SUPPLEMENTARY MATERIAL

Supplementary section 1: Search algorithms.

Supplementary section 2: Flow diagram for the identification and selection of randomised controlled trials comparing TAVI vs. SAVR.

Supplementary section 3: Risk of bias assessment according to the Cochrane Risk of Bias tool.

Supplementary section 4: Number of events and risk estimates across the trials for the primary outcome of all-cause mortality up to 2 years and for longer follow-up where available.

Supplementary section 5: Risk estimates across the trials for stratified analysis of the primary outcome of all-cause mortality.

Supplementary section 6: Number of events and risk estimates across the trials for secondary outcomes.

Supplementary section 7: Random-effects meta-analysis of all-cause mortality for the longest available follow-up period.

Supplementary section 1: Search algorithms.

Medline
1 TRANSCATHETER AORTIC VALVE REPLACEMENT/ 3363
2 "transcatheter aortic valve".ab,ti. 7369
3 (TAVI or TAVR).ab,ti. 5444
4 1 or 2 or 3 8542
5 AORTIC VALVE/su 14219
6 AORTIC VALVE STENOSIS/su 10719
7 "surgical aortic valve".ab,ti. 1523
8 SAVR.ab,ti. 655
9 5 or 6 or 7 or 8 21810
10 4 and 9 4790
11 limit 10 to (clinical trial, all or clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial) 269
12 trial.ti. 195624
13 10 and 12 106
14 11 or 13 299
15 limit 14 to yr="2016-Current" 125

Embase
1 TRANSCATHETER AORTIC VALVE IMPLANTATION/ 17159
2 "transcatheter aortic valve".ab,ti. 13753
3 (TAVI or TAVR).ab,ti. 12742
4 1 or 2 or 3 19241
5 AORTA VALVE REPLACEMENT/ 18424
6 AORTIC VALVE REPLACEMENT/ 3042
7 AORTIC STENOSIS/ 4075
8 AORTIC VALVE STENOSIS/ 1997
9 SURGERY/ 478704
10 5 or 6 or 7 or 8 26350
11 9 and 10 2786
12 SURGICAL AORTIC VALVE REPLACEMENT/ 219
13 "surgical aortic valve".ab,ti. 2795
14 SAVR.ab,ti. 1304
15 11 or 12 or 13 or 14 5413
16 4 and 15 2877
17 limit 16 to (clinical trial or randomized controlled trial or controlled clinical trial) 171
18 trial.ti. 263178
19 16 and 18 105
20 17 or 19 227
21 limit 20 to yr="2016-Current 115"

