

**Is Mortality Really an Issue for
Prolonged DAPT and
2nd Generation DES? Yes!
Increased Mortality Is a Serious
Concern**

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant/Research Support
- Consulting Fees/Honoraria

Company

- Eli Lilly
- Abbott Vascular

DAPT trial

Outcome	Continued Thienopyridine (N=5020)	Placebo (N=4941)	Hazard Ratio, Thienopyridine vs. Placebo (95% CI) [†]	P Value [†]
	<i>no. of patients (%)</i>			
Stent thrombosis [‡]	19 (0.4)	65 (1.4)	0.29 (0.17–0.48)	<0.001
Definite	15 (0.3)	58 (1.2)	0.26 (0.14–0.45)	<0.001
Probable	5 (0.1)	7 (0.1)	0.71 (0.22–2.23)	0.55
Major adverse cardiovascular and cerebrovascular events [§]	211 (4.3)	285 (5.9)	0.71 (0.59–0.85)	<0.001
Death	98 (2.0)	74 (1.5)	1.36 (1.00–1.85)	0.05
Cardiac	45 (0.9)	47 (1.0)	1.00 (0.66–1.52)	0.98
Vascular	5 (0.1)	5 (0.1)	0.98 (0.28–3.39)	0.98
Noncardiovascular	48 (1.0)	22 (0.5)	2.23 (1.32–3.78)	0.002
Myocardial infarction	99 (2.1)	198 (4.1)	0.47 (0.37–0.61)	<0.001
Stroke	37 (0.8)	43 (0.9)	0.80 (0.51–1.25)	0.32
Ischemic	24 (0.5)	34 (0.7)	0.68 (0.40–1.17)	0.16
Hemorrhagic	13 (0.3)	9 (0.2)	1.20 (0.50–2.91)	0.68
Type uncertain	0	1 (<0.1)	—	0.32

Mauri et al, NEJM 2014

Fourteen RCTs and 69,644 pts

	Study group	Control group	HR for all-cause mortality	HR (95% CI)
	N (events)	N (events)		
CASPAR	425 (24)	426 (17)		1.44 (0.77-2.68)
SPS3	1503 (113)	1517 (77)		1.52 (1.14-2.04)

8 DES trials

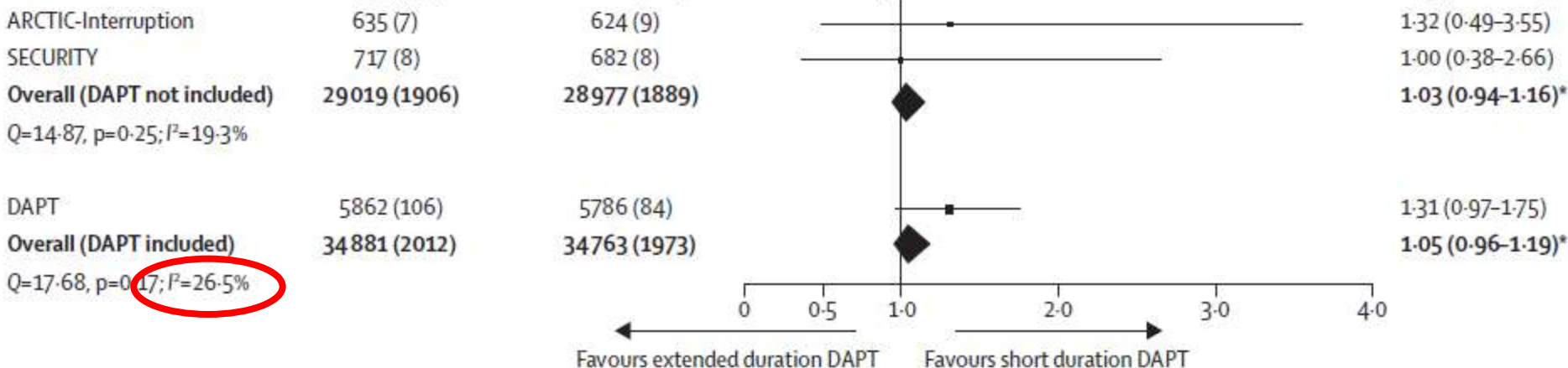
1 BMS trial

2 secondary prevention trials

1 atrial fibrillation trial

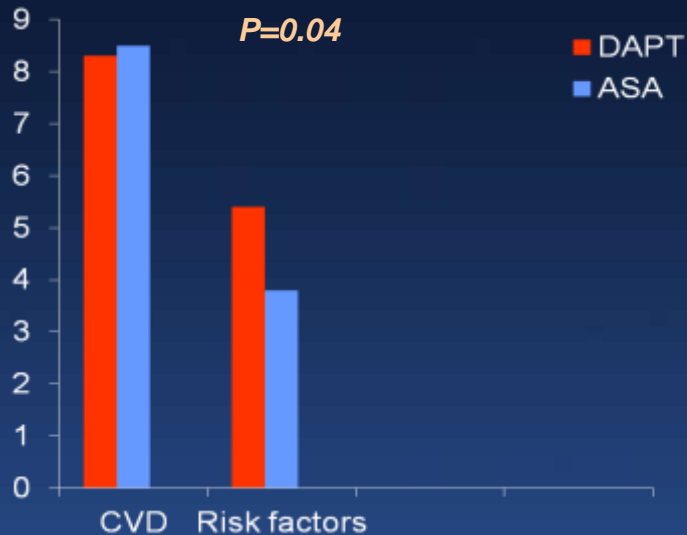
1 peripheral arterial disease trial

1 trial with a mixed population (multiple RF or established CV disease)



Treatment effect may be disease specific

CHARISMA Trial



Baht et al; NEJM 2006

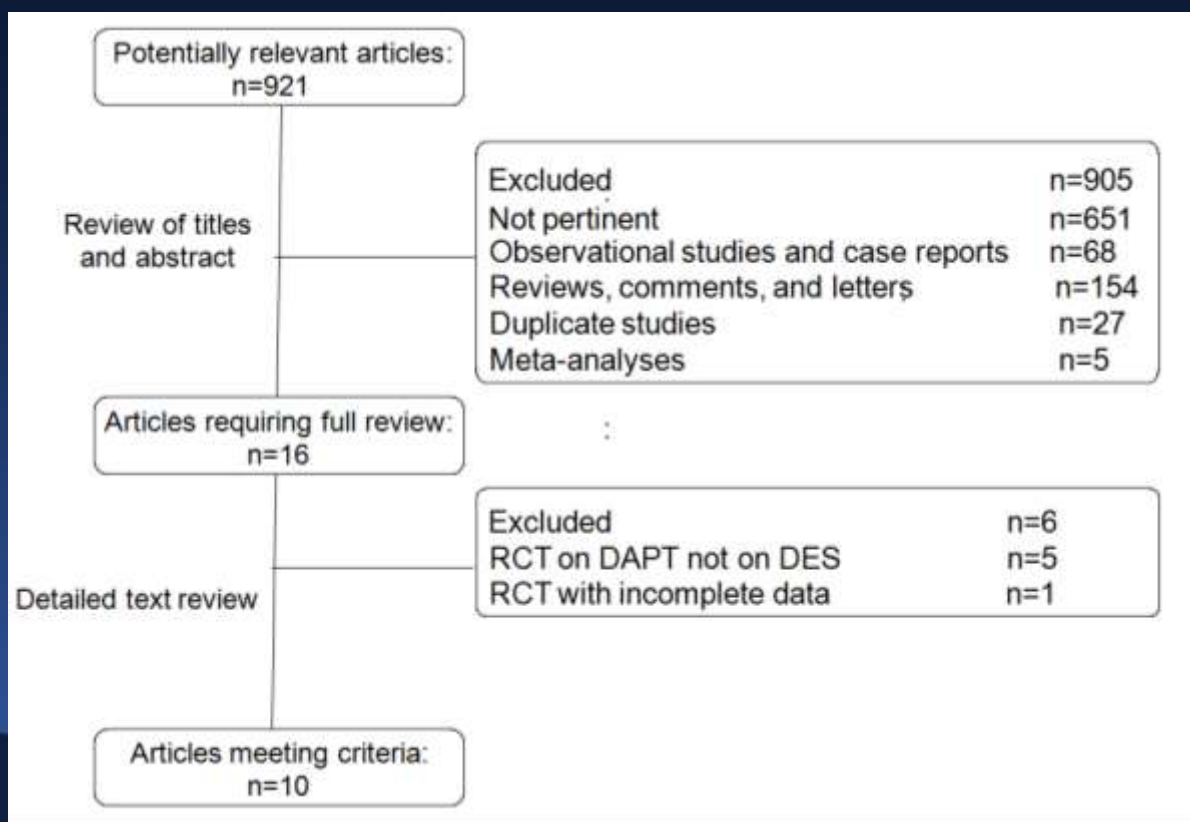
SPS trial

Outcome	Aspirin plus Placebo (N=1503)		Aspirin plus Clopidogrel (N=1517)		Hazard Ratio (95% CI)	P Value
	no.	rate (%/yr)	no.	rate (%/yr)		
All strokes (ischemic and hemorrhagic)	138	2.7	125	2.5	0.92 (0.72-1.16)	0.48
Ischemic stroke	124	2.4	100	2.0	0.82 (0.63-1.09)	0.13
Intracranial hemorrhage	13	0.25	21	0.42	1.65 (0.83-3.11)	0.15
Unknown†	1	0.02	4	0.08	3.97 (0.44-35.47)	0.22
Disabling or fatal stroke‡	40	0.78	42	0.84	1.06 (0.69-1.64)	0.79
Transient ischemic attack without stroke	39	0.78	28	0.57	0.73 (0.45-1.18)	0.19
Myocardial infarction	38	0.71	31	0.59	0.84 (0.52-1.35)	0.47
Other thromboembolic events§	12	0.22	21	0.40	1.81 (0.89-3.68)	0.10
Major vascular event¶	174	3.4	153	3.1	0.89 (0.72-1.11)	0.29
All deaths	77	1.4	113	2.1	1.52 (1.14-2.04)	0.004
Vascular causes	19	0.35	27	0.51	1.46 (0.81-2.64)	0.20
Cerebral	9	0.17	10	0.19	1.13 (0.46-2.78)	0.79
Noncerebral	10	0.18	17	0.32	1.77 (0.81-3.87)	0.15
Probable vascular causes	6	0.11	18	0.34	3.09 (1.23-7.80)	0.02
Nonvascular causes	31	0.57	39	0.73	1.31 (0.82-2.10)	0.26
Uncertain	21	0.39	29	0.55	1.41 (0.82-2.52)	0.21

SPS 3 Investigators

Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials

Tullio Palmerini, Umberto Benedetto, Letizia Bacchi-Reggiani, Diego Della Riva, Giuseppe Biondi-Zoccai, Fausto Feres, Alexandre Abizaid, Myeong-Ki Hong, Byeong-Keuk Kim, Yangsoo Jang, Hyo-Soo Kim, Kyung Woo Park, Philippe Genereux, Deepak L Bhatt, Carlotta Orlandi, Stefano De Servi, Mario Petrou, Claudio Rapezzi, Gregg W Stone

