Terapia combinata anticoagulanti-antiaggreganti

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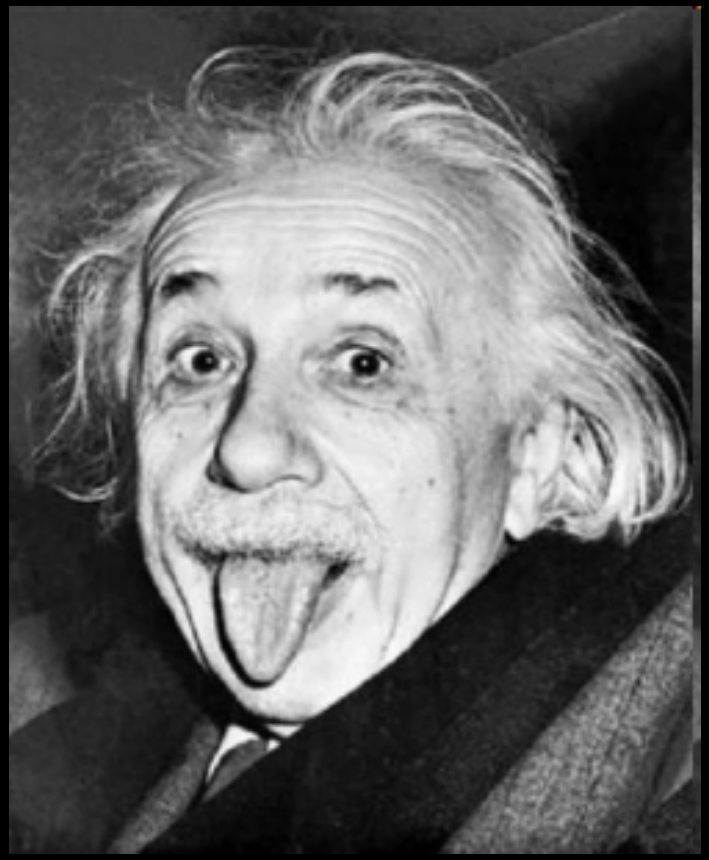
FCSA, Bologna – 5 ottobre 2017



"Non pretendiamo che le cose cambino se continuiamo a farle nello stesso modo"

Albert Einstein 1879-1955

Giovanni M, 76 anni

- NSTEMI con coronarie indenni: trombo-aspirazione; episodio di FA
- Dimesso in terapia con: ASA, Clopidogrel, Enoxaparina 8,000x2, Warfarin, Atorvastatina 40, Omeprazolo, Amiodarone, Metoprololo
- A 24 ore dalla dimissione accesso in PS: dolore addome e arto inf sin, Hb 7.8 e Creatinina 1.55
- Ematoma m. ileo-psoas 10x8x19 cm

Premesse

- L’associazione antiaggreganti-anticoagulanti viene proposta:
  - per incrementare l’efficacia
  - per nuova indicazione a terapia antiaggregante in paziente già anticoagulato (o vice-versa)
- Tuttavia, l’efficacia antitrombotica non può essere disgiunta da un incremento del rischio emorragico
- L’associazione inizialmente più studiata è stata, ovviamente, ASA + VKA

VKA + ASA: in quali pazienti?

- Una metanalisi del 2007 evidenziava che:
  - il vantaggio clinico riguarda i pazienti con protesi valvolari meccaniche
  - non vi sono vantaggi per i pazienti con sola FA (OR 0.99, 95% CI 0.47-2.07)
  - VKA+ASA determina un aumentato rischio emorragico (OR 1.43, 95% CI 1.00-2.02)

Dentali F et al. Arch Intern Med 2007;167:117-124

Antiplatelet and anticoagulation for patients with prosthetic heart valves

Massel DR & Little SH, Cochrane Syst Rev. 2013

- In total, 4122 patients, 13 studies (published between 1971 and 2011)
- The addition of an antiplatelet agent:
  - reduced thromboembolic events (OR 0.43, CI 0.32-0.59; P < 0.00001) and total mortality (OR 0.57, CI 0.42-0.78; P = 0.0004)
  - increased major bleeding (OR 1.58, 95% CI 1.14 to 2.18; P = 0.006)


HEALTH TECHNOLOGY ASSESSMENT
VOLUME 17 ISSUE 30 JULY 2013
ISSN 1366-5278
Combined anticoagulation and antiplatelet therapy for high-risk patients with atrial fibrillation: a systematic review
DA Lane, S Raichand, D Moore, M Connock, A Fry-Smith and DA Fitzmaurice on behalf of the Steering Committee
NHS
National Institute for Health Research
DOI 10.3310/hta17300

208 pagine !

