La gestione del paziente in terapia con antiaggreganti-anticoagulanti

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SISET – Abano Terme, 12 novembre 2016

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

Qualche “semplice” domanda

- Quando associare anticoagulanti e antiaggreganti
- Quali farmaci scegliere
- Come seguire il paziente
- Che cosa fare in caso di emorragia

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 più studiata è, ad oggi, ASA + VKA

VKA + ASA: in quali pazienti?

- Una metanalisi evidenzia 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)

Conclusions

- Either dipyridamole or low-dose aspirin + VKA decrease the risk of systemic embolism or death, but increase the risk of bleeding
- These results apply to patients with mechanical prosthetic valves or those with biological valves and indicators of high risk such as AF or prior thromboembolic events


HEALTH TECHNOLOGY ASSESSMENT
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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 !

Objectives

- To determine if the addition of APT to ACT is beneficial compared with ACT alone in patients with AF who are considered to be at a high risk of TEs

Results

- 5 RCTs, different doses of anticoagulant plus antiplatelet, patients at variable (or unspecified) stroke risks
- The type and dosage of both ACT and APT differed in the studies
- The quality of the 18 studies that reported non-randomised comparisons was generally poor

Conclusions

- There are not sufficient data to conclude whether or not there are patients with AF who would benefit from combined ACT and APT compared with ACT alone
- A definitive prospective randomised controlled trial needs to be undertaken with a sufficient follow-up

A ten arms study

Dea Kalì Trial

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+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

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

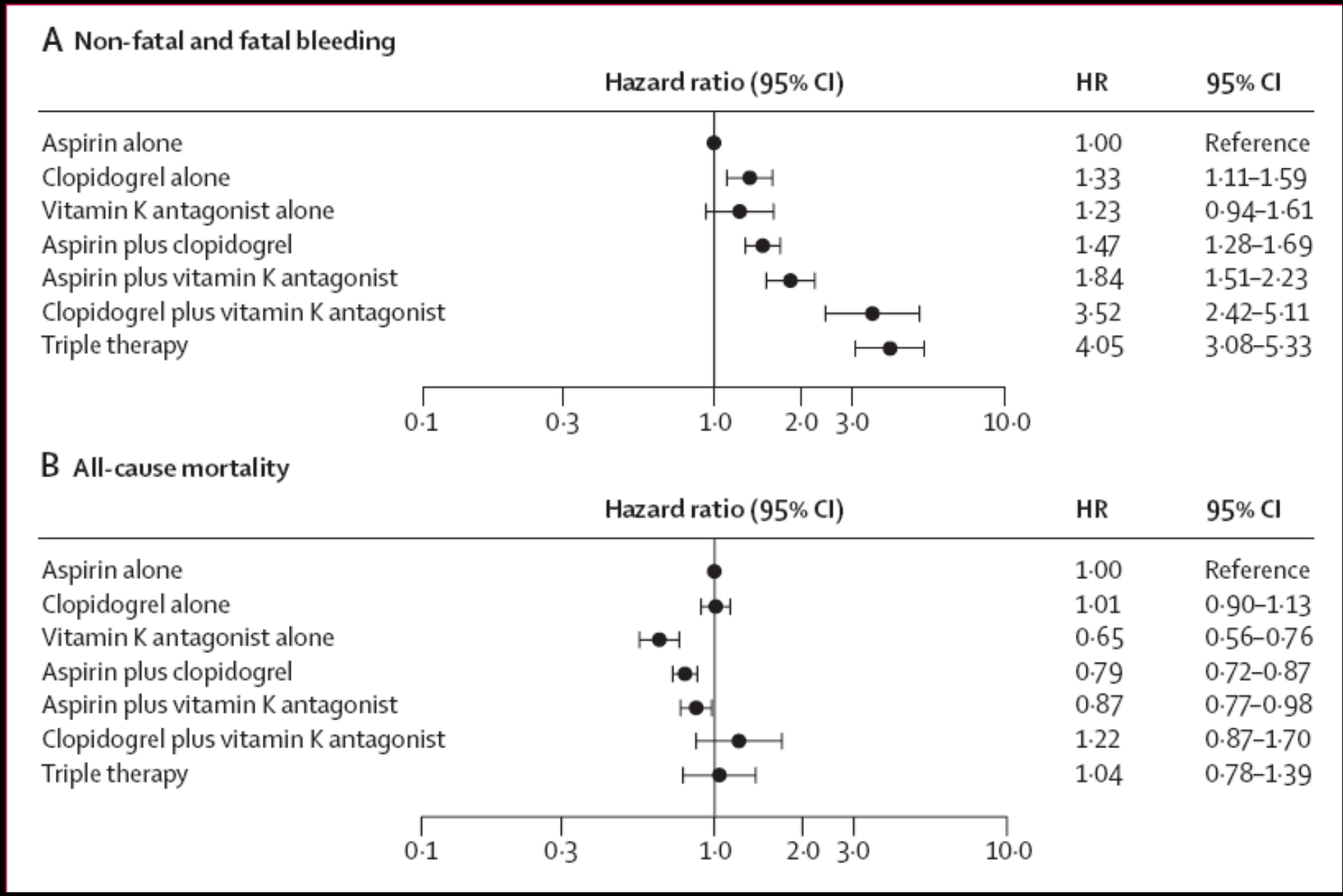
Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data