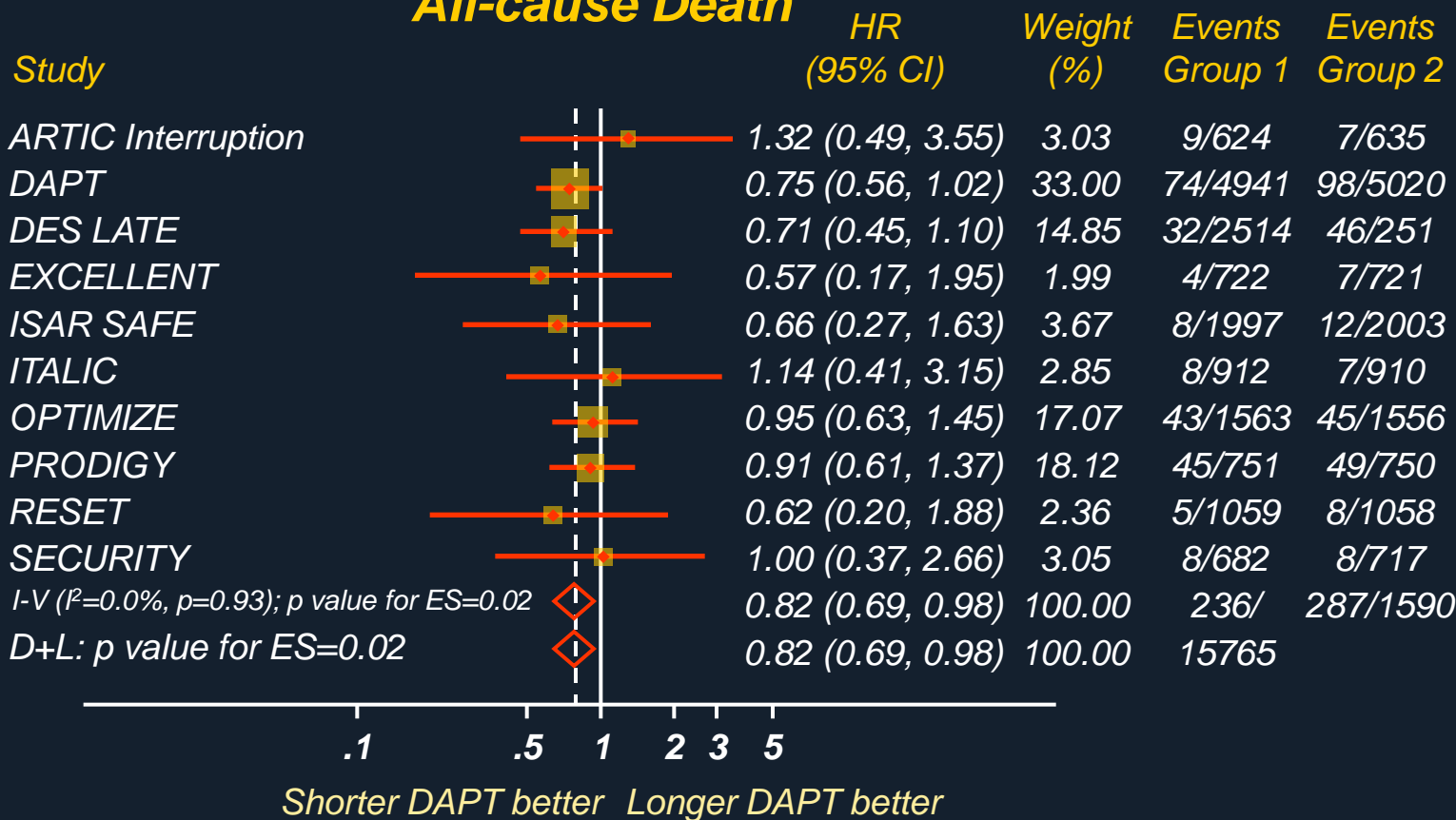


10 RCT
31,666 pts

Lancet 2015

Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

All-cause Death

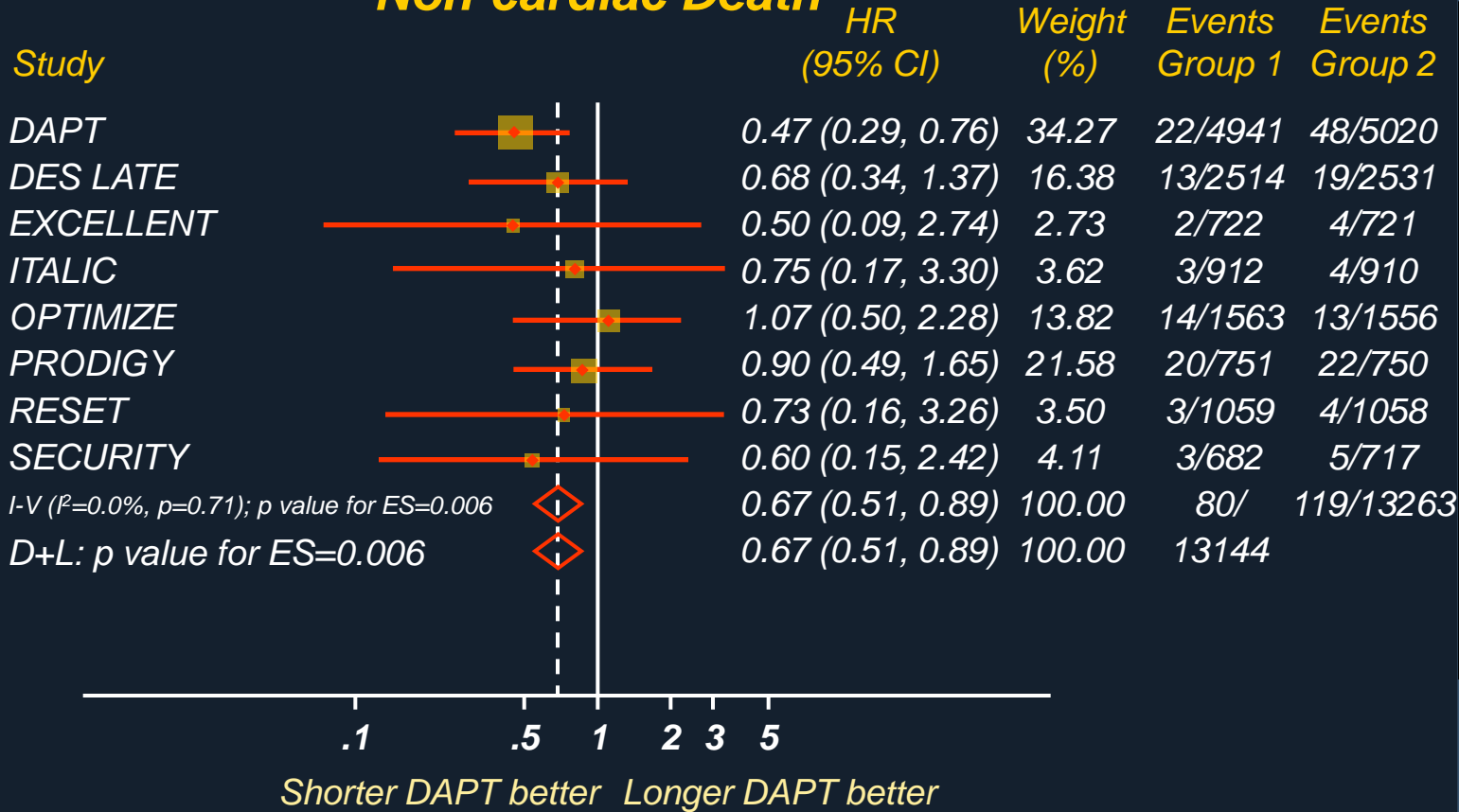


**22% ↑
mortality
with
prolonged
DAPT
($p=0.02$)**

ES=effect size

Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

Non-cardiac Death

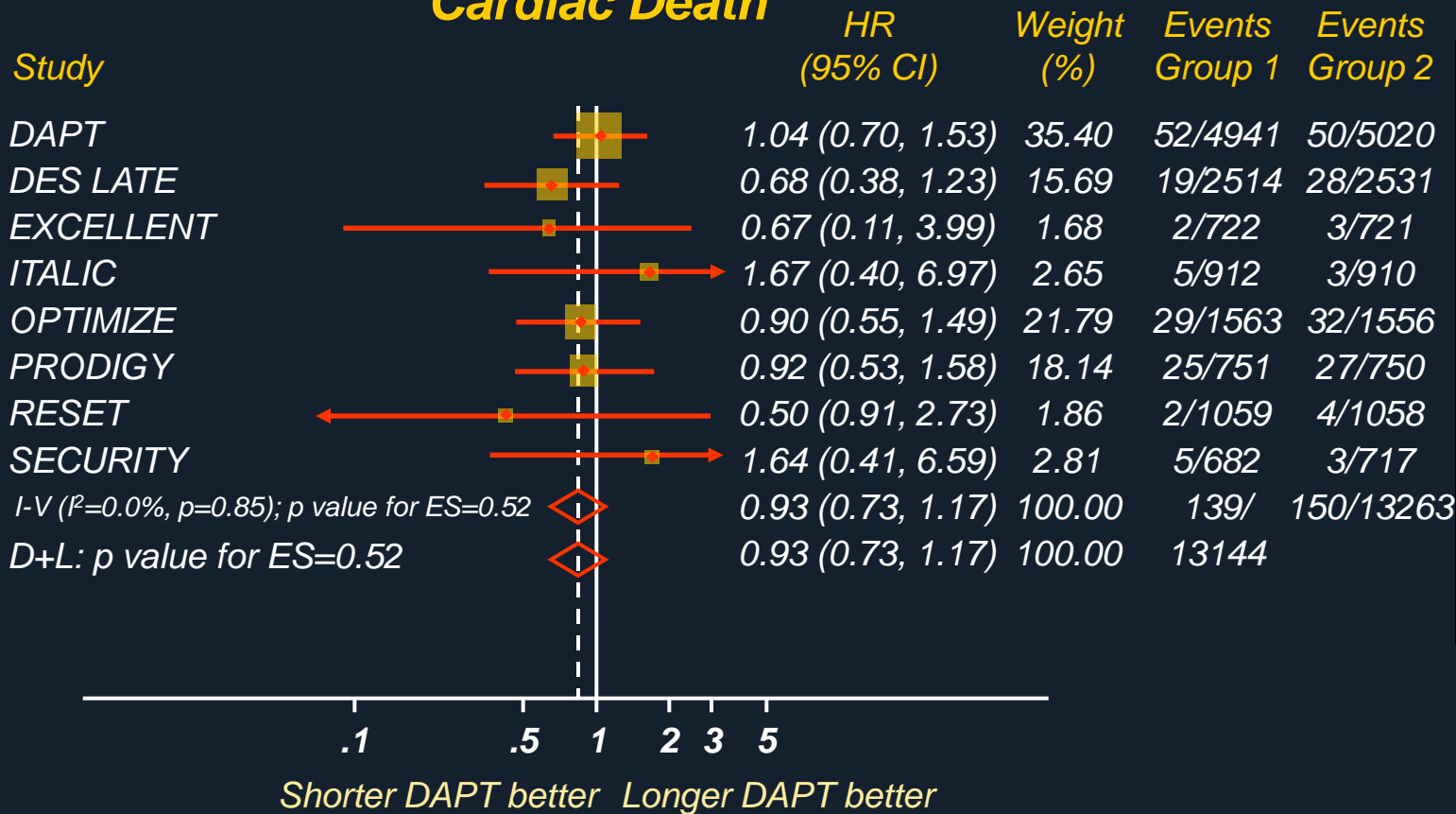


49% ↑
Non-cardiac mortality with prolonged DAPT (p=0.006)

ES=effect size

Mortality with Extended Duration DAPT After DES: A Pairwise and Bayesian Network Meta-Analysis of 10 RCTs and 31,666 Pts

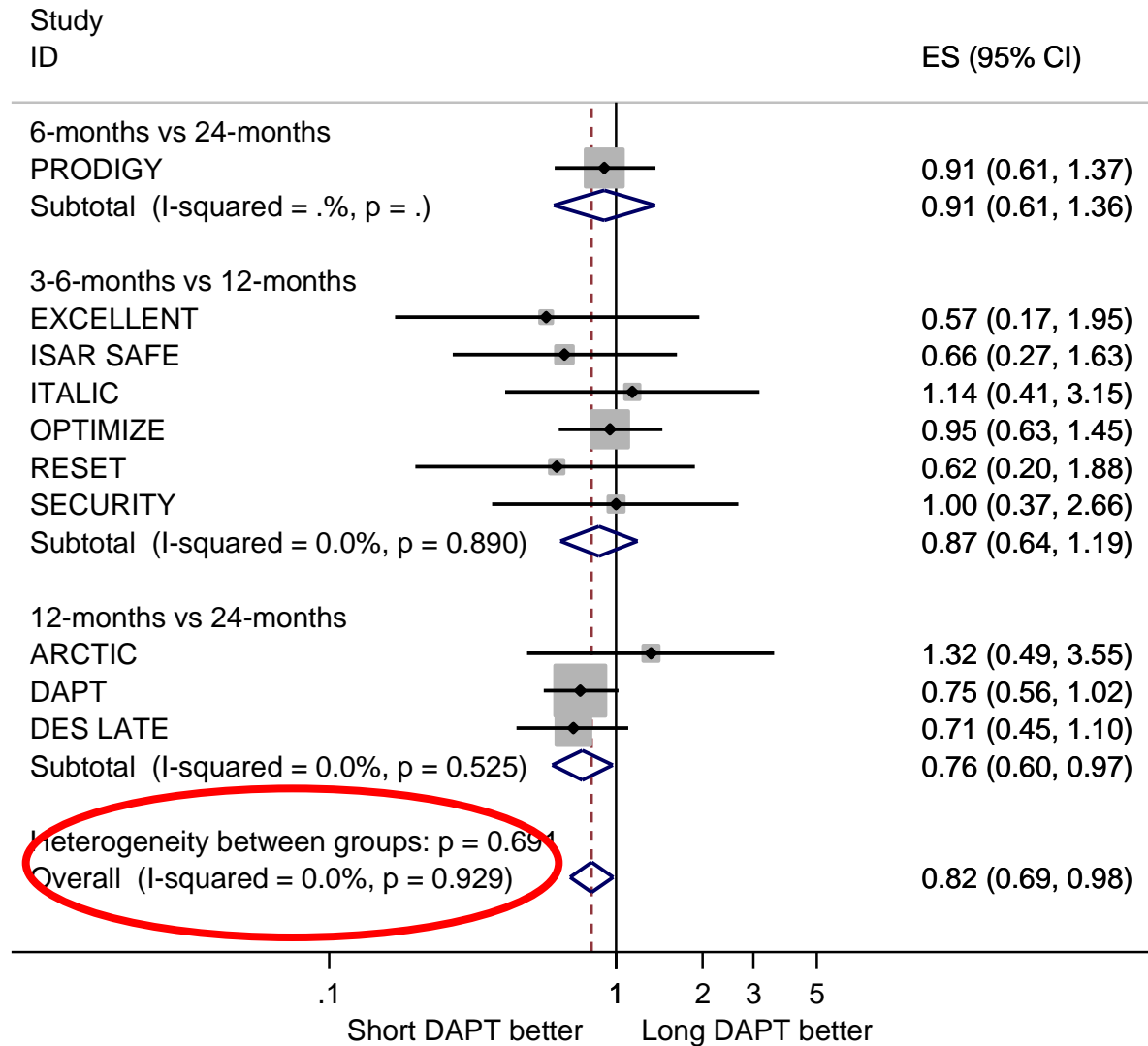
Cardiac Death



**8% ↑
cardiac
mortality
with
prolonged
DAPT
($p=NS$)**

ES=effect size

Death



DAPT trials: 15 RCTs

≤6 months vs ≥ 1 year (n=10)

- RESET 2 RCT: 3 months vs 1 year

- OPTIMIZE

- EXCELLENT

- ISAR SAFE

- SECURITY 5 RCT 6 months vs 1 year

- I LOVE IT

- IVUS XPL

- PRODIGY

- ITALICS 3 RCT 6 months vs > 1 year

- NIPPON

1 year vs > 1 year (n=5)

- DAPT trial

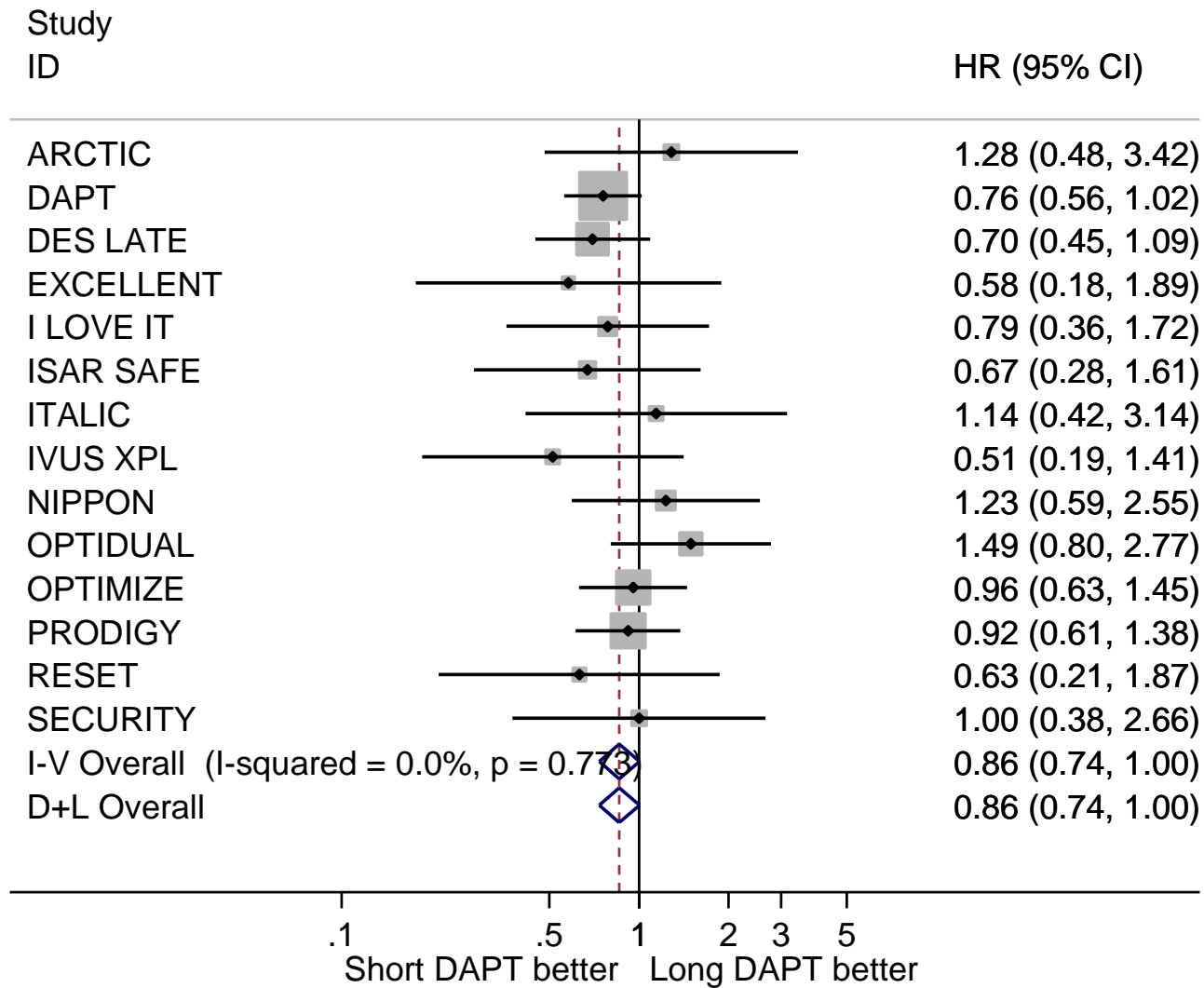
- DES LATE

- ARCTIC INTERRUPTION

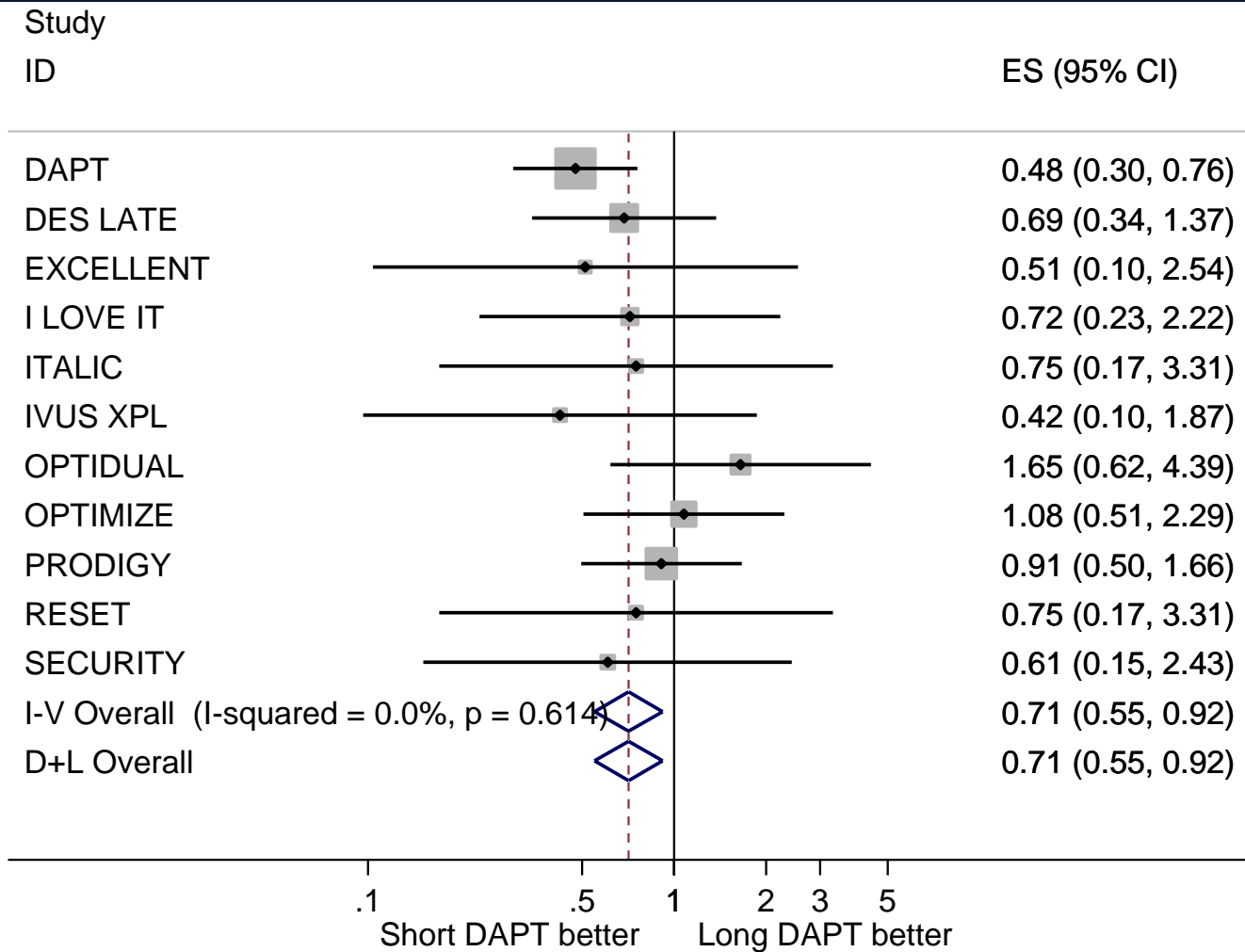
- OPTIDUAL

- Dadjou et al

All-cause mortality

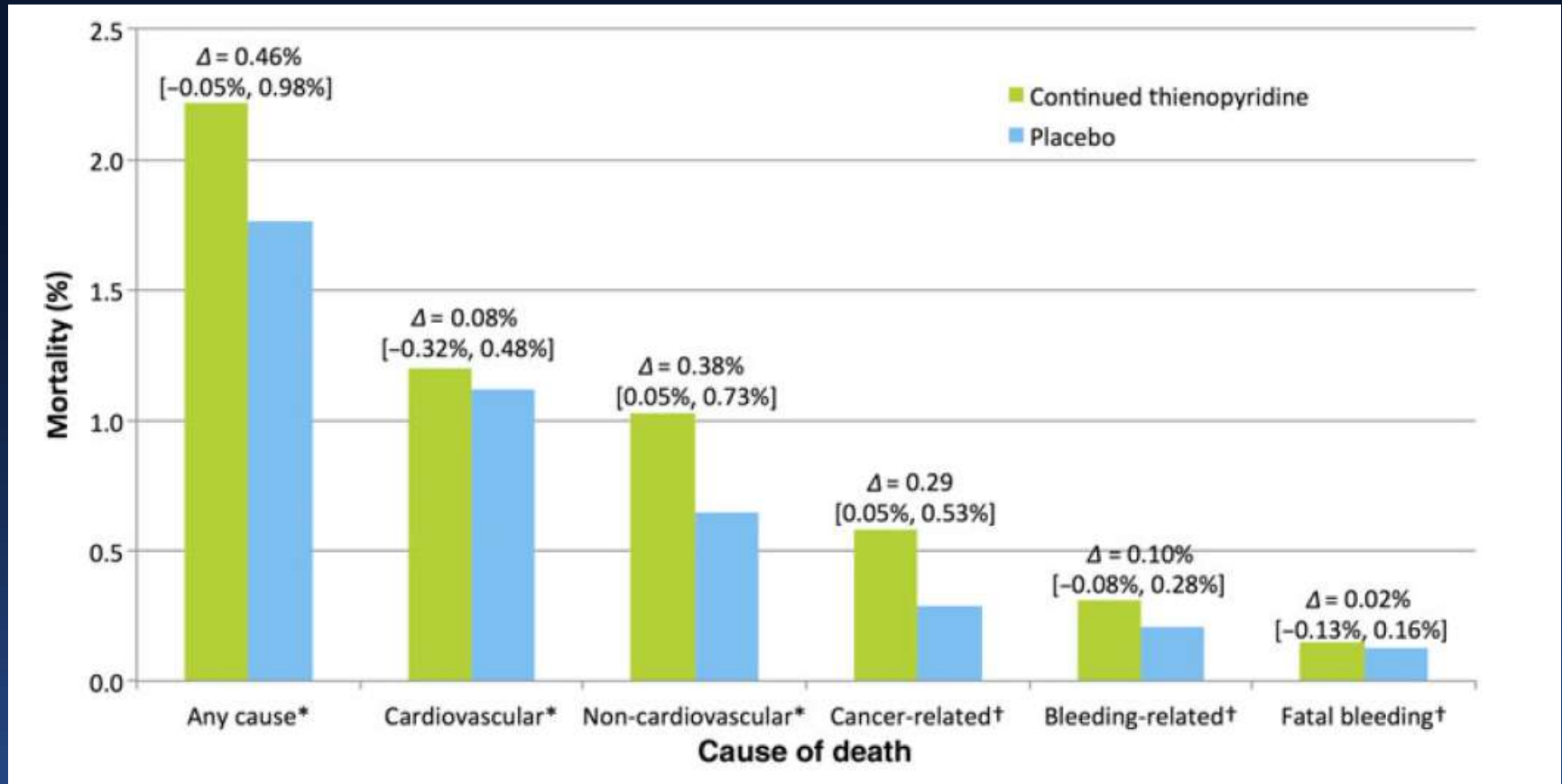


Non-cardiac mortality



- **Is there a biological plausibility behind these findings?**

Causes of mortality in the DAPT trial

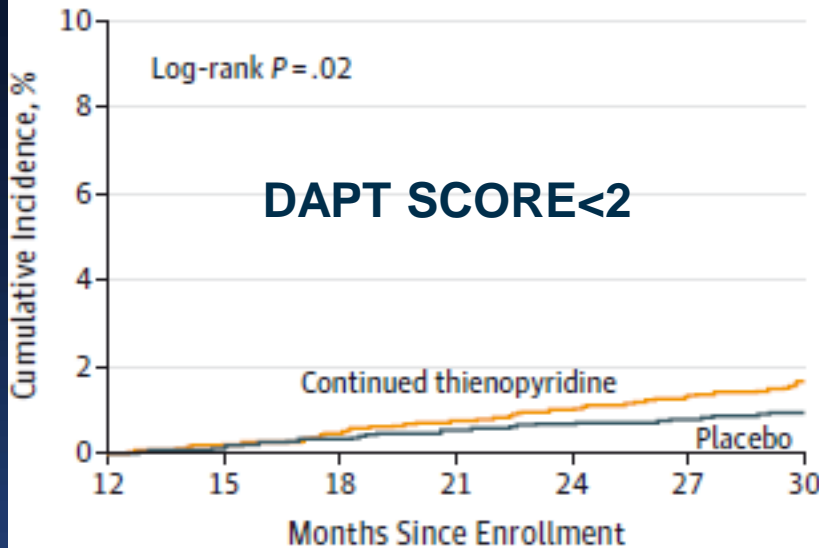


Continued Thienopyridine vs. Placebo High vs. Low DAPT Score

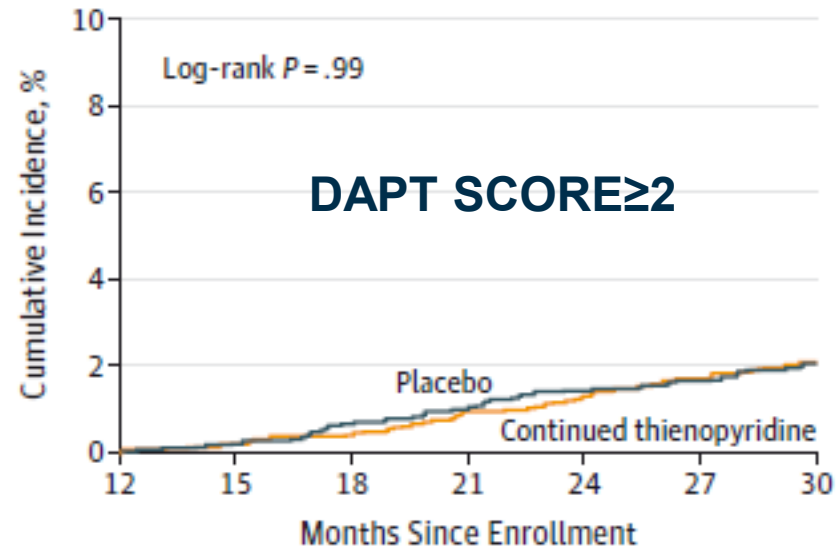


OM 4,0% Myocardial Infarction or Stent Thrombosis GUSTO Moderate or Severe Bleed Net Adverse Events Mortality

Death



Death

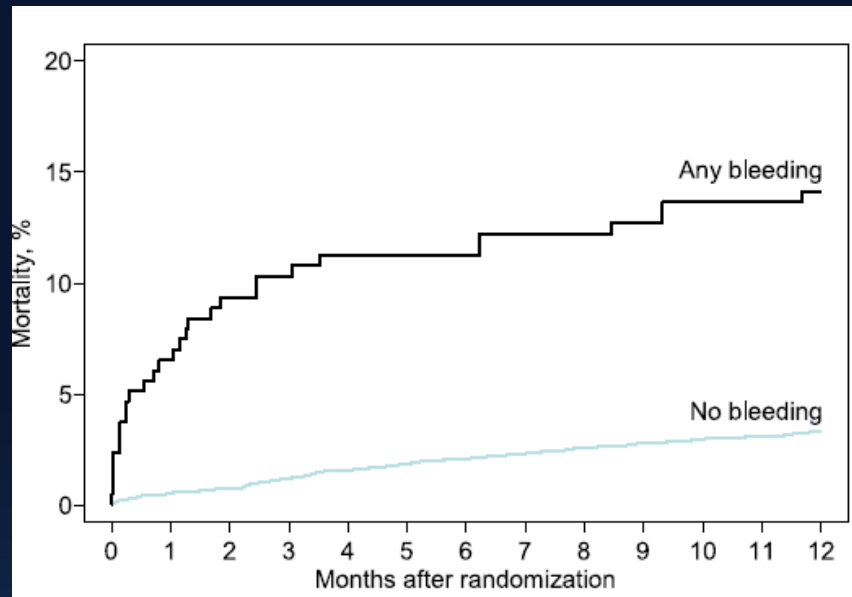


(Conti) -3,0% -3,02% -4,0%

-2,70%

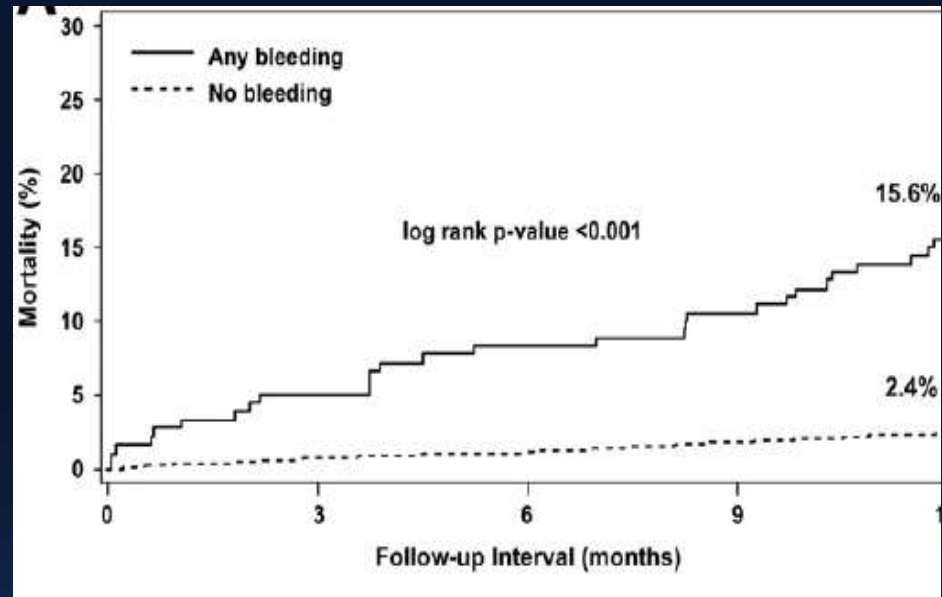
P values are for comparison of risk differences across DAPT Score category (interaction).

