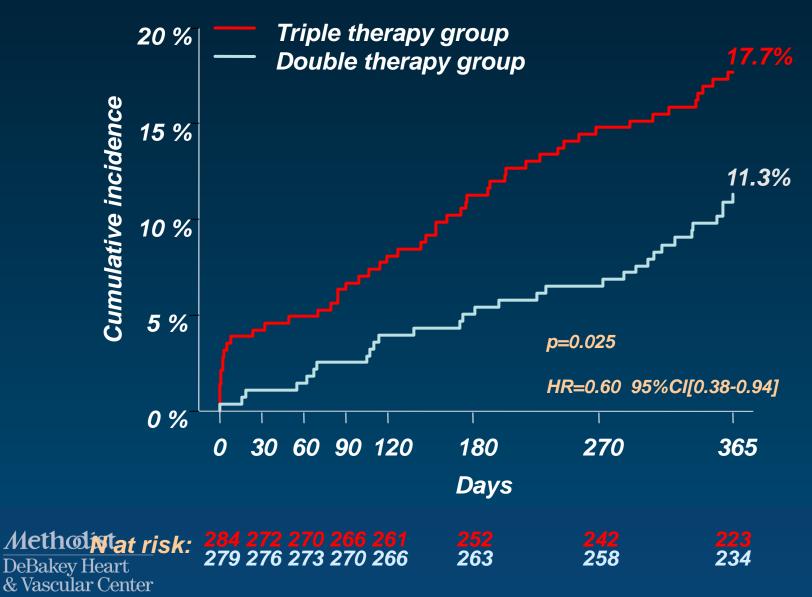
\* withdrawn informed consent; in double group 2 patients and triple group 1 patient were included in intention to treat analysis until the day of withdrawal Vascular Center

#### **WOEST** Primary Endpoint: Total number of Bleeding Events (TIMI)





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



### **WOEST- Secondary Endpoints**

	Double	Triple	HR	Р
Death				
All Cause	7 (2.5)	18 (6.3)	0.39 (.1093)	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 (.1040)	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

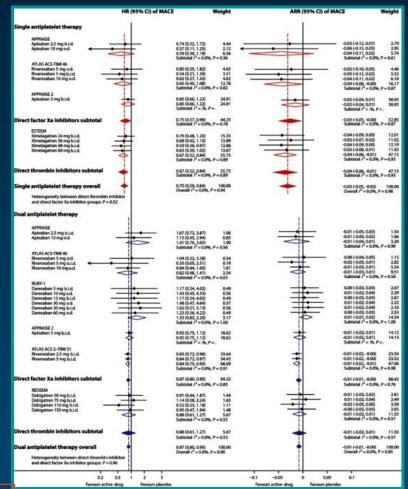
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### Meta-Analysis of New OACs and Antiplatelet Therapy

