Dabigatran: nuove conferme di sicurezza. Da Recruit a ReDual-PCI







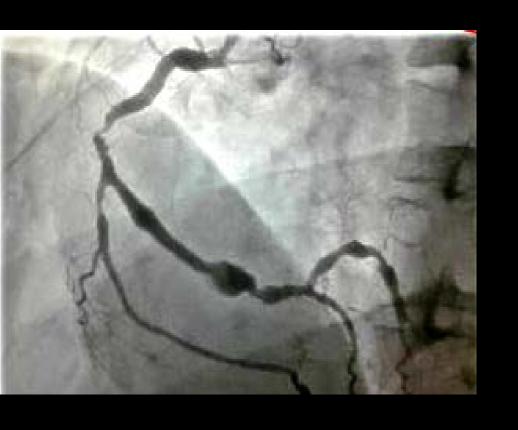
Maurizio Tespili

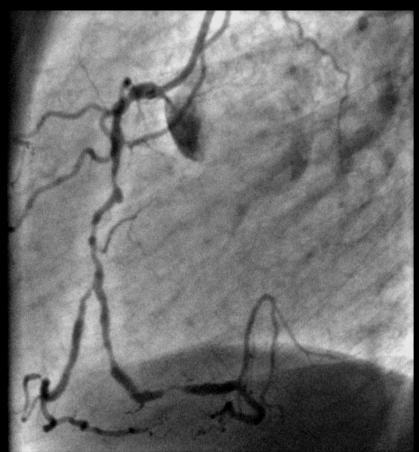
Dip.Cardiotoracico
Istituto Clinico Sant'Ambrogio
Milano





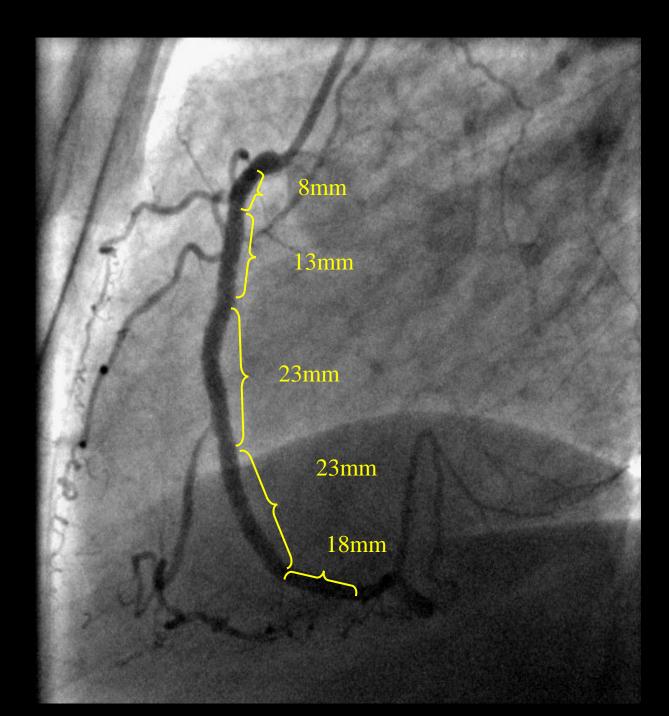








5 stents (sirolimus)



Safety of Short-Term Discontinuation of Antiplatelet Therapy in Patients With Drug-Eluting Stents

Mark J. Eisenberg, MD, MPH; Pierre R. Richard, BSc; Danielle Libersan, PhD; Kristian B. Filion, MSc

Conclusions

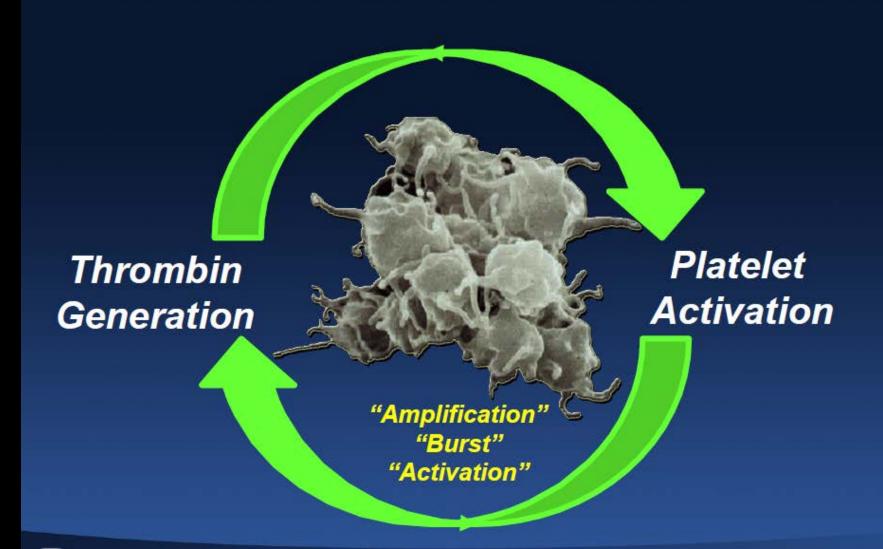
Our study was designed to examine the safety of short-term discontinuation of antiplatelet therapy in patients with DES. We found that very few cases of LST occurred within 10 days of stopping a thienopyridine if ASA was maintained. These data suggest that it may potentially be feasible for patients with DES to stop their thienopyridine therapy for a short period of time if required for invasive or surgical procedures. Although there is still a risk for LST with this strategy, short-term cessation of thienopyridine therapy may be relatively safe if ASA is maintained.

(Circulation. 2009;119:000-000.)