ISAR REACT, SWEET, SMART 2, REACT 2



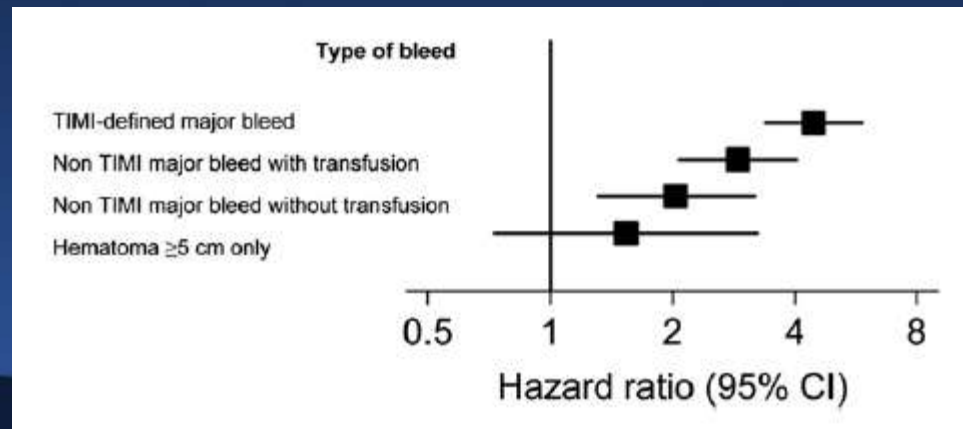
Ndrepepa et al; JACC 2008

EVENT trial



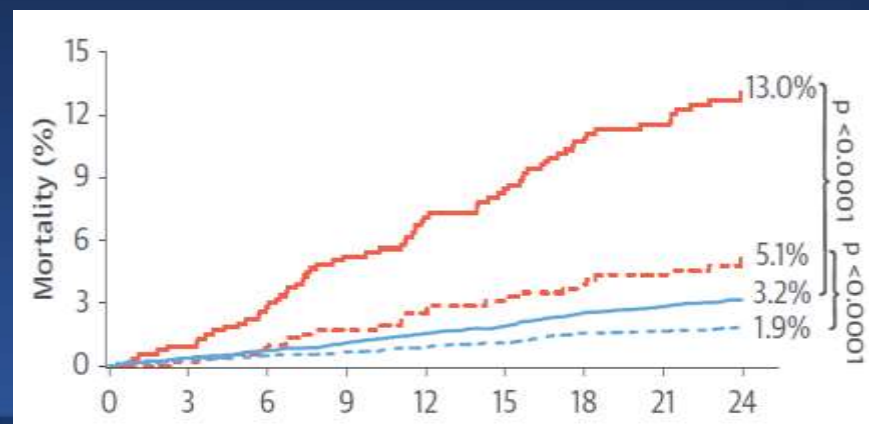
Lindsey et al; JACC Int 2009

ACUITY trial



Mehran et al; JACC 2010

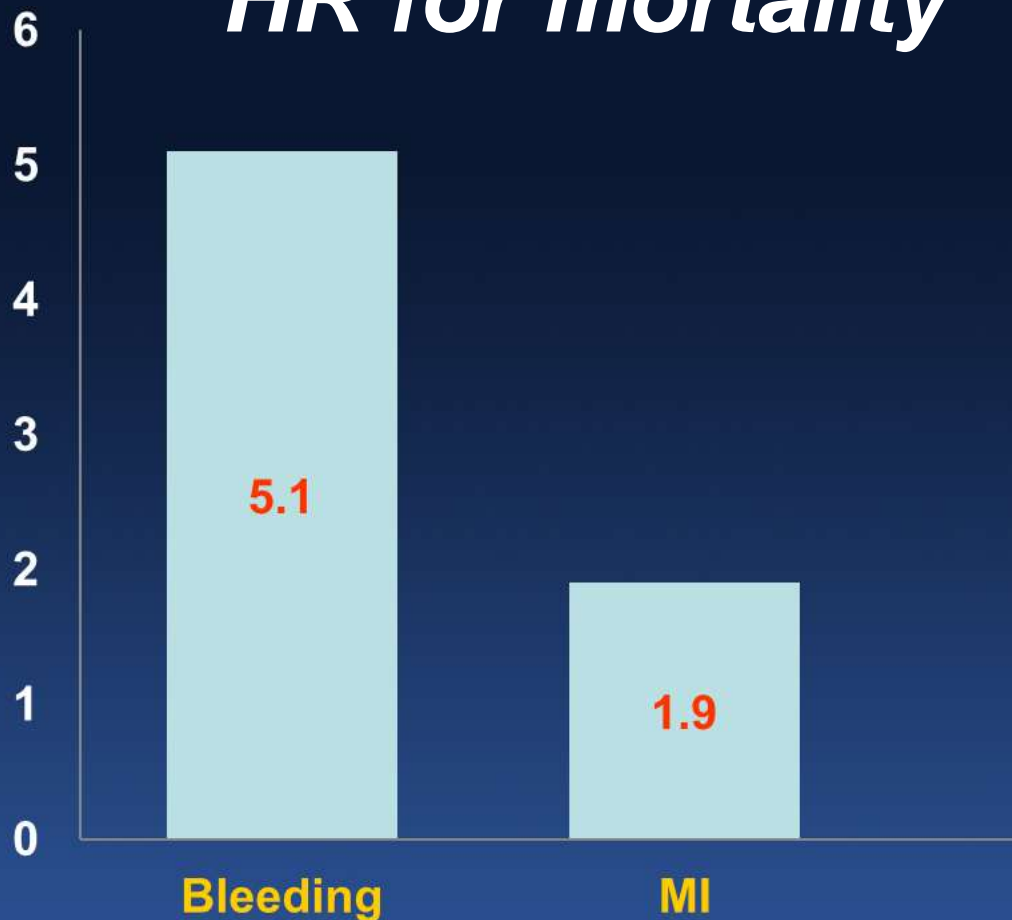
ADAPT DES



Genereux et al; JACC 2015

Bleeding and mortality in ADAPT DES

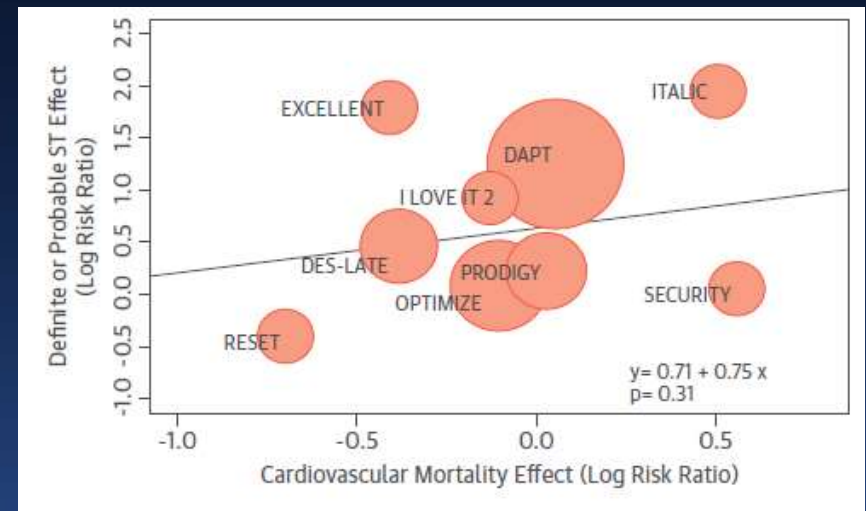
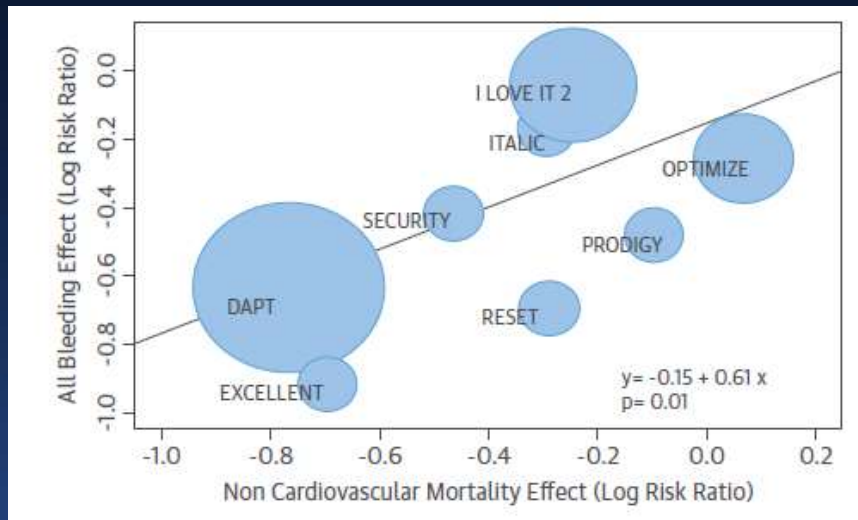
HR for mortality



Genereux et al; JACC 2015

Effect of bleeding or stent thrombosis on mortality

9 RCTs with 28,236 patients



The missing link

- **Shorter DAPT is associated with lower bleeding**

Is shorter DAPT associated with lower rates of bleeding-related deaths?