CENTRAL
1 "Transcatheter aortic valve" (MeSH) 684
2 TAVI or TAVR 568
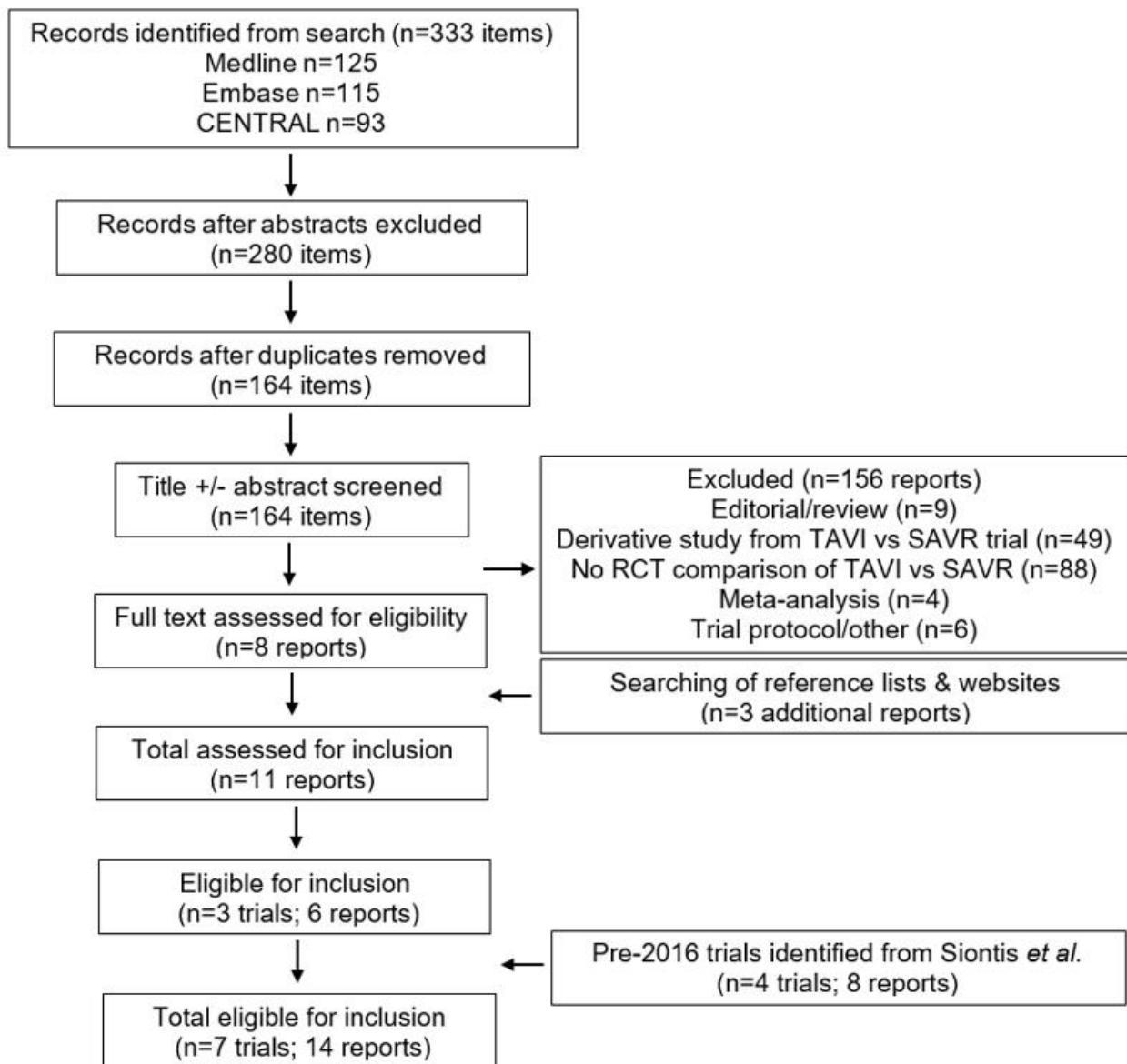
3 "Surgical aortic valve" 187
4 SAVR 110
5 #1 or #2 734
6 #3 or #4 195
7 #5 and #6 93
with Publication Year from 2016 to 2019, in Trials

Supplementary section 2: Flow diagram for the identification and selection of randomised controlled trials comparing TAVI vs. SAVR.

Records identified from search (n=333 items)
Medline n=125
Embase n=115
CENTRAL n=93

↓

Records after abstracts excluded
(n=280 items)

↓

Records after duplicates removed
(n=164 items)

↓

Title +/- abstract screened
(n=164 items)

→ Excluded (n=156 reports)
Editorial/review (n=9)
Derivative study from TAVI vs SAVR trial (n=49)
No RCT comparison of TAVI vs SAVR (n=88)
Meta-analysis (n=4)
Trial protocol/other (n=6)

↓

Full text assessed for eligibility
(n=8 reports)

← Searching of reference lists & websites
(n=3 additional reports)

↓

Total assessed for inclusion
(n=11 reports)

↓

Eligible for inclusion
(n=3 trials; 6 reports)

← Pre-2016 trials identified from Siontis *et al.*
(n=4 trials; 8 reports)

↓

Total eligible for inclusion
(n=7 trials; 14 reports)

Supplementary section 3: Risk of bias assessment according to the Cochrane Risk of Bias tool.

TRIAL	Sequence generation	Allocation concealment	Blinding of oucome assessment	Incomplete outcome data	Selective outcome reporting
PARTNER 1A	✓	?	✓	✓	✓
US CoreValve high risk	✓	?	?	✓	✓
NOTION	✓	✓	X	✓	✓
PARTNER 2A	✓	?	?	✓	✓
SURTAVI	✓	?	?	✓	✓
PARTNER 3	✓	?	✓	✓	✓
Evolut low risk	✓	?	X	✓	✓

Low risk
Unclear risk
High risk

Supplementary section 4: Number of events and risk estimates across the trials for the primary outcome of all-cause mortality up to 2 years and for longer follow-up where available.

