Title page

Five-year outcomes in trials comparing trans-catheter aortic valve implantation vs surgical aortic valve replacement: a pooled analysis of Kaplan-Meier derived individual patient data

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ABSTRACT **(word count: 308)**

Objectives. We planned a pooled analysis of Kaplan-Meier-estimated individual patient data from trials comparing TAVI and SAVR to evaluate their effects on long-term composite of death for any cause and stroke, all-cause mortality, stroke and re-hospitalization.

Methods. Trials comparing TAVI vs. SAVR were identified through Medline, Embase, Cochrane databases and specialist websites. The primary outcome was death from any cause at follow-up. Enhanced secondary analysis of survival curves was performed estimating individual patient time-to-event data from published Kaplan-Meier curves. Comparison between treatments was done with grouped frailty Cox models in a landmark framework, and fully parametric models.

Results. In the six included trials, 7770 participants were randomly assigned to undergo TAVI (3977) or SAVR (3793). At landmark analysis, incidence of mortality in the first 24 months after implantation was significantly lower in TAVI group (risk-profile stratified HR 0.87, 95%CI 0.77 – 0.99, p 0.03), while there was a reversal of HR after 24 months (risk-profile stratified HR 1.18; 95%CI 1.03-1.35; p 0.01) favoring SAVR. Randomisation to TAVI was associated with a significantly lower incidence of the composite outcome in the first 6 months (Risk-stratified HR 0.66, 95% CI 0.56 – 0.77, p-value < 0.001) but there was a reversal of HR after 24 months favoring SAVR (Risk-stratified HR 1.25; 95%CI 1.08-1.46; p-value 0.003). This outcomes has been confirmed also by comparison of all-cause death, with randomization to TAVI being associated with mortality after 24 months (Risk-stratified HR 1.25; 95%CI 1.08-1.46; p-value 0.003). TAVI was also associated with an increased incidence of re-hospitalization after 1 year (Risk-stratified HR 1.69; 95%CI 1.33-2.15; p-value < 0.001).

Conclusions. The meta-analysis describes an early advantaged associated with randomization to TAVI, an advantage which decreases over time, with randomisation to TAVI becoming a risk factor for all-cause mortality and the composite of all-cause mortality and stroke after 24 months.

Keywords: Aortic valve, Trans-catheter aortic valve implantation, Surgical aortic valve replacement

TEXT

Introduction

Trans-catheter aortic valve implantation (TAVI) has been recognized as the primary choice for the treatment of aortic valve stenosis in prohibitive risk and high risk patients and an alternative to surgery in the intermediate risk patients [1]. The encouraging results up to 5 years in the high/intermediate risk profile has led to increased interest also in low-risk patients, making critical an appraisal of longer-term outcomes [2-8].

We recently performed an individual patient data (IPD)-derived meta-analysis on all-cause mortality to overcome the limitation of the individually underpowered studies and describe changing relative hazards over time, revealing an early survival advantage of TAVI, followed by a survival disadvantage after 40 months. This that is in contrast with single RCTs and other published meta-analyses which use summary data [9]. The relatively short follow-up time in RCTs on intermediate and low risk groups limited results between 2 and 5 years, as only the two trials on high risk and one small trial on low risk reached 5-year follow-up [2, 3, 7], leaving opened the concerns on intermediate risk [5, 10]. However, in the last months, the 5-year update of the PARTNER 2A trial as well as the 2-year follow-up of PARTNER 3 [12] have been published or presented [4, 11, 12]. These data increased the 5-year sample size by 2.14 times, as the PARTNER 2A increased the 5-year follow-up population from 1776 patients to 3808 [4] permitting our analysis to be more informative not only on intermediate but also on low-risk trials.

To date, all RCTs have been designed on composite primary outcomes but and advantage of meta analysis of multiple trials is that it can enable the examination of rarer components of these composite outcomes.[cite] All-cause mortality and neurological events are frequently included in composite endpoints and our meta analysis provides an opportunity to examine these events individually [2, 4-8, 13]. Another endpoint that hasgained a critical role for comparing TAVI and SAVR is the incidence of re-hospitalization which may provide further insights into the effects of TAVI over time [2, 4, 10, 14].

We planned a pooled analysis of Kaplan-Meier-estimated individual patient data (IPD) from trials comparing TAVI and SAVR to evaluate their effects on long-term composite of death for any cause or stroke,

all-cause mortality, stroke and re-hospitalization, focusing on the potential time-varying effect and modelling their Hazard Ratio over time.

Materials and Methods

Search strategy and selection criteria.

A systematic review of the literature was performed by two independent researchers to identify eligible studies published between January 1st, 2007 and August 30th, 2020 in MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL). The search algorithm is detailed in eTable 1 in the Supplement. We also checked websites (www.clinicaltrials.gov, www.cardiosource.com, www.escardio.org) for unpublished data.

The inclusion criteria were: 1) randomized controlled trials with random allocation to TAVI or SAVR; 2) at least 1-year follow-up; 3) the report of Kaplan-Meier curves of a composite of all-cause mortality or stroke, all-cause-mortality, stroke and re-hospitalization in Text or Appendix or presented in selected international meetings.

The meta-analysis endpoint were the composite of all-cause mortality or stroke at follow-up, death from any cause at follow-up, stroke at follow-up and rehospitalization at follow-up. The Hazard Ratio (HR) was considered as the effect size. Hazards Ratios were estimated from Kaplan Meier curves-derived Individual Patient Data (KMd-IPD) with Cox models and fully parametric models. We pooled data from intention-to-treat (ITT) populations, choosing data from as-treated population when ITT data were not available. For each enclosed trial, we selected the longest available follow-up report for each endpoint.

Data extraction and analysis.

Two independent investigators (F.B. and F.M.) identified trials that fulfilled the pre-specified inclusion criteria. Eligible trials were then reviewed in duplicate and disagreement was solved by a third investigator (M.R.). Extracted data from Text and Appendix were previously reported [9].

Data extraction from Kaplan-Meier graphs was performed as described by Guyot and Colleagues [9, 15, 16], employing a dedicated software (Plot Digitized 2.6.2 for Macintosh) to digitize KM curves and a KM-data reconstruction algorithm developed in R language (R 3.6.0; R Development Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

ISBN 3-900051-07-0, URL http://www.R-project.org/) to estimate the individual patient data.

Risk of bias and quality assessment /certainty of evidence.

The risk of bias among included trials was estimated by two Authors using the revised Cochrane risk of bias tool for randomized controlled trials [17]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was employed to grade the certainty of evidence (very low, low, moderate, high).

Statistical analysis.

Cumulative incidence of outcomes at follow-up in the two treatment arms was evaluated with Kaplan-Meier estimates. Unadjusted and risk-profile stratified HRs in the pooled dataset were calculated with grouped frailty semi-parametric (Cox) model, accounting for heterogeneity among trials with a random-intercept parameter, as previously described [9]. Proportionality of hazards of the Cox models was checked with the Grambsch-Therneau test and diagnostic plots based on Shoenfeld residuals. We planned to perform landmark analysis in the case of evidence of non constant proportional hazards from test results or visual inspection of Kaplan-Meier curves.

Time-dependency of treatments' effect was approached with landmark analysis, applying Kaplan-Meier analysis and Cox regression to evaluate endpoints in the groups (TAVI/SAVR) at time-frames. The cutoffs were chosen on the basis of visual inspection of the scaled Shoenfeld residuals and of the Kaplan Meier curves. Moreover, the time-varying Hazard Ratio of endpoints for TAVI vs SAVR was modeled with fully parametric generalized survival models (Royston-Parmar models) with baseline smoother and time-varying variables based on b-splines.

Quality assessment of Kaplan-Meier derived IPD data was performed graphically checking the derived Kaplan-Meier curves with the original ones. Moreover, the accuracy was evaluated comparing the estimated and reported (when available) HRs. We assessed potential publication bias with visual interpretation of funnel plot.

Analyses were performed with R language (R 3.6.0; R Development Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/).

We adhere to the Preferred Reporting Items for Systematics Reviews and Meta-analyses (PRISMA) statement (PRISMA checklist, eTable 2 in the Supplement) [18].

Role of funding source.

This study was done without funding. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Trials characteristic and risk of bias.