- **Shorter DAPT is associated with lower mortality**

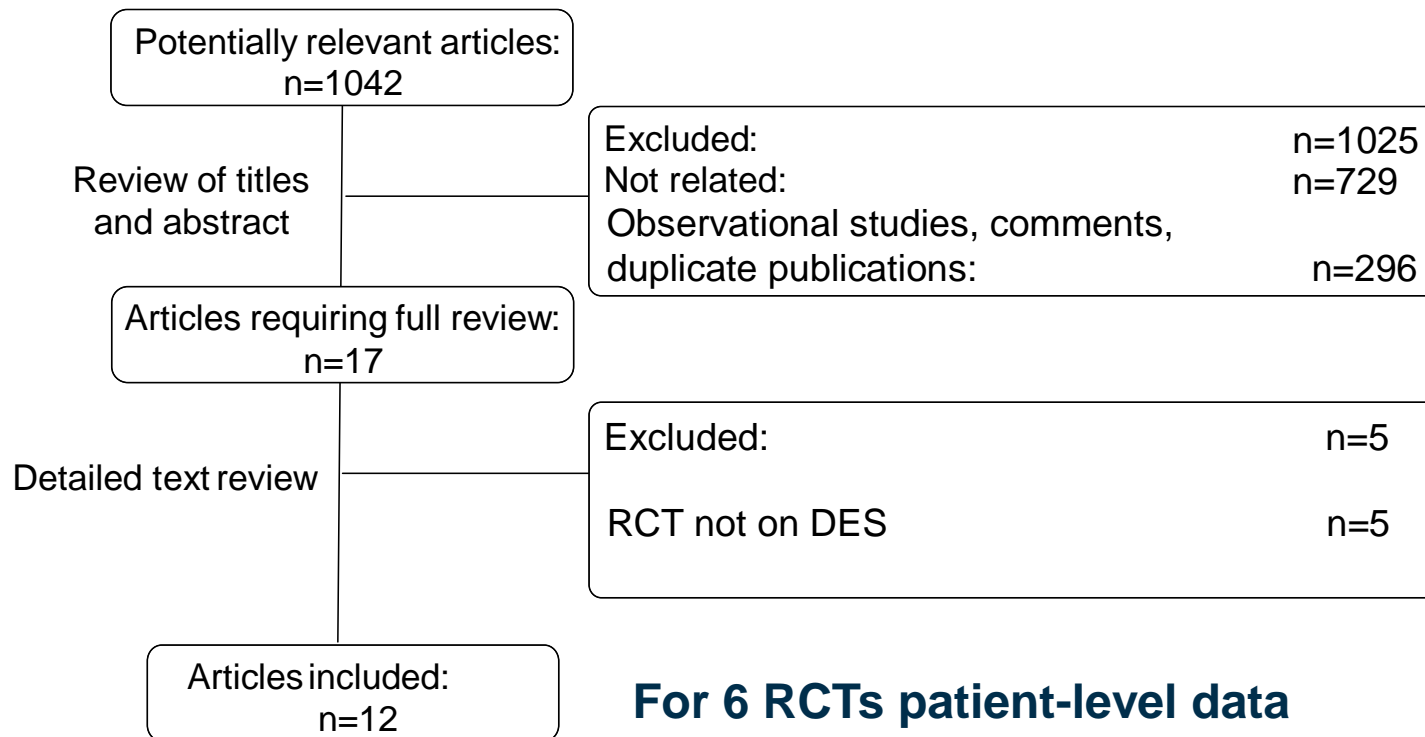


Bleeding-Related Deaths in Relation to the Duration of Dual-Antiplatelet Therapy After Coronary Stenting

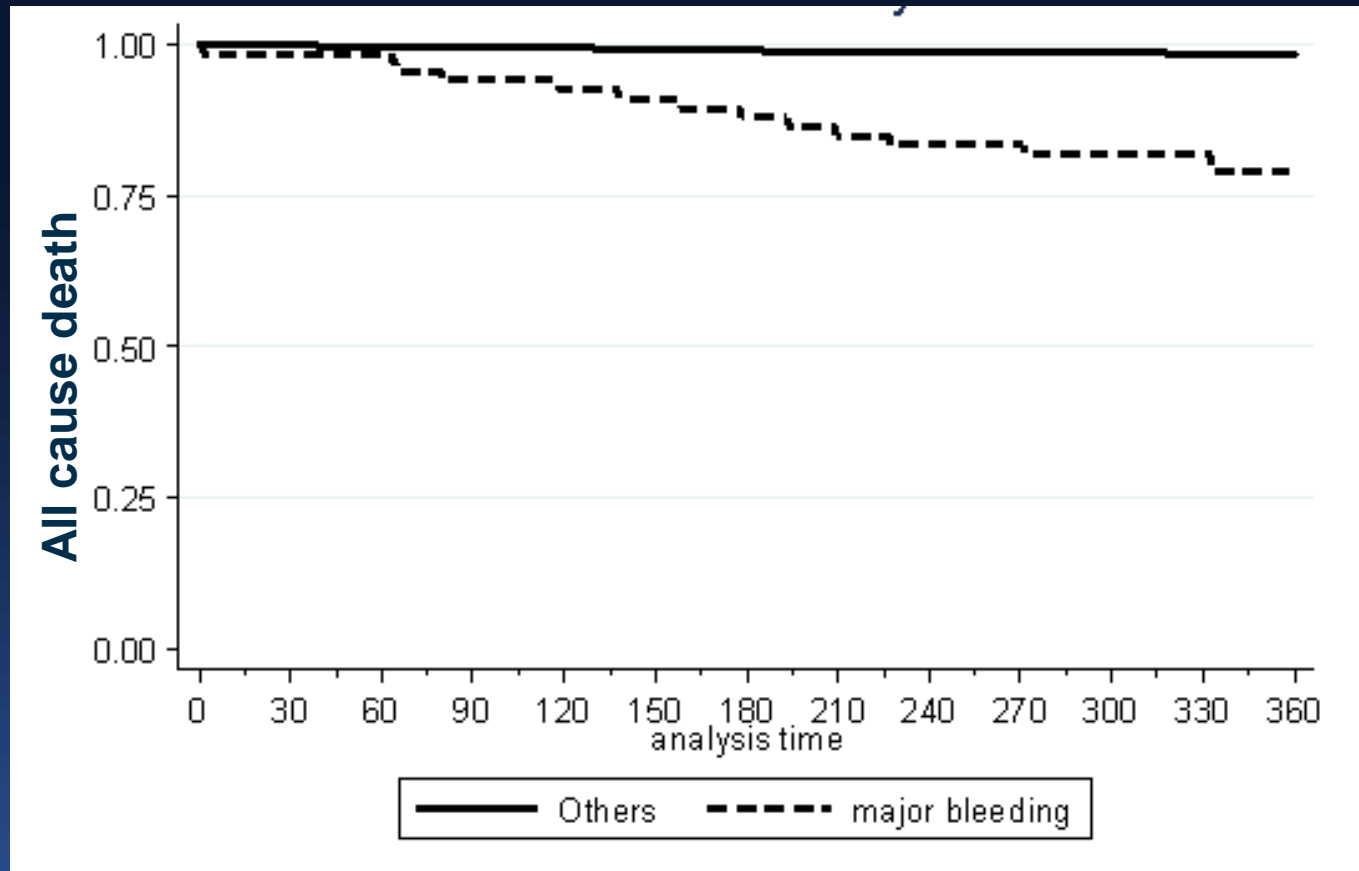
Tullio Palmerini, MD,^a Letizia Bacchi Reggiani, MSTAT,^a Diego Della Riva, MD,^a Mattia Romanello, MD,^a Fausto Feres, MD,^b Alexandre Abizaid, MD,^b Martine Gilard, MD,^c Marie-Claude Morice, MD,^d Marco Valgimigli, MD, PhD,^e Myeong-Ki Hong, MD, PhD,^f Byeong-Keuk Kim, MD, PhD,^f Yangsoo Jang, MD, PhD,^f Hyo-Soo Kim, MD, PhD,^g Kyung Woo Park, MD,^g Antonio Colombo, MD,^h Alaide Chieffo, MD,^h Jung-Min Ahn, MD,ⁱ Seung-Jung Park, MD,ⁱ Stefanie Schüpke, MD,^j Adnan Kastrati, MD,^j Gilles Montalescot, MD,^k Philippe Gabriel Steg, MD,^l Abdourahmane Diallo, MD,^m Eric Vicaut, MD,^m Gerard Helft, MD,ⁿ Giuseppe Biondi-Zoccai, MD, MSTAT,^o Bo Xu, MD,^p Yaling Han, MD,^q Philippe Genereux, MD,^r Deepak L. Bhatt, MD, MPH,^s Gregg W. Stone, MD^r