Trial	Analysis	Follow-up	TAVI	SAVR	Events TAVI	Events SAVR	Metric	Estimate (95%CI)
PARTNER 1A	Intention-to-treat	2 years	348	351	116	114	HR	0.90 (0.71-1.15)
PARTNER 1A	Intention-to-treat	5 years	348	351	229	198	HR	1.04 (0.86-1.24)
US CoreValve high risk	Intention-to-treat	2 years	394	401	55	75	RR	0.79 (0.61-1.01)
US CoreValve high risk	As treated	5 years	391	359	208	184	HR	0.93 (0.77-1.14)
NOTION	Intention-to-treat	2 years	145	135	11	14	HR	0.72 (0.33-1.59)
NOTION	Intention-to-treat	5 years	145	135	40	39	RR	0.96 (0.66-1.39)
PARTNER 2A	Intention-to-treat	2 years	1011	1021	166	170	HR	0.92 (0.74-1.13)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	IRR	0.98 (0.72-1.34)
PARTNER 3	As treated	1 year	496	454	5	11	HR	0.41 (0.14-1.17)
Evolut low risk	Intention-to-treat	1 year	734	734	nd	nd	IRR	0.83 (0.41-1.67)

Abbreviations: TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; RR, risk ratio; IRR, incidence rate ratio; CI, confidence interval.

Supplementary section 5: Risk estimates across the trials for stratified analysis of the primary outcome of all-cause mortality.

	Trial	Follow-up	Subgroup	Estimate (95%CI)
Surgical risk	PARTNER 1A	2 years	High-risk	0.90 (0.71-1.15)
	US CoreValve high risk	2 years	High-risk	0.79 (0.61-1.01)
	NOTION	2 years	Low-risk	0.72 (0.33-1.59)
	PARTNER 2A	2 years	Intermediate risk	0.92 (0.74-1.13)
	SURTAVI	2 years	Intermediate risk	0.98 (0.72-1.34)
	PARTNER 3	1 year	Low-risk	0.41 (0.14-1.17)
	Evolut low risk	1 year	Low-risk	0.83 (0.41-1.67)
Access route	PARTNER 1A	2 years	Transfemoral	0.84 (0.63-1.13)
	PARTNER 1A	2 years	Transthoracic	1.06 (0.69-1.63)
	US CoreValve high risk	2 years	Transfemoral	0.79 (0.61-1.01)
	NOTION	2 years	Transfemoral	0.72 (0.33-1.59)
	PARTNER 2A	2 years	Transfemoral	0.80 (0.62-1.04)
	PARTNER 2A	2 years	Transthoracic	1.26 (0.86-1.86)
	SURTAVI	2 years	Transfemoral	0.98 (0.72-1.34)
	PARTNER 3	1 year	Transfemoral	0.41 (0.14-1.17)
	Evolut low risk	1 year	Transfemoral	0.83 (0.41-1.67)
THV system	PARTNER 1A	2 years	Balloon-expandable	0.90 (0.71-1.15)
	US CoreValve high risk	2 years	Self-expandable	0.79 (0.61-1.01)
	NOTION	2 years	Self-expandable	0.72 (0.33-1.59)
	PARTNER 2A	2 years	Balloon-expandable	0.92 (0.74-1.13)
	SURTAVI	2 years	Self-expandable	0.98 (0.72-1.34)
	PARTNER 3	1 year	Balloon-expandable	0.41 (0.14-1.17)
	Evolut low risk	1 year	Self-expandable	0.83 (0.41-1.67)

Abbreviations: THV, transcatheter heart valve; CI, confidence interval.

Supplementary section 6: Number of events and risk estimates across the trials for secondary outcomes.