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

Adjusted risk of non-fatal and fatal bleeding and all-cause mortality in pts. treated with antithrombotic drugs after first MI



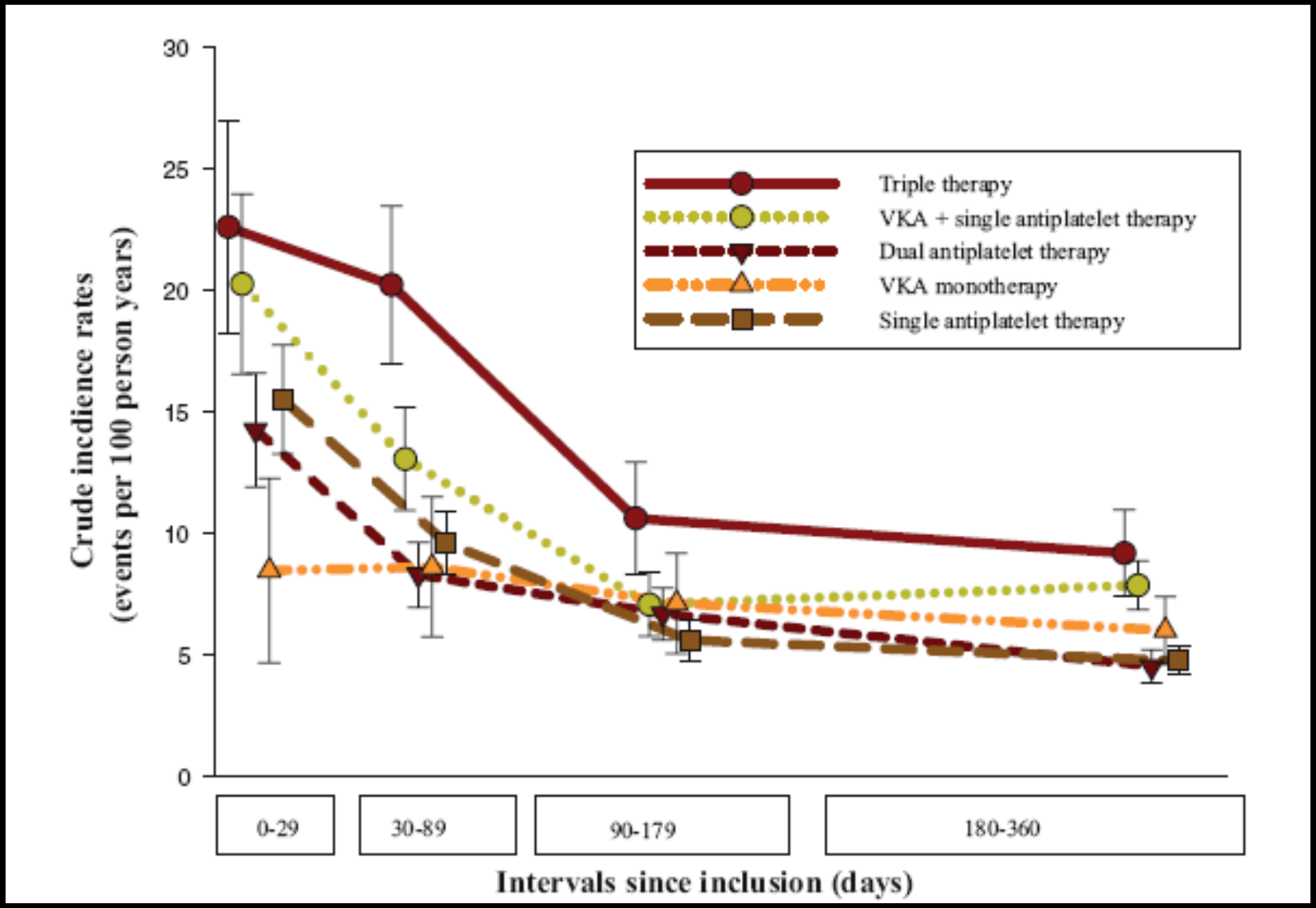
Bleeding After Initiation of Multiple Antithrombotic Drugs, Including Triple Therapy, in Atrial Fibrillation Patients Following Myocardial Infarction and Coronary Intervention

A Nationwide Cohort Study

Morten Lamberts, MD; Jonas Bjerring Olesen, MD; Martin Huth Ruwald, MD; Carolina Malta Hansen, MD; Deniz Karasoy, MD; Søren Lund Kristensen, MD; Lars Køber, MD, DMSc; Christian Torp-Pedersen, MD, DMSc; Gunnar Hilmar Gislason, MD, PhD; Morten Lock Hansen, MD, PhD

Circulation. 2012;126:1185-1193

Crude incidence rates of fatal and nonfatal bleeding



Conclusions

- A continually elevated risk associated with triple therapy indicates no safe therapeutic window
- No benefit was present for the combined thromboembolic end point for triple therapy *vs* VKA plus a single antiplatelet agent
- Until data from randomised trials are available, our results suggest that triple therapy should only be prescribed after careful evaluation of bleeding risk

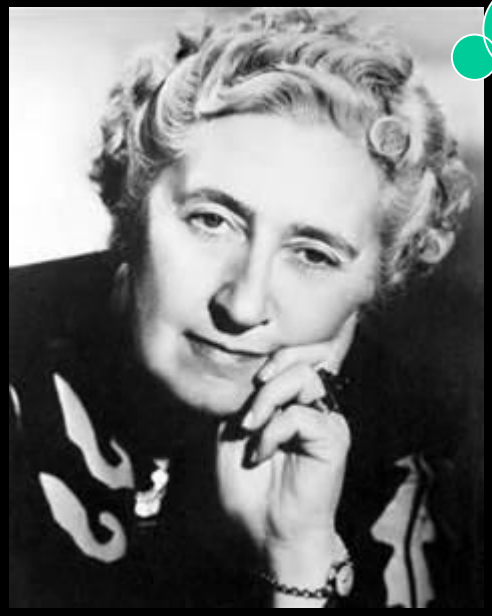
Antithrombotic regimens in patients with indication for long-term anticoagulation undergoing coronary interventions-systematic analysis, review of literature, and implications on management.