#### Bleeding

	HR (95% CI) of bleeding	Weight	ARR (95% CI) of bleeding	Weight
ngle antiplatelet therapy				
APPRAISE Apkaban 2,5 mg b.i.d		0.82 (0.15, 4.49) 0.83		-0.00(-0.05, 0.04) 10.16
Apkaban 2,5 mg b.ud		1.08 (0.20, 5.88) 0.84		-0.00(-0.05, 0.04) 10.16 0.01(-0.04, 0.07) 9.33
-		0.94 (0.28, 3.13) 1.66 Subtotal /* = 0.0%, P = 0.82		0.00 (-0.03, 0.04) 19.49 Subtotal / <sup>2</sup> = 0.0%, / <sup>2</sup> = 0.60
ATLAS ACS-TIMI 46				
Rivaroxaban 5 mg o.d		1.67 (0.31, 9.07) 0.84 0.81 (0.09, 7.26) 0.50		0.01 (-0.03, 0.05) 10.44 -0.00 (-0.03, 0.03) 10.99
Riveroxaben 10 mg o.d.		474(139.16.18) 1.59		0.05 (0.00, 0.11) 9.46
		2.50 (0.93, 6.67) 2.93 Subtotal / <sup>0</sup> = 11.8%, P = 0.32		0.02 (-0.02, 0.05) 30.90 Subtotal / <sup>2</sup> = 57.8%, P = 0.09
APPRAISE 3		Subjortan /* = 11.8%, P = 0.32		SUDIOTAI /* = 57.8%, P = 0.09
Apixaban 5 mg b.i.d		3.78 (1.25, 11.41) 1.96		0.01 (0.00, 0.03) 11.73
		3.78 (1.25, 11.41) 1.96 Subtotal / <sup>2</sup> = .%, P = .	0	0.01 (0.00, 0.03) 11.73 Subtotal / <sup>2</sup> = .%, P = .
irect factor Xa inhibitors subtotal		2.21 (1.18, 4.13) 6.56 Subtotal / <sup>2</sup> = 5.5%, P = 0.38	-	0.01 (0.00, 0.02) 62.13 Subtotal / <sup>2</sup> =0.0%, P=0.48
ESTEEM				
Ximelagatran 24 mg b.i.d Ximelagatran 36 mg b.i.d		1.47 (1.05, 2.05) 21.43 1.60 (1.15, 2.23) 21.87		0.06 (0.00, 0.11) 9.61 0.07 (0.02, 0.12) 9.51
Ximelagatran 48 mg b.i.d		1.99(1.46, 2.71) 25.07		0.12 (0.06, 0.17) 9.33
Ximelagatran 60 mg b.l.d	1	1.99 (1.46, 2.71) 25.07 1.76 (1.50, 2.07) 93.44	1	0.11 (0.05, 0.16) 9.43
	Ψ	1.76 (1.50, 2.07) 93.44 Subtotal / <sup>2</sup> = 0.0%, P 0.45		0.09 (0.06, 0.11) 37.87 Subtotal / <sup>2</sup> = 13.7%, P = 0.32
Firect thrombin inhibitors subtotal				
rect thrombin inhibitors subtotal	+	1.76 (1.50, 2.07) 93.44 Subtotal / <sup>2</sup> = 0.0%, P = 0.45	-	0.09 (0.06, 0.11) 37.87 Subtotal I <sup>2</sup> = 13.7%, P = 0.32
ingle antiplatelet therapy overall	4			0.04 (0.01, 0.08) 100.00
	T	1.79 (1.54, 2.09) 300.00 Overall / <sup>2</sup> =0.0%, P=0.48	1	Overall J <sup>4</sup> =89.5%, P<0.001
Heterogeneity between direct thrombin inf and direct factor Xa inhibitor groups: $P = 0.4$	NBMOF 15		1.254	
ual antiplatelet therapy	10			
APPRAISE				
Apikaban 2,5 mg b.i.d		2.27 (1.11, 4.64) 3.00		0.04 (0.00, 0.08) 5.26
Apikaban 10 mg o.d.		2.96 (1.52, 5.83) 3.37 2.62 (1.61, 4.28) 6.36 Subtotal (* =0.0%, P = 0.59	1	0.06 (0.02, 0.10) 4.95 0.05 (0.02, 0.08) 10.21 Subtotal /*=0.0%, p=0.45
		Subtotal /* = 0.0%, P = 0.59	the second se	Subtotal /2 = 0.0%, P = 0.45
ATLAS ACS-TIMI 46 Riveroseben 5 mg o.d.	i i i i i i i i i i i i i i i i i i i	3.28 (1.57, 6.85) 2.84		0.08 (0.01, 0.15) 2.46