Safety of Short-Term Discontinuation of Antiplatelet Therapy in Patients With Drug-Eluting Stents

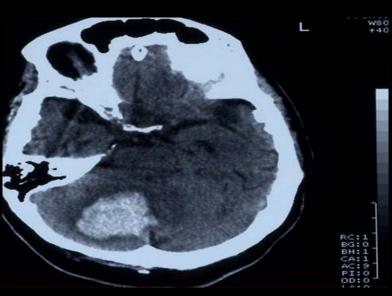
Mark J. Eisenberg, MD, MPH; Pierre R. Richard, BSc; Danielle Libersan, PhD; Kristian B. Filion, MSc

Positive Feedback Loop: Thrombin Begets Platelet Activation Which Begets Thrombin

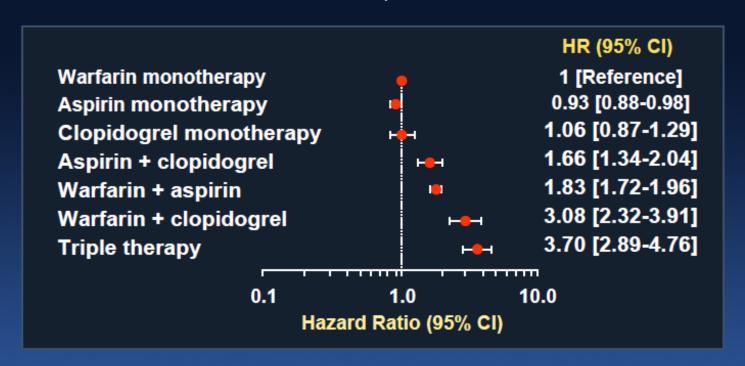








Bleeding Associated with Warfarin, Aspirin, Clopidogrel in Patients with AF n=82,854









573 pts Randomisation 1:1

2/2

Double therapy group:

OAC + 75mg Clopidogrel qd

Triple therapy group:

OAC + 75mg Clopidogrel qd + 80mg Aspirin qd

1 month minimum after BMS

1 year after DES

1 month minimum after BMS

1 year after DES

Follow up: 1 year

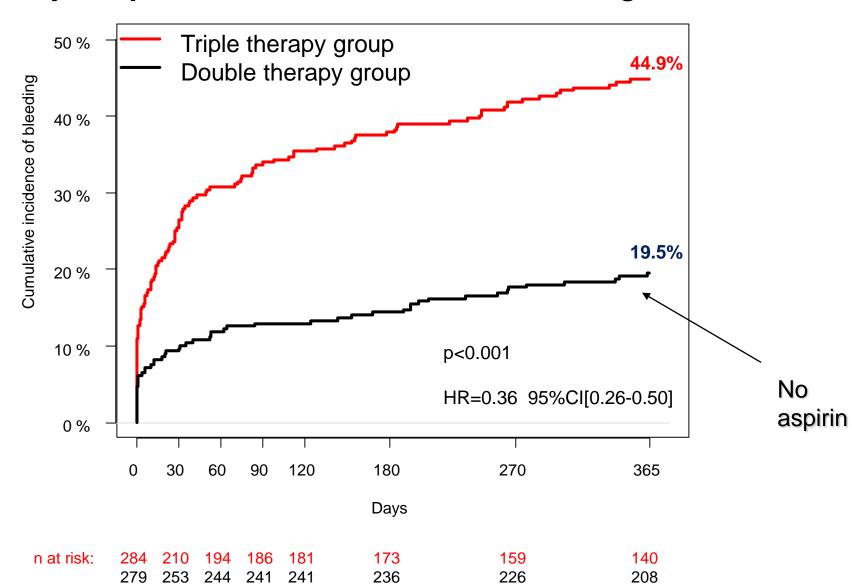
<u>Primary Endpoint:</u> The occurence of all bleeding events (TIMI criteria)

Secondary Endpoints:

- Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation
- All individual components of primary and secondary endpoints

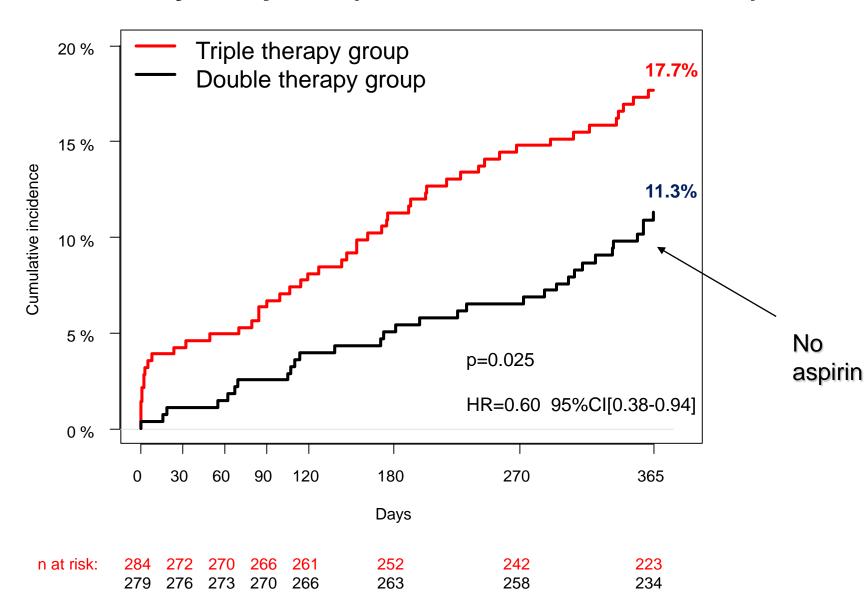
WOEST

Primary Endpoint: Total number of TIMI bleeding events

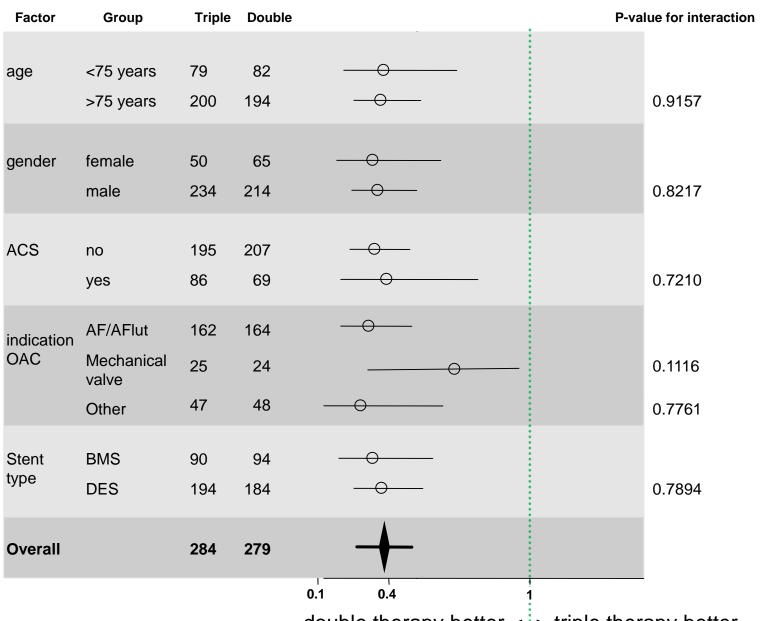




Secondary Endpoint (Death, MI,TVR, Stroke, ST)



WOEST



double therapy better <=> triple therapy better

Bleeding Complications of Triple Antithrombotic Therapy after Percutaneous Coronary Interventions

Nadeen N. Faza, Amgad Mentias, Akhil Parashar, Pulkit Chaudhury, Amr F. Barakat, Shikhar Agarwal, Siddharth Wayangankar, Stephen G. Ellis, E. Murat Tuzcu, and Samir R. Kapadia*

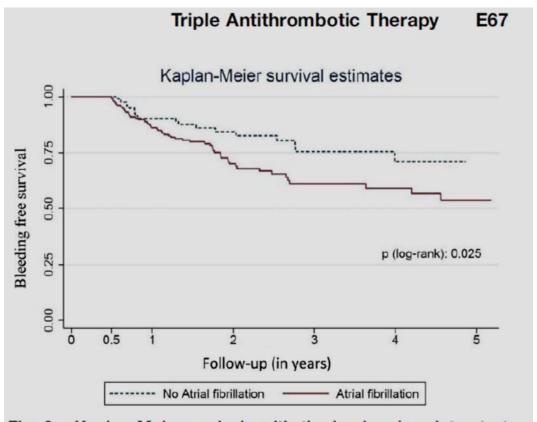
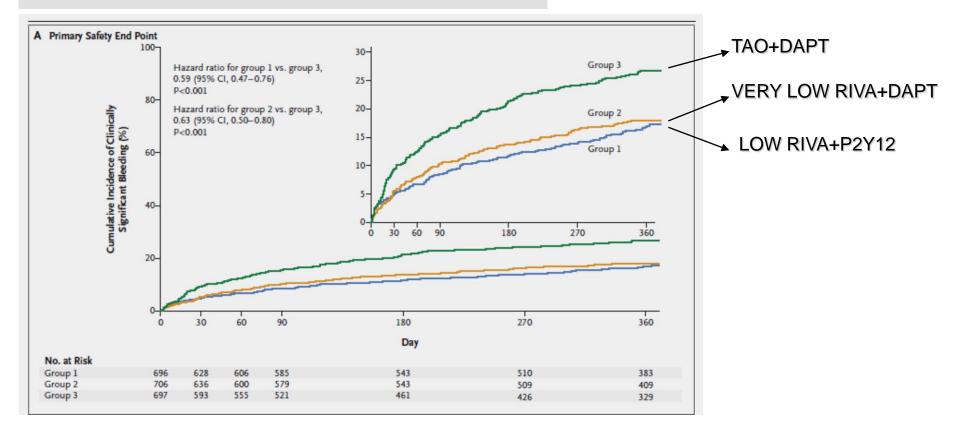


Fig. 3. Kaplan Meier analysis with the landmark point set at six months after index PCI.

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

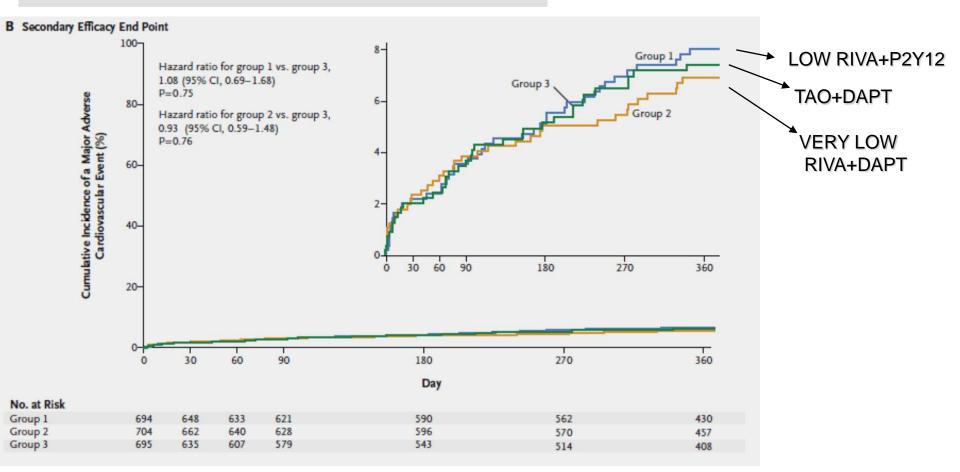




Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

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EDITORIALS



Atrial Fibrillation and PCI — Do We Still Need Aspirin?

Sanjit S. Jolly, M.D., and Madhu K. Natarajan, M.D.

who undergo percutaneous coronary intervention (PCI) is a common clinical dilemma. Approximately 10 to 15% of patients undergoing PCI have a history of atrial fibrillation.1 Patients with atrial fibrillation are at increased risk for stroke, and warfarin has been shown to be superior to dual antiplatelet therapy (DAPT) with clopido-However, DAPT has been shown to be markedly superior to aspirin plus warfarin for the prevention of stent thrombosis.3 This has led to the adoption of triple therapy with DAPT plus warfarin in patients with atrial fibrillation undergoing PCL

The challenge is that triple therapy is associated with high rates of bleeding.1 A potential solution is to eliminate aspirin, and this solution was tested in the WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting), which showed a lower rate of bleeding higher rate of bleeding than either therapy with with clopidogre! plus warfarin than with triple a single P2Y,, inhibitor plus low-dose rivaroxaban therapy.4 Although this finding is intriguing, 573 patients were involved in the WOEST trial, very-low-dose rivaroxaban (2.5 mg twice daily). and larger trials would be needed to ensure the There were no significant differences among the safety of stopping aspirin after PCL

Novel oral anticoagulant drugs have been shown to have at least similar efficacy to warfarin for stroke prevention and to be safer (associated with lower rates of intracranial hemorrhage) than warfarin in patients with atrial fibrillation.5 Specifically, rivaroxaban, an oral factor Xa inhibitor, administered at a dose of 20 mg daily was proven to be noninferior to warfarin for stroke prevention.5 In addition, in a randomized trial involving patients with acute coronary syndromes,

The treatment of patients with atrial fibrillation rivaroxaban administered at a dose of 2.5 or 5 mg twice daily was superior to placebo for the prevention of death from cardiovascular causes, myocardial infarction, or stroke and the prevention of stent thrombosis, but the rate of major bleeding with rivaroxaban plus background DAPT (clopidogrel plus aspirin) was three times as high as the rate with placebo plus background gre! plus aspirin for the prevention of stroke.2 DAPT.6 It is important to note that these doses of rivaroxaban are not approved for use in the United States.