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



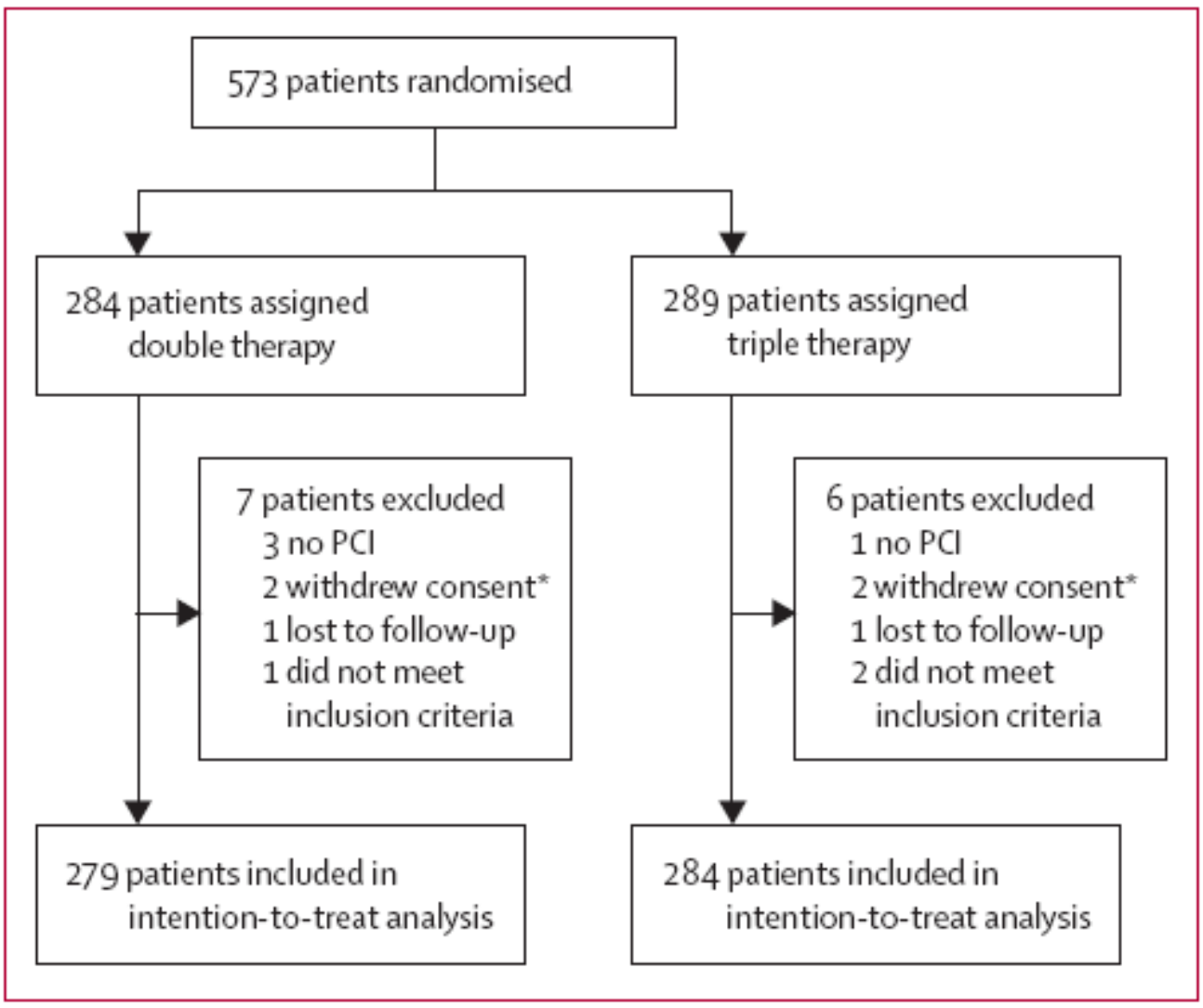
Agatha Christie

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

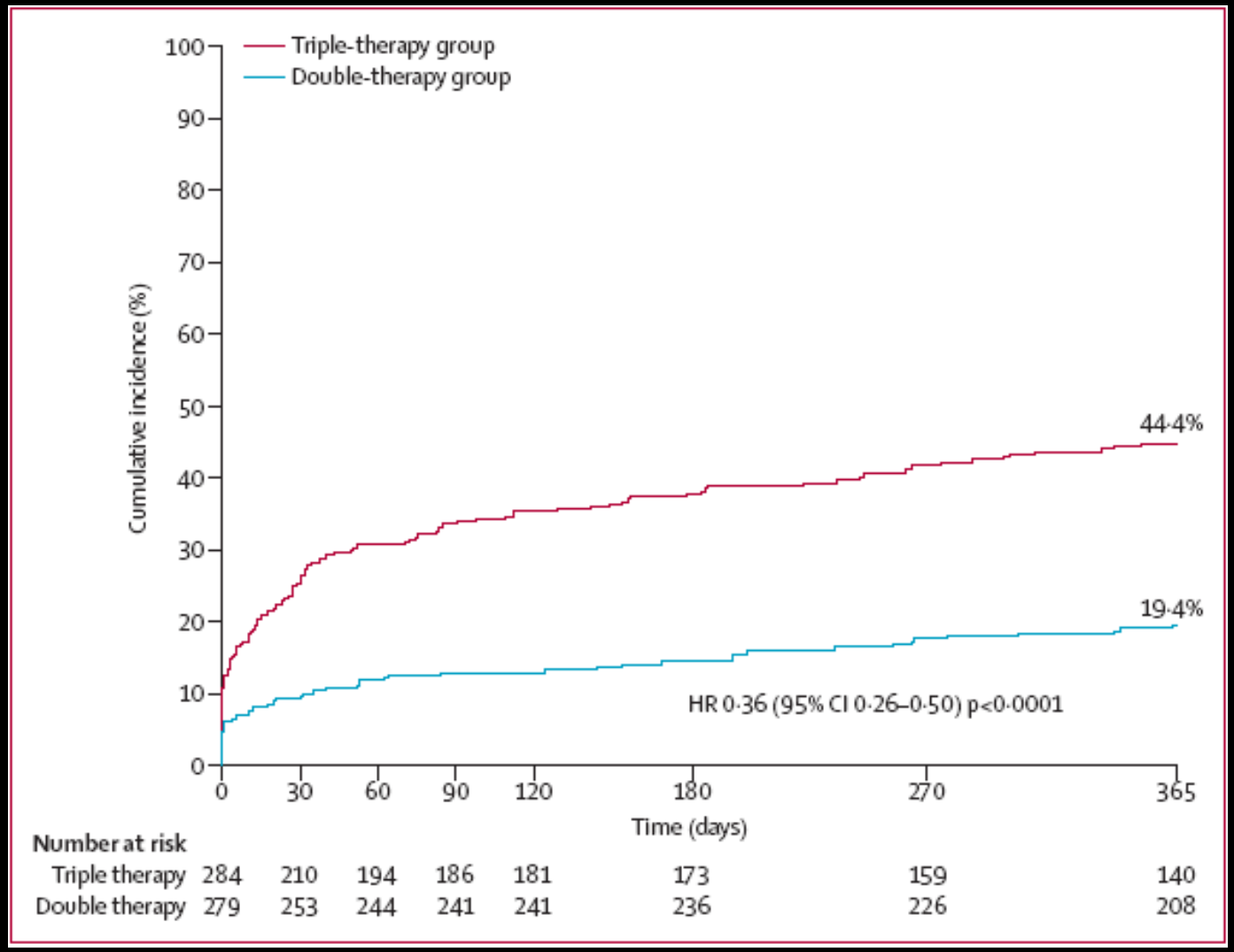
WOEST Study - Lancet 2013; 381: 1107–15

WOEST Study Design



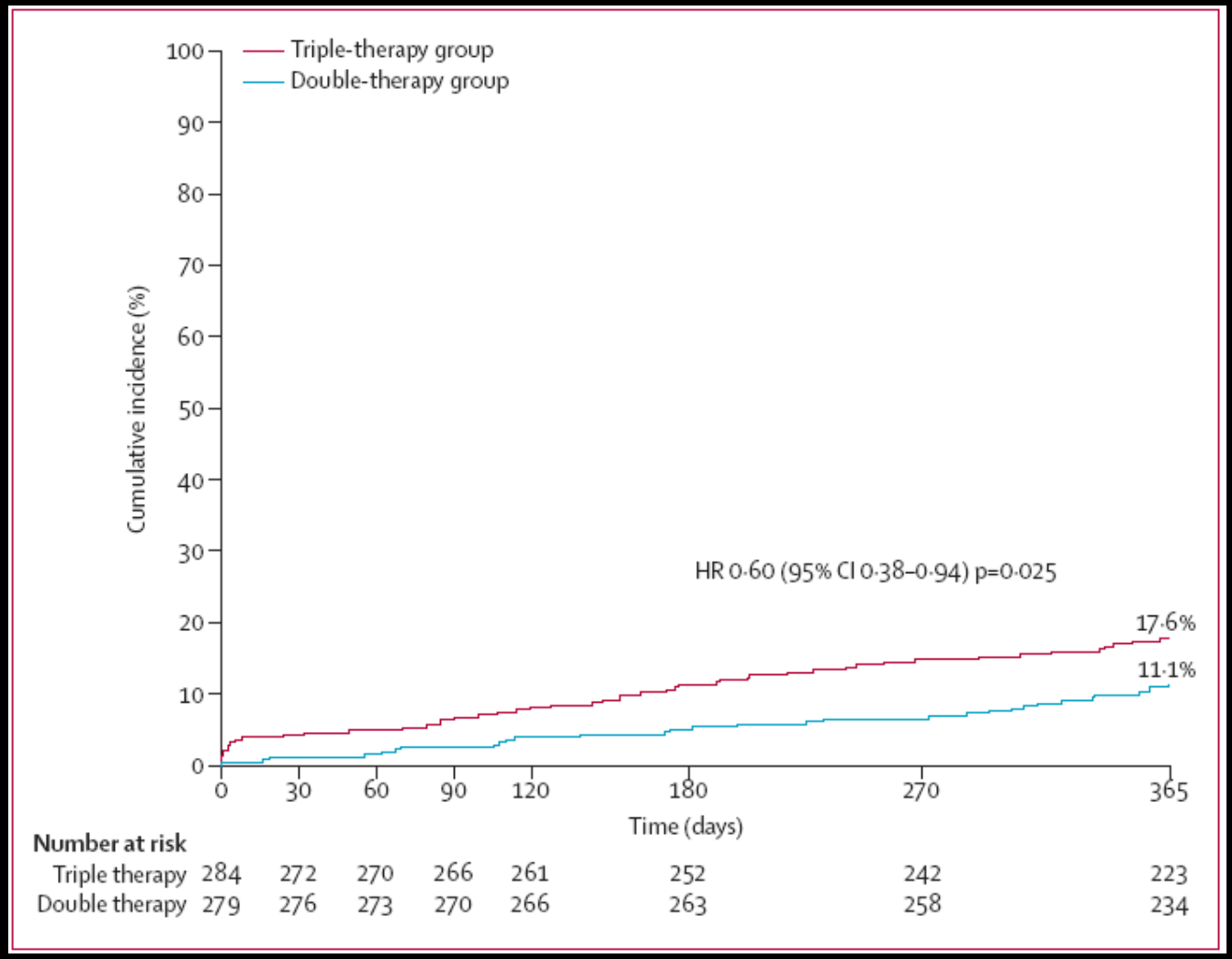
Lancet 2013; 381: 1107–15

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

Sicurezza ed efficacia di ASA associato a DOAC

- E’ stato ipotizzato che l’associazione di ASA con i “nuovi anticoagulanti” possa offrire un miglior rapporto beneficio/rischio rispetto alla associazione ASA+TAO
- Tuttavia questa ipotesi (e l’associazione con altri antiaggreganti) deve ancora essere studiata in modo adeguato

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

Phase III trials of 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	Rocket AF	n.a.	n.a.
Apixaban	Aristotle	1.90	2.70
Edoxaban 30 mg	Engage AF	1.46	2.00
Edoxaban 60 mg	Engage AF	2.41	3.62