After literature search, eligibility evaluation and duplicates' exclusion, 8 trials were checked for further assessment. We excluded the STACCATO trial as only 30-day follow-up was reported. Seven trials (PARTNER 1A, PARTNER 2A, PARTNER 3, NOTION, US CoreValve High Risk, SURTAVI and EVOLUT Low-risk Trial) fulfilled the pre-specified inclusion criteria and were included in the meta-analysis (eFigure 1 in the Supplement) [2-8, 10-14].

Table 1 reports baseline characteristics of the study groups. All studies were multicenter randomized trials and the longest available follow-up was published between 2015 and 2020. Four of 7 studies reported 5-year follow-up (a cohort of 3808 patients). Kaplan-Meier graphs from ITT data were available from PARTNER 1A, PARTNER 2A and SURTAVI. As-treated population data were available from PARTNER 3, CoreValve U.S. Pivotal trial, Evolut R Low-Risk trial and NOTION.

Overall, 7770 patients were randomly assigned to undergo TAVI (n=3977) or SAVR (n=3793). In the 7 trials, both balloon-expanding (Edwards SAPIEN, SAPIEN XT and SAPIEN 3) and self-expanding TAVI devices (Medtronic CoreValve) were under study. The TAVI approaches were different, however the most common access was transfemoral.

The risk of bias of the included trials was detailed in eTable 3 .

Quality assessment of estimated IPD data.

No major graphical differences were shown at visual comparison between original reported Kaplan-Meier curves and estimated KM curves. Hazards Ratios estimated from KMd-IPD were compared to HRs in the paper, when available. NOTION, EVOLUT R Low-Risk and SURTAVI did not calculate TAVI vs SAVR HRs, while comparison between reported and estimated HRs was possible for PARTNER 1A, PARTNER 2A, PARTNER 3 and CoreValve US Pivotal Trials. As shown in eFigure 2 in the Supplement, HRs estimated from Kaplan Meier-derived IPD data were not different to those reported in the trials, confirming a high accuracy of the IPD-deriving method.

Analysis of composite of death from any cause or stroke up to 5 years.

Six of the seven RCTs reported Kaplan-Meier graphs of the composite endpoint. The NOTION trial was not included as reported a composite of death, stroke and myocardial infarction [7]. Moreover, only the 3-year graph of the composite endpoint was available for the CoreValve U.S. Pivotal trial, although 5-year results have been published [3, 13]. Summarizing, the included trials were PARTNER 1A (5 years), CoreValve U.S. Pivotal trial (3 years), PARTNER 2A (5 years), SURTAVI (2 years), PARTNER 3 (2 years) and EVOLUT LR (2 years) [2, 4-6, 8, 13]

The risk-stratified Cox-estimated HR for all-cause mortality was not significant (0.98; 95% CI 0.90 - 1.08, p-value 0.73). The heterogeneity was significant ($\theta = 0.05$, p-value < 0.001). However, the assumption of hazard-proportionality was not fulfilled based on the analysis of Shoenfeld residuals and the Grambsch-Therneau test for time-invariant effect (p-value < 0.001); hence models accounting for time-varying HRs were required as, in the absence of constant proportional hazards, the Cox model output is biased.

The cutoffs selected for landmarking by visual inspection of the scaled Shoenfeld residuals and the Kaplan-Meier curve were 6 and 24 months. Figure 1 Panel A shows the Kaplan-Meier estimates of all-cause mortality by landmark analysis. In the first 6 months after implantation, TAVI was related to significant lower incidence of the composite outcome (risk profile stratified HR 0.66, 95% CI 0.56 – 0.77, p-value < 0.001).Although randomization to SAVR was associated with a numerically improved survival in 6 to 24 months this difference in the incidence of composite outcome between TAVI and SAVR not statistically significant (6 - 24 months Risk-stratified HR 1.16, 95%CI 0.97 – 1.38; p-value 0.099). Landmark analysis of composite outcome after 24 months described a significant reversal of HR (Risk-stratified HR 1.25; 95%CI 1.08-1.46; p-value 0.003) favoring SAVR.

The analysis of HR trend over time of TAVI vs SAVR estimated by fully parametric generalized survival models confirmed results by landmark analysis (Figure 1, Panel B). TAVI was superior to surgery in the early months with the advantage decreasing over time to 2 years, when SAVR became clearly superior.

Analysis of all-cause mortality up to 5 years.

The risk-stratified Cox-estimated HR for all-cause mortality was 1.00 (95% CI 0.92 -1.10, p-value 0.9). with a significant heterogeneity (θ = 0.10, p-value < 0.001). The assumption of hazard-proportionality was not fulfilled (p-value 0.001).

The Kaplan-Meier estimates of all-cause mortality by landmark analysis shows similar results to those of composite outcome (Figure 2). TAVI was associated with a survival advantage over surgery in the first 6 months (HR 0.70, 95%CI 0.59 - 0.83, p-value < 0.001), while no difference in mortality was shown between 6 and 24 months (HR 1.09, 95%CI 0.91 – 1.31, p-value 0.33). Again, a reversal of HR (Risk-stratified HR 1.18; 95%CI 1.03-1.35; p-value 0.01) favoring SAVR over TAVI was evident after 24 months.

The analysis of HR trend over time for all-cause death is concordant with the landmark outputs, showing that the TAVI survival advantage in the first months turns into a significant worst incidence of death after 2 years.

As expected, the HR trend including only trials with 5 years follow-up was largely superimposable to that of the total group. (eFigure 4).

Analysis of stroke incidence up to 5 years.

Analysis of stroke in the two groups was limited by the low incidence together with the reduced sample size. Most of the RCTs presented the composite outcome alone and Kaplan Meier curves at 5 years for stroke were reported only by PARTNER 1A and NOTION trial [2, 7].

The risk-stratified Cox-estimated HR for stroke favored TAVI over surgery (0.73; 95% CI 0.58 – 0.93, p-value 0.01). The heterogeneity was significant (θ = 0.09, p-value 0.02) and the assumption of hazard-proportionality was not fulfilled (p-value 0.03).

The cutoff selected was 3 months (Figure 3A). In the first 3 months after implantation, TAVI showed a significant lower incidence of stroke (risk profile stratified HR 0.90, 95% CI 0.65 – 1.27, p-value 0.56). There was no difference in stroke incidence between groups after 3 months (risk profile stratified HR 0.60, 95% CI 0.43 – 0.84, p-value 0.002).

The landmark analysis results were concordant with HR trend analysis shown in Figure 3B.

Analysis of re-hospitalization incidence up to 5 years.

Four of the seven RCTs reported Kaplan-Meier graphs of the re-hospitalization. The included trials were PARTNER 1A (5 years), PARTNER 2A (5 years), PARTNER 3 (2 years) and EVOLUT LRT (1 years) [2, 4, 10, 14].

The risk-stratified Cox-estimated HR for all-cause mortality was not significant (1.06; 95% CI 0.93 - 1.22, p-value 0.34). The heterogeneity was significant ($\theta = 0.24$, p-value < 0.001) and the assumption of hazard-proportionality was not fulfilled (p-value < 0.001).

The cutoffs selected were 6 and 12 months. In the first 6 months after implantation, TAVI was related to significant lower incidence of re-hospitalization (risk profile stratified HR 0.80, 95% CI 0.67 – 0.96, p-value 0.02). Incidence of re-hospitalization after 12 months was significantly favorable to surgery (Risk-stratified HR 1.69; 95%CI 1.33-2.15; p-value < 0.001).

The landmark analysis results were concordant with the HR trend analysis. The advantage of TAVI appears to be limited in the first months after implantation while after 1 year the hazard of re-hospitalization is significantly lower in the surgical group.