> In this issue of the Journal, Gibson et al.? report the results of the PIONEER AF-PCI trial (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), in which triple therapy with DAPT plus a vitamin K antagonist (warfarin) was shown to be associated with a significantly (15 mg once daily) or therapy with DAPT plus three groups in the rate of death from cardiovascular causes, myocardial infarction, or stroke or the rate of stent thrombosis; however, the trial was not powered to assess these outcomes. Ischemic stroke occurred in 7 patients receiving a P2Y,, inhibitor plus low-dose rivaroxaban, in 6 receiving DAPT plus very-low-dose rivaroxaban, and in 2 receiving DAPT plus warfarin. These differences were not statistically significant; however, the confidence intervals were wide.

PIONEER AF-PCI was designed primarily to

EDITORIALS



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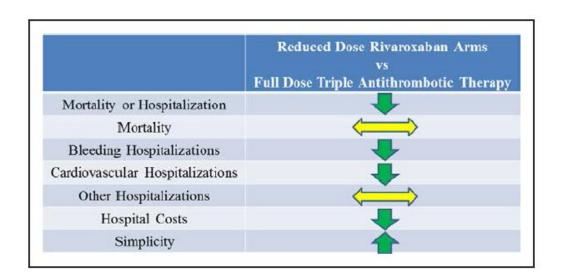
According to the results of PIONEER AF-PCI, the elimination of aspirin from triple therapy or the use of very-low-dose rivaroxaban with DAPT resulted in a lower rate of bleeding than did the use of triple therapy. However, the efficacy of these strategies for the prevention of stroke or stent thrombosis is still uncertain.

EDITORIAL

O PIONEERs!

The Beginning of the End of Full-Dose Triple Therapy with Warfarin?

Deepak L. Bhatt, MD, MPH



EDITORIAL

O PIONEERs!

The Beginning of the End of Full-Dose Triple Therapy with Warfarin?

Deepak L. Bhatt, MD, MPH

For the time being, in patients not in clinical trials, full-dose oral triple therapy with dual antiplatelet agents and full-dose anticoagulation should be avoided as a routine practice.

EDITORIALS



Atrial Fibrillation and PCI — Do We Still Need Aspirin?

Sanjit S. Jolly, M.D., and Madhu K. Natarajan, M.D.

Table 1. Major Randomized Trials Comparing Anticoagulation Strategies for Patients with Atrial Fibrillation Undergoing PCI.*											
Trial	No. of Participants	Control	Intervention	Primary Outcome	ClinicalTrials.gov No.						
REDUAL-PCI	2800	Aspirin, P2Y ₁₂ inhibitor, and vitamin K antagonist	Dabigatran (either 110 mg twice daily or 150 mg twice daily) plus P2Y ₁₂ inhibitor	Major bleeding and clinically relevant nonmajor bleeding, defined ac- cording to ISTH criteria	NCT02164864						
ENTRUST-AF-PCI	1500	Aspirin, P2Y ₁₂ inhibitor, and vitamin K antagonist	Edoxaban (60 mg once daily) plus P2Y ₁₂ inhibitor	Major bleeding and clinically relevant nonmajor bleeding, defined ac- cording to ISTH criteria	NCT02866175						
AUGUSTUS	4600	Either aspirin or vitamin K antagonist (2-by-2 factorial design)	Either apixaban (5 mg twice daily) or placebo	Major bleeding and clinically relevant nonmajor bleeding, defined according to ISTH criteria	NCT02415400						

RE-DUAL PCI

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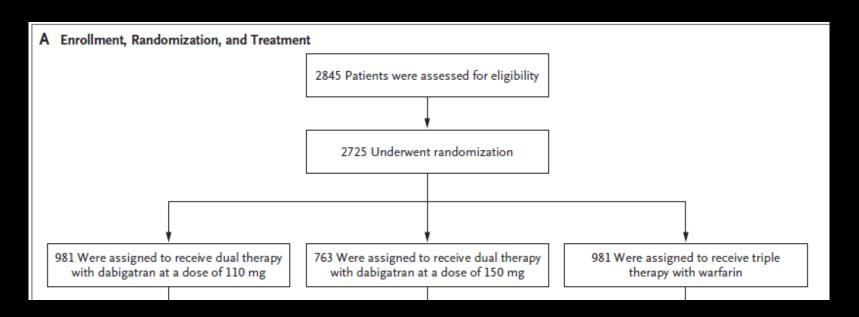
ORIGINAL ARTICLE

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H.,



August 2017



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August 2017

RE-DUAL PCI

Italy: L. Bolognese, M.T. Cardillo, F. Crea, C. Cuccia, C. Mauro, M. Menichelli, G. Colonna,

A. Montinaro, C. Moretti, G. Musumeci, M. Senni, C. Tamburino, N. Maddestra,

F. Romeo, M. Tespili, S. Berti, D. Nassiacos, and A. Picchi.

RE-DUAL PCI tested the safety and efficacy of two regimens of dual therapy with dabigatran without ASA vs triple therapy with warfarin

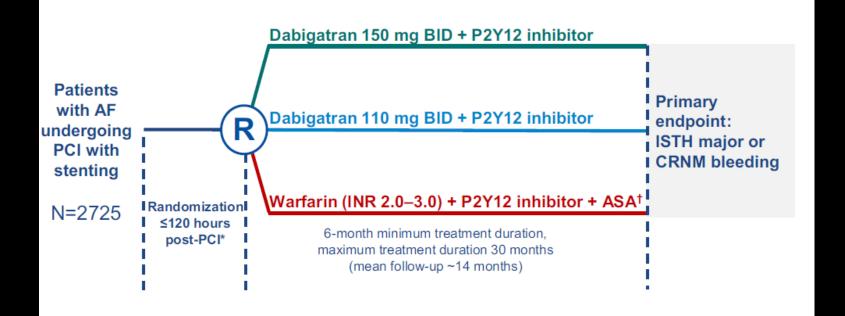


Table 1. Baseline Characteristics of the Patients.*

Characteristic

Other

Male sex — no. (%)

