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DOUBLE *VS.* TRIPLE ANTITHROMBOTIC THERAPY: A META-ANALYSIS OF THE REAL-LIFE EFFECT IN ABOUT 20,000 PATIENTS WITH ATRIAL FIBRILLATION UNDERGOING CORONARY ARTERY STENTING

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ABSTRACT – *Objective:* The aim of the present meta-analysis is to assess and quantify the effectiveness in the current clinical practice of double antithrombotic therapy (DAT) *vs.* triple antithrombotic treatment (TAT) regimens in patients affected by atrial fibrillation undergoing coronary artery stenting, complementing findings based on randomized clinical trials (RCT) with those based on observational studies and registries.

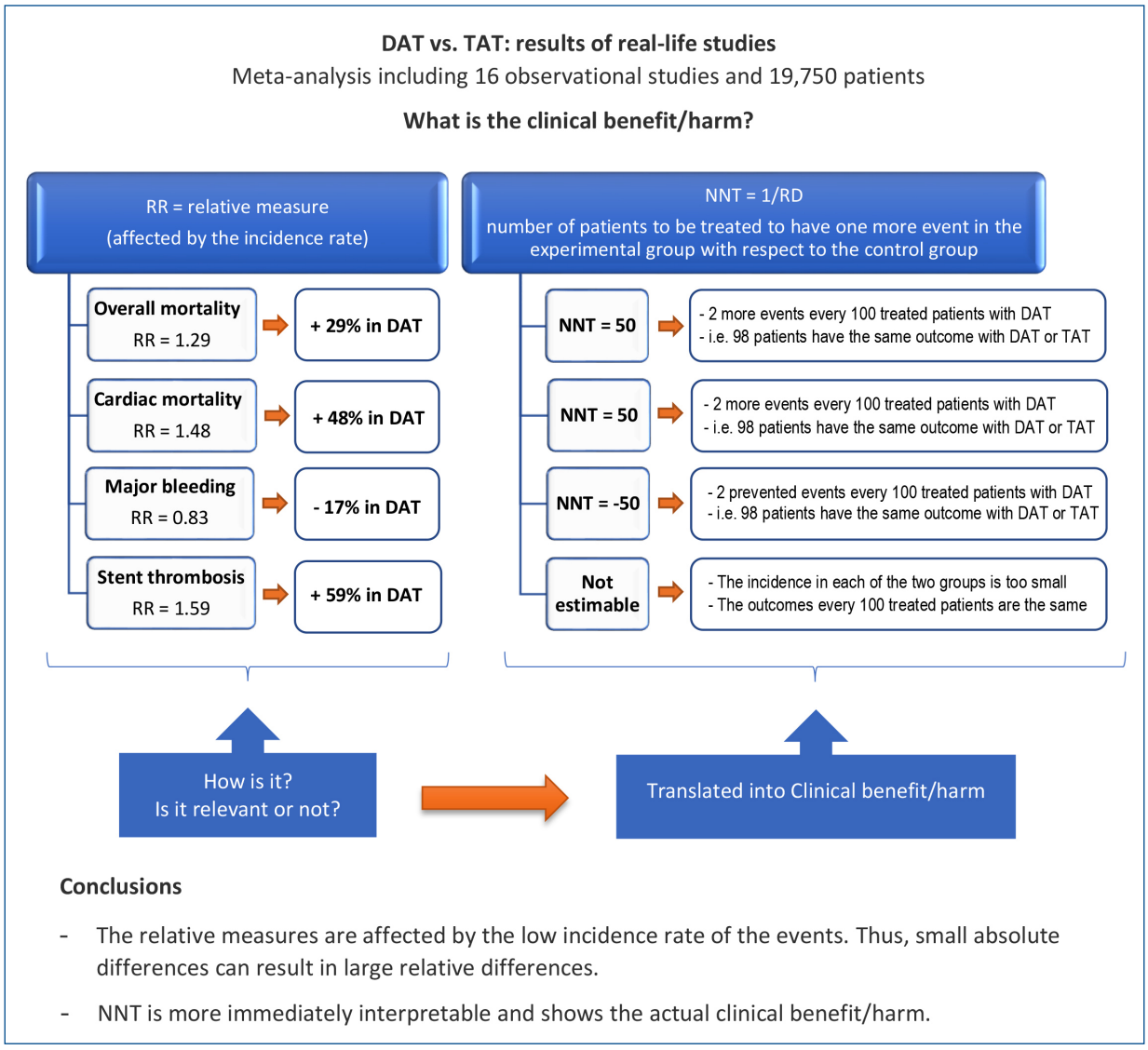
Materials and Methods: Sixteen observational studies were retrieved through the PubMed database. Risk ratio (RR) and absolute risk reduction (RD) with 95% confidence interval, together with the number needed to treat (NNT), were computed to compare the examined endpoints (mortality, major bleeding, intracranial hemorrhage, stroke, and stent thrombosis).

Results: The meta-analysis on RR in DAT in comparison to TAT demonstrated a significant reduction in bleeding risk, as expected. On the contrary, a significant increase in the risk of overall and cardiovascular death and of stent thrombosis was shown.

The RD and the derived NNT ruled out that, due to the lower incidence of the events, the real benefit of DAT *vs.* TAT was a reduction of 2 major bleeding cases every 100 treated patients. On the contrary, the overall and cardiovascular mortality was increased in DAT, with two more deaths every 100 treated patients.

Conclusions: Our meta-analysis demonstrates that, to be appropriate for use in clinical practice, guidelines must be based on solid scientific evidence from RCTs, complemented by observational studies that better represent real-world patients and treatment adherence. Furthermore, in case of rare events, RR can amplify the size of an effect that is clinically not relevant. Efficacy measures that take into account the low incidence of the event, such as RD and NNT, are desirable. Furthermore, the NNT allows for the direct quantification of the number of patients who benefit or suffer harm from the study treatment and should therefore be preferred.

KEYWORDS: Dual antithrombotic therapy, Triple antithrombotic therapy, Atrial fibrillation, Percutaneous coronary intervention, Number needed to treat.



Graphical Abstract. Effectiveness of DAT *vs*. TAT in AF patients undergoing PCI. DAT: dual antithrombotic therapy; NNT: Number Needed to Treat; RD: risk difference; RR: relative risk; TAT: triple antithrombotic therapy.

INTRODUCTION

Randomized controlled trials (RCTs) are the most reliable studies for assessing causal relationships between interventions and outcomes[1]. This is because: i) random assignment of participants to treatment and control groups helps to ensure comparability of the study groups, ii) the strict inclusion criteria reduce the possibility that external factors may influence outcomes.

On the other hand, real-world data are increasingly being used to complement RCT findings and provide a more complete picture of treatment effectiveness and safety, because they are representative of the widest spectrum of patients available in routine clinical practice[1-4].

At the present time, in patients with non-valvular atrial fibrillation (AF) undergoing percutaneous coronary artery intervention (PCI), the recommended antithrombotic therapy to be prescribed was modified[5-9] based on the evidence coming from the RCTs performed in this setting[10-17], even if the reference trials were not powered to achieve comprehensive results for all the examined endpoints[10-15,18,19].

In particular, the RCTs on which the current guideline recommendations are based consistently demonstrated a significant reduction in major bleeding when, in patients requiring long-term oral anticoagulation (OAC), a double antithrombotic therapy (DAT) consisting of OAC plus a single antiplatelet agent was used instead of the triple antithrombotic therapy (TAT) including dual antiplatelet treatment[10-17]. On the contrary, they did not have a sufficient sample size (and consequently, an adequate power) to evaluate the efficacy of DAT *vs*. TAT in preventing stent thrombosis[16-18].

On these grounds, the present meta-analysis, which includes a larger sample (about 20,000 patients) from real-life studies and registries, could contribute to comparing the efficacy/safety of DAT *vs.* TAT in patients with non-valvular AF undergoing percutaneous revascularization with stent implantation.

MATERIALS AND METHODS

The meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[20]. The observational studies (Obs) published from January 1, 2013 to December 31, 2024 were selected from a literature search of the PubMed computerized database in order to include real-life studies published in English language, comparing the risk/benefit of DAT (OAC plus a single antiplatelet agent) *vs.* TAT (OAC and a double antiplatelet agent) at ≥1year follow-up in patients with non-valvular AF after PCI with stent. The study selection process was performed independently by two reviewers, with an additional reviewer brought in on occasion if there were significant disagreements between the initial reviewers.

RCTs, case reports, letters to the editor, or articles unrelated to the aim of the present meta-analysis were excluded. The retrieved Obs were excluded in case of duplicates, when not providing sufficient data for risk estimation or in case of a follow-up of less than 12 months.

Study outcomes

The examined endpoints at ≥12 months of follow-up were cardiac and all-cause death, all major bleedings, intracranial hemorrhage, stroke, and stent thrombosis. The bleeding criteria for each study are reported in Table I.

Statistical analysis

The meta-analysis was performed using Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020[21]. The risk ratios (RRs) with 95% Confidence Intervals (CIs) were computed using a random-effect Mantel-Haenszel model to correct the effect estimate in case of heterogeneity among individual studies.

The results are presented graphically in the Forest plot reporting the effect estimates for i) each individual study and ii) the overall measure of the effect, together with iii) the Cochran's Q test and I^2 statistics computed to quantify the homogeneity/heterogeneity among the individual studies.

Due to the low weighted incidence of the events in both groups, the Absolute risk reduction (RD) using the random-effect model was also computed together with the 95% CI. The effect was then translated into the Number Needed to Treat (NNT) in order to quantify the effective benefit/harm of DAT *vs.* TAT for each endpoint under evaluation[22]. A bidirectional alpha error <0.05 was considered statistically significant.

RESULTS

Out of the 1,804 articles identified at the initial screening, after detailed review, 16 Obs[23-38], including about 20,000 patients (exactly 5,544 in DAT and 14,206 in TAT), were selected (Figure 1, Table I). Details about the main characteristics of these studies are reported in Table I.

Primary endpoints

All-cause death

The analysis on all-cause death included 18,348 patients from 15 studies (5,287 in DAT, 13,061 in TAT). The incidence rate of all-cause deaths was greater in DAT (12.46%) than in TAT (9.15%). The RR of DAT *vs.* TAT was significantly greater than 1 (RR: 1.29; 95% CI 1.08 to 1.54; p=0.005; Figure 2a) with a moderate heterogeneity (I^2=50%). On the contrary, the RD did not show significant differences between DAT and TAT (RD: 0.02; 95% CI -0.01 to 0.04; p=0.14; Table II).

The NNT was equal to 50, meaning that there are 2 more deaths in DAT every 100 treated patients (Table II).

Cardiovascular death

Data on cardiovascular mortality was available in 8 studies and included 5,128 patients (DAT: 1,461; TAT: 3,667). The risk of cardiovascular death was significantly higher in DAT *vs.* TAT (RR=1.48; 95% CI 1.07 to 2.06; p=0.02). A slight heterogeneity was observed among studies (I^2=23%, Figure 2b). The incidence rate of cardiac mortality was 7.11% in DAT and 4.61% in TAT, with an NNT equal to 50, i.e., 2 more deaths in DAT every 100 treated patients.

The RD did not show significant differences between DAT *vs.* TAT (RD: 0.02; 95% CI -0.01 to 0.04; p=NS; Table II).

Major bleeding

The analysis included 18,500 patients (DAT: 5,372; TAT: 13,128) from 16 studies (Figure 3) with a mild heterogeneity among studies (I^2=25%). The risk of major bleeding was significantly reduced in patients receiving *DAT vs.* TAT (RR: 0.83; 95% CI 0.69 to 0.99; p=0.04) with an incidence

Table I. Characteristics of the studies included in the meta-analysis.

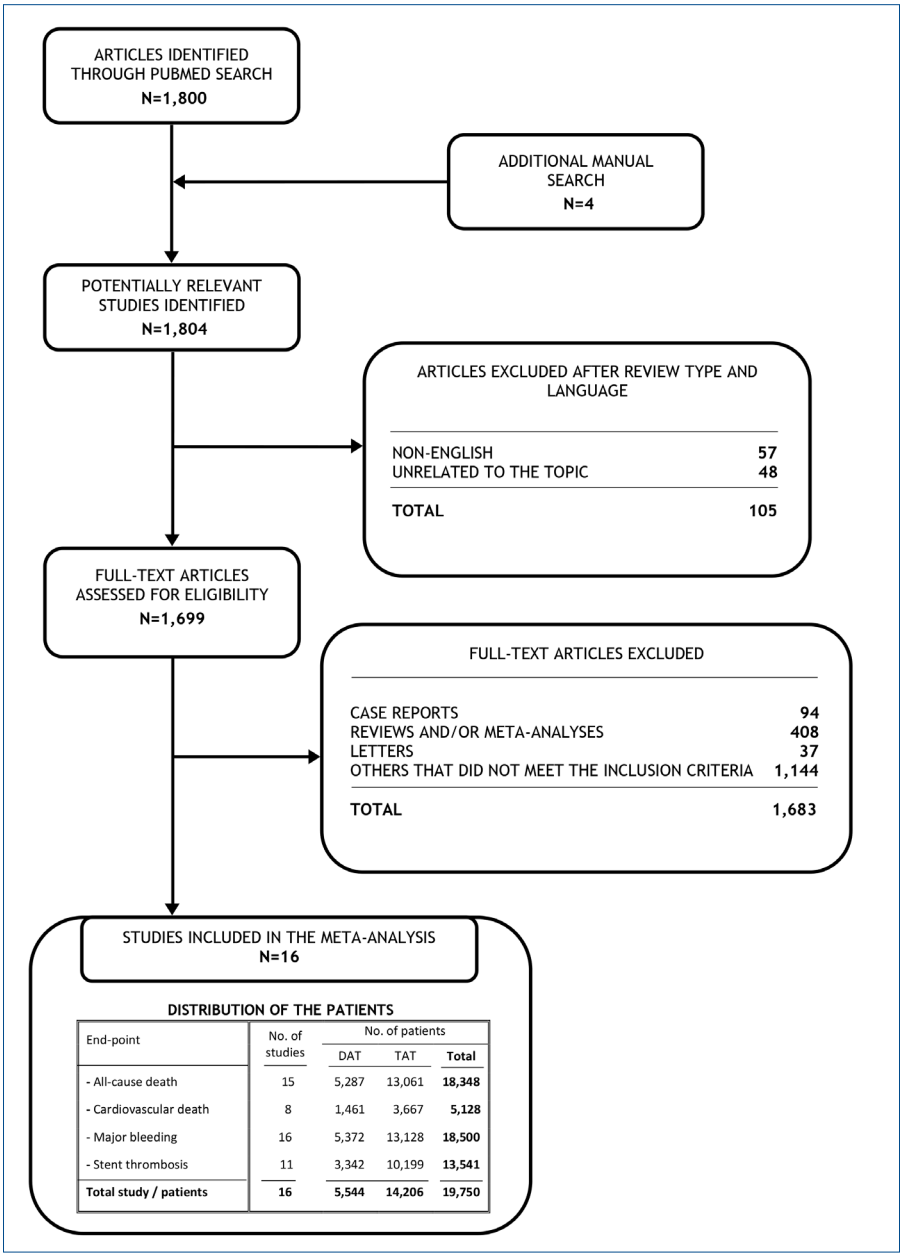
Study (NCT* registry number)	Publication year	Study design and setting	Period	Pts characteristics	Study population	Bleeding criteria	Follow-up (months)	Pts included in the meta-analysis			OAC	
								DAT	TAT	Total	DAT	TAT
Lamberts et al[23]	2013	Retrospective study. Data collected using nationwide Danish Registries	Jan 2001-Dec 2009	Pts with AF hospitalized for MI or PCI	12,165	NA	12	548	1,896	2,444	- VKA	- VKA
Rubboli et al[24] - *AFCAS Registry (NCT00596570)*	2014	Prospective, multicenter Registry. Pts from 17 institutions in 5 European countries (Italy, Germany, Finland, Spain, United Kingdom)	Oct 2008-Aug 2010	AF pts undergoing PCI with stent	975 enrolled 914 included	BARC	12	73	679	752	- VKA	- VKA
Rubboli et al[25] - *WAR-STENT Registry (NCT00722319)*	2014	Prospective registry including 37 Italian centers	Nov 2008-Jun 2010	Pts with OAC undergoing PCI with stent	411	TIMI	12	20	339	359	- VKA	- VKA
Sindet-Pedersen et al[26]	2018	Prospective study including pts identified from Danish nationwide administrative registries	Aug 2011-Jun 2017	AF pts under OAC therapy hospitalized with MI and/or PCI	3,222	NA	12	1,470	1,752	3,222	- VKA: n=875 - NOAC: n=595	- VKA: n=1,074 - NOAC: n=678
Wustrow et al[27]	2018	Cohort study, 2 centers in München, Germany	Jan 2013-Dec 2013	Pts with OAC undergoing PCI with stent	237	BARC, TIMI	12	89	148	237	- VKA: n=60 - NOAC: n=29	- VKA: n=139 - NOAC: n=9
Heger et al[28]	2020	Retrospective, single center, cohort study in Germany	Apr 2013-May 2018	Pts with AF undergoing PCI	259	BARC, ISTH	Until 36 Mdn=13.3	127	132	259 - VKA: 126 - NOAC: 133	- VKA: NR - NOAC: NR	- VKA: NR - NOAC: NR
De La Torre Hernandez et al[29] - *PACO-PCI Registry*	2021	Retrospective, multicenter (20 centers) in Spain	Jan 2016-May 2019 with stent	AF pts (>75 years) undergoing PCI	1,249	ISTH	12	228	1,021	1,249	- VKA: n=67 - NOAC: n=161	- VKA: n=527 - NOAC: n=494
Bor et al[30] - *WEST 2 Registry (NCT02635230)*	2022	Prospective registry performed in 10 PCI centers in the Netherlands an Belgium	2014-2021	Pts undergoing PCI with indication to long term OAC therapy	1,075	BARC	12	644	415	1,059	- VKA: n=314 - NOAC: n=331	- VKA: n=182 - NOAC: n=232

Continued

Table I *(Continued)*. Characteristics of the studies included in the meta-analysis.

Study (NCT* registry number)	Publication year	Study design and setting	Period	Pts characteristics	Study population	Bleeding criteria	Follow-up (months)	Pts included in the meta-analysis			OAC	
								DAT	TAT	Total	DAT	TAT
Chandrasekhar et al[31] - *AVIATOR 2 Registry (NCT02362659)*	2022	Prospective multicenter registry from 11 international sites (5 in USA, 4 in Italy, 1 in Germany, 1 in Greece)	Jun 201-Nov 2017	AF pts undergoing PCI	514	BARC	12	65	338	403	- VKA: n=18 - NOAC: n=47	- VKA: n=155 - NOAC: n=183
Berteotti et al[32]	2023	Prospective single center registry (Italy)	Apr 2018-Mar 2021	AF pts undergoing PCI	147	ISTH	12	56	91	147	- VKA: n=9 - NOAC: n=47	- VKA: n=38 - NOAC: n=53
Kitahara et al[33] - *CHIBA AF-PCI Registry*	2023	Multicenter (15 institutions) in Japan, prospective and retrospective	Jan 2015-Mar 2021	AF pts undergoing PCI	710	BARC	12	157	471	628	- OAC: n=157	- OAC: n=471
Zhou et al[34]	2023	Retrospective, single center in China	Jan 2016-Dec 2018	AF pts undergoing PCI	272	TIMI	~ 21	42	61	103	- OAC: n=42	- OAC: n=61
Durand et al[35]	2024	Retrospective study of the FRANCE PCI Registry	2014-2020	PCI pts discharged with OAC	7,277	BARC	12	1,700	5,577	7,277	- VKA: n=342 - NOAC: n=1,358	- VKA: n=2,090 - NOAC: n=3,48
Saad et al[36]	2024	Retrospective in a single Malaysian cohort	Jan 2020-May 2022	Non-valvular AF and ACS	206	NA	12	103	103	206	- VKA	- VKA
Wang et al[37]	2024	Prospective, single center study in China	2017-2019	AF and CCS undergoing PCI	516	TIMI	Mdn=36	25	165	190	- VKA: n=5 - NOAC: n=20	- VKA: n=43 - NOAC: n=122
Sciahbasi et al[38]	2024	Prospective PERSEO Registry (NCT03392948) enrolling 25 Italian centers	Feb 201-Feb 2022	PCI pts discharged with OAC	1,234	BARC	12	197	1018	1,215	NA	NA
			Total		**30,408**			**5,544**	**14,206**	**19,750**		

*NCT: National Clinical Trial (https://www.clinicaltrials.gov). ACS: acute coronary syndrome; AF: atrial fibrillation; ASA: acetylsalicylic acid; CCS: chronic coronary syndrome; DAPT: dual antiplatelet therapy; DAT: dual antithrombotic therapy; Mdn: median; MI: myocardial infarction: NA: not available; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; pts: patients; SAPT: single antiplatelet therapy; TAT: triple antithrombotic therapy; VKA: vitamin K antagonist.



End-point	No. of studies	No. of patients		
		DAT	TAT	Total
- All-cause death	15	5,287	13,061	**18,348**
- Cardiovascular death	8	1,461	3,667	**5,128**
- Major bleeding	16	5,372	13,128	**18,500**
- Stent thrombosis	11	3,342	10,199	**13,541**
Total study / patients	**16**	**5,544**	**14,206**	**19,750**

Figure 1. Flowchart of the study selection process.

rate of major bleeding of 7.05% in DAT against 9.11% in TAT. The NNT equal to -50 means that 2 fewer major bleeds occur in DAT *vs.* TAT every 100 treated patients.

Also, the RD showed a significantly lower bleeding in DAT *vs.* TAT (RD: -0.02; 95% CI -0.03 to -0.01, p=0.008; Table II).

Intracranial hemorrhage

The analysis included 3,638 patients (DAT: 1,373; TAT: 2,265; Figure 4a) from 6 studies that had homogeneous results (I^2=0%) with a reduction in the risk for intracranial hemorrhage in DAT *vs.* TAT, although not statistically significant (RR: 0.81; 95% CI 0.40 to 1.65; p=0.56; Figure 4a). The RD showed no benefit of DAT *vs.* TAT with respect to the incidence of intracranial hemorrhage (RD: -0.00; 95% CI -0.01 to 0.00; p=0.38). The NNT was not estimable (Table II).

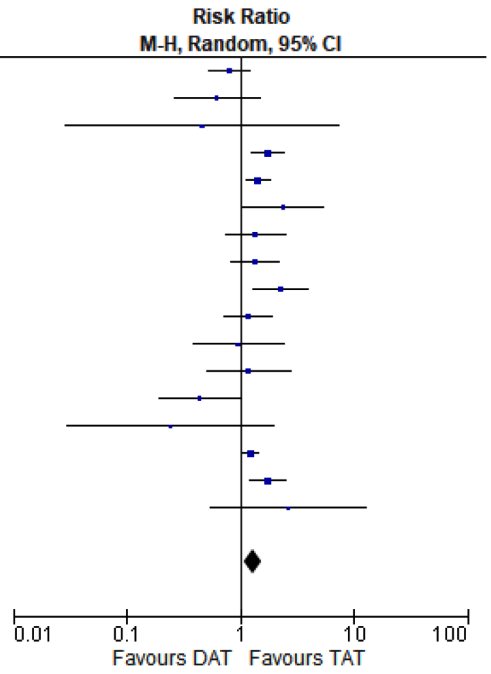
Stroke

The analysis on stroke incidence was performed on 17,916 patients (DAT: 5,103; TAT: 12,813; Figure 4b) from 13 studies. The risk of stroke was lower in TAT *vs.* DAT, although not statistically significant (RR: 1.09; 95% CI 0.82 to 1.43; p=0.56). The RD equal to 0 shows the same occurrence of stroke in DAT and in TAT (RD: 0.00; 95% CI -0.01 to 0.01; p=0.90). The NNT was not estimable (Table II).

a) All-cause death

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Lamberts	28	394	76	854	8.5%	0.80 [0.53, 1.21]	2013
Rubboli - AFCAS Registry	5	73	75	679	3.3%	0.62 [0.26, 1.48]	2014
Rubboli - WAR STENT	0	20	17	339	0.4%	0.46 [0.03, 7.43]	2014
Sindet-Petersen, NOAC	80	595	52	678	10.2%	1.75 [1.26, 2.44]	2018
Sindet-Petersen, VKA	125	875	108	1074	12.2%	1.42 [1.12, 1.81]	2018
Wustrow	13	89	9	148	3.7%	2.40 [1.07, 5.39]	2018
Heger	21	127	16	132	5.6%	1.36 [0.75, 2.49]	2020
de laTorre Hernandez - PACO-PCI Registry, NOAC	21	161	48	494	7.4%	1.34 [0.83, 2.17]	2021
de laTorre Hernandez - PACO-PCI Registry, VKA	13	67	45	527	6.2%	2.27 [1.29, 3.99]	2021
Bor - WOEST2 Registry	42	644	23	415	7.2%	1.18 [0.72, 1.93]	2022
Chandrasekhar - AVIATOR 2 Registry	5	65	27	338	3.1%	0.96 [0.39, 2.41]	2022
Berteotti	8	56	11	91	3.5%	1.18 [0.51, 2.76]	2023
Kitahara - CHIBA AF-PCI Registry	6	157	41	471	3.5%	0.44 [0.19, 1.01]	2023
Zhou	1	42	6	61	0.7%	0.24 [0.03, 1.94]	2023
Durand	167	1700	446	5577	13.8%	1.23 [1.04, 1.46]	2024
Sciahbasi - PERSEO Registry	33	197	97	1018	9.5%	1.76 [1.22, 2.53]	2024
Wang	2	25	5	165	1.2%	2.64 [0.54, 12.88]	2024
Total (95% CI)		**5287**		**13061**	**100.0%**	**1.29 [1.08, 1.54]**	
Total events	570		1102				

Heterogeneity: Tau² = 0.05; Chi² = 31.88, df = 16 (P = 0.01); I² = 50%
Test for overall effect: Z = 2.80 (P = 0.005)



b) Cardiovascular death

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Wustrow	11	89	8	148	11.0%	2.29 [0.96, 5.47]	2018
de laTorre Hernandez - PACO-PCI Registry, NOAC	13	161	15	494	14.5%	2.66 [1.29, 5.47]	2021
de laTorre Hernandez - PACO-PCI Registry, VKA	6	67	29	527	11.6%	1.63 [0.70, 3.78]	2021
Bor - WOEST2 Registry	28	644	16	415	18.5%	1.13 [0.62, 2.06]	2022
Chandrasekhar - AVIATOR 2 Registry	5	65	20	338	9.7%	1.30 [0.51, 3.34]	2022
Berteotti	4	56	8	91	6.9%	0.81 [0.26, 2.57]	2023
Kitahara - CHIBA AF-PCI Registry	3	157	21	471	6.5%	0.43 [0.13, 1.42]	2023
Sciahbasi - PERSEO Registry	12	197	37	1018	17.4%	1.68 [0.89, 3.16]	2024
Wang	2	25	5	165	3.9%	2.64 [0.54, 12.88]	2024
Total (95% CI)		**1461**		**3667**	**100.0%**	**1.48 [1.07, 2.06]**	
Total events	84		159				

Heterogeneity: Tau² = 0.06; Chi² = 10.37, df = 8 (P = 0.24); I² = 23%
Test for overall effect: Z = 2.37 (P = 0.02)

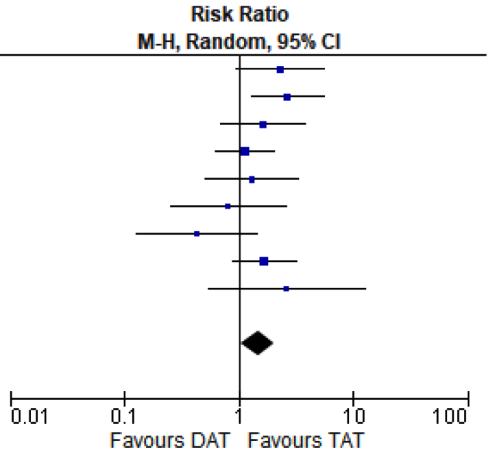


Figure 2. Meta-analysis on RR of **(a)** all-cause death and **(b)** cardiovascular death between patients with DAT *vs.* those with TAT. CI: confidence interval; DAT: dual antithrombotic therapy; M-H: Mantel-Haenszel; TAT: triple antithrombotic therapy.

Table II. Total events occurring in DAT and TAT and incidence of events weighted according to study population.

Endpoint	N. of studies	DAT		TAT		Weighted incidence (%)		RR (95% CI)	RD (95% CI)	NNT	Meaning: benefit/harm in DAT every 100 treated patients
		Events	Total	Events	Total	DAT	TAT				
All cause death	15	570	5,287	1,102	13,061	12.46	9.15	1.29 (1.08, 1.54)	0.02 (-0.01, 0.04)	50	2 more all cause deaths in DAT
Cardiovascular death	8	84	1,461	159	3,667	7.11	4.61	1.48 (1.07, 2.06)	0.02 (-0.01, 0.04)	50	2 more cardiovascular deaths in DAT
Major bleeding	16	312	5,372	826	13,128	7.05	9.11	0.83 (0.69, 0.99)	-0.02 (-0.03, -0.01)	-50	2 less major bleeding in DAT
Intracranial hemorrhage	6	11	1,373	28	2,265	1.22	1.53	0.81 (0.40, 1.65)	-0.00 (-0.01, 0.00)	Not estimable	Not estimable
Stroke	13	97	5,103	207	12,813	2.13	2.22	1.09 (0.82, 1.43)	-0.00 (-0.01, 0.01)	Not estimable	Not estimable
Stent thrombosis	11	34	3,342	66	10,199	1.54	0.89	1.59 (1.01, 2.49)	0.00 (-0.00, 0.00)	Not estimable	Not estimable

CI: confidence interval; DAT: dual antithrombotic therapy; NNT, number needed to treat; RD, risk difference; RR, risk ratio; TAT: triple antithrombotic therapy.

Major bleeding

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Lamberts	41	376	117	818	13.9%	0.76 [0.55, 1.06]	2013
Rubboli - WAR STENT	1	20	14	339	0.8%	1.21 [0.17, 8.75]	2014
Rubboli - AFCAS Registry	5	73	69	679	3.6%	0.67 [0.28, 1.62]	2014
Sindet-Petersen, VKA	54	875	98	1074	14.5%	0.68 [0.49, 0.93]	2018
Sindet-Petersen, NOAC	31	595	27	678	8.6%	1.31 [0.79, 2.17]	2018
Wustrow	3	89	7	148	1.7%	0.71 [0.19, 2.69]	2018
Heger	4	127	4	132	1.6%	1.04 [0.27, 4.07]	2020
de laTorre Hernandez - PACO-PCI Registry, NOAC	10	161	42	494	5.7%	0.73 [0.38, 1.42]	2021
de laTorre Hernandez - PACO-PCI Registry, VKA	4	67	62	527	3.0%	0.51 [0.19, 1.35]	2021
Bor - WOEST2 Registry	49	644	33	415	10.7%	0.96 [0.63, 1.46]	2022
Chandrasekhar - AVIATOR 2 Registry	4	65	18	338	2.6%	1.16 [0.40, 3.30]	2022
Berteotti	5	56	9	91	2.6%	0.90 [0.32, 2.56]	2023
Zhou	0	42	5	61	0.4%	0.13 [0.01, 2.31]	2023
Kitahara - CHIBA AF-PCI Registry	4	157	27	471	2.7%	0.44 [0.16, 1.25]	2023
Saad	16	103	26	103	7.4%	0.62 [0.35, 1.08]	2024
Wang	0	25	4	165	0.4%	0.71 [0.04, 12.79]	2024
Sciahbasi - PERSEO Registry	3	197	52	1018	2.2%	0.30 [0.09, 0.95]	2024
Durand	78	1700	212	5577	17.6%	1.21 [0.94, 1.56]	2024
Total (95% CI)		**5372**		**13128**	**100.0%**	**0.83 [0.69, 0.99]**	
Total events	312		826				

Heterogeneity: Tau² = 0.03; Chi² = 22.61, df = 17 (P = 0.16); I² = 25%

Test for overall effect: Z = 2.10 (P = 0.04)

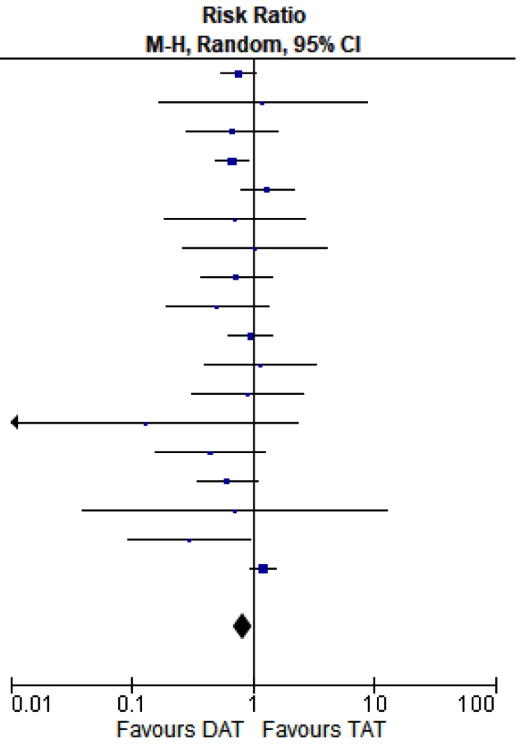
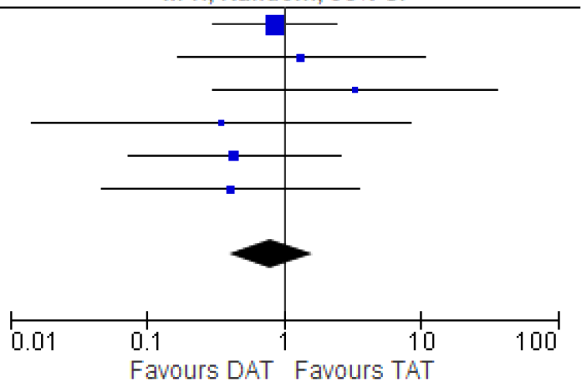


Figure 3. Meta-analysis on RR of major bleeding between patients with DAT *vs.* those with TAT. CI: confidence interval; DAT: dual antithrombotic therapy; M-H: Mantel-Haenszel; TAT: triple antithrombotic therapy.

a) Intracranial hemorrhage

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Lamberts	5	384	12	800	47.4%	0.87 [0.31, 2.45]	2013
Rubboli - AFCAS Registry	1	73	7	679	11.8%	1.33 [0.17, 10.65]	2014
Wustrow	2	89	1	148	8.9%	3.33 [0.31, 36.15]	2018
Heger	0	127	1	132	5.0%	0.35 [0.01, 8.42]	2020
Bor - WOEST2 Registry	2	644	3	415	16.0%	0.43 [0.07, 2.56]	2022
Berteotti	1	56	4	91	10.9%	0.41 [0.05, 3.54]	2023
Total (95% CI)		**1373**		**2265**	**100.0%**	**0.81 [0.40, 1.65]**	
Total events	11		28				

Heterogeneity: Tau² = 0.00; Chi² = 2.73, df = 5 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)



b) Stroke

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Lamberts	11	393	34	829	14.7%	0.68 [0.35, 1.33]	2013
Rubboli - WAR STENT	0	20	5	339	0.9%	1.47 [0.08, 25.73]	2014
Rubboli - AFCAS Registry	1	73	14	679	1.8%	0.66 [0.09, 4.98]	2014
Sindet-Petersen, NOAC	10	595	21	678	12.2%	0.54 [0.26, 1.14]	2018
Sindet-Petersen, VKA	28	875	24	1074	21.1%	1.43 [0.84, 2.45]	2018
Wustrow	2	89	1	148	1.3%	3.33 [0.31, 36.15]	2018
de laTorre Hernandez - PACO-PCI Registry, NOAC	5	161	5	494	4.8%	3.07 [0.90, 10.46]	2021
de laTorre Hernandez - PACO-PCI Registry, VKA	1	67	6	527	1.7%	1.31 [0.16, 10.72]	2021
Chandrasekhar - AVIATOR 2 Registry	2	65	5	338	2.8%	2.08 [0.41, 10.49]	2022
Bor - WOEST2 Registry	12	644	5	415	6.7%	1.55 [0.55, 4.36]	2022
Kitahara - CHIBA AF-PCI Registry	3	157	19	471	5.0%	0.47 [0.14, 1.58]	2023
Zhou	1	42	2	61	1.3%	0.73 [0.07, 7.75]	2023
Durand	19	1700	45	5577	21.4%	1.39 [0.81, 2.36]	2024
Sciahbasi - PERSEO Registry	2	197	10	1018	3.2%	1.03 [0.23, 4.68]	2024
Wang	0	25	11	165	1.0%	0.28 [0.02, 4.57]	2024
Total (95% CI)		**5103**		**12813**	**100.0%**	**1.09 [0.82, 1.43]**	
Total events	97		207				

Heterogeneity: Tau² = 0.02; Chi² = 14.92, df = 14 (P = 0.38); I² = 6%
Test for overall effect: Z = 0.59 (P = 0.56)

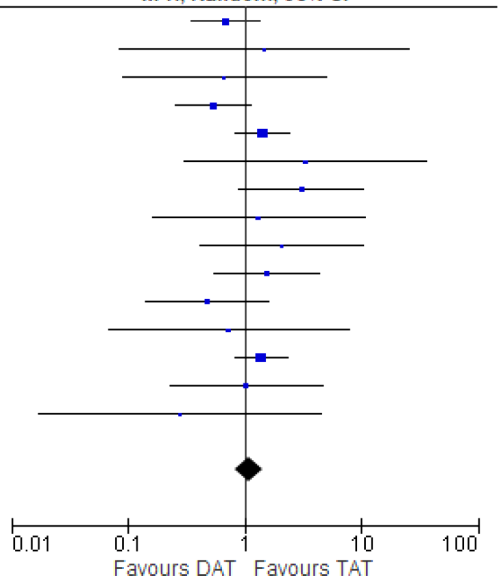


Figure 4. Meta-analysis on RR of **(a)** intracranial hemorrhage and **(b)** stroke between patients with DAT *vs*. those with TAT. CI: confidence interval, DAT: dual antithrombotic therapy, M-H: Mantel-Haenszel, TAT: triple antithrombotic therapy.

Stent thrombosis

The analysis of stent thrombosis was performed in 13,541 patients (DAT: 3,342; TAT: 10,199) across 11 studies. The analysis showed homogeneous results in the Obs (I^2=0%) and a significantly greater risk for stent thrombosis in patients treated with DAT than in TAT (RR=1.59; 95% CI 1.01 to 2.49; p=0.05; Figure 5). With an incidence rate of stent thrombosis of 1.54% in DAT against 0.89% in TAT, the RD did not show differences between DAT *vs.* TAT (RD=0.00; 95% CI -0.00 to 0.00; p=0.33; Table II). The NNT was not estimable.

DISCUSSION

Patients with AF and acute coronary syndrome (ACS) or undergoing PCI require antithrombotic therapy with a combination of i) OAC, to prevent atrial fibrillation-related thromboembolic events[39,40], and ii) dual antiplatelet therapy (aspirin in association with a P2Y12 inhibitor), to prevent ischemic events[41].

However, the increased prevalence trend of AF in patients with coronary disease requiring PCI, due to population aging[42], made it necessary to find a best therapeutic strategy able to reduce the risks related to TAT administration[5-9].

For this reason, supported by the results of RCTs, the guideline recommendations were revised for both acute and chronic coronary syndromes, advocating a very short course of TAT followed by DAT[5-9].

However, the results of RCTs assess efficacy under ideal conditions and need to be validated in real-world clinical practice, where patients are often more complex[3,4]. Indeed, integrating RCT evidence with observational data, obtained in more realistic contexts, offers a valuable source of supplementary information to RCTs[1-4].

Our meta-analysis, which includes almost 20,000 patients from Obs, had the statistical power for detecting the impact of DAT *vs.* TAT, demonstrating a significant RR for overall and cardiac mortality with a higher weighted mortality rate in DAT than in TAT (all-cause: DAT 12.46%, TAT 9.15%; cardiac: DAT 7.11%, TAT 4.61%). As for stent thrombosis, even if the occurrence of this event was low, the rate was higher in DAT than in TAT (DAT 1.54%, TAT 0.89%; Table II). On the contrary, a lower rate of major bleeding was confirmed in DAT (DAT 7.05%, TAT 9.11%; Table II).

It should also be noted that comparisons between groups are typically expressed using relative measures, such as relative risk or odds ratio, which show the size of change as a ratio compared to the baseline risk[22]. However, the relative measures are sensitive to the prevalence of the underlying condition (event incidence). In low-incidence situations, the clinical significance may be overestimated by RR[43]; thus, in order to have more comprehensive and practical information, the risk needs to be translated into absolute terms, like RD or NNT. In particular, NNT quantifies how many patients need to be treated with a specific intervention (e.g., a drug or therapy) for one of them to experience a beneficial or detrimental outcome, compared to a control group (e.g., a placebo or standard treatment)[22,44].

More than other parameters, NNT helps doctors and patients decide the acceptable risk level and choose the best interventions, from a public health benefits perspective, to which to allocate the limited financial resources.

For these reasons, relative and absolute measures provide complementary information: relative measures help to understand the magnitude of the effect, while absolute measures help to understand the real clinical benefit, i.e., the actual impact on population health[43,45,46].

As shown in Table II, in our meta-analysis, only in front of a greater incidence rate of the events (as for all-cause and cardiovascular death), the significant differences observed at RR were confirmed in absolute terms at RD, showing a different and effective impact of the two treatments.

On the contrary, the lower incidence rate of stent thrombosis observed in TAT produces a significant difference at RR not confirmed at RD. Moreover, as it can be seen from Table II, the NNT calculation shows that the actual benefit of DAT *vs.* TAT is almost irrelevant. For major bleeding, there are only two fewer events with DAT *vs.* TAT per 100 patiens treated, while there are two more events for all-cause and cardiovascular death per 100 patiens treated. Therefore, the benefit observed with DAT regarding major bleeding appears to be offset by the harm regarding the overall and cardiovascular death, thus raising doubts about the actual superiority of DAT *vs.* TAT in the overall evaluation of both safety and efficacy.

Limitations

The possible limitations of our meta-analysis could stem from greater heterogeneity among the patients and studies included from Obs. However, the I^2 test shows only a low/moderate heterogeneity for all the examined endpoints. In addition, during our meta-analysis, we applied the random Mantel-Haenszel model to make the analysis more conservative and to correct the effect estimate in cases of heterogeneity among individual studies greater than expected by chance.

Stent thrombosis

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Rubboli - AFCAS Registry	2	73	9	679	9.0%	2.07 [0.46, 9.39]	2014
Rubboli - WAR STENT	0	20	3	339	2.4%	2.31 [0.12, 43.33]	2014
Wustrow	4	89	1	148	4.3%	6.65 [0.76, 58.58]	2018
Heger	0	127	1	132	2.0%	0.35 [0.01, 8.42]	2020
de laTorre Hernandez - PACO-PCI Registry, NOAC	2	161	6	494	8.1%	1.02 [0.21, 5.02]	2021
de laTorre Hernandez - PACO-PCI Registry, VKA	2	67	4	527	7.3%	3.93 [0.73, 21.06]	2021
Chandrasekhar - AVIATOR 2 Registry	1	65	4	338	4.3%	1.30 [0.15, 11.44]	2022
Bor - WOEST2 Registry	11	644	4	415	15.9%	1.77 [0.57, 5.53]	2022
Zhou	1	42	1	61	2.7%	1.45 [0.09, 22.58]	2023
Kitahara - CHIBA AF-PCI Registry	1	157	4	471	4.3%	0.75 [0.08, 6.66]	2023
Durand	7	1700	17	5577	26.6%	1.35 [0.56, 3.25]	2024
Sciahbasi - PERSEO Registry	3	197	12	1018	13.0%	1.29 [0.37, 4.54]	2024
Total (95% CI)		**3342**		**10199**	**100.0%**	**1.59 [1.01, 2.49]**	
Total events	34		66				

Heterogeneity: Tau² = 0.00; Chi² = 4.90, df = 11 (P = 0.94); I² = 0%

Test for overall effect: Z = 1.99 (P = 0.05)

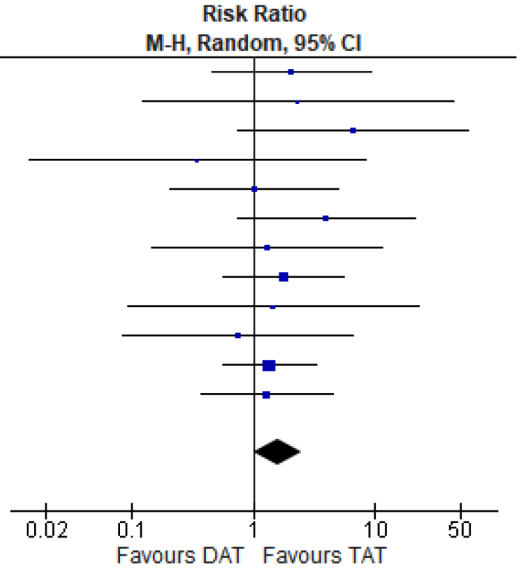


Figure 5. Meta-analysis on RR risk ratio of stent thrombosis between patients with DAT *vs*. those with TAT. CI: confidence interval, DAT: dual antithrombotic therapy, M-H: Mantel-Haenszel, TAT: triple antithrombotic therapy.

Another limitation is that the literature search was conducted exclusively in the PubMed database. This choice, however, was based on its recognized reliability and primary focus on medicine and biomedical sciences, as well as its inclusion of online-first publications not yet available in SCOPUS or Web of Science.

CONCLUSIONS

Our meta-analysis shows that, for guidelines to be useful in clinical practice, it is necessary to: (i) verify that RCTs are robust and sufficiently powered to evaluate the hypotheses under study; (ii) assess whether the clinical characteristics of the patients being studied correspond to those of the general population targeted by the intervention under consideration; and (iii) take into account evidence from observational studies to confirm and complement the results of the RCTs[47,48].

In addition, guidelines must be understandable to clinicians. To this end, as recently reported in the 2023 Canadian Cardiovascular Society Antiplatelet Guidelines[9], results should not only be reported as RR or RD, but also translated into a metric, such as NNT, which provides a more direct and understandable measure of a treatment's effectiveness.

Conflict of Interest
The authors have no conflicts of interest to declare.

Funding
None.

Ethics Committee and Informed Consent
Not applicable.

Availability of Data and Materials
All data reported in this meta-analysis are extracted or derived from the selected studies and reported in the Forest plots and/or in Tables I and II; further inquiries can be directed to the corresponding author.

Authors' Contributions
Maria Cristina Acconcia contributed to the conception and design of the study, acquisition and analysis of the data, and drafted the manuscript and prepared the figures.
Quintilio Caretta contributed to the conception and design of the study, drafted the manuscript, and prepared the figures.
Gaetano Tanzilli contributed to the conception and design of the study.
Giuseppe Pannarale contributed to the acquisition and analysis of data.
Flavia Chiarotti contributed to the acquisition and analysis of the data and drafted the text.
All authors critically revised the manuscript, proofread, and approved the final manuscript.
The corresponding author attests that all listed authors meet the authorship criteria and that no other individuals meeting the criteria have been omitted.

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