Discussion

The rapid development and wider indication to TAVI in younger and lower-risk patients has led to increased attention on long-term follow-up, as feasibility and safety of the procedure are increasingly well described at least in clinical trials [2-8, 10-14]. Short term results have shown that the appeal of less invasive approach is not only aesthetic but it is also substantive, as it leads to lower complication rates and faster "recovery", which may be particularly valuable in older and frailty patients [2-8, 10-14]. A shorter in-hospital stay, as well as lower incidence of readmission in the very first months after the procedure, are a direct confirmation of the better outcomes of TAVI within the first months [6]. Nonetheless, the short-term outcome cannot be necessarily confirmed at longer follow-up as the forces that drive outcomes are different and the durability of a new prosthesis compared to the gold standard should be evaluated over a prolonged period of time, usually more than 5 and at least 10 years. Indeed, it is standard for the FDA to require 10 year follow up for pivotal trials. Our results indicate that the advantage of TAVI over SAVR is not constant over time and is reversed at longer follow-up, favoring surgery. The increase in patient numbers of the 5-year cohort, as well as the follow up to 2 year of low-risk trials, stabilized the results of our previous analyses on all-cause death [9] and gave more precise estimates, indicating that the reversal of HR favoring surgery may be anticipated at about 2 years and most of the TAVI advantage on survival can be confined in the first months. This message is reinforced also by the analysis of the composite of all-cause mortality and stroke at follow-up and re-hospitalization at follow-up. Their HRs trend to have the same pattern and overturn the widespread hypothesis that good short term results indicate good long-term results.

Our results are in contrast to most of the meta-analyses performed on the same issue and with almost the same included studied [19-21], that showed superiority or at least no inferiority of TAVI at follow-up. As we previously demonstrated, these contrasting results are related to the use of standard meta-analysis methodologies to outcomes that are time-to-event where the data are front loaded to short term trials. This circumstance of non linear effects requires specific methods. Summarizing Cox-estimated HR as a simple dichotomy (such as a OR, for an example) poorly represents these data and their time varying effects [9]. Moreover, mixing HRs and ORs in the same meta-analysis is a forced operation that can substantially bias the

summary effect [19]. Also heterogeneity due to time varying effects could be highly misleading when treatment effects are estimated employing traditional meta-analysis [9].

Our results are congruent with the individual studies included but provide considerably greater statistical certainty. The graphical analysis of Kaplan-Meier curves as well as the landmark analysis performed in some studies reveal a different effect of TAVI vs SAVR over time [2-4]. In the PARTNER 2A at five years, TAVI has been associated to a significant survival disadvantage between 2 and 5 years not only in the total cohort (HR 1.27, 95%CI 1.06-1.53, $p<0.05$) but also in the trans-femoral (HR 1.23 95%CI 1.00-1.52) and trans-apical subgroups (1.45, 95%CI 1.01-2.07) [4, 11, 22].

The explanation of the time-varying effect of TAVR/SAVR on outcomes at 5 years is far beyond the aims of the present study. Durability of the prosthesis, as well as paravalvular leaks and higher incidence of pace-maker implantation has been considered as potential factors affecting mid-term outcomes [23]. Newer prostheses are claimed to be more performant and with a lower incidence of structural and non-structural valve deterioration although there is limited evidence to support these arguments. Further a last-generation device in low-risk patients has been associated to significant valve-thrombosis at 2-year, compared to surgery (2.6% vs 0.7%, p-value 0.02) [12].

Limitations

Our analysis of pooled KM-derived IPD data has some intrinsic limitations. The duration of follow-up is limited up to 5 years and only 1 study in the low-risk profile describes 5-year outcomes. The longer follow-up is available for older devices and results should be validated also in trials with newer ones that potentially could demonstrate better follow-up for improvement in valve design and technical aspects; nonetheless, the question over durability and worse outcomes at longer follow-up times of time overcomes by far the expectations associated to newer TAVI prostheses. No comparison between balloon-expanding and self-expanding TAVI devices has been performed. Moreover, this analysis can be stratified only for risk-profile by STS score and EuroSCORE at the study level, and the potential impact of singular comorbidities on both heterogeneity and outcomes cannot be extrapolated.

Conclusions.

This pooled analysis of Kaplan-Meier derived individual patient data comparing outcomes at 5 years between TAVI and SAVR in RCTs indicates that TAVI is associated with an advantage in the first months after implantation; nonetheless this advantage decreases quickly over time, with TAVI becoming a risk factor for all-cause mortality and the composite of all-cause mortality and stroke after 24 months. TAVI is also related to a 69% increased hazard of re-hospitalization beginning from 1 year after implantation.

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Contributors

Conceptualization: FB, NF, AP, DP. *Data curation*: FM, MR. *Formal analysis*: FB and NF. *Funding Acquisition*: None. Investigation: FB, NF, MR, GG, AP. *Methodology*: FB and AP. *Project administration*: GG, MR. *Resources*: DP, FM, AP. *Software*: FB, AP. *Supervision*: AP, NF, DP. *Visualization*: FB. *Writing – original draft*: FB. *Writing – review & editing*: All Authors.

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Conflict of interest

Dr. Barili reports personal fees from Abbott Medical, outside the submitted work.
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1 **Tables**

2 **Table 1. Baseline characteristics of the 7 trials.**

Risk Profile	HIGH								LOW				INTERMEDIATE								LOW						LOW			
Trial name	**PARTNER 1A 5y**				**CORE VALVE US 5y**				**NOTION**				**PARTNER 2A 2y**				**SURTAVI 2y**				**PARTNER 3 1y**						**EVOLUT LOW RISK 2y**			
Treatment group	**TAVR**		**AVR**		**TAVR**		**AVR**		**TAVR**		**AVR**		**TAVR**		**AVR**		**TAVR**		**AVR**		**TAVR**		**AVR**				**TAVR**		**AVR**	
Trial's Characteristics																														
Numbers of centres	25				45				3				57				87				71						86			
Recruitment period	2007-09				2011-12				2009-13				2011-13				2012-2016				2016-2017						2016-2018			
Longest follow up, y	5				5				5				2				2				1						1			
design	Non-inferiority				Non-inferiority				Superiority				Non-inferiority				Non-inferiority				Non-inferiority						Non-inferiority			
ITT patients, n	348		351		395		402		145		135		1011		1021		864		796								734		734	
As-treated patients, n	344		313		391		359		142		134		994		944		863		764		496		454				725		678	
Patient's Characteristics																														
Age, mean (SD)	83,6 ± 6,8		84,5 ± 6,4		83.2 ± 7.1		83.3 ± 6.3		79,2 ± 4,9		79,0 ±4,7		81,5 ± 6,7		81,7 ± 6,7		79,9 ± 6,2		79,8 ± 6,0		73,3 ± 5,8		73,6 ± 6,1				74,0 ± 5,9		73,8 ± 6,0	
Women, n	147	42,2%	153	43,6%	184	47,1%	171	47,6%	67	46,2%	64	47,4%	463	45,8%	461	45,2%	366	42,4%	438	55,0%	161	32,5%	131	28,9%			266	36,2%	246	33,5
NYHA Class III or IV	328	94,3%	328	93,4%	334	85,4%	312	86,9%	70	48,3%	61	45,2%	782	77,3%	776	76,0%	520	60,2%	463	58,2%	155	31,3%	108	23,8%			181	24,6%	205	27,9
STS, mean (SD)	11,8 ± 3,3		11,7 ± 3,5		7,3 ± 3,0		7,5 ± 3,2		2,9 ± 1,6		3,1 ± 1,7		5,8 ± 2,1		5,8 ± 1,9		4,4 ± 1,5		4,5 ± 1,6		1,9 ± 0,7		1,9 ± 0,6				1,9 ± 0,7		1,9 ± 0,7	
Logistic EuroSCORE	29,3 ± 16,5		29,2 ± 15,6		17,7 ± 13,0		18,8 ± 13,2		8,4 ± 4,0		8,9 ± 5,5		-		-		11,9 ± 7,6		11,6 ± 8,0		-		-				-		-	
Logistic EuroSCORE II	-		-		-		-		1,9 ± 1,2		2,0 ± 1,3		-		-		-		-		1,5 ± 1,2		1,5 ± 0,9				-		-	
Hypertension	-	-	-	-	372	95,1%	345	96,1%	103	71,0%	103	76,3%	-	-	-	-	801	92,7%	719	90,3%	-	-	-	-			622	84,9%	608	82,9
Diabetes Mellitus	-	-	-	-	136	34,8%	162	45,1%	26	17,9%	28	20,7%	381	37,7%	349	34,2%	295	34,1%	277	34,8%	155	31,3%	137	30,2%			228	31,1%	224	30,5
Chronic kidney	38	10,9%	24	6,8%	48	12,3%	45	12,5%	2	1,4%	1	0,7%	51	5,0%	53	5,2%	14	1,6%	17	2,1%	1	0,2%	1	0,2%			0	0%	1	1%
COPD any	152	43,7%	151	43,0%	-	-	-		17	11,7%	16	11,9%	321	31,8%	306	30,0%	-	-	-	-	25	5,1%	28	6,2%			106	15,1%	121	17,2
COPD - O2 dependent	38	10,9%	38	10,8%	-	-	-		-	-	-	-	34	3,4%	32	3,1%	-	-	-	-	-	-	-	-			-	-	-	-
Peripheral vascular disease, n	148	42,5%	142	40,5%	159	40,7%	150	41,8%	6	4,1%	9	6,7%	282	27,9%	336	32,9%	266	30,8%	238	29,9%	34	6,9%	33	7,3%			55	7,6%	62	8,5
Prior cerebrovascular event, n	95	27,3%	87	24,8%	49	12,5%	50	13,9%	24	16,6%	22	16,3%	325	32,1%	317	31,0%	115	13,3%	103	12,9%	17	3,4%	23	5,1%			74	10%	84	11,4
Coronary artery disease, no (%)	260	74,7%	266	75,8%	295	75,4%	273	76,0%					700	69,2%	679	66,5%	541	62,6%	511	64,2%	137	27,6%	127	28,0%			-	-	-	-
Previous myocardial infarction - no (%)	92	26,4%	103	29,3%	99	25,3%	91	25,3%	8	5,5%	6	4,4%	185	18,3%	179	17,5%	125	14,5%	111	13,9%	28	5,6%	26	5,7%			49	6,7%	39	5,3
Prior CABG, n	147	42,2%	152	43,3%	115	29,4%	113	31,5%	-	-	-	-	239	23,6%	261	25,6%	138	16,0%	137	17,2%	-	-	-	-			18	2,5%	17	2,3
Prior PCI, n 1	116	33,3%	110	31,3%	134	34,3%	135	37,6%	11	7,6%	12	8,9%	274	27,1%	282	27,6%	184	21,3%	169	21,2%	-	-	-	-			102	13,9%	93	12,7
Known atrial fibrillation or flutter, n	80	23,0%	73	20,8%	160	40,9%	165	46,0%	40	27,6%	34	25,2%	313	31,0%	359	35,2%	243	28,1%	211	26,5%	78	15,7%	85	18,8%			113	15,5%	109	14,9
Prior pacemaker, n	69	19,8%	76	21,7%	91	23,3%	76	21,2%	5	3,4%	6	4,4%	118	11,7%	123	12,0%	84	9,7%	72	9,0%	12	2,4%	13	2,9%			25	3,4%	28	3,8
Pulmonary hypertension	126	36,2%	111	31,6%	-	-	-	-	-		-		-		-		-	-	-	-	-	-	-	-			-	-	-	-
Left ventricular ejection fraction - % (SD)	52,5 ± 13,5		53,3 ± 12,8		-	-	-	-					56,2 ± 10,8		55,3 ± 11,9						65,7 ± 9.0		66.2 ± 8.6				61,7 ± 7,9		61,9 ± 7,7	
Intervention's characteristics																														