	Analysis	Follow-up	TAVI	SAVR	Events TAVI	Events SAVR	Metric	Estimate (95%CI)
Any stroke								
PARTNER 1A	Intention-to-treat	2 years	348	351	24	14	HR	1.22 (0.67-2.23)
US CoreValve high risk	As treated	2 years	391	359	40	52	RR	0.70 (0.48-1.04)
NOTION	Intention-to-treat	2 years	145	135	5	7	RR	0.65 (0.21-2.05)
PARTNER 2A	Intention-to-treat	2 years	1011	1021	91	85	HR	0.93 (0.65-1.33)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	IRR	0.74 (0.51-1.07)
PARTNER 3	As treated	1 year	496	454	6	14	HR	0.38 (0.15-1.00)
Evolut low risk	Intention-to-treat	1 year	734	734	nd	nd	IRR	0.95 (0.56-1.63)
Disabling stroke								
PARTNER 1A	Intention-to-treat	30 days	348	351	13	7	RR	1.87 (0.76-4.64)
US CoreValve high risk	As treated	2 years	391	359	25	30	RR	0.77 (0.46-1.28)
PARTNER 2A	Intention-to-treat	2 years	1011	1021	59	61	RR	0.98 (0.69-1.38)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	IRR	0.58 (0.32-1.04)
PARTNER 3	As treated	1 year	496	454	1	4	HR	0.22 (0.03-2.00)
Evolut low risk	Intention-to-treat	1 year	734	734	nd	nd	IRR	0.38 (0.14-1.04)
Cardiovascular death								
PARTNER 1A	Intention-to-treat	2 years	348	351	67	59	RR	1.15 (0.83-1.57)
US CoreValve high risk	As treated	2 years	391	359	58	64	RR	0.83 (0.60-1.15)
NOTION	As treated	2 years	142	134	9	12	RR	0.71 (0.31-1.63)
PARTNER 2A	Intention-to-treat	2 years	1011	1021	97	104	RR	0.94 (0.72-1.23)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	IRR	0.96 (0.66-1.40)
PARTNER 3	As treated	1 year	496	454	4	9	HR	0.40 (0.12-1.30)
Evolut low risk	Intention-to-treat	1 year	734	734	nd	nd	IRR	0.65 (0.30-1.42)

Myocardial infarction

PARTNER 1A	Intention-to-treat	2 years	348	351	0	4	RR	0.11 (0.01-2.07)
US CoreValve high risk	As treated	2 years	391	359	7	7	RR	0.92 (0.32-2.58)
NOTION	Intention-to-treat	2 years	145	135	8	7	HR	1.06 (0.38-2.92)
PARTNER 2A	Intention-to-treat	2 years	1011	1021	33	37	RR	0.90 (0.57-1.43)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	IRR	1.27 (0.63-2.57)
PARTNER 3	As treated	1 year	496	454	6	10	HR	0.54 (0.20-1.49)
Evolut low risk	Intention-to-treat	1 year	734	734	nd	nd	IRR	1.06 (0.44-2.56)

Acute kidney injury

PARTNER 1A	Intention-to-treat	2 years	348	351	20	21	RR	0.96 (0.53-1.74)
US CoreValve high risk	As treated	2 years	391	359	24	54	RR	0.41 (0.26-0.64)
NOTION	Intention-to-treat	2 years	145	135	2	3	RR	0.61 (0.10-3.67)
PARTNER 2A	Intention-to-treat	2 years	1011	1021	36	57	RR	0.64 (0.42-0.96)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	IRR	nd
PARTNER 3	As treated	1 year	496	454	nd	nd	ND	nd
Evolut low risk	As treated	1 year	734	734	nd	nd	IRR	0.32 (0.14-0.76)

New-onset atrial fibrillation

PARTNER 1A	Intention-to-treat	2 years	348	351	42	60	RR	0.71 (0.49-1.02)
US CoreValve high risk	As treated	2 years	391	359	71	121	RR	0.54 (0.42-0.69)
NOTION	Intention-to-treat	2 years	145	135	32	80	HR	0.28 (0.18-0.43)
PARTNER 2A	Intention-to-treat	2 years	1011	1021	110	273	RR	0.41 (0.33-0.50)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	.	nd
PARTNER 3	As treated	1 year	496	454	29	150	HR	0.13 (0.09-0.20)
Evolut low risk	As treated	1 year	734	734	nd	nd	IRR	0.26 (0.21-0.32)

Major bleeding

PARTNER 1A	Intention-to-treat	2 years	348	351	60	95	RR	0.64 (0.48-0.85)