Riveroxaben 5 mg b.d		2.17 (0.91, 5.18) 2.06		0.04 (-0.02, 0.10) 3.04
Riveroxaben 10 mg o.d.	++-	3.21 (2.06, 5.00) 6.93	· · · · · ·	0.08(0.04.0.11) 5.87
	$\diamond$	3.03 (2.14, 4.29) 11.86 Subtotal / <sup>1</sup> =0.0%, P=0.71		0.07 (0.04, 0.10) 11.37 Subtotal / <sup>2</sup> = 0.0%, P = 0.63
RUBY-1				
Darexaban 5 mg b.i.d	+++	2.05 (0.81, 5.16) 1.85		0.03 (-0.01, 0.07) 4.88
Darexalban 10 mg o.d. Darexalban 15 mg b.i.d		1.78 (0.68, 4.62) 1.74 2.27 (0.92, 5.59) 1.94		0.02 (-0.02, 0.06) 5.07 0.03 (-0.01, 0.08) 4.70
Davesaban 30 mg o.d.		1.83 (0.71, 4.74) 1.76		0.02 (-0.02, 0.06) 5.01
Darexalban 30 mg b.i.d		3.80 (1.66, 8.66) 2.29		0.07 (0.02, 0.12) 3.80 0.04 (-0.01, 0.04) 4.57
Derevalban 60 mg o.d.		2.42 (0.96, 5.99) 1.93 2.33 (1.61, 3.30) 11.51 Subtotal / =0.0%, P=0.85		0.03 (0.02, 0.05) 28.10
	T	Subtotal / =0.0%, P =0.85		Subtotal / <sup>2</sup> = 0.0%, P = 0.74
APPRAISE 2 Apixaban 5 mg b.i.d		2.53 (1.76, 3.63) 9.54	+	0.02 (0.01, 0.03) 8.68
	$\diamond$	2.53 (1.76, 3.63) 9.54 Subtotal / = %, P =	\$	0.02 (0.01, 0.03) 8.68 Subtotal / <sup>#</sup> = .%, P = .
ATLAS ACS 2-TIMI 51		autodat / = . %, / = .		anagodat 1. a '40' b. a '
Rivarosaban 2,5 mg b.i.d	+	1.79 (1.55, 2.07) 25.90	-	0.04 (0.03, 0.05) 8.51
Rivaroxaban 5 mg b.Ld	1	2.39 (2.08, 2.75) 26.49	+	0.07 (0.06, 0.08) 8,44 0.06 (0.03, 0.08) 16,95
	9	2.07 (1.56, 2.75) 52.38 Subtotal /*=87.4%, P=0.005		0.06 (0.03, 0.08) 16.95 Subtotal /* = 92.8%, P < 0.001
Firect factor Xa inhibitors subtotal	1	1100001100		
rect rector As inhibitors subtotal	•	2.29 (2.00, 2.61) 91.65 Subtotal /*=21.3%, P=0.22	-	0.04 (0.03, 0.06) 75.31 Subtotal / <sup>2</sup> = 82.2%, P< 0.001
REDEEM				
Debigatran 50 mg b.Ld Debigatran 75 mg b.Ld		1.77 (0.70, 4.49) 1.83 2.17 (0.88, 5.33) 1.95		0.01 (-0.01, 0.04) 6.94 0.02 (-0.00, 0.05) 6.72
Debigatran 110 mg b.i.d		3.92 (1.72, 8.94) 2.30	· + • - · · · · · · · · · · · · · · · · · ·	0.06 (0.03, 0.09) 6.13
Dabigatran 150 mg b.Ld		4.27 (1.96, 9.81) 2.26		0.08 (0.04, 0.12) 4.90 0.04 (0.01, 0.07) 24.69
		2.94 (1.91, 4.54) 8.35 Subtotal / = 0.0%, P = 0.42		0.04 (0.01, 0.07) 24.69 Subtotal I <sup>2</sup> = 76.8%, P = 0.005
the state of the latest statest sta				
irect thrombin inhibitors subtotal	-	2.94 (1.91, 4.54) 8.35 Subtotal /*=0.0%, P=0.42	-	0.04 (0.01, 0.07) 24.69 Subtotal / <sup>2</sup> = 76.8%, P = 0.005
ual antiplatelet therapy overall	•	2.34 (2.06, 2.66) 100.00 Overall / <sup>2</sup> = 19.2%, P = 0.22	-	0.04 (0.03, 0.06) 100.00 Overall /* = (0.5%, P < 0.001
Heterogeneity between direct thrombin inh	libitor			
and direct factor Xa inhibitor groups: $P = 0.2$	19			
	1 1 1 1			
0.2	01 1 2 5	-0.1 -0.0		
Fevours active	trug Favours placebo	Fevours activ	ve rug Favours placebo	

#### MACE

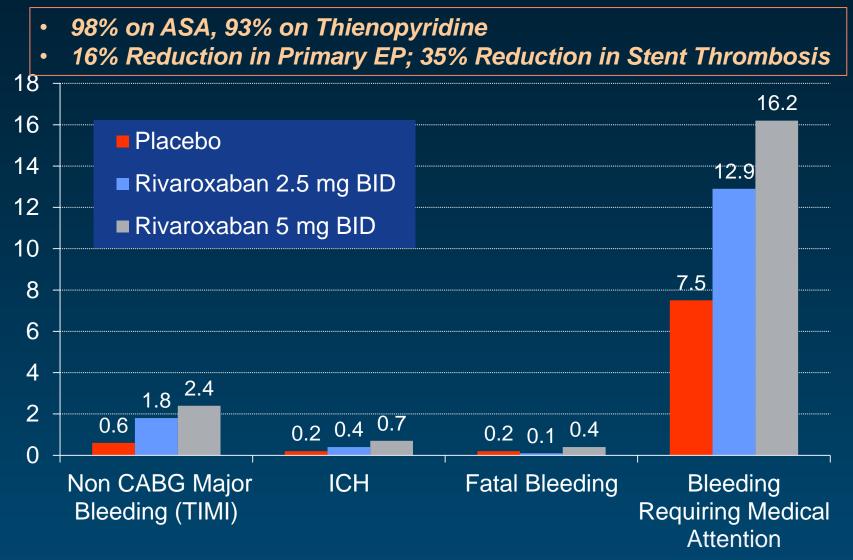


"Favors Placebo"

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DeBakey Heart & Vascular Center *Oldgren. Eur Heart J. 20*13;34:1670

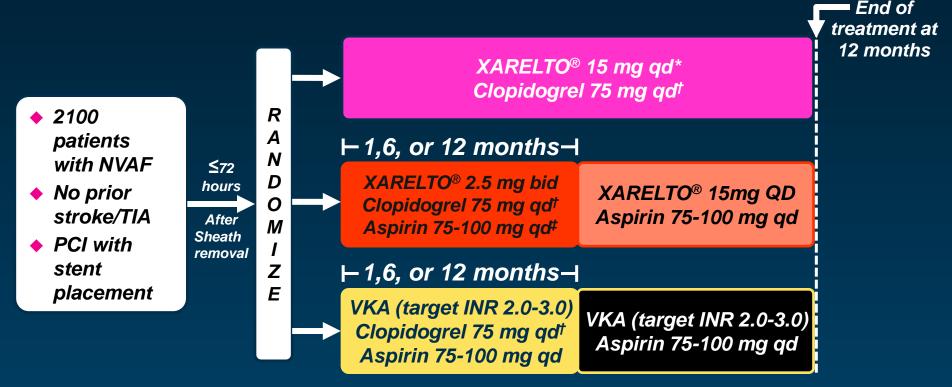
### **ATLAS ACS 2 Trial of Rivaroxiban and DAPT**



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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<sup>®</sup> dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min. <sup>†</sup>Alternative P2Y<sub>12</sub> inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor. <sup>‡</sup>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



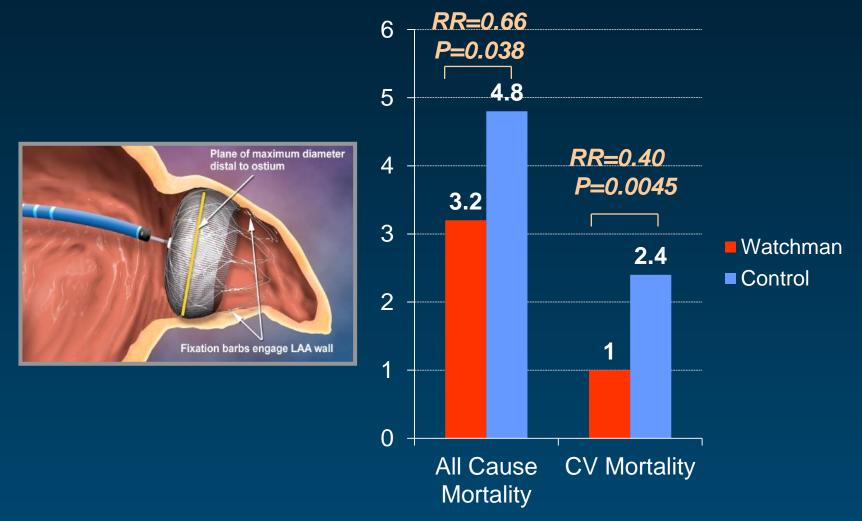


Safety and Efficacy of Ticlopidine for Only 2 Weeks After Successful Intracoronary Stent Placement Peter B. Berger, Malcolm R. Bell, David Hasdai, Diane E. Grill, Steve Melby and David R. Holmes, Jr

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 Copyright © 1999 American Heart Association, Inc. All rights reserved. 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

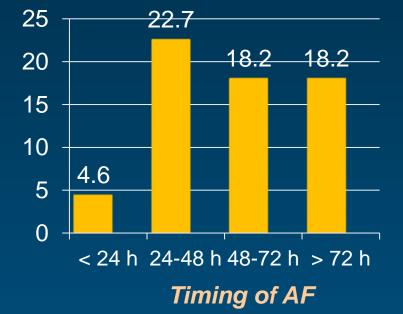
New Onset AF 31.9%



Amat Santos. JACC. 2012;50:178

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#### **LESS IS MORE**

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

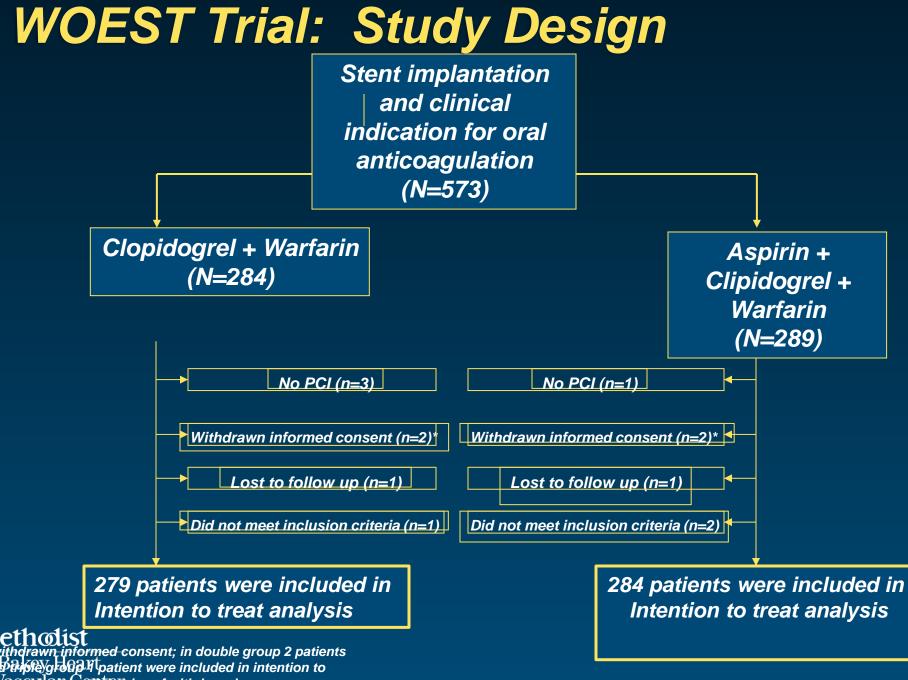
Morten L. Hansen, MD, PhD; Rikke Sørensen, MD; Mette T. Clausen, MSc Pharm; Marie Louise Fog-Petersen, MSc Pharm; Jakob Raunsø, MD; Niels Gadsbøll, MD, DMSc; Gunnar H. Gislason, MD, PhD; Fredrik Folke, MD; Søren S. Andersen, MD; Tina K. Schramm, MD; Steen Z. Abildstrøm, MD, PhD; Henrik E. Poulsen, MD, 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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DeBakey Heart & Vascular Center Hansen. Arch Int Med. 2010;170:1433



&reason and the wanter 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)

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