TAVI Valve system	Edwards SAPIEN		NA	NA	Medtronic CoreValve		NA	NA	Medtronic CoreValve		NA	NA	Sapien XT		NA	NA	Corevalve or Evolut R		NA	NA	SAPIEN 3		NA	NA	Corevalve, Evolut R or Evolut PRO		NA	
Access site																												
Trans-femoral	244	70,1%	NA	NA	394	99,7%	NA	NA	137	96,5%	NA	NA	775	76,7%	NA	NA	808	93,6%	NA	NA	496	100,0%	NA	NA	718	99%	NA	NA
Trans thoracic	104	29,9%	NA	NA	0	0,0%	NA	NA	0	0,0%	NA	NA	236	23,3%	NA	NA	35	4,1%	NA	NA	0	0,0%	NA	NA	3	0,4%	NA	NA
Trans Subclavian	0	0%	NA	NA	0	0%	NA	NA	5	3,5%	NA	NA	0	0%	NA	NA	20	2,3%	NA	NA	0	0%	NA	NA	4	0,6%	NA	NA

1

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Figure legends.

Figure 1. Panel A: Landmark analysis of all-cause mortality or stroke in TAVI and SAVR groups. Panel B: HR trend over time for all-cause mortality or stroke of TAVI vs SAVR estimated by fully parametric generalized survival models.

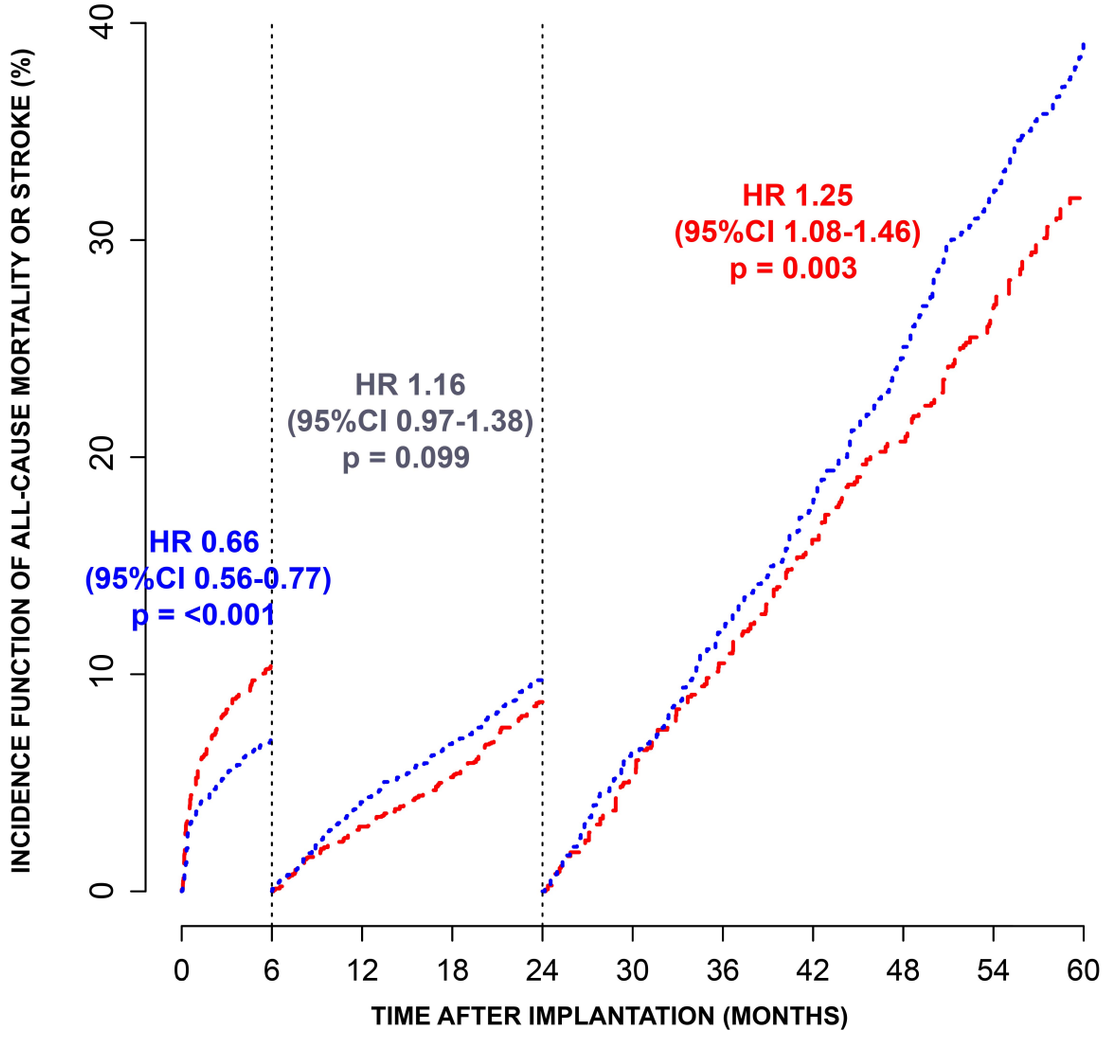
Figure 2. Panel A: Landmark analysis of all-cause mortality in TAVI and SAVR groups. Panel B: HR trend over time for mortality of TAVI vs SAVR.