US CoreValve high risk	As treated	2 years	391	359	123	135	RR	0.83 (0.68-1.02)
NOTION	Intention-to-treat	2 years	145	135	nd	nd	RR	0.54 (0.31-0.95)
PARTNER 2A	Intention-to-treat	2 years	1011	1021	169	471	RR	0.36 (0.31-0.42)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	.	nd
PARTNER 3	As treated	1 year	496	454	38	117	HR	0.25 (0.17-0.37)
Evolut low risk	As treated	1 year	734	734	nd	nd	IRR	0.36 (0.22-0.58)

Major vascular complications

PARTNER 1A	Intention-to-treat	2 years	348	351	40	13	RR	3.10 (1.69-5.70)
US CoreValve high risk	As treated	2 years	391	359	27	7	RR	3.53 (1.56-8.01)
NOTION	Intention-to-treat	2 years	145	135	nd	nd	RR	3.77 (0.82-17.46)
PARTNER 2A	Intention-to-treat	2 years	1011	1021	86	55	RR	1.58 (1.14-2.19)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	.	nd
PARTNER 3	As treated	1 year	496	454	14	7	HR	1.83 (0.74-4.55)
Evolut low risk	As treated	1 year	734	734	nd	nd	IRR	1.09 (0.63-1.88)

Valve endocarditis

PARTNER 1A	Intention-to-treat	2 years	348	351	4	3	RR	1.34 (0.30-5.96)
US CoreValve high risk	As treated	2 years	391	359	3	5	RR	0.55 (0.13-2.28)
NOTION	Intention-to-treat	2 years	145	135	9	2	RR	4.21 (0.91-19.49)
PARTNER 2A	Intention-to-treat	2 years	1011	1021	11	6	RR	1.85 (0.69-4.99)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	.	nd
PARTNER 3	As treated	1 year	496	454	1	2	HR	0.44 (0.04-4.89)
Evolut low risk	Intention-to-treat	1 year	734	734	nd	nd	IRR	0.50 (0.05-4.76)

Permanent pacemaker implantation

PARTNER 1A	Intention-to-treat	2 years	348	351	23	19	RR	1.22 (0.68-2.20)
US CoreValve high risk	As treated	2 years	391	359	96	42	RR	2.09 (1.50-2.92)
NOTION	Intention-to-treat	2 years	145	135	55.0	5.0	RR	10.38 (4.29-25.14)

PARTNER 2A	Intention-to-treat	2 years	1011	1021	114	96	RR	1.20 (0.93-1.55)
SURTAVI	Intention-to-treat	30 days	879	867	nd	nd	IRR	3.92 (3.08-4.99)
SURTAVI	Intention-to-treat	2 years	879	867	nd	nd	.	nd
PARTNER 3	As treated	1 year	496	454	36	24	HR	1.38 (0.82-2.32)
Evolut low risk	As treated	1 year	734	734	nd	nd	IRR	2.90 (2.16-3.88)

Abbreviations: TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; HR, hazard ratio; RR, risk ratio; IRR, incidence rate ratio; CI, confidence interval.

Supplementary section 7: Random-effects meta-analysis of all-cause mortality for the longest available follow-up period.

All-cause mortality – longest follow-up

Trial	HR (95% CI)	P
PARTNER 1A	1.04 (0.86 - 1.24)	
US CoreValve high risk	0.93 (0.77 - 1.14)	
NOTION	0.96 (0.66 - 1.39)	
PARTNER 2A	0.92 (0.74 - 1.13)	
SURTAVI	0.98 (0.72 - 1.34)	
PARTNER 3	0.41 (0.14 - 1.17)	
Evolut low risk	0.83 (0.41 - 1.67)	
Overall	**0.96 (0.87 - 1.06)**	**0.402**

(*Heterogeneity* $\tau^2<0.001$, p = 0.725)