(J Am Coll Cardiol 2017;69:2011-22)

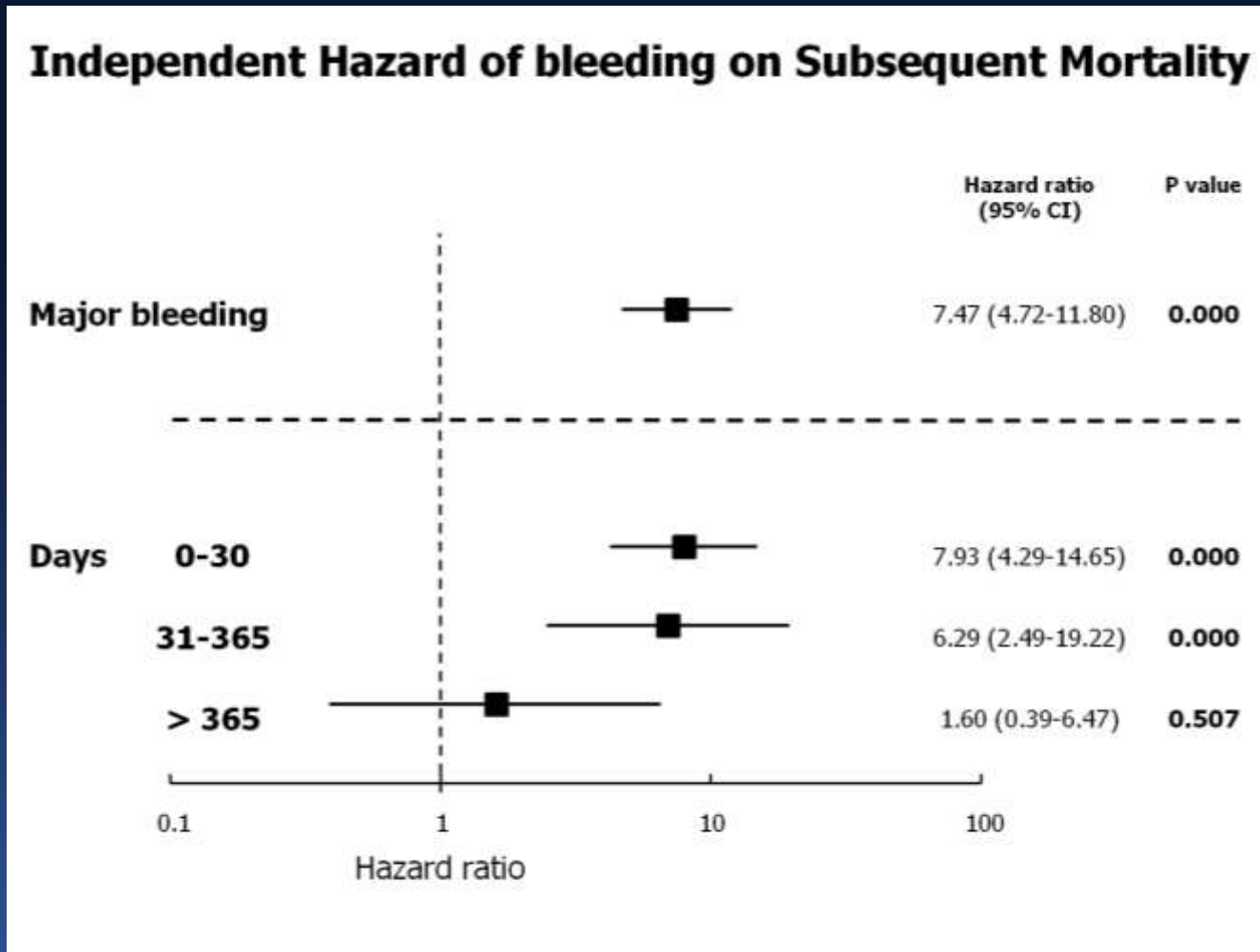
Flow chart



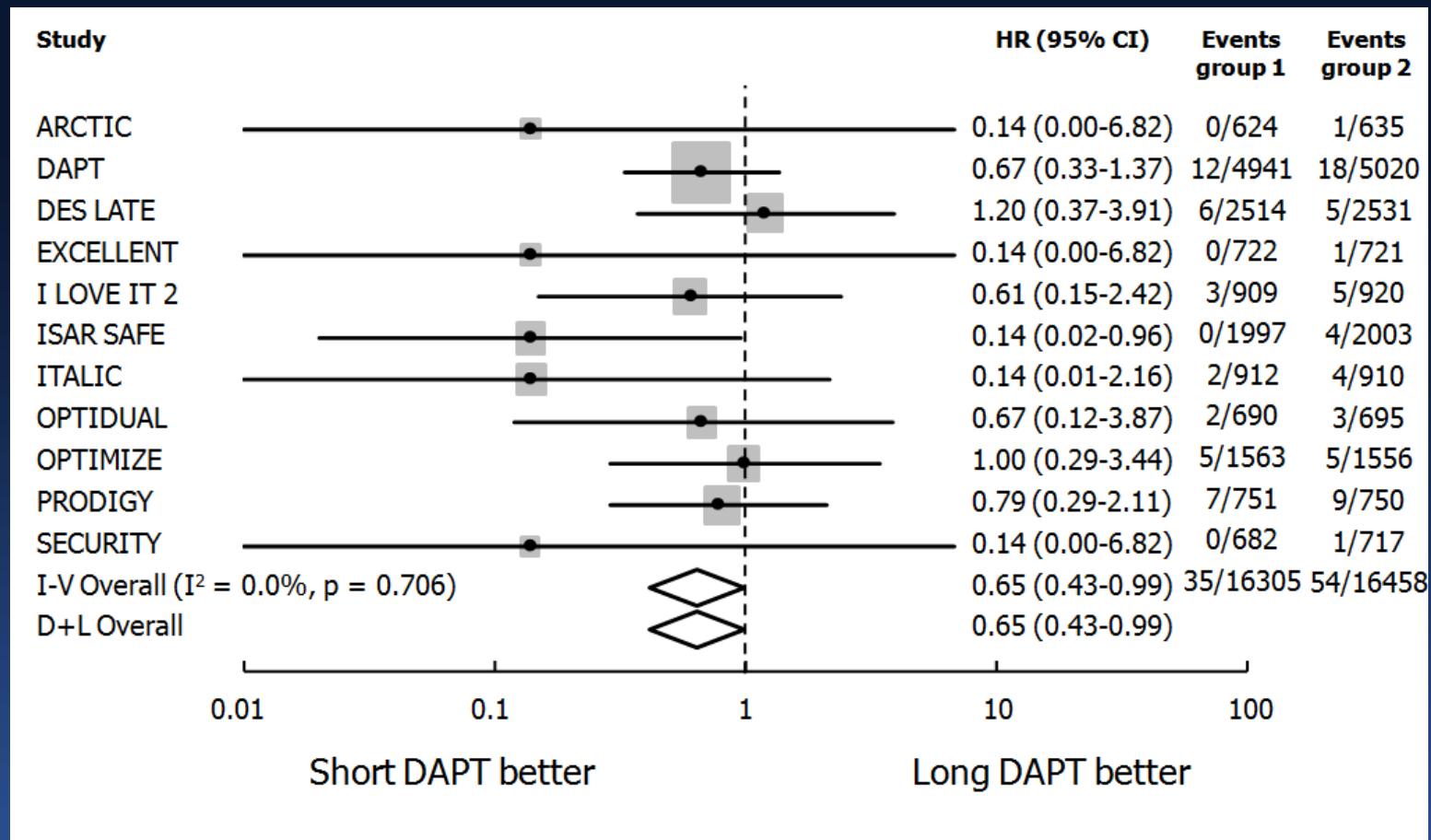
Pooled dataset of 6 RCTs and 11,473 pts



Pooled dataset of 6 RCTs and 11,473 pts



Bleeding related death in a meta-analysis of 12 RCTs and 34,880 pts



Conclusions

- **Prolonged DAPT (> 1 year) significantly reduce the risk stent thrombosis and myocardial infarction, but significantly increase the risk of bleeding and bleeding-related deaths.**
- **The risk of mortality with prolonged DAPT is a serious concern and should be taken into account when deciding the optimal DAPT duration after DES placement.**