Figure 3. Panel A: Landmark analysis of stroke in TAVI and SAVR groups. Panel B: HR trend over time for stroke of TAVI vs SAVR.

Figure 4. Panel A: Landmark analysis of re-hospitalization in TAVI and SAVR groups. Panel B: HR trend over time for re-hospitalization of TAVI vs SAVR.

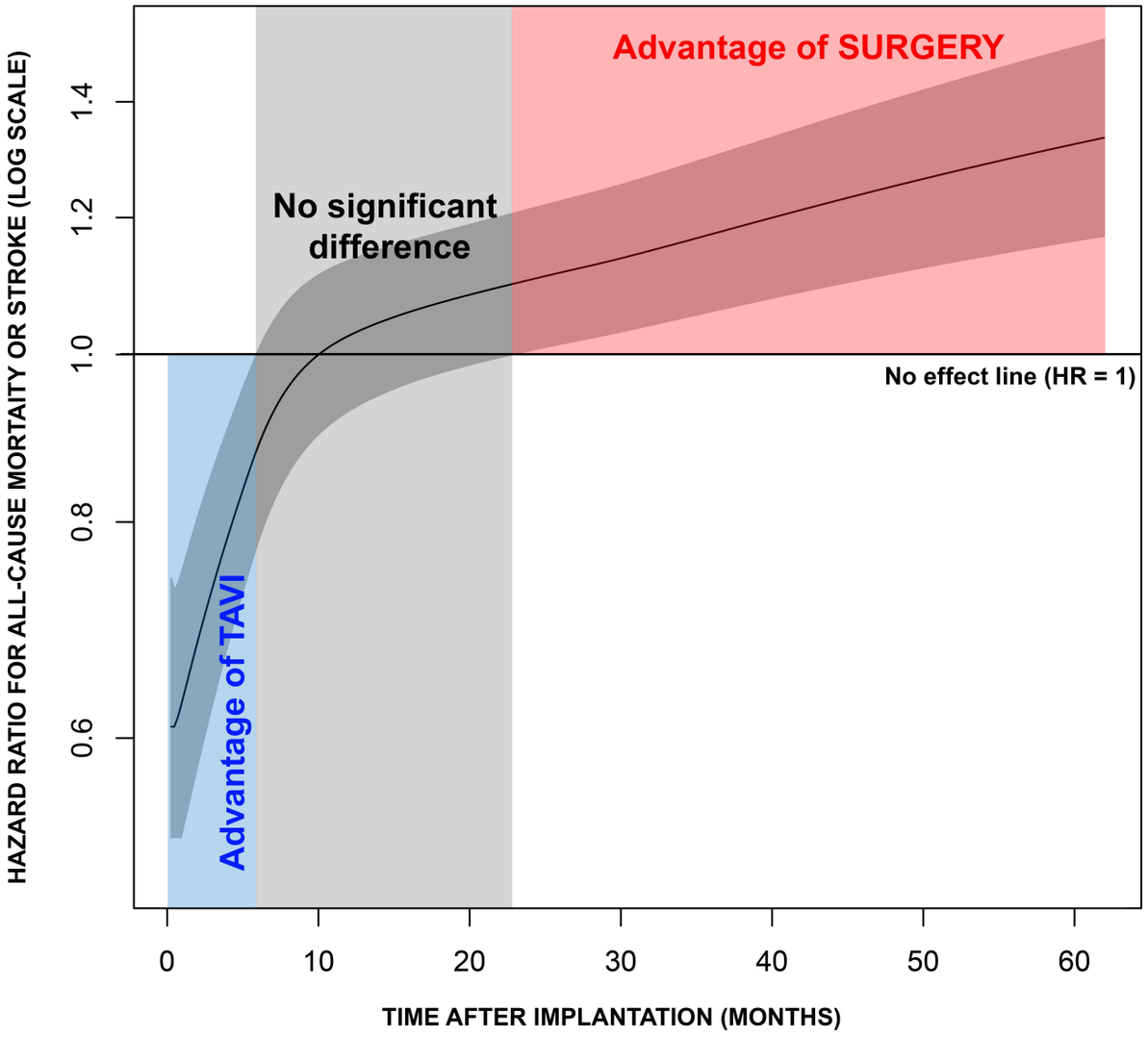
COMPOSITE OUTCOME (All cause death and stroke)

Landmark Analysis



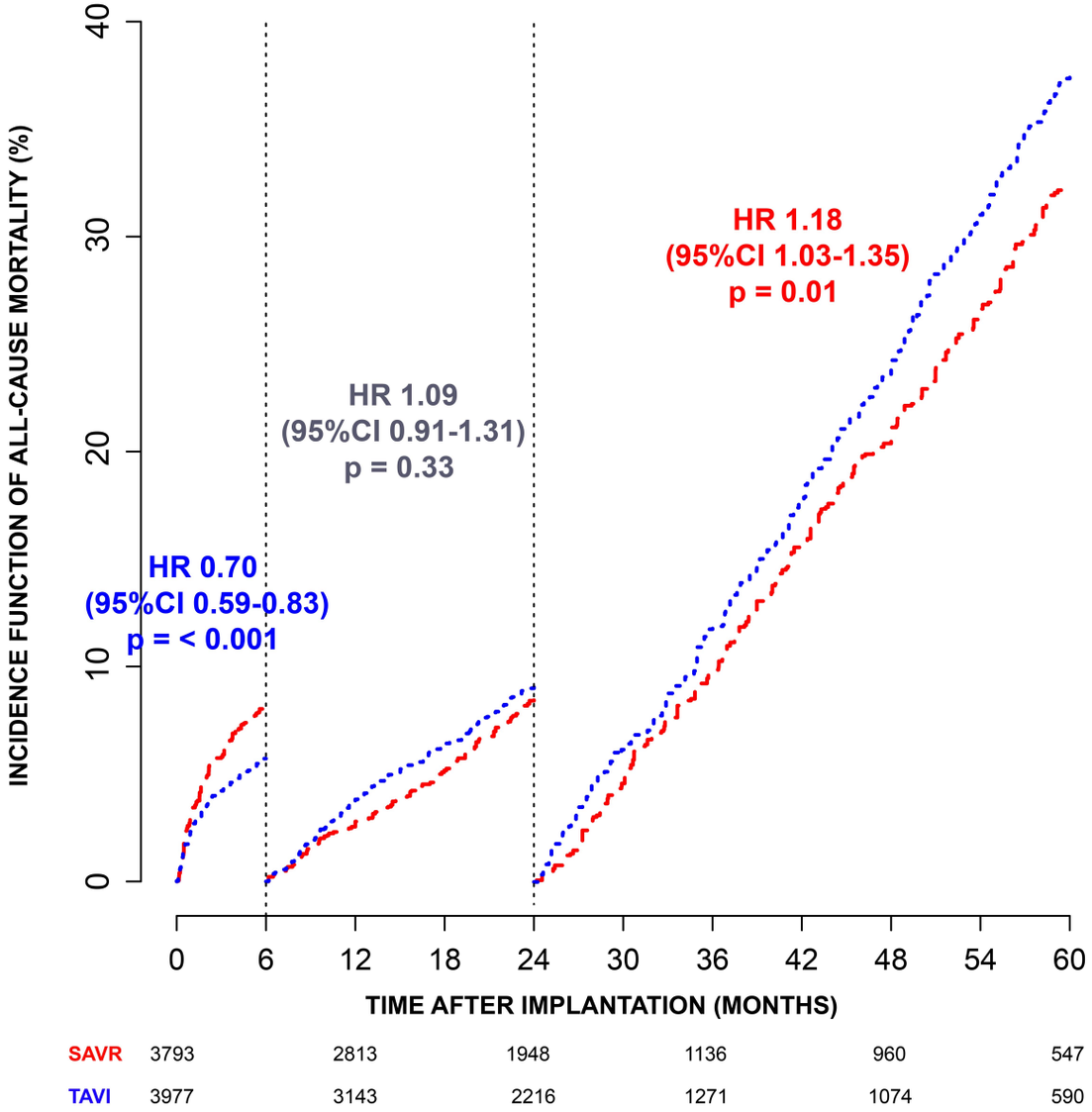
SAVR	3659	2602	1822	922	675	504
TAVI	3835	2949	2090	1033	725	531