0.2   0.5   1   2   5

Favours TAVI   Favours SAVR
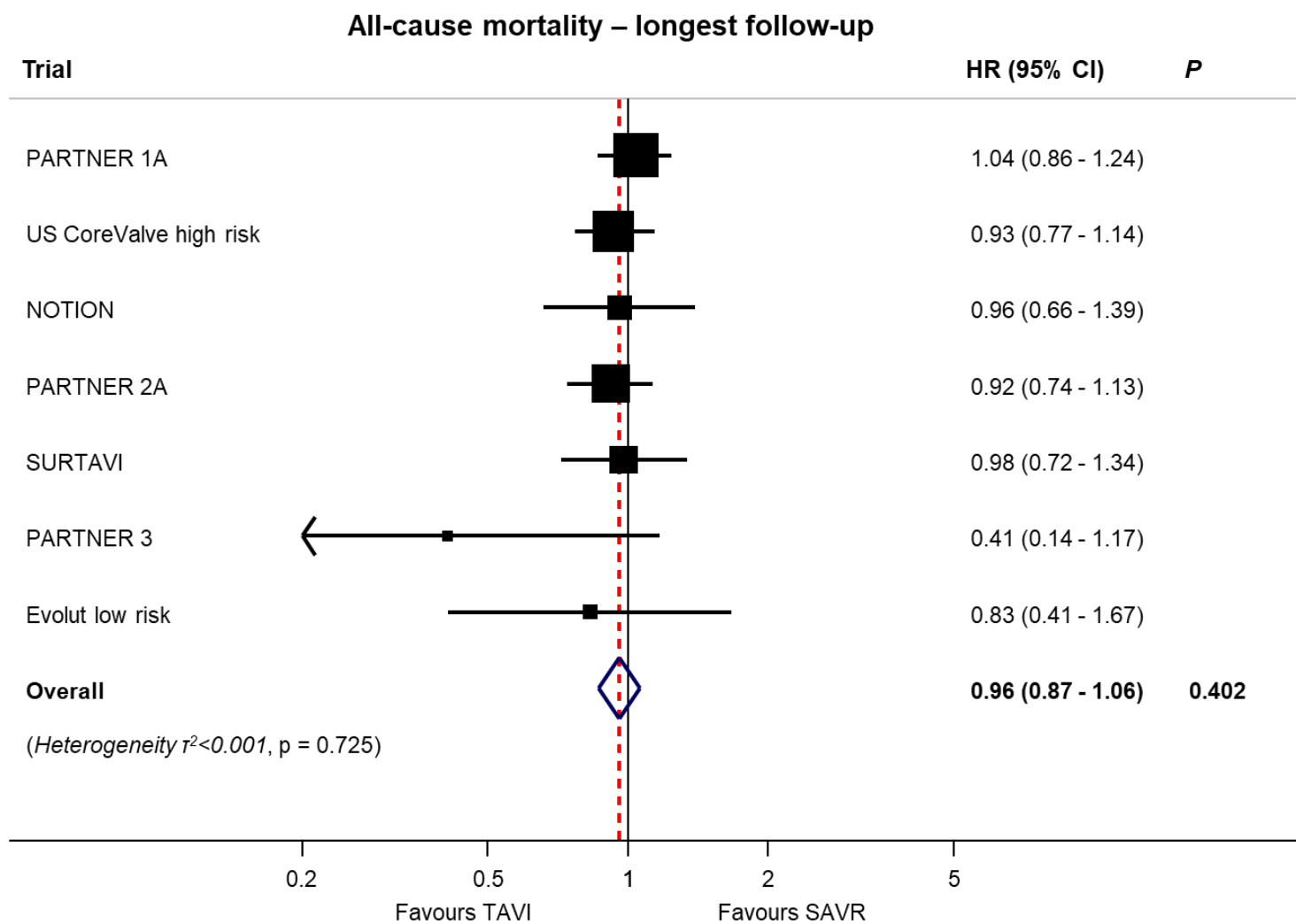
For each trial, boxes and horizontal lines correspond to the respective point estimate and accompanying 95% confidence interval. The size of each box is proportional to weight of that trial result. The vertical solid line on the forest plot represents the point estimate of hazard ratio=1. The vertical dashed line on the plot represents the point estimate of overall hazard ratio derived from random-effects meta-analysis. The diamond represents the 95% confidence interval of the summary pooled estimate of the effect and is centred on pooled hazard ratios. Heterogeneity estimate of τ^2 accompanies the summary estimate. Details of the data from individual trials are available in Supplementary section 4. Five year data are included for PARTNER 1A, US CoreValve High Risk, and NOTION trials.
Abbreviations: HR, hazard ratio; CI, confidence interval; TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement.