EFFICACIA E SICUREZZA DELLA DOPPIA VS. TRIPLICE TERAPIA ANTITROMBOTICA IN PAZIENTI FIBRILLANTI SOTTOPOSTI AD ANGIOPLASTICA CORONARICA

REVISIONE E METANALISI DEI TRIAL RANDOMIZZATI SUGLI ANTICOAGULANTI ORALI DIRETTI

BACKGROUND

- Most patients with atrial fibrillation (AF) and risk factors for stroke require oral anticoagulation (OAC) to prevent cerebrovascular or systemic embolism.

- Frequently AF coincides with coronary artery disease (CAD) and microcirculatory flow abnormalities, so many of these patients present with acute coronary syndrome or stable CAD requiring percutaneous coronary intervention (PCI).

- The optimal antithrombotic treatment regimen for patients with AF undergoing PCI is a clinical conundrum. Dual antiplatelet therapy (DAPT) is recommended to reduce the risk of ischaemic complications in patients undergoing PCI and the combination of OAC with DAPT, a strategy generally called triple antithrombotic therapy (TAT), increases the bleeding risks compared with the use of OAC or DAPT alone.

Safety and efficacy outcomes of double vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of non-vitamin K antagonist oral anticoagulant-based randomized clinical trials

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METHODS

- A systematic review and meta-analysis was performed using PubMed to search for non-vitamin K antagonist oral anticoagulant (NOAC)-based randomized clinical trials comparing DAT vs. TAT in AF patients undergoing PCI

- Four trials encompassing 10234 patients (DAT = 5496 vs. TAT = 4738) were included

	PIONEER AF-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST AF-PCI
Trial name	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	Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention	Open-Label, 2×2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention	EdoxabaN TReatment versUS VKA in paTients with AF undergoing PCI
N. of patients	2124	2725	4614	1506
Patient population	AF patients within 72 hours after PCI with stenting	AF patients from 6 to 120 hours after successful PCI	AF patients within 14 days after having an ACS and/or undergoing PCI	AF patients from 4 hours to 5 days after PCI
Median time to randomization	Unknown	Unknown	6 days (IQR 3 to 10)	45.1 h (IQR 22.2 to 76.2)
Treatment strategies	- Rivaroxaban 15 mg + P2Y12 inhibitor (clopidogrel 75 mg) vs - Rivaroxaban 2.5 mg bid + DAPT (aspirin 75-100 mg and clopidogrel 75 mg) vs - Warfarin + DAPT	- Dabigatran etexilate 110mg bid + P2Y12 inhibitor (clopidogrel or Ticagrelor) vs - Dabigatran etexilate 150mg bid + P2Y12 inhibitor (clopidogrel or Ticagrelor) vs - Warfarin (INR 2.0-3.0) + DAPT (aspirin ≤100mg and clopidogrel or Ticagrelor)	- Apixaban 5 mg bid + DAPT (aspirin 81 mg and a P2Y12 inhibitor) vs - Apixaban 5 mg bid + P2Y12 inhibitor vs - Warfarin (INR 2.0-3.0) + DAPT (aspirin 81 mg and a P2Y12 inhibitor) vs - Warfarin (INR 2.0-3.0) + P2Y12 inhibitor	- Edoxaban 60 mg + P2Y12 inhibitor vs - VKA + DAPT (aspirin 100 mg and a P2Y12 inhibitor)

From supplementary table 1, G. Gargiulo et al. EHJ (2019) 0, 1–11

	PIONEER AF-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST AF-PCI
Year of publication	2016	2017	2019	2019
Enrolment time	May 2013-July 2015	July 2014-October 2016	September 2015-April 2018	February 2017-May 2018
Follow-up	12 months	14 months	6 months	12 months
Analysis	Modified ITT	ITT	Modified ITT and ITT	ITT
Primary safety endpoint	A composite of major bleeding or minor bleeding according to the TIMI or bleeding requiring medical attention	A composite of major or clinically relevant nonmajor bleeding event according to ISTH	A composite of major or clinically relevant nonmajor bleeding event according to ISTH	A composite of major or clinically relevant nonmajor bleeding event according to ISTH
MACE definition	A composite of cardiovascular death, MI, or stroke	A composite of all-cause death or ischemic event (including stroke, MI, SE, or unplanned revascularization	A composite of all-cause death or ischemic event (including stroke, MI, ST definite/probable, urgent revascularization)	A composite of cardiovascular death or ischemic event (including stroke, MI, ST definite, SE)
Stent thrombosis	Definite ST (not clearly reported)	Definite ST	Definite/probable ST	Definite ST
Sponsor	Janssen Scientific Affairs and Bayer Pharmaceuticals	Boehringer Ingelheim	Bristol-Myers Squibb and Pfizer	Daiichi Sankyo