Hazard Ratio Trend

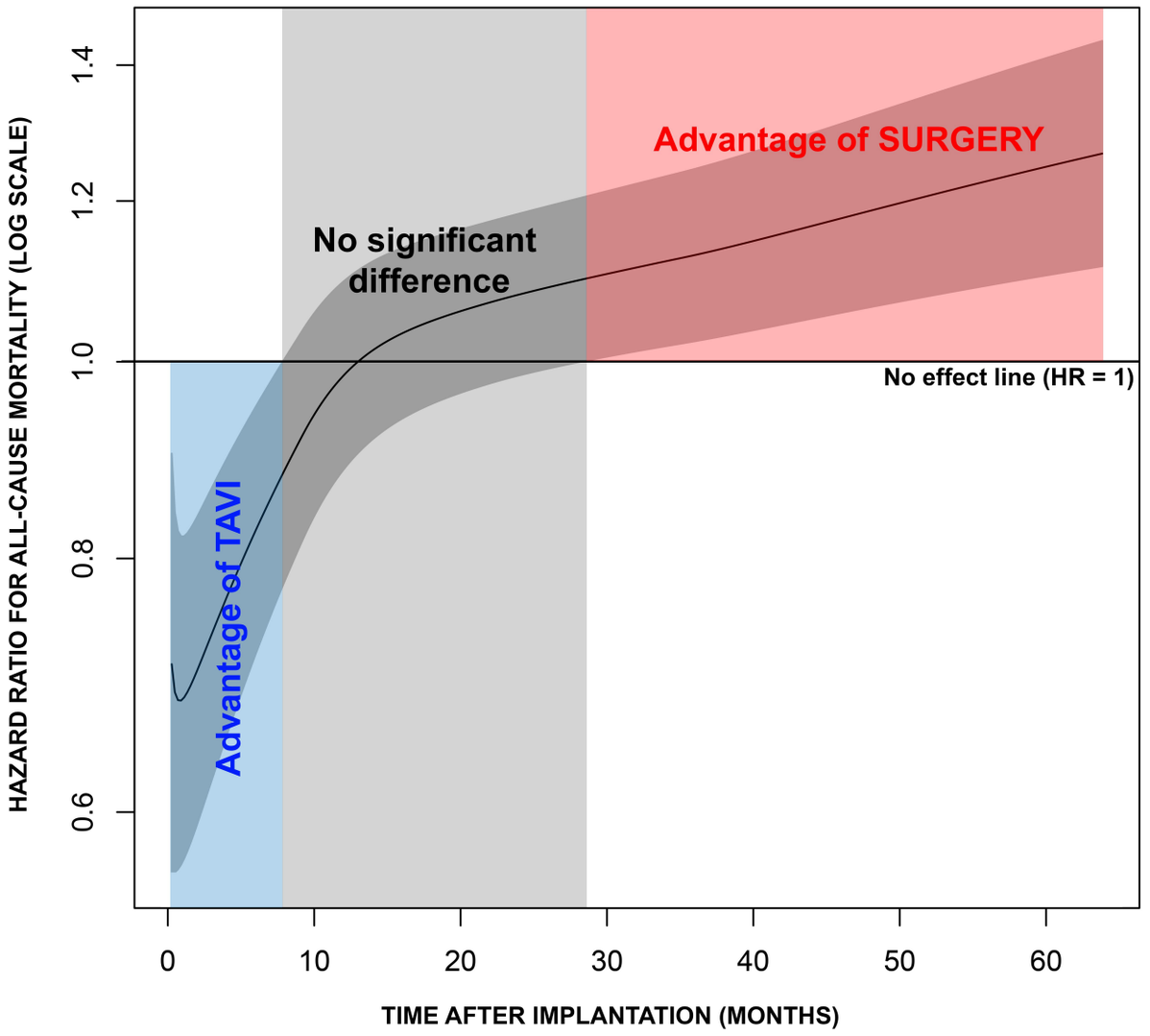


ALL-CAUSE MORTALITY

Landmark Analysis

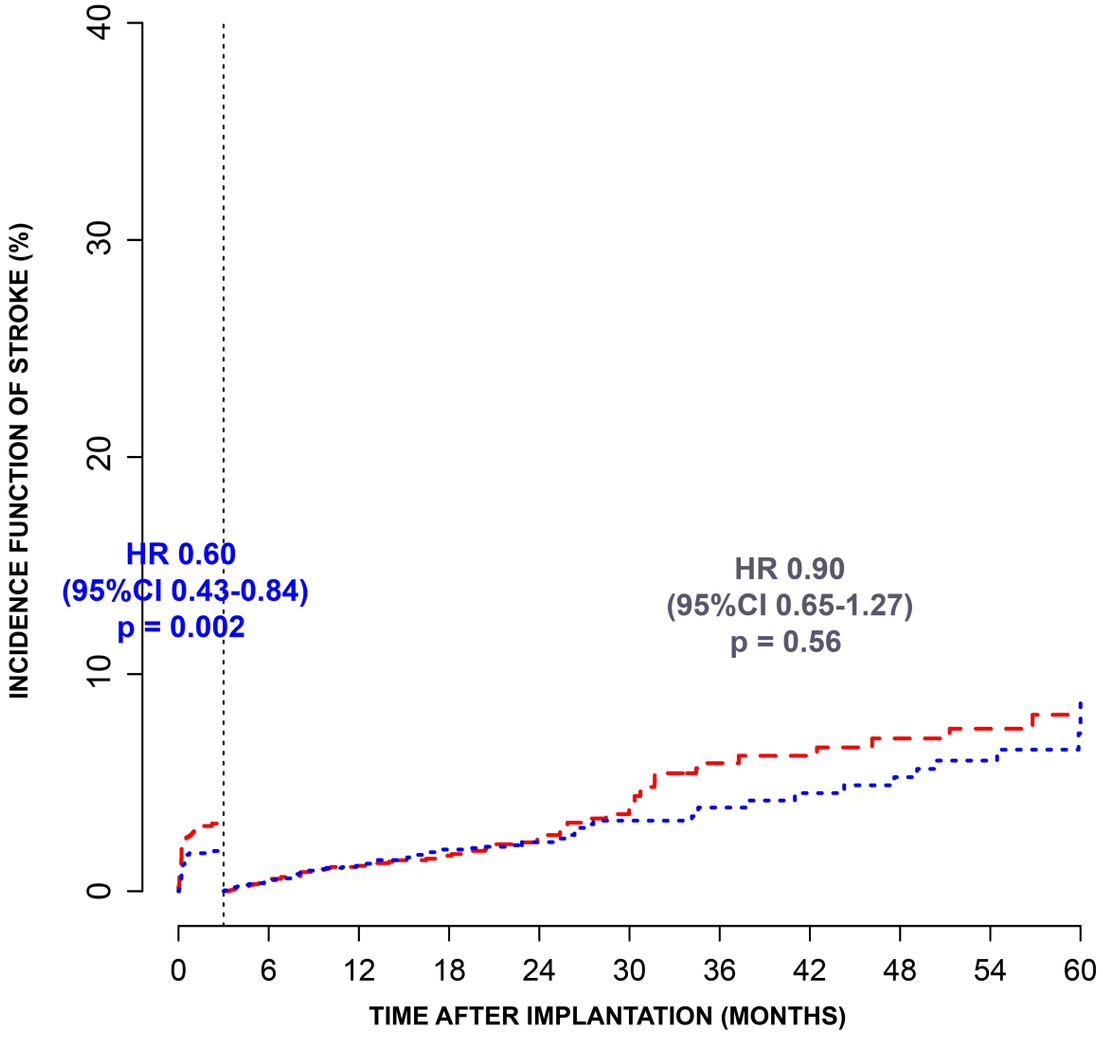


Hazard Ratio Trend