Elderly age group - no. (%):

Age -yr

()	· /	\ /	· /	· /
Diabetes mellitus — no./total no. (%)	362/981 (36.9)	371/980 (37.9)	260/763 (34.1)	303/763 (39.7)
Previous stroke — no./total no. (%)	74/981 (7.5)	100/980 (10.2)	52/763 (6.8)	77/763 (10.1)
CHA₂DS₂-VASc score§	3.7±1.6	3.8±1.5	3.3±1.5	3.6±1.5
HAS-BLED score¶	2.7±0.7	2.8±0.8	2.6±0.7	2.7±0.8
Creatinine clearance — ml/min	76.3±28.9	75.4±29.1	83.7±31.0	81.3±29.6
Previous myocardial infarction — no. (%)	237 (24.2)	268 (27.3)	194 (25.4)	211 (27.6)
Previous PCI — no./total no. (%)	326/981 (33.2)	347/980 (35.4)	239/763 (31.3)	272/763 (35.6)
Previous CABG — no./total no. (%)	97/981 (9.9)	111/980 (11.3)	79/763 (10.4)	87/763 (11.4)
Indication for PCI — no. (%)				
Stable angina or positive stress test	433 (44.1)	429 (43.7)	320 (41.9)	339 (44.4)
Acute coronary syndrome	509 (51.9)	475 (48.4)	391 (51.2)	369 (48.3)
Staged procedure	156 (15.9)	168 (17.1)	138 (18.1)	134 (17.5)

Dual Therapy

with Dabigatran,

110 mg

(N = 981)

71.5±8.9

225 (22.9)

728 (74.2)

Dual Therapy

with Dabigatran,

150 mg

(N = 763)

68.6±7.7

8 (1.0)

592 (77.6)

65 (8.5)

Triple Therapy

with Warfarin

(N = 981)

71.7±8.9

225 (22.9)

750 (76.5)

62 (6.3)

Corresponding

Triple Therapy

with Warfarin†

(N = 764)

68.8±7.7

8 (1.0)

594 (77.7)

50 (6.5)

43 (4.4)

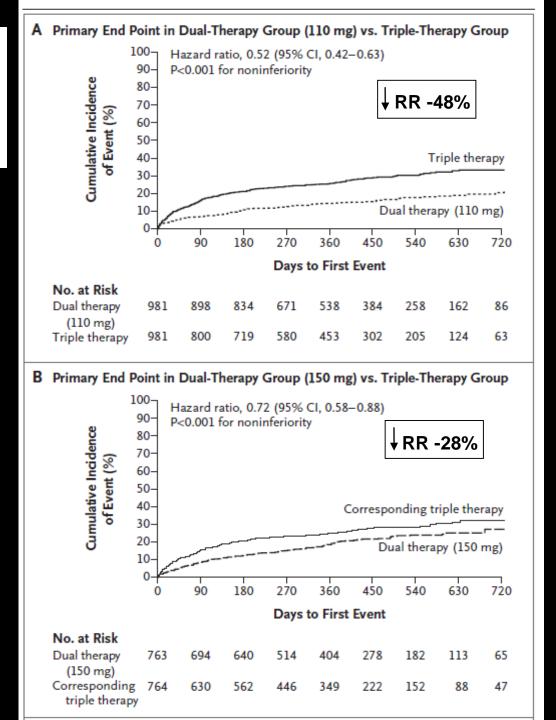
[†] The corresponding triple-therapy group included only patients who had been eligible to be assigned to the 150-mg dual-therapy group (i.e., did not include elderly patients outside the United States).

‡ Elderly was defined as 80 years of age or older (≥70 years of age in Japan). Stratification according to age group was performed with the use of an interactive voice-response system.

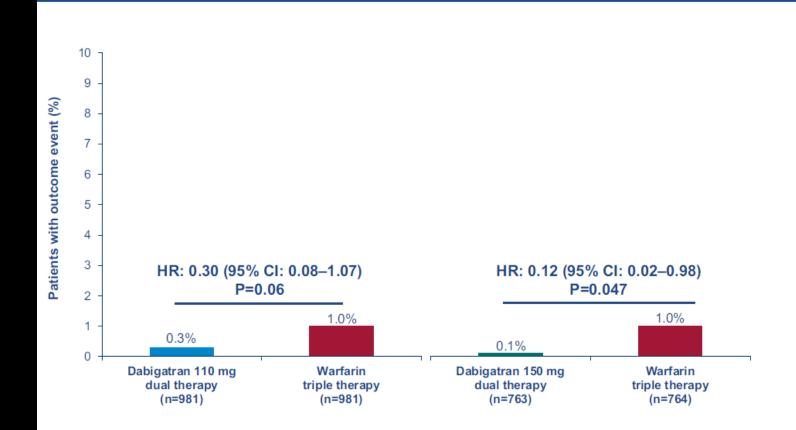
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ORIGINAL ARTICLE

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

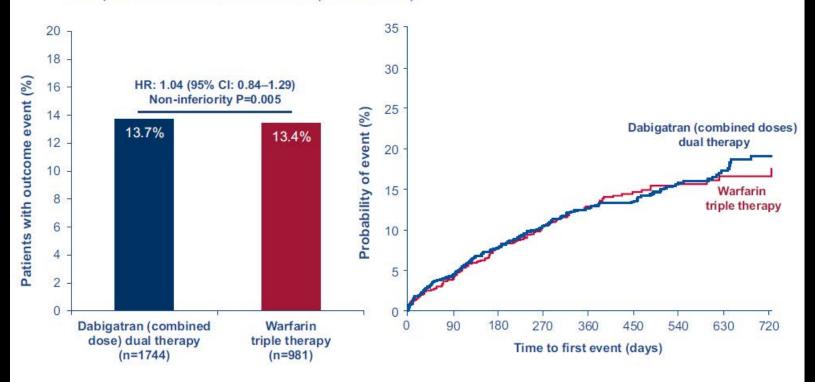


Intracranial haemorrhage: fewer events with dabigatran dual therapy



Dabigatran dual therapy was non-inferior to warfarin triple therapy in the composite efficacy endpoint