Conclusions

- There are not sufficient data from the 5 randomised comparisons and 18 non-randomised comparisons to conclude whether or not there are patients with AF who would benefit from combined ACT and APT compared with ACT alone

Dabigatran *vs* Warfarin in Patients with Atrial Fibrillation

Moia M & Mannucci PM
N Engl J Med, 2009, letter

- The yearly incidence of major bleeding in the warfarin group was 3.36%
- We surmise that the high percentage of patients concomitantly treated with aspirin (more than 20%) contributed substantially to the unusually high incidence of bleeding

Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Trial

Antonio L. Dans, MD, MSc; Stuart J. Connolly, MD; Lars Wallentin, MD, PhD; Sean Yang, MSc; Juliet Nakamya, PhD; Martina Brueckmann, MD; Michael Ezekowitz, MBChB, DPhil; Jonas Oldgren, MD, PhD; John W. Eikelboom, MD; Paul A. Reilly, PhD; Salim Yusuf, DPhil, FRCPC, FRSC

Circulation. 2013;127:634-640

- Concomitant antiplatelet drugs appeared to increase the risk for major bleeding in RE-LY without affecting the advantages of dabigatran over warfarin

Terapia combinata nei pazienti con FA

- Nonostante non vi sia evidenza di una migliore efficacia, vi è un progressivo incremento dei pazienti trattati con VKA (o DOAC) +ASA

Trials con i DOAC nella FA: % di pazienti trattati con ASA (ache nel braccio di controllo)

DOAC	Studio, anno	% ASA +
ximelagatran	SPORTIF III, 2003	10
ximelagatran	SPORTIF V, 2005	15
idraparinux	Amadeus, 2008	20
dabigatran	RE-LY, 2009	21
rivaroxaban	ROCKET, 2011	18
apixaban	ARISTOTLE, 2011	31
edoxaban	Engage AF, 2013	29

DOAC in patients with AF: percentage of major bleeding in patients without (-) or with (+) combined DOAC-ASA treatment

Drug	Trial	Major bleeding, %/y ASA -	Major bleeding, %/y ASA +
Ximelagatran	SPORTIF	2.35	5.09
Dabigatran etexilate	RE-LY 110mg	2.2	3.9
	150mg	2.6	4.4
Rivaroxaban	Real life (Tamayo)	2.2	2.9
Apixaban	Aristotle	1.90	2.70
Edoxaban 30 mg	Engage AF	1.46	2.00
Edoxaban 60 mg	Engage AF	2.41	3.62

VKA + antiaggreganti: elevato rischio emorragico

- 2 studi Danesi evidenziano l'elevato rischio di emorragie gravi nei pazienti trattati con antiaggreganti-anticoagulanti (ricovero in ospedale con diagnosi di emorragia fatale o non-fatale)
- L'aggiunta di un secondo antiaggregante incrementa ulteriormente il rischio

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

Lancet 2009; 374: 1967–74

	Incidence (% per person-year)	Unadjusted risk ratio (95% CI)	Number needed to harm§	
			Unadjusted	Adjusted¶
Monotherapy				
Aspirin alone	2·6%	Reference	Reference	Reference
Clopidogrel alone	4·6%	1·75 (1·75–1·76)	50·8	115·7
Vitamin K antagonist alone	4·3%	1·63 (1·62–1·65)	60·2	165·9
Dual therapy				
Aspirin plus clopidogrel	3·7%	1·43 (1·43–1·43)	89·3	81·2
Aspirin plus vitamin K antagonist	5·1%	1·94 (1·94–1·95)	40·5	45·4
Clopidogrel plus vitamin K antagonist	12·3%	4·68 (4·64–4·74)	10·4	15·2
Triple therapy				
Aspirin, clopidogrel, and vitamin K antagonist	12·0%	4·57 (4·55–4·61)	10·7	12·5

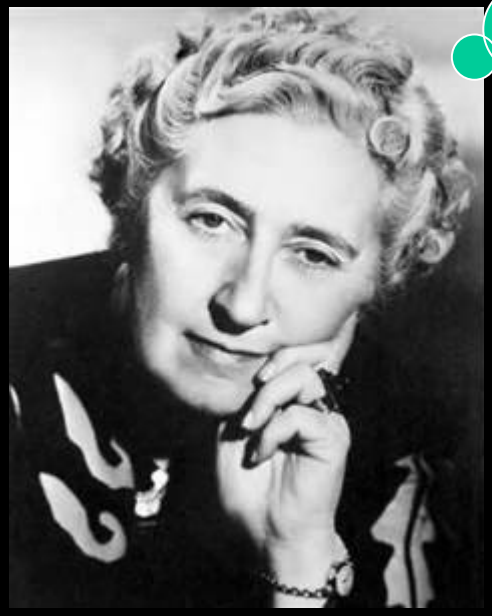
Antithrombotic regimens in patients with indication for long-term anticoagulation undergoing coronary interventions-systematic analysis, review of literature, and implications on management.

Deshmukh A et al, Am J Ther 2013;20:654-63

- Ten retrospective studies, 1 post hoc analysis of a major registry, and 2 prospective studies

- Major bleeding at 1 year:
  - Triple antithrombotic therapy: 5,2 %
  - Dual antiplatelet therapy: 2,4 %

*un **indizio** è un **indizio**,*
***due indizi** sono una*
coincidenza, ma
tre indizi fanno una
prova