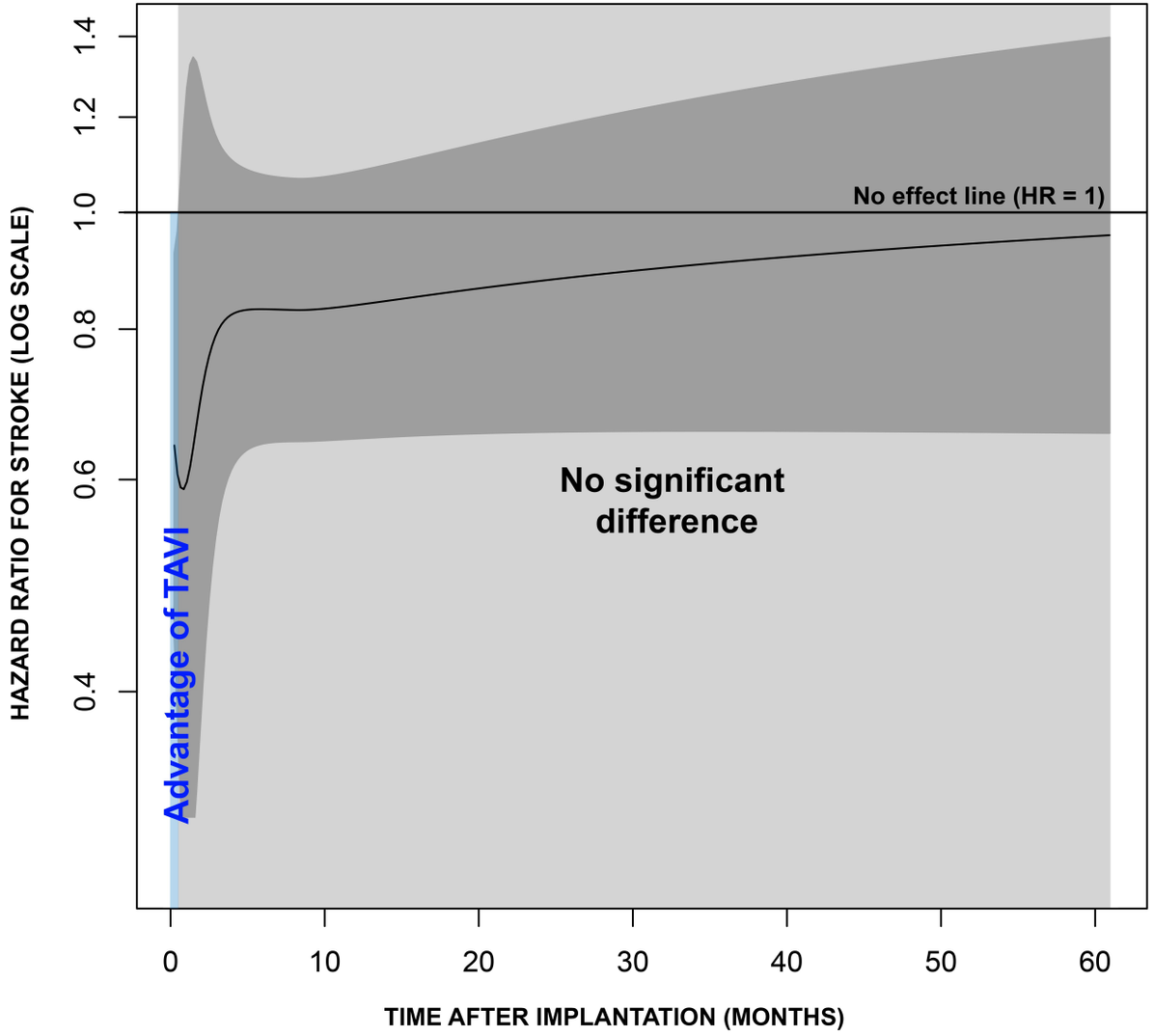
STROKE

Landmark Analysis



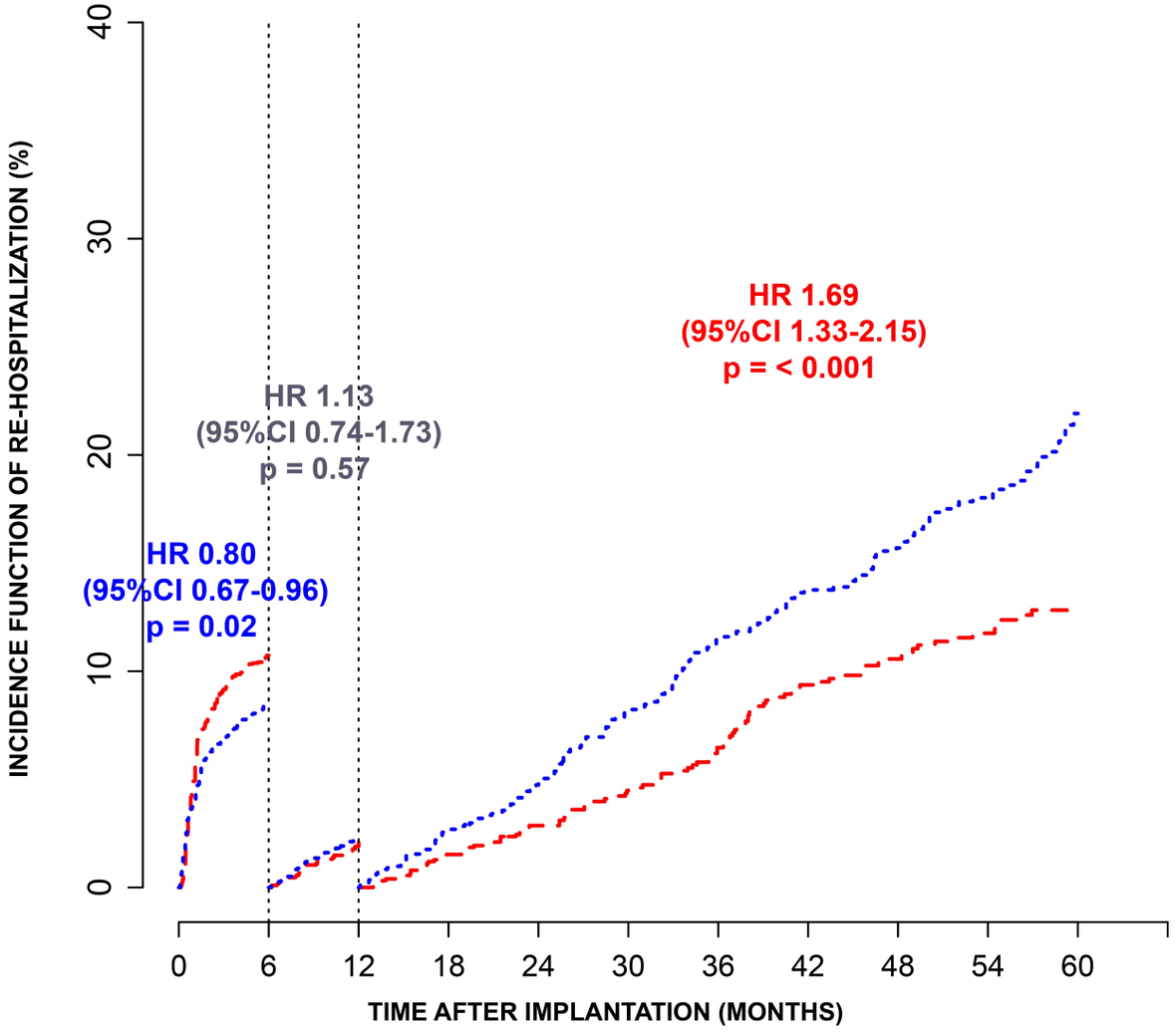
SAVR	2772	1941	1155	405	224	138
TAVI	2966	2233	1344	460	253	124