Composite endpoint of death or thromboembolic event (MI, stroke or systemic embolism) or unplanned revascularization (PCI/CABG)



CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; Cannon et al. N Engl J Med 2017; Cannon et al ESC 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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Table 3. Efficacy End Points.*												
End Point			abigatran (Co py with Warf	Dual Therapy with Dabigatran (110 mg) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (150 mg) vs. Triple Therapy with Warfarin				
	Combined Dual- The rapy Groups (N=1744)	Triple- The rapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	110-mg Dual- Therapy Group (N=981)	Triple- Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	150-mg Dual- Therapy Group (N=763)	Corresponding Triple-Therapy Group (N=764)	Hazard Ratio (95% CI)	P Value
no. (%)				no. (%)					no. (%)			
Composite efficacy end point: thromboembolic events, death, or unplanned revas- cularization	239 (13.7)	131 (13.4)	1.04 (0.84–1.29)	0.74 (0.005 for noninferiority)	149 (15.2)	131 (13.4)	1.13 (0.90–1.43)	0.30	90 (11.8)	98 (12.8)	0.89 (0.67–1.19)	0.44
Thromboembolic events or death	168 (9.6)	83 (8.5)	1.17 (0.90–1.53)	0.25 (0.11 for noninferiority)	108 (11.0)	83 (8.5)	1.30 (0.98–1.73)	0.07	60 (7.9)	60 (7.9)	0.97 (0.68–1.39)	0.88
Death					55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Myocardial infarction					44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stroke					17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Definite stent thrombosis					15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

ORIGINAL ARTICLE

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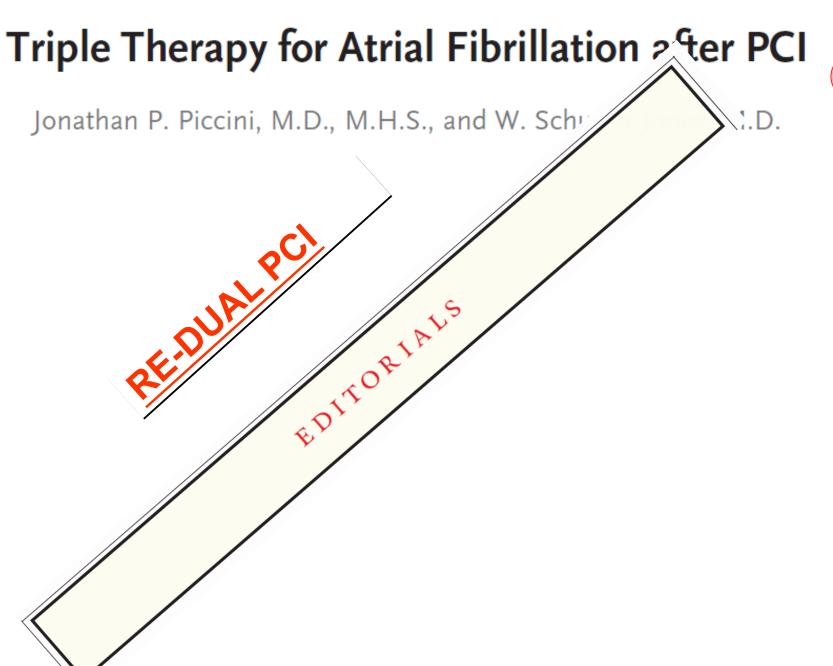
ORIGINAL ARTICLE

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Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H.,

CONCLUSIONS

Among patients with atrial fibrillation who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with dabigatran and a P2Y₁₂ inhibitor than among those who received triple therapy with warfarin, a P2Y₁₂ inhibitor, and aspirin. Dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events. (Funded by Boehringer Ingelheim; RE-DUAL PCI Clinical Trials.gov number, NCT02164864.)



EDITORIALS



Atrial Fibrillation and PCI — Do We Still Need Aspirin?

Sanjit S. Jolly, M.D., and Madhu K. Natarajan, M.D.

The treatment of patients with atrial fibrillation rivaroxaban administered at a dose of 2.5 or 5 mg who undergo percutaneous coronary intervention (PCI) is a common clinical dilemma. Approximately 10 to 15% of patients undergoing PCI have a history of atrial fibrillation.1 Patients with atrial fibrillation are at increased risk for stroke, and warfarin has been shown to be superior to dual antiplatelet therapy (DAPT) with clopidogrel plus aspirin for the prevention of stroke.2 However, DAPT has been shown to be markedly superior to aspirin plus warfarin for the prevention of stent thrombosis,3 This has led to the adoption of triple therapy with DAPT plus warfarin in patients with atrial fibrillation undergoing PCL

The challenge is that triple therapy is associated with high rates of bleeding.1 A potential solution is to eliminate aspirin, and this solution was tested in the WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting), which showed a lower rate of bleeding with clopidogrel plus warfarin than with triple therapy.4 Although this finding is intriguing, 573 patients were involved in the WOEST trial, and larger trials would be needed to ensure the There were no significant differences among the safety of stopping aspirin after PCI.

Novel oral anticoagulant drugs have been shown to have at least similar efficacy to warfarin for stroke prevention and to be safer (associated with lower rates of intracranial hemorrhage) than warfarin in patients with atrial fibrillation.5 Specifically, rivaroxaban, an oral factor Xa inhibitor, administered at a dose of 20 mg daily was proven to be noninferior to warfarin for stroke prevention,5 In addition, in a randomized trial involving patients with acute coronary syndromes,

twice daily was superior to placebo for the prevention of death from cardiovascular causes, myocardial infarction, or stroke and the prevention of stent thrombosis, but the rate of major bleeding with rivaroxaban plus background DAPT (clopidogrel plus aspirin) was three times as high as the rate with placebo plus background DAPT.6 It is important to note that these doses of rivaroxaban are not approved for use in the United States.

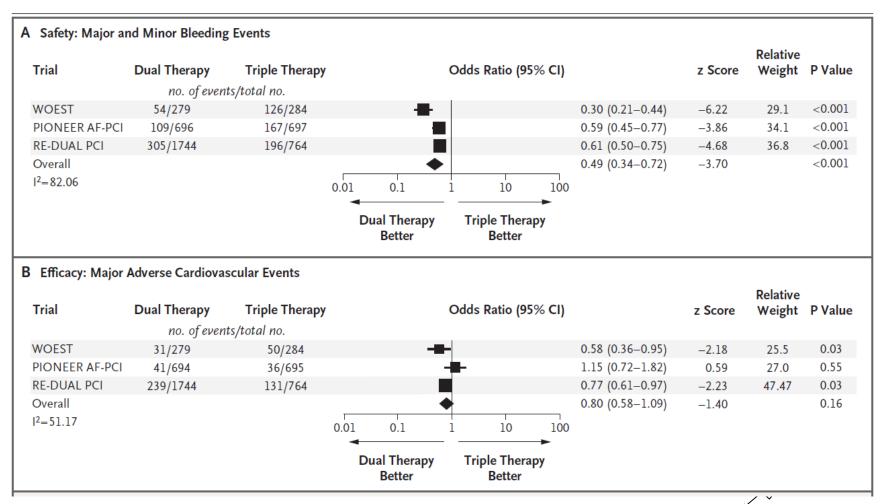
In this issue of the Journal, Gibson et al.? report the results of the PIONEER AF-PCI trial (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention), in which triple therapy with DAPT plus a vitamin K antagonist (warfarin) was shown to be associated with a significantly higher rate of bleeding than either therapy with a single P2Y,, inhibitor plus low-dose rivaroxaban (15 mg once daily) or therapy with DAPT plus very-low-dose rivaroxaban (2.5 mg twice daily). three groups in the rate of death from cardiovascular causes, myocardial infarction, or stroke or the rate of stent thrombosis; however, the trial was not powered to assess these outcomes. Ischemic stroke occurred in 7 patients receiving a P2Y,, inhibitor plus low-dose rivaroxaban, in 6 receiving DAPT plus very-low-dose rivaroxaban, and in 2 receiving DAPT plus warfarin. These differences were not statistically significant; however, the confidence intervals were wide.

PIONEER AF-PCI was designed primarily to

Triple Therapy for Atrial Fibrillation after PCI



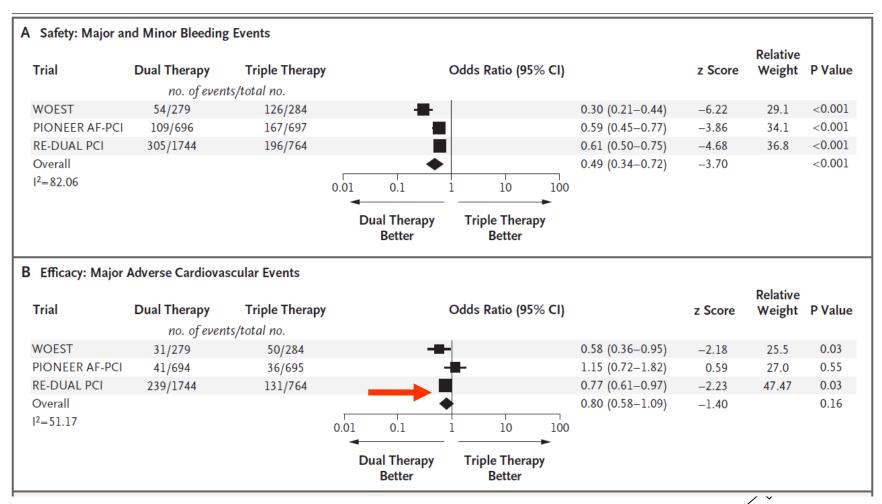
Jonathan P. Piccini, M.D., M.H.S., and W. Schuyler Jones, M.D.



Triple Therapy for Atrial Fibrillation after PCI



Jonathan P. Piccini, M.D., M.H.S., and W. Schuyler Jones, M.D.



Triple Therapy for Atrial Fibrillation after PCI



Jonathan P. Piccini, M.D., M.H.S., and W. Schuyler Jones, M.D.

However, the consistency across these three major trials and the significantly lower risk of bleeding with dual therapy make it hard to argue that triple therapy should be used routinely. The aggregate evidence suggests that the net clinical benefit of dual therapy should give cardiologists confidence to drop aspirin when they are using a contemporary PCI strategy with drug-eluting stents. Moving forward, the key questions will be: What combination of drugs should be included in dual therapy, and how will we test this strategy?

Sistema Tolemaico

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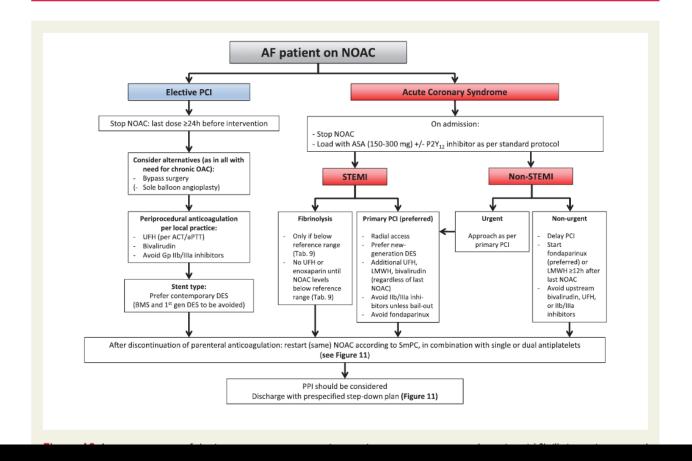


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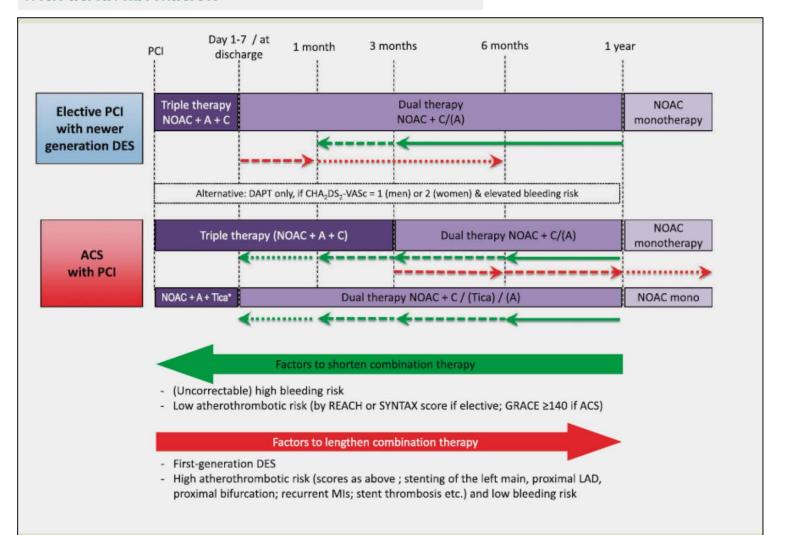