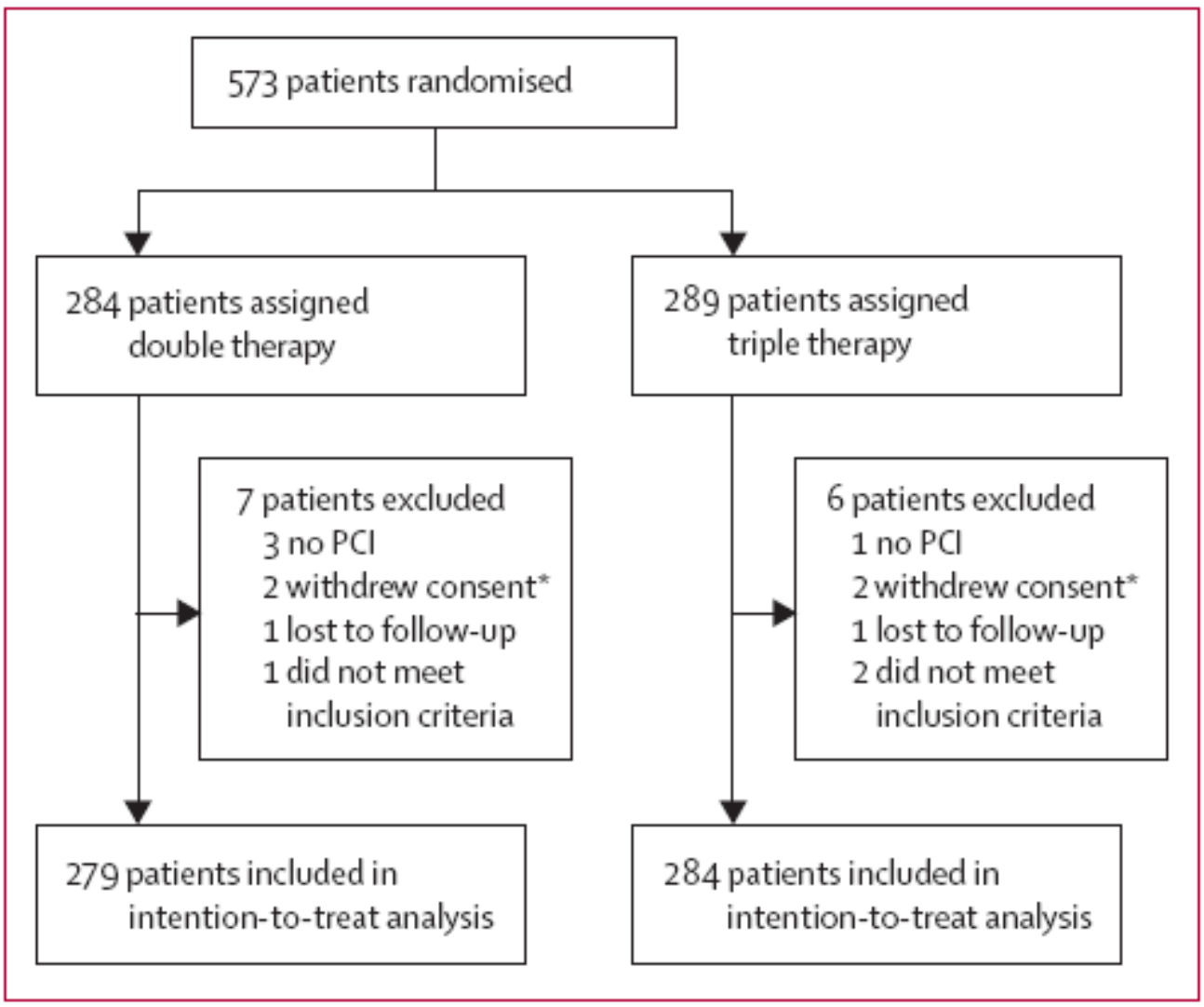
Agatha Christie

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Willem J M Dewilde, Tom Oirbans, Freek W A Verheugt, Johannes C Kelder, Bart J G L De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius A C M Heestermans, Marije M Vis, Jan G P Tijsen, Arnoud W van 't Hof, Jurriën M ten Berg, for the WOEST study investigators

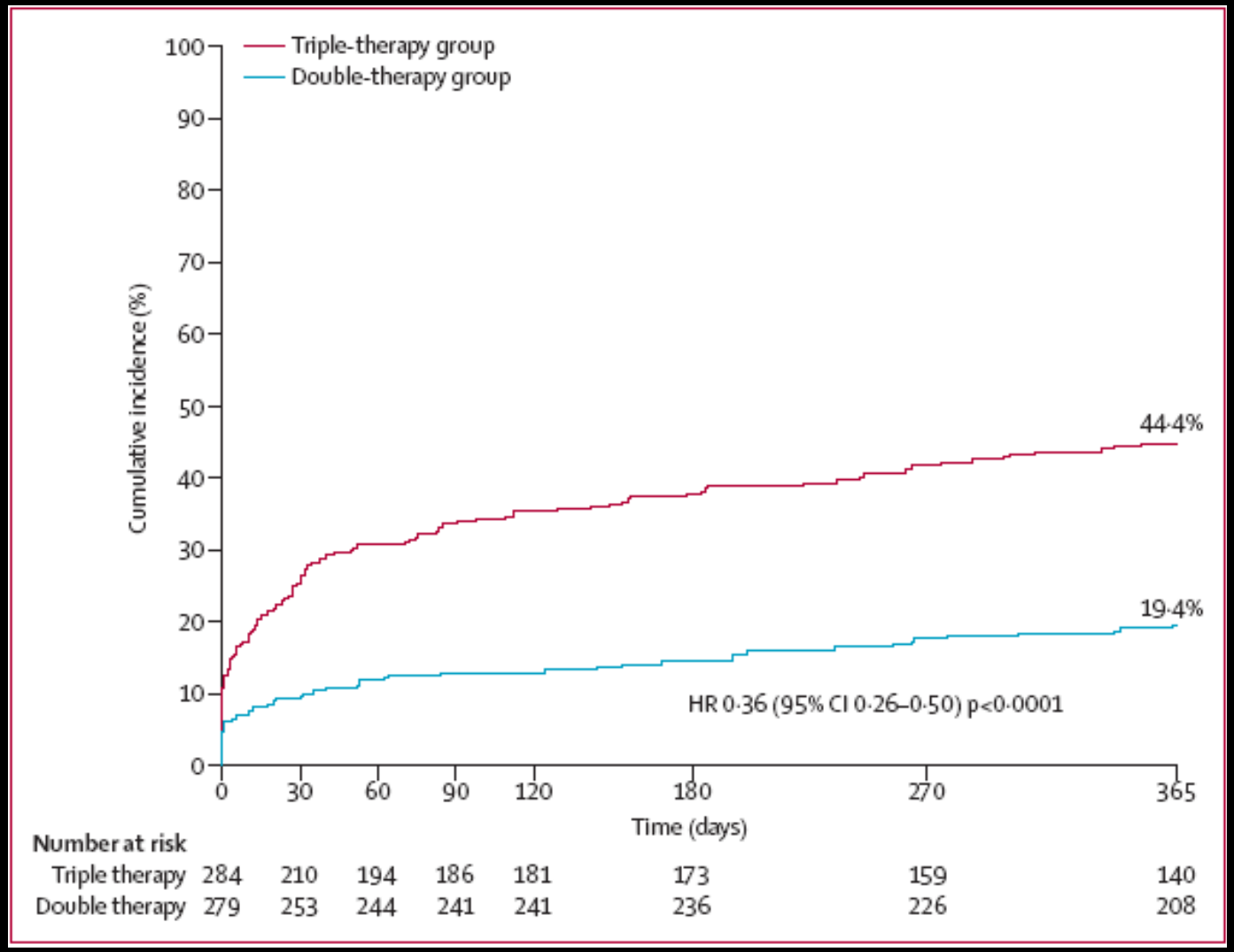
WOEST Study - Lancet 2013; 381: 1107–15

WOEST Study Design



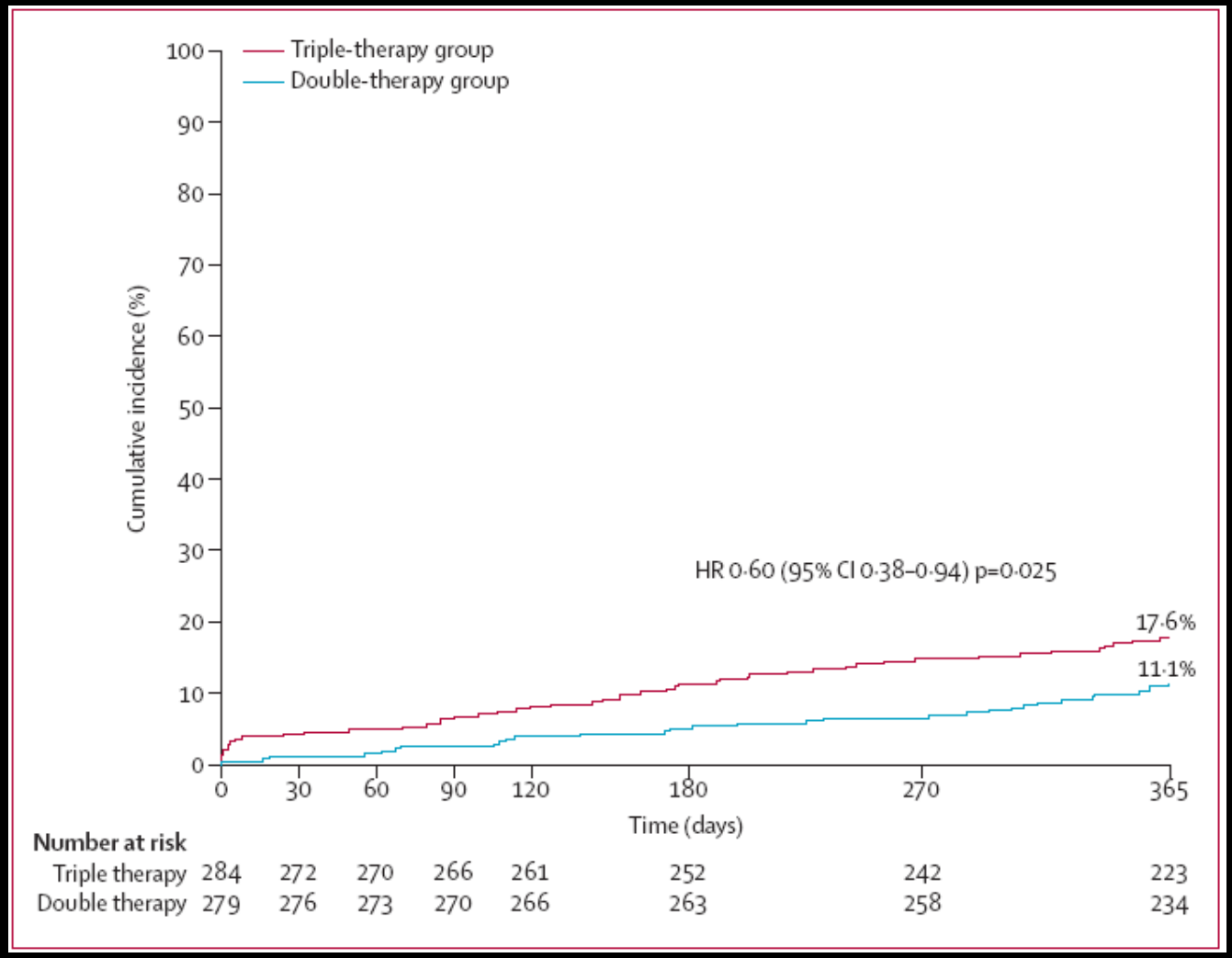
Lancet 2013; 381: 1107–15

Incidence of the primary endpoint (any bleeding)



Lancet 2013; 381: 1107–15

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



Lancet 2013; 381: 1107–15

Conclusion

- Clopidogrel + VKA was associated with a significantly lower risk of bleeding complications than Clopidogrel + ASA + VKA
- No evidence of increased thrombotic risk without the use of ASA

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 22, 2016 VOL. 375 NO. 25

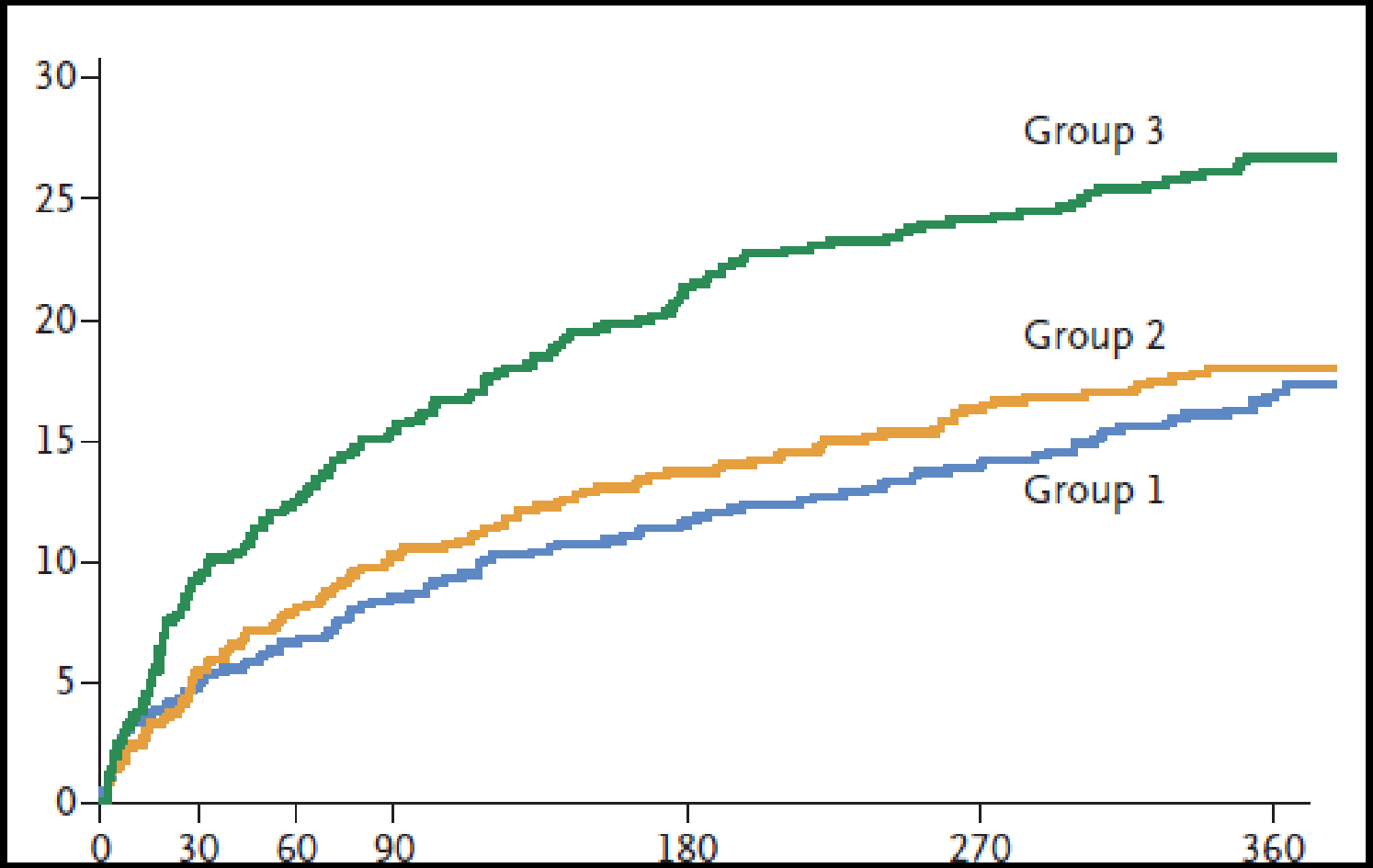
Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

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.

PIONEER AF-PCI Study

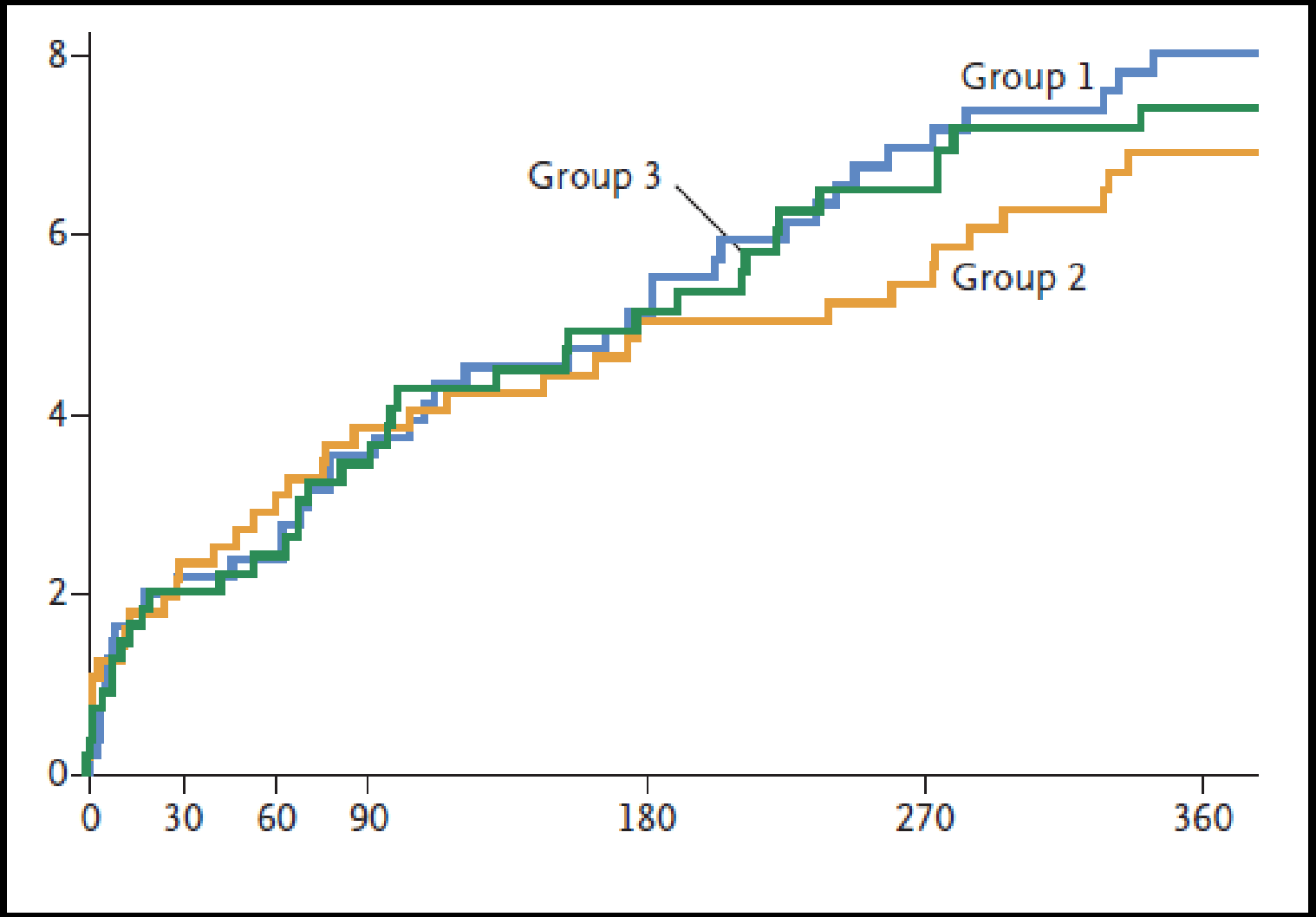
- 2024 patients: AF with PCI
- Group 1: rivaroxaban 15 mg + P2Y
- Group 2: rivaroxaban 2,5 x 2 + P2Y
- Group 3: warfarin (INR 2-3) + DAPT
- Primary end point: clinically significant bleeding
- Conclusion: lower rate of bleeding for rivaroxaban groups

Safety



Group 1: rivaroxaban 15 mg + P2Y
Group 2: rivaroxaban 2,5 x 2 + P2Y
Group 3: warfarin (INR 2-3) + DAPT

Efficacy



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Group 3: warfarin (INR 2-3) + DAPT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

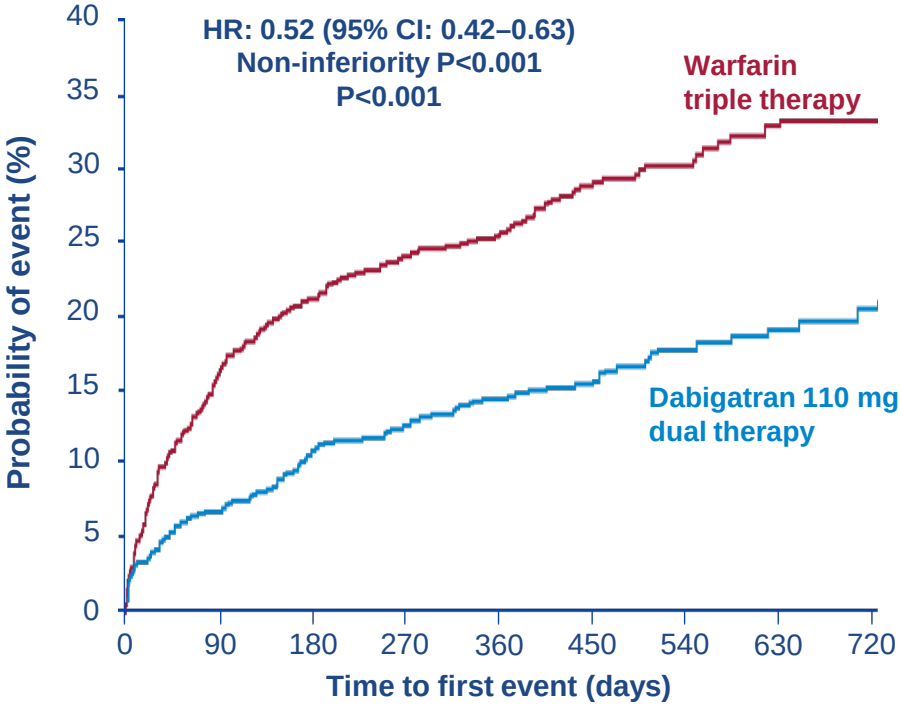
Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D., Stephen G. Ellis, M.D., Takeshi Kimura, M.D., Michael Maeng, M.D., Ph.D., Bela Merkely, M.D., Uwe Zeymer, M.D., Savion Gropper, M.D., Ph.D., Matias Nordaby, M.D., Eva Kleine, M.Sc., Ruth Harper, Ph.D., Jenny Manassie, B.Med.Sc., James L. Januzzi, M.D., Jurrien M. ten Berg, M.D., Ph.D., P. Gabriel Steg, M.D., and Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*

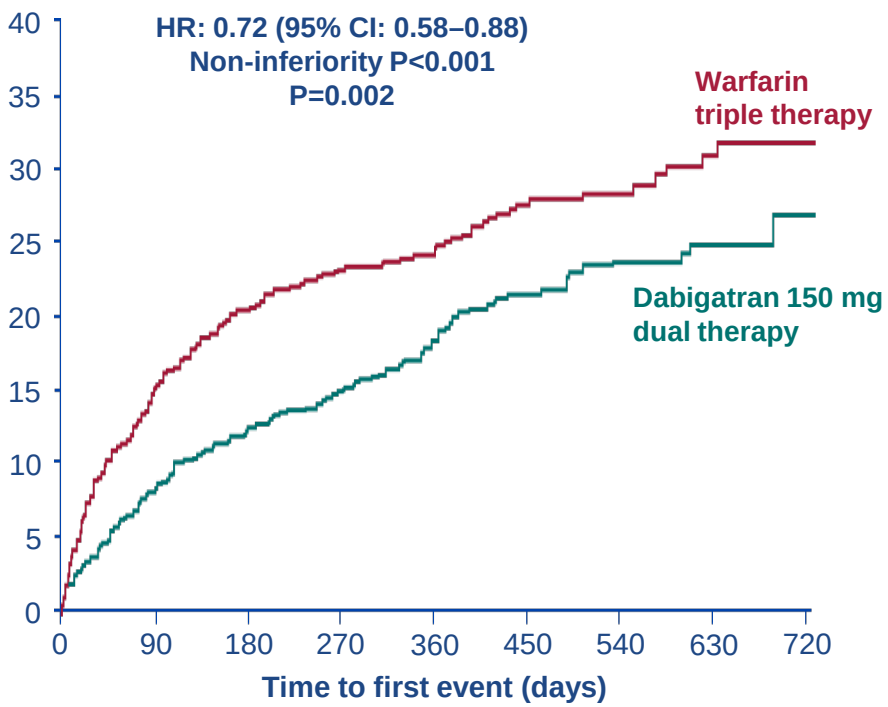
NEJM, August 2017

RE-DUAL PCI Study

- 2725 patients: AF with PCI
- Group 1: dabigatran 110 mg x 2 + P2Y
- Group 2: dabigatran 150 mg x 2 + P2Y
- Group 3: warfarin (INR 2-3) + DAPT
- Primary end point: major or clinically relevant non major bleeding
- Conclusions: lower rate of bleeding for dabigatran, non inferior to triple therapy for thrombotic events

Significantly lower rates of ISTH major bleeding or CRNMBE with dabigatran dual therapy



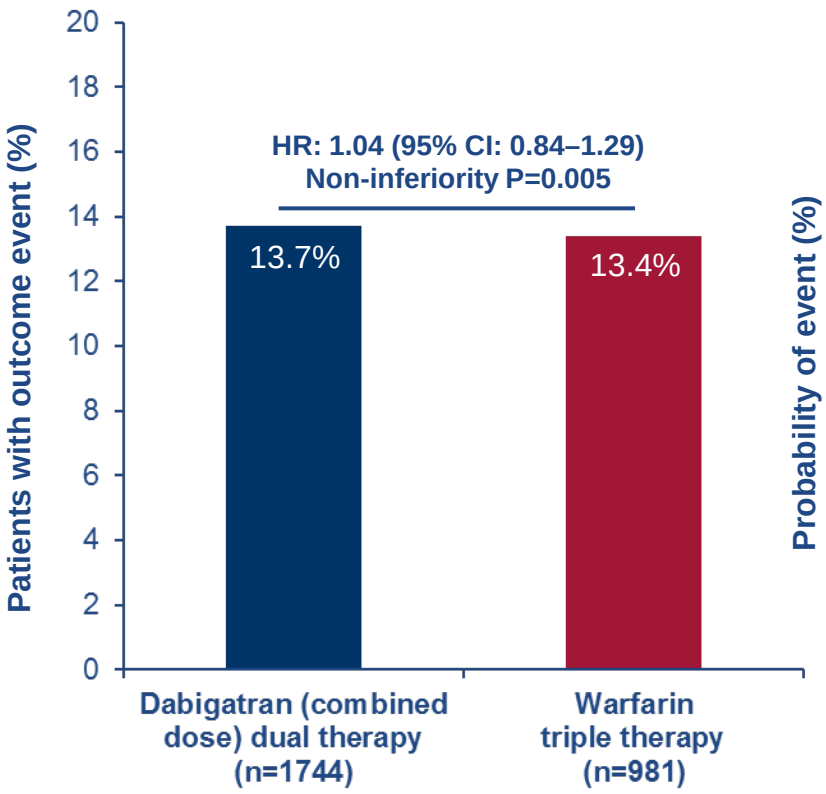


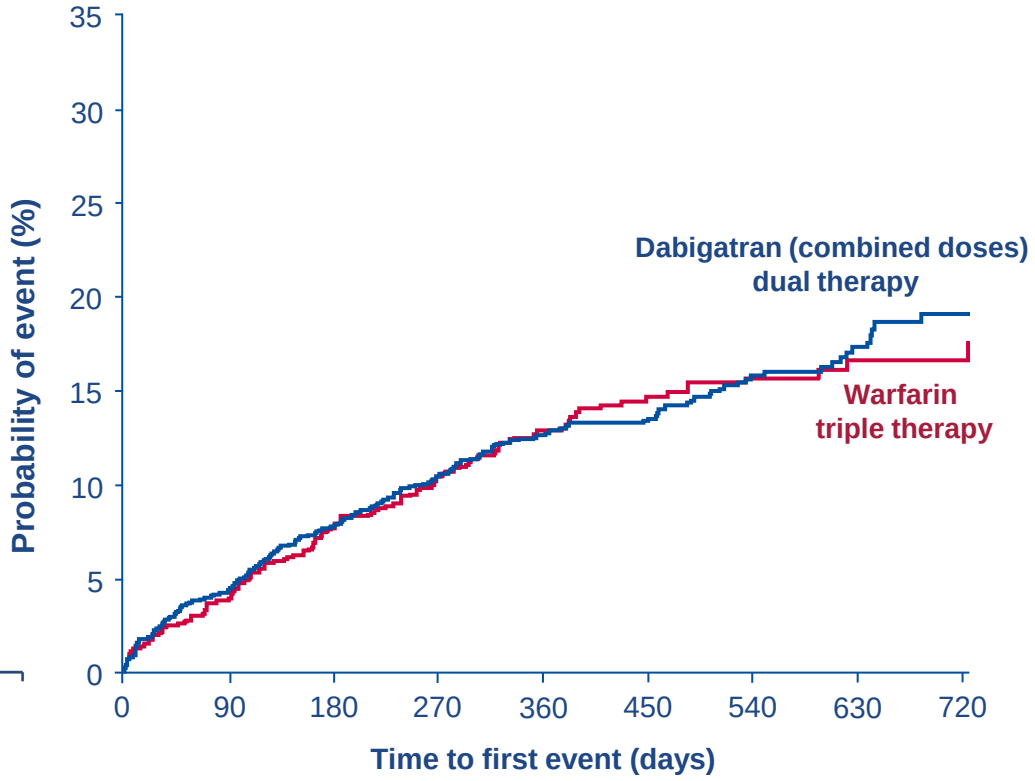
For the dabigatran 150 mg vs warfarin comparison, elderly patients outside the USA (≥80 years) and Japan (≥70 years) are excluded. Full analysis set presented

CRNMBE, clinically relevant non-major bleeding event; ISTH, International Society on Thrombosis and Haemostasis; Cannon et al. ESC 2017; Cannon et al. N Engl J Med 2017

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

"Primum non nocere"

- Ogni volta che il beneficio di un'associzione anticoagulante+antiaggregante risulta incerto ricordiamo che…

… un evento emorragico maggiore richiede la sospensione di ogni farmaco anticoagulante e/o antiaggregante, ed espone il paziente ad un prolungato rischio tromboembolico

Paolo Q, 72 anni

- SCA con PCI primaria e posizionamento di 2 stent medicati: FA comparsa peri-manovra
- Introdotta terapia con ASA, Clopidogrel, dabigatran 150x2
- A 48 h dalla manovra shock cardiogeno a bassa portata -> emopericardio con tamponamento
- Correzione d’urgenza con idarucizumab, coronarografia con sealing di leak vascolare
- Dimissione: dabigatran 110x2 + clopidogrel

Domande e (mie) risposte “semplici”

- Quali farmaci scegliere? Quelli con maggiore sperimentazione, a dosi ridotte
- Come seguire il paziente? Informare, motivare, dare disponibilità per urgenze
- Che cosa fare in caso di emorragia grave? Neutralizzare anticoagulante, eventuale supporto di piastrine
- Ma soprattutto: quando associare anticoagulanti e antiaggreganti?

il più raramente possibile!

Emmo za daeto !