Hazard Ratio Trend



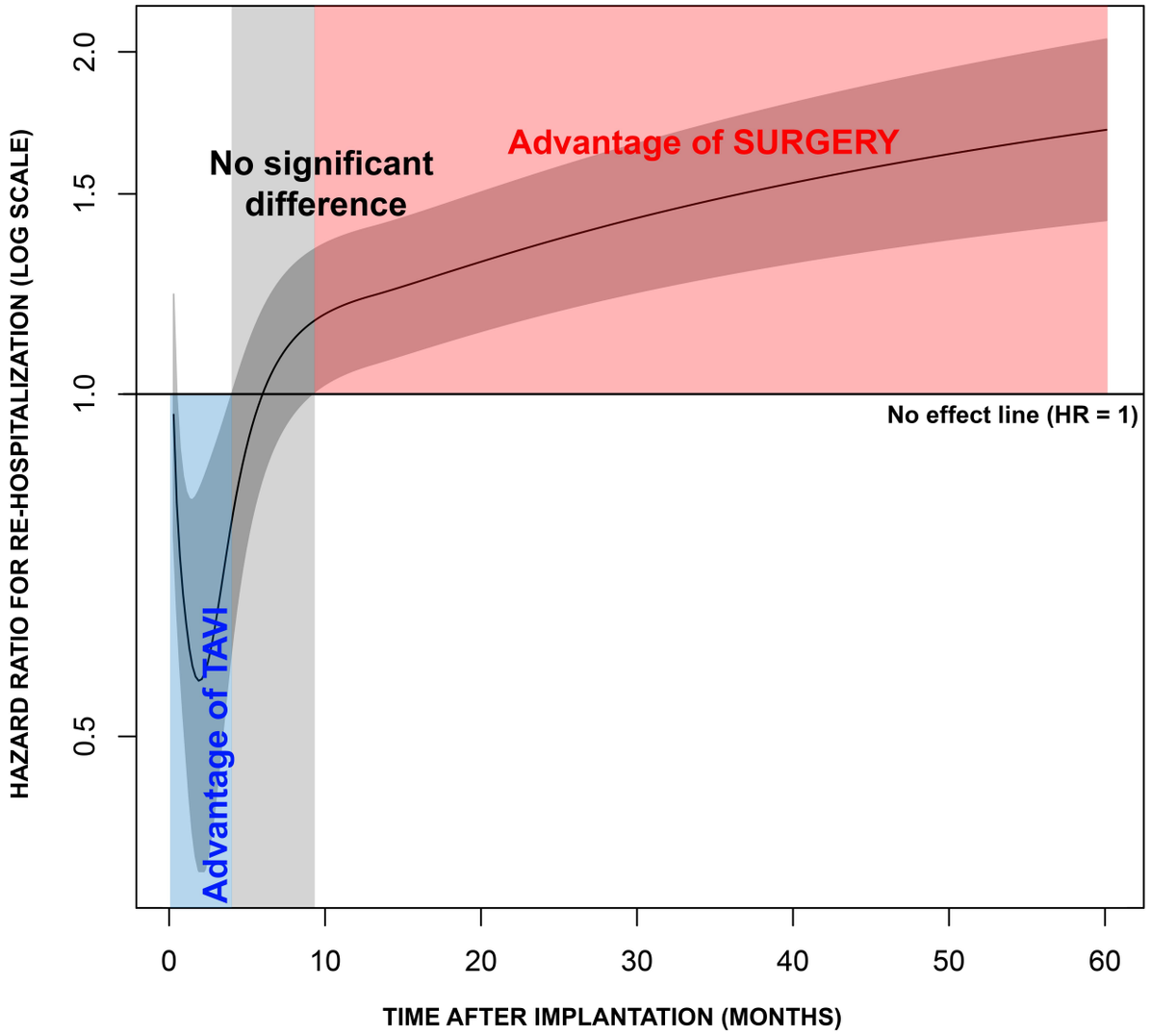
RE-HOSPITALIZATION

Landmark Analysis



SAVR	2504	1638	1114	694	576	308
TAVI	2580	1855	1284	722	594	291

Hazard Ratio Trend



Supplemental material.

Five-year survival in trials comparing trans-catheter aortic valve implantation vs surgical aortic valve replacement: an updated pooled meta-analysis of Kaplan-Meier derived individual patient data

eTable 1. Search algorithms (last search 03/07/2020).

MEDLINE		
#1	“aortic valve”	68770
#2	transcatheter	26281
#3	random*	1371807
#4	clinic*	6063941
#5	trial	1723057
#6	surgical	3769147
#7	#1 AND #2 AND #3 AND #4 AND #5 AND #6	**497**
EMBASE		
#1	'aortic valve'/exp OR 'aortic valve' OR (aortic AND ('valve'/exp OR valve))	**118,906**
#2	Transcatheter	**55,830**
#3	Trial	**2,151,907**
#4	Random*	**1,761,087**
#5	surgical	**1,969,825**
#6	#1 AND #2 AND #3 AND #4 AND #5	**789**
CENTRAL		
#1	aortic valve	2823
#2	transcatheter	2512
#3	trial	1216299
#4	random*	1144565
#5	surgical	102068
#6	#1 AND #2 AND #3 AND #4 AND #5	**299**

MEDLINE		
#1	“aortic valve”	65478
#2	transcatheter	23555
#3	random*	1300742
#4	clinic*	5163136
#5	trial	1346752

#6	surgical	3586768
#7	#1 AND #2 AND #3 AND #4 AND #5 AND #6	**310**
	EMBASE	
#1	'aortic valve'/exp OR 'aortic valve' OR (aortic AND ('valve'/exp OR valve))	111583
#2	Transcatheter	50638
#3	Trial	2047905
#4	Random*	1658994
#5	surgical	1873669
#6	#1 AND #2 AND #3 AND #4 AND #5	**685**
	CENTRAL	
#1	“aortic valve”	2818
#2	transcatheter	2513
#3	trial	1176293
#4	random*	1072182
#5	surgical	98668
#6	#1 AND #2 AND #3 AND #4 AND #5	**290**

eTable 2. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	no registration number
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4, 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4, 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4, 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4, 5

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5, 6

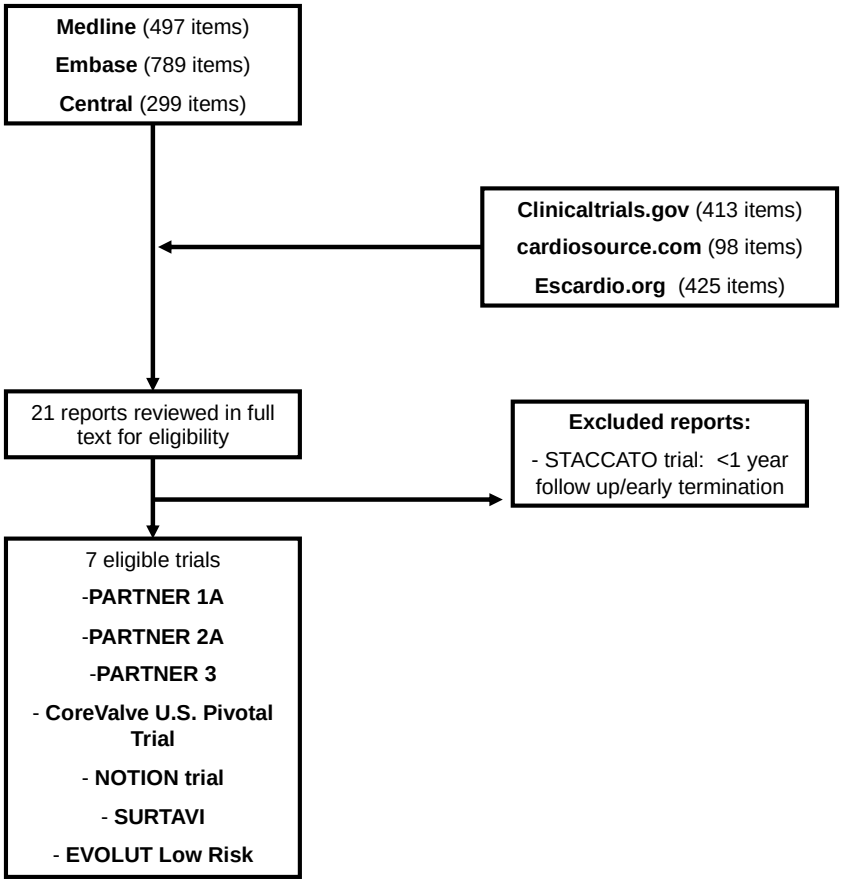
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

eTable3. Revised Cochrane risk of bias tool for randomized controlled trials.