From supplementary table 1, G. Gargiulo et al. EHJ (2019) 0, 1–11

	PIONEER AF-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST AF-PCI
Major inclusion criteria	Age ≥18 years; Patients with documented non-valvular AF within last 1 year and who had just undergone PCI with stent placement for atherosclerotic disease or more than 1 year before screening if the subject has been receiving OAC for the AF for 3 months immediately before the index PCI	Age ≥ 18 years; Patients with non-valvular AF who have been receiving an OAC or who are treatment-naïve prior to PCI; AF not secondary to a reversible disorder unless long-term anticoagulation was planned; ACS or unstable angina successfully treated by PCI and stenting or stable CAD with ≥1 lesion eligible for PCI that was successfully treated by elective PCI and stenting	Age ≥ 18 years; Patients with either active or a history of AF or flutter with planned or existing use of an OAC for prophylaxis of thromboembolism; Patients who have had an ACS and/or a PCI within the prior 14 days; Planned use of an approved P2Y12 inhibitor for at least 6 months	Age ≥ 18 years; OAC indication for AF for a period of at least 12 m following successful PCI with stenting.
Major exclusion criteria	History of stroke/TIA, significant gastrointestinal bleeding within 12 months before randomization, eGFR<30 ml/min, Hb<10 g/dl	Mechanical or biological heart valves, cardiogenic shock, prior stroke, surgery, gastrointestinal bleeding, major bleeding within 1 month prior to randomization, Hb<10 g/dl, eGFR<30 ml/min, active liver disease	Patients with other conditions requiring OAC (such as prosthetic valves or moderate or severe mitral stenosis); Severe renal insufficiency; History of intracranial haemorrhage	Bleeding risk or systemic conditions; Medication-related factors (INR>2.5, contraindications to study drugs, concomitant antithrombotics, fibrinolytic agents, etc.); concomitant conditions (critically ill or hemodynamically unstable, prior mechanical valvular prosthesis, ischaemic stroke within 2 weeks, moderate or severe mitral stenosis, planned coronary or vascular intervention or major surgery within 12 m, creatinine clearance <15 mL/min or on dialysis, known abnormal liver function, Hb<8 g/dl or Platelets <50x10^9/L, etc.)

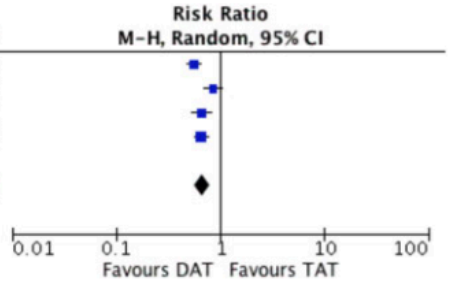
From supplementary table 1, G. Gargiulo et al. EHJ (2019) 0, 1–11

MAIN BLEEDING ENDPOINTS IN DOUBLE VS. TRIPLE ANTITHROMBOTIC THERAPY

A ISTH MAJOR OR CLINICALLY RELEVANT NONMAJOR BLEEDING

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	204	2279	367	2277	26.8%	0.56 [0.47, 0.65]
ENTRUST AF-PCI	128	751	152	755	22.3%	0.85 [0.68, 1.05]
PIONEER AF-PCI	117	696	178	697	22.7%	0.66 [0.53, 0.81]
RE-DUAL PCI	305	1744	264	981	28.2%	0.65 [0.56, 0.75]
Total (95% CI)		**5470**		**4710**	**100.0%**	**0.66 [0.56, 0.78]**
Total events	754		961			

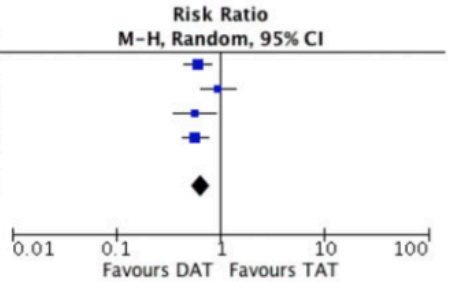
Heterogeneity: Tau² = 0.02; Chi² = 9.65, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 5.03 (P < 0.00001)