The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation





No published data ...not existing data



While awaiting the results of trials with apixaban and edoxaban the 150 mg dabigatran dual therapy appears to be the preferred choice over triple therapy for the majority of patients based on both the results from RE-LY²⁸ and RE-DUAL PCI¹⁴¹; dual therapy using 110 mg dabigatran or rivaroxaban 15 mg (10 mg in renal insufficiency) appears as a viable alternative for patients with estimated high bleeding risk—provided that dabigatran or rivaroxaban per se appear as a good choice for this individual patient based on age (see **chapter 18.1**), comorbidities (e.g. renal insufficiency; see **chapter 6**), interactions (see **chapter 5**), and others.

Patients with A.F. that <u>underwent PCI</u>
(Nao+PY12 i)

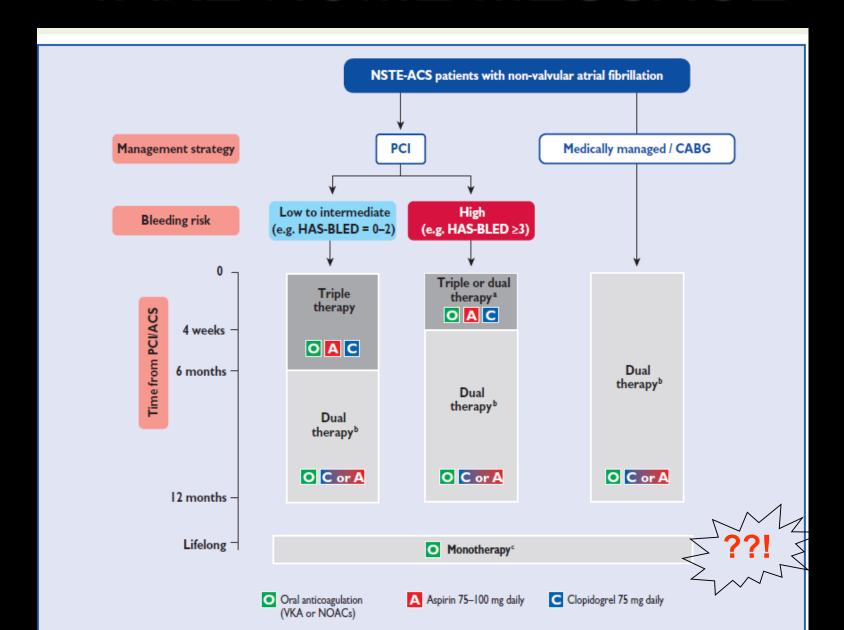
Safety — OK REDUAL, PIONEER

Efficacy — OK REDUAL

..until now the only DOAC that showed reduction of bleeding events and total cardiovascular events is Dabigatran..
Cannon C.P.

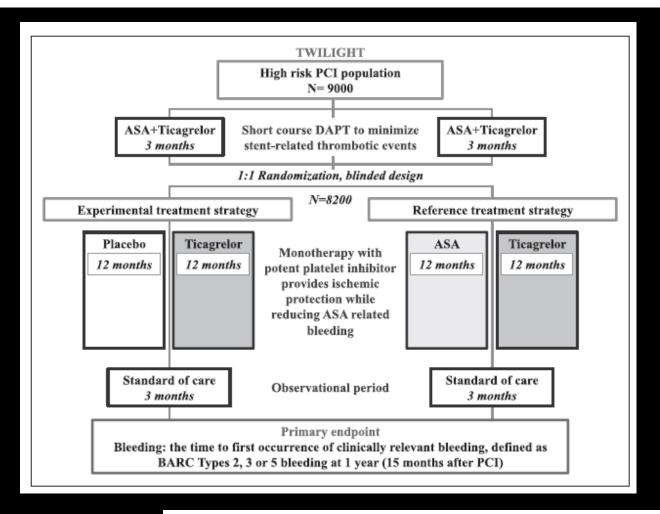
ESC 2017 Barcelona





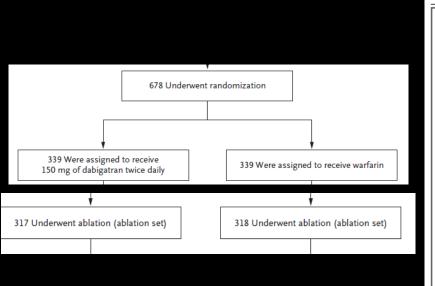
A Critical Appraisal of Aspirin in Secondary Prevention

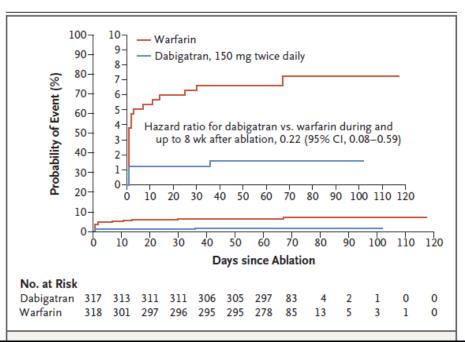
Is Less More?



Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation

Hugh Calkins, M.D., Stephan Willems, M.D., Edward P. Gerstenfeld, M.D., Atul Verma, M.D., Richard Schilling, M.D., Stefan H. Hohnloser, M.D., Ken Okumura, M.D., Ph.D., Harvey Serota, M.D., Matias Nordaby, M.D., Kelly Guiver, M.Sc., Branislav Biss, M.D., Marc A. Brouwer, M.D., Ph.D., and Massimo Grimaldi, M.D., Ph.D., for the RE-CIRCUIT Investigators*





Grazie per l'attenzione