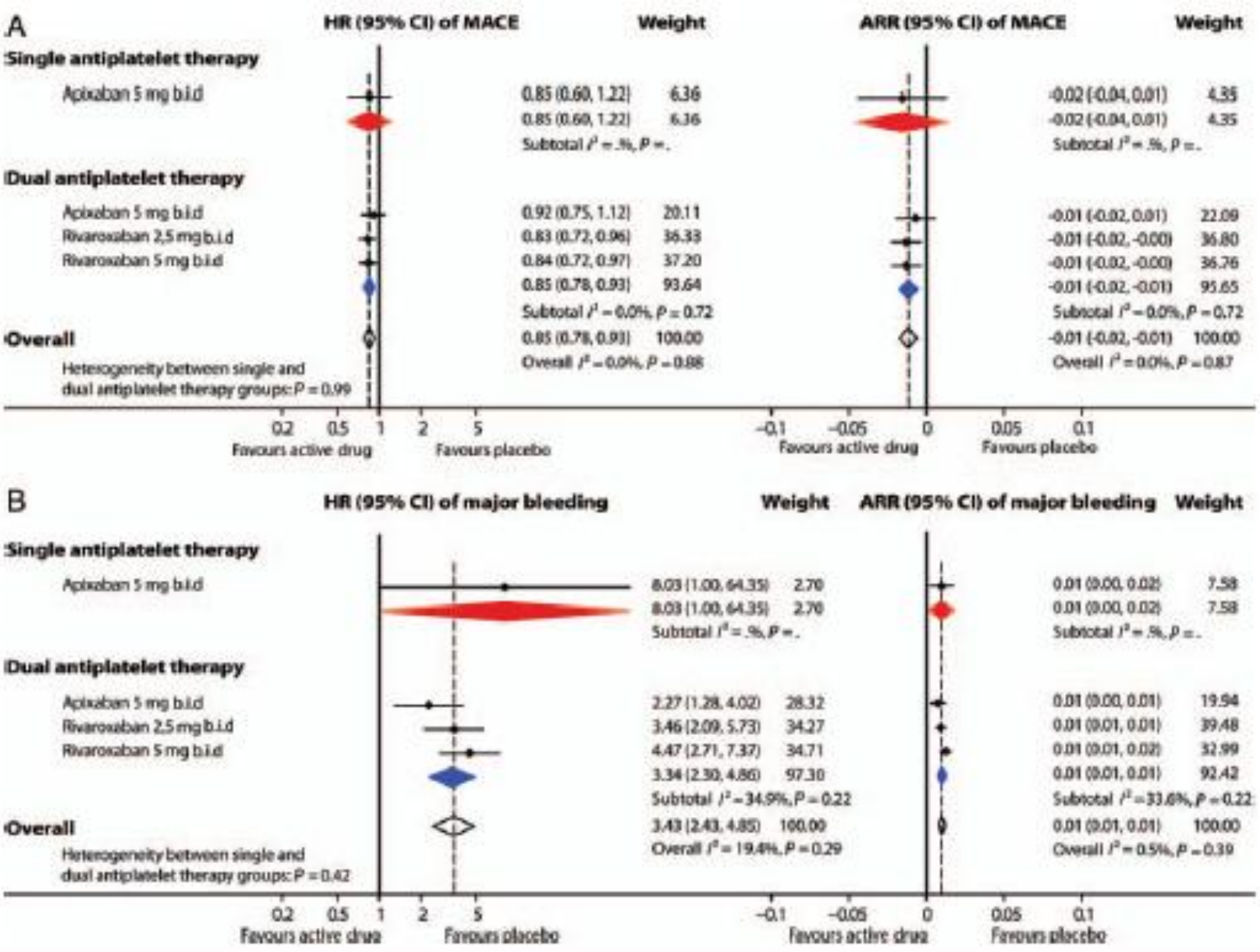
European Heart Journal Advance Access published March 6, 2013

European Heart Journal
doi:10.1093/eurheartj/eht049

CLINICAL RESEARCH

New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis

Jonas Oldgren[1,2*], Lars Wallentin[1,2], John H. Alexander[3], Stefan James[1,2], Birgitta Jönelid[1], Gabriel Steg[4,5,6], and Johan Sundström[1,2]