B ISTH MAJOR BLEEDING

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	65	2279	108	2277	29.6%	0.60 [0.44, 0.81]
ENTRUST AF-PCI	45	751	48	755	21.2%	0.94 [0.64, 1.40]
PIONEER AF-PCI	27	696	48	697	17.0%	0.56 [0.36, 0.89]
RE-DUAL PCI	92	1744	90	981	32.2%	0.57 [0.43, 0.76]
Total (95% CI)		**5470**		**4710**	**100.0%**	**0.64 [0.52, 0.80]**
Total events	229		294			

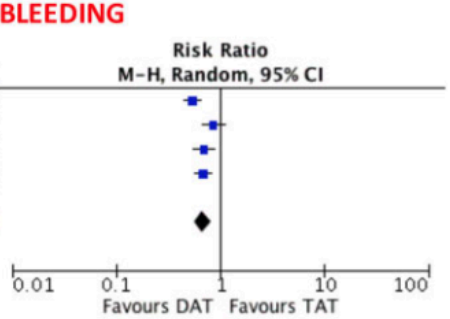
Heterogeneity: Tau² = 0.02; Chi² = 4.73, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 3.94 (P < 0.0001)



C CLINICALLY RELEVANT NONMAJOR BLEEDING

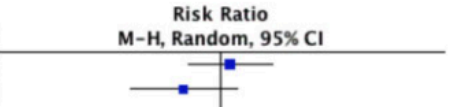
Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	148	2279	275	2277	27.1%	0.54 [0.44, 0.65]
ENTRUST AF-PCI	97	751	114	755	22.4%	0.86 [0.67, 1.10]
PIONEER AF-PCI	90	696	130	697	22.7%	0.69 [0.54, 0.89]
RE-DUAL PCI	213	1744	174	981	27.7%	0.69 [0.57, 0.83]
Total (95% CI)		**5470**		**4710**	**100.0%**	**0.68 [0.56, 0.82]**
Total events	548		693			

Heterogeneity: Tau² = 0.02; Chi² = 8.87, df = 3 (P = 0.03); I² = 66%
Test for overall effect: Z = 4.12 (P < 0.0001)



D INTRACRANIAL HAEMORRHAGE

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	10	2279	8	2277	30.6%	1.25 [0.49, 3.16]
ENTRUST AF-PCI	4	751	9	755	24.2%	0.45 [0.14, 1.44]



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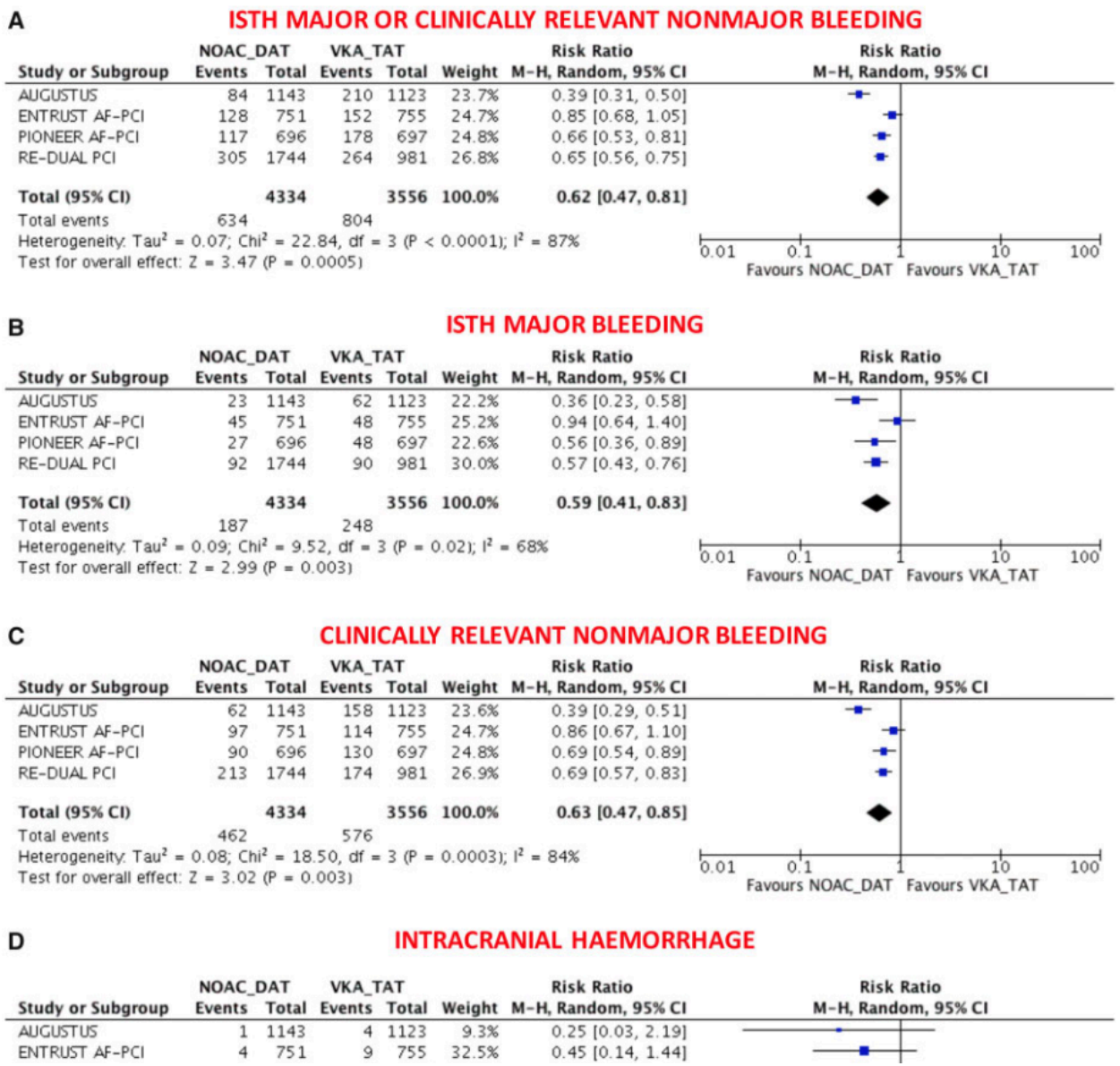
MAIN BLEEDING ENDPOINTS IN NOAC BASED DOUBLE ANTITHROMBOTIC THERAPY VS. VKA- BASED TRIPLE ANTITHROMBOTIC THERAPY



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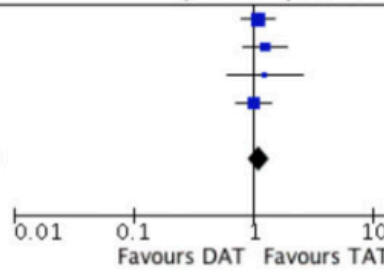
DEATH AND MAJOR ADVERSE CARDIOVASCULAR EVENTS IN DOUBLE VS. TRIPLE ANTITHROMBOTIC THERAPY

A **ALL-CAUSE DEATH**

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	79	2307	72	2307	38.9%	1.10 [0.80, 1.50]
ENTRUST AF-PCI	46	751	37	755	21.6%	1.25 [0.82, 1.90]
PIONEER AF-PCI	16	694	13	695	7.3%	1.23 [0.60, 2.54]
RE-DUAL PCI	85	1744	48	981	32.2%	1.00 [0.71, 1.41]
Total (95% CI)		**5496**		**4738**	**100.0%**	**1.10 [0.91, 1.34]**
Total events	226		170			

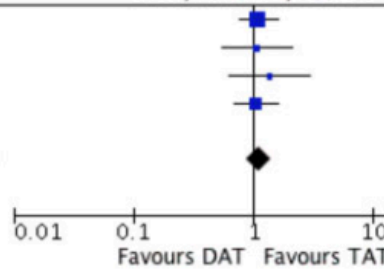
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.77$, df = 3 (P = 0.86); $I^2 = 0\%$
Test for overall effect: Z = 0.98 (P = 0.32)



B **CARDIOVASCULAR DEATH**

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	58	2307	53	2307	44.2%	1.09 [0.76, 1.58]
ENTRUST AF-PCI	17	751	16	755	13.1%	1.07 [0.54, 2.10]
PIONEER AF-PCI	15	694	11	695	10.1%	1.37 [0.63, 2.95]
RE-DUAL PCI	58	1744	31	981	32.5%	1.05 [0.69, 1.62]
Total (95% CI)		**5496**		**4738**	**100.0%**	**1.10 [0.86, 1.41]**
Total events	148		111			

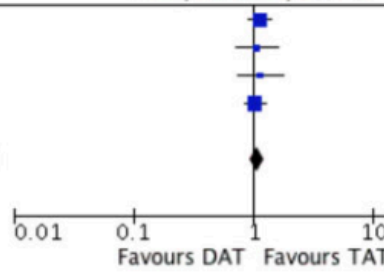
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.35$, df = 3 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 0.77 (P = 0.44)



C **TRIAL-DEFINED MACE**

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	168	2307	149	2307	37.1%	1.13 [0.91, 1.40]
ENTRUST AF-PCI	49	751	46	755	11.1%	1.07 [0.73, 1.58]
PIONEER AF-PCI	41	694	36	695	8.9%	1.14 [0.74, 1.76]
RE-DUAL PCI	239	1744	131	981	42.9%	1.03 [0.84, 1.25]
Total (95% CI)		**5496**		**4738**	**100.0%**	**1.08 [0.95, 1.23]**
Total events	497		362			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.47$, df = 3 (P = 0.92); $I^2 = 0\%$
Test for overall effect: Z = 1.13 (P = 0.26)



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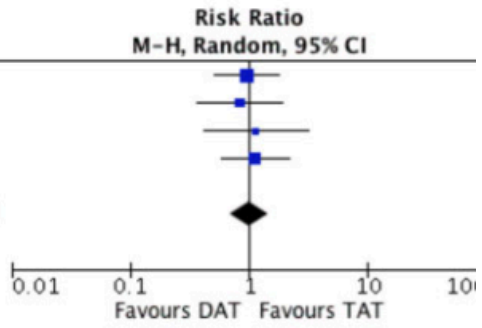
ISCHAEMIC ENDPOINTS IN DOUBLE VS. TRIPLE ANTITHROMBOTIC THERAPY

STROKE

or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
TUS	19	2307	20	2307	35.2%	0.95 [0.51, 1.78]
ST AF-PCI	10	751	12	755	19.8%	0.84 [0.36, 1.93]
ER AF-PCI	8	694	7	695	13.5%	1.14 [0.42, 3.14]
AL PCI	26	1744	13	981	31.5%	1.13 [0.58, 2.18]
95% CI)		5496		4738	100.0%	1.00 [0.69, 1.45]
vents	63		52			

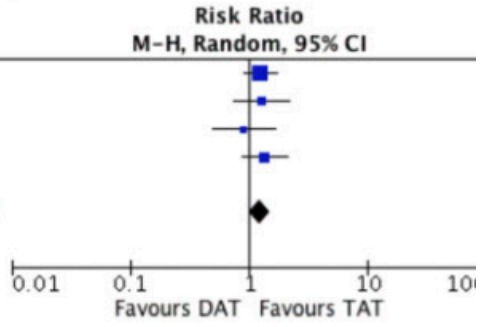
geneity: Tau² = 0.00; Chi² = 0.39, df = 3 (P = 0.94); I² = 0%
r overall effect: Z = 0.01 (P = 0.99)



MYOCARDIAL INFARCTION

or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
TUS	84	2307	68	2307	46.5%	1.24 [0.90, 1.69]
ST AF-PCI	29	751	23	755	15.9%	1.27 [0.74, 2.17]
ER AF-PCI	19	694	21	695	12.3%	0.91 [0.49, 1.67]
AL PCI	70	1744	29	981	25.4%	1.36 [0.89, 2.08]
95% CI)		5496		4738	100.0%	1.22 [0.99, 1.52]
vents	202		141			

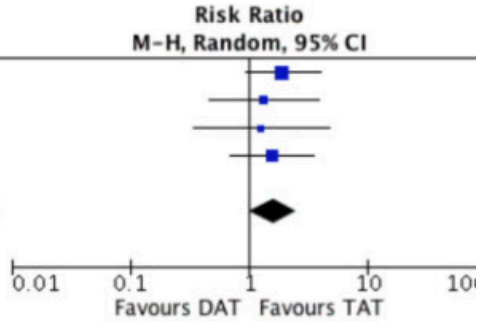
geneity: Tau² = 0.00; Chi² = 1.18, df = 3 (P = 0.76); I² = 0%
r overall effect: Z = 1.84 (P = 0.07)



STENT THROMBOSIS

or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
TUS	21	2307	11	2307	38.5%	1.91 [0.92, 3.95]
ST AF-PCI	8	751	6	755	18.3%	1.34 [0.47, 3.84]
ER AF-PCI	5	694	4	695	11.8%	1.25 [0.34, 4.64]
AL PCI	22	1744	8	981	31.4%	1.55 [0.69, 3.46]
95% CI)		5496		4738	100.0%	1.59 [1.01, 2.50]
vents	56		29			

geneity: Tau² = 0.00; Chi² = 0.48, df = 3 (P = 0.92); I² = 0%
r overall effect: Z = 2.02 (P = 0.04)



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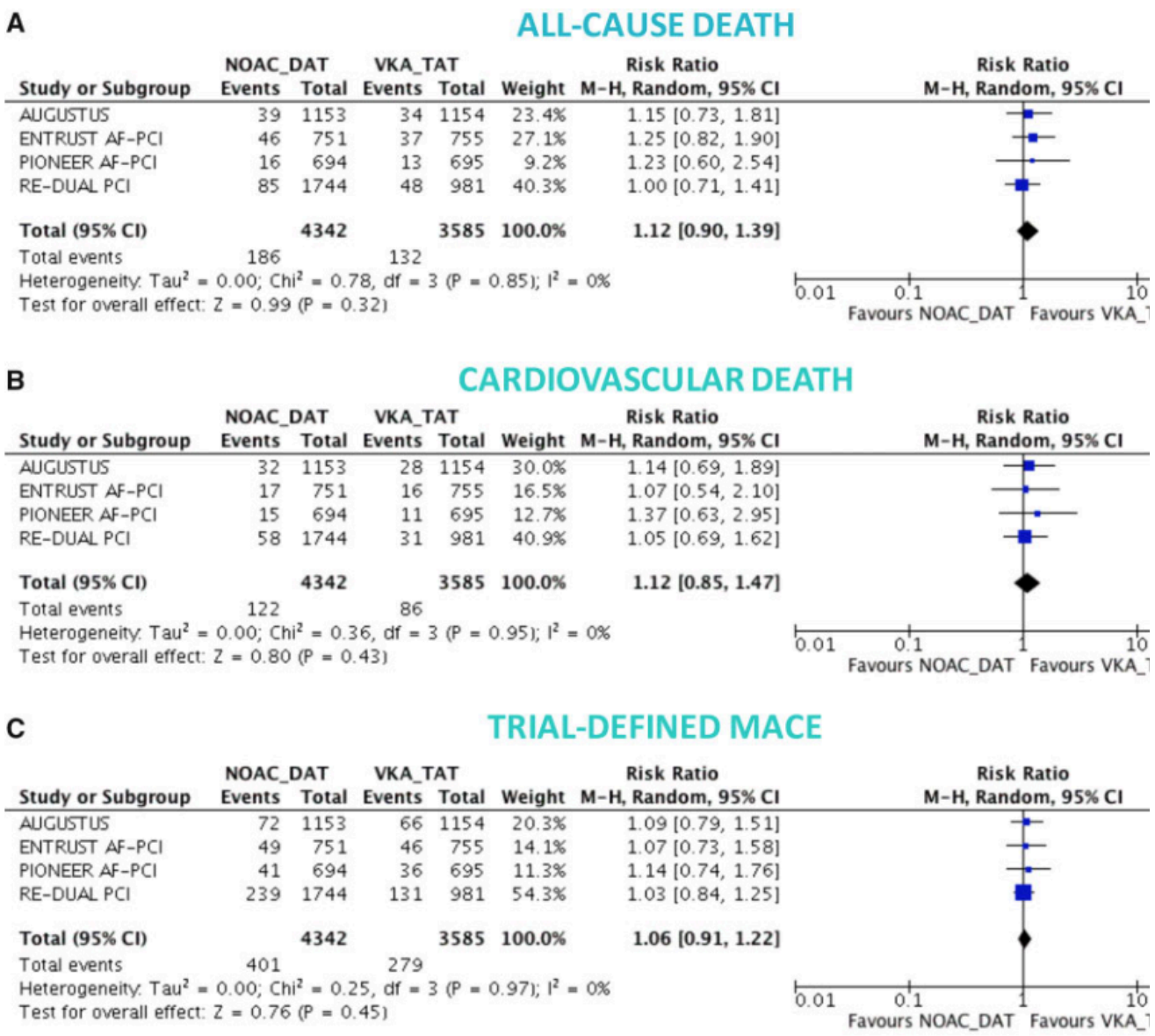

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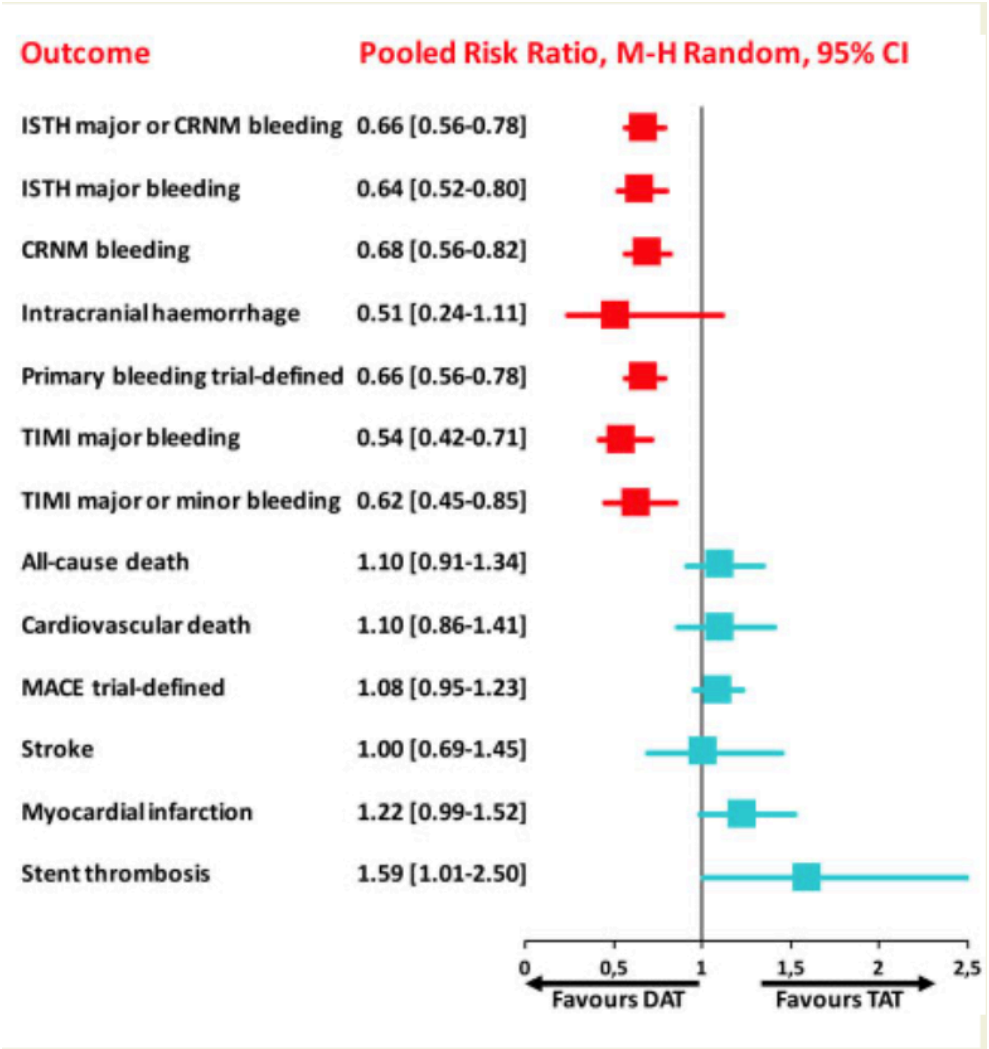

SUMMARY OF SAFETY AND EFFICACY END- POINTS IN DOUBLE VS. TRIPLE ANTITHROMBOTIC THERAPY

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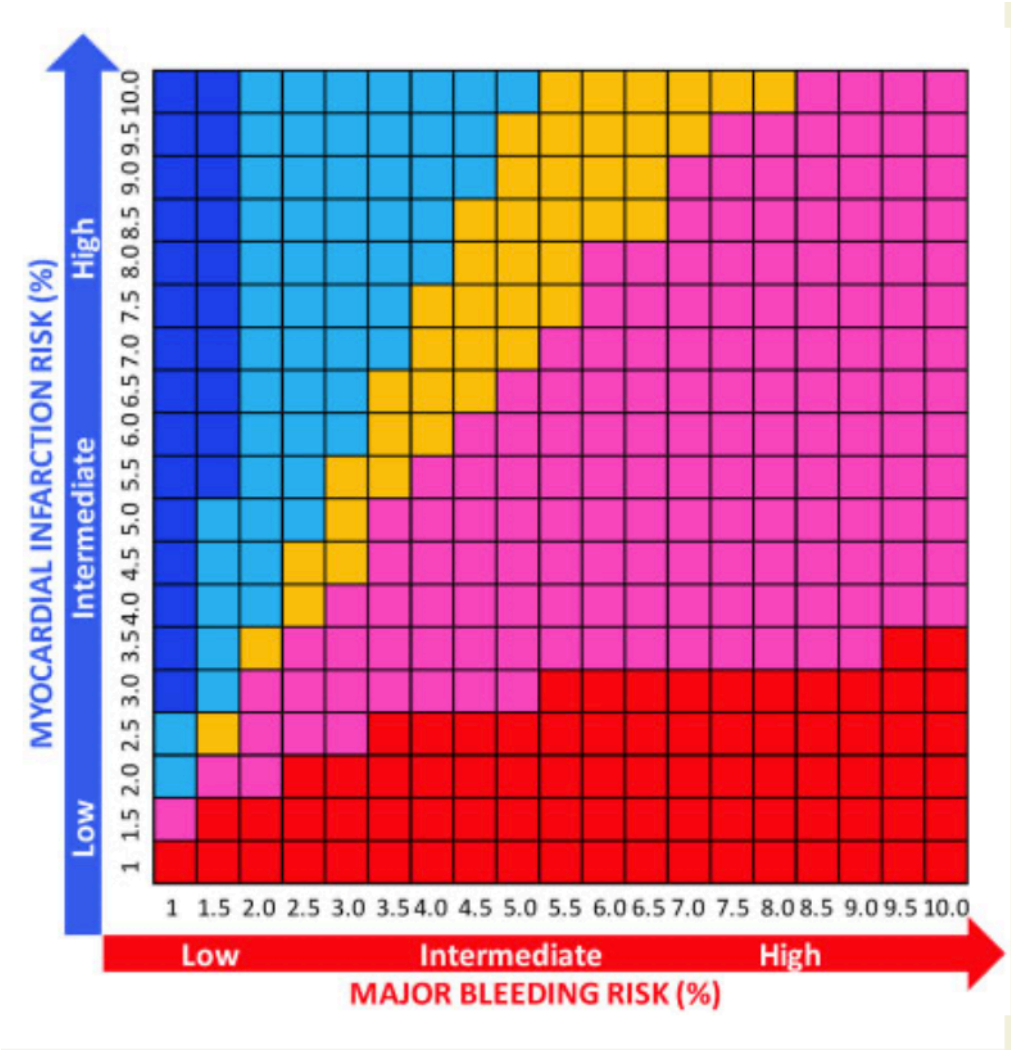

NUMBER NEEDED TO TREAT FOR BENEFIT OR HARM FOR DOUBLE VS. TRIPLE ANTITHROMBOTIC THERAPY ACCORDING TO RISK OF MAJOR BLEEDING AND MYOCARDIAL INFARCTION.

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LIMITATIONS

- Individual patient data are not publicly available at the time, therefore, subgroup analyses exploring specific subsets of patients or the role of different variables across the trials is highly desirable.
- Stent thrombosis definition implemented was not fully uniform across trials.
- Absence of secondary analysis on PCI-only patients because full outcome data from the AUGUSTUS in this population (by excluding .23.9% of medically-managed patients with ACS) are not yet available.

CONCLUSIONS

- Compared with TAT, DAT, particularly when based on NOACs, is associated with a reduction in bleeding complications, including major and intracranial haemorrhages.

- However, this benefit is counterbalanced by a higher risk of ischaemic, mainly stent-related, events.