A
HR (95% CI) of MACE
Weight
ARR (95% CI) of MACE
Weight
Single antiplatelet therapy
Apixaban 5 mg b.i.d
0.85 (0.60, 1.22) 6.36
0.85 (0.60, 1.22) 6.36
Subtotal I² = .%, P = .
-0.02 (-0.04, 0.01) 4.35
-0.02 (-0.04, 0.01) 4.35
Subtotal I² = .%, P = .
Dual antiplatelet therapy
Apixaban 5 mg b.i.d
Rivaroxaban 2.5 mg b.i.d
Rivaroxaban 5 mg b.i.d
0.92 (0.75, 1.12) 20.11
0.83 (0.72, 0.96) 36.33
0.84 (0.72, 0.97) 37.20
0.85 (0.78, 0.93) 93.64
Subtotal I² = 0.0%, P = 0.72
-0.01 (-0.02, 0.01) 22.09
-0.01 (-0.02, -0.00) 36.80
-0.01 (-0.02, -0.00) 36.76
-0.01 (-0.02, -0.01) 95.65
Subtotal I² = 0.0%, P = 0.72
Overall
0.85 (0.78, 0.93) 100.00
Overall I² = 0.0%, P = 0.88
-0.01 (-0.02, -0.01) 100.00
Overall I² = 0.0%, P = 0.87
Heterogeneity between single and dual antiplatelet therapy groups: P = 0.99
0.2 0.5 1 2 5
Favours active drug
Favours placebo
-0.1 -0.05 0 0.05 0.1
Favours active drug
Favours placebo
B
HR (95% CI) of major bleeding
Weight
ARR (95% CI) of major bleeding
Weight
Single antiplatelet therapy
Apixaban 5 mg b.i.d
8.03 (1.00, 64.35) 2.70
8.03 (1.00, 64.35) 2.70
Subtotal I² = .%, P = .
0.01 (0.00, 0.02) 7.58
0.01 (0.00, 0.02) 7.58
Subtotal I² = .%, P = .
Dual antiplatelet therapy
Apixaban 5 mg b.i.d
Rivaroxaban 2.5 mg b.i.d
Rivaroxaban 5 mg b.i.d
2.27 (1.28, 4.02) 28.32
3.46 (2.09, 5.73) 34.27
4.47 (2.71, 7.37) 34.71
3.34 (2.30, 4.86) 97.30
Subtotal I² = 34.9%, P = 0.22
0.01 (0.00, 0.01) 19.54
0.01 (0.01, 0.01) 39.48
0.01 (0.01, 0.02) 32.99
0.01 (0.01, 0.01) 92.42
Subtotal I² = 33.6%, P = 0.22
Overall
3.43 (2.43, 4.85) 100.00
Overall I² = 19.4%, P = 0.29
0.01 (0.01, 0.01) 100.00
Overall I² = 0.5%, P = 0.39
Heterogeneity between single and dual antiplatelet therapy groups: P = 0.42
0.2 0.5 1 2 5
Favours active drug
Favours placebo
-0.1 -0.05 0 0.05 0.1
Favours active drug
Favours placebo

Conclusion

- The addition of a DOAC to antiplatelet therapy leads to a modest reduction in cardiovascular events but a substantial increase in bleeding
- These results are most pronounced when DOAC are combined with dual anti-platelet therapy with aspirin and clopidogrel

Dual or single antiplatelet therapy with anticoagulation?

- Clinicians are becoming increasingly aware of the importance of reducing bleeding risk
- "More potent is not always better"

Keith A A Fox

Centre for Cardiovascular Science,

University of Edinburgh, UK

Lancet, 2013

"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

Qualche “semplice” risposta

- Quando associare anticoagulanti e antiaggreganti: il più raramente possibile
- Quali farmaci scegliere: quelli con maggiore sperimentazione
- Come seguire il paziente: informazione, motivazione, disponibilità per urgenze
- Che cosa fare in caso di emorragia grave: neutralizzazione anticoagulante, eventuale supporto di piastrine

Chi ci aiuterà a comprendere meglio come gestire un paziente in terapia con antiaggreganti-anticoagulanti ?

https://www.whitehouse.gov/precision-medicine

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"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if

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ITA 14:35 11/11/2016

What is the Precision Medicine Initiative?

Mission statement:

To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care.


Health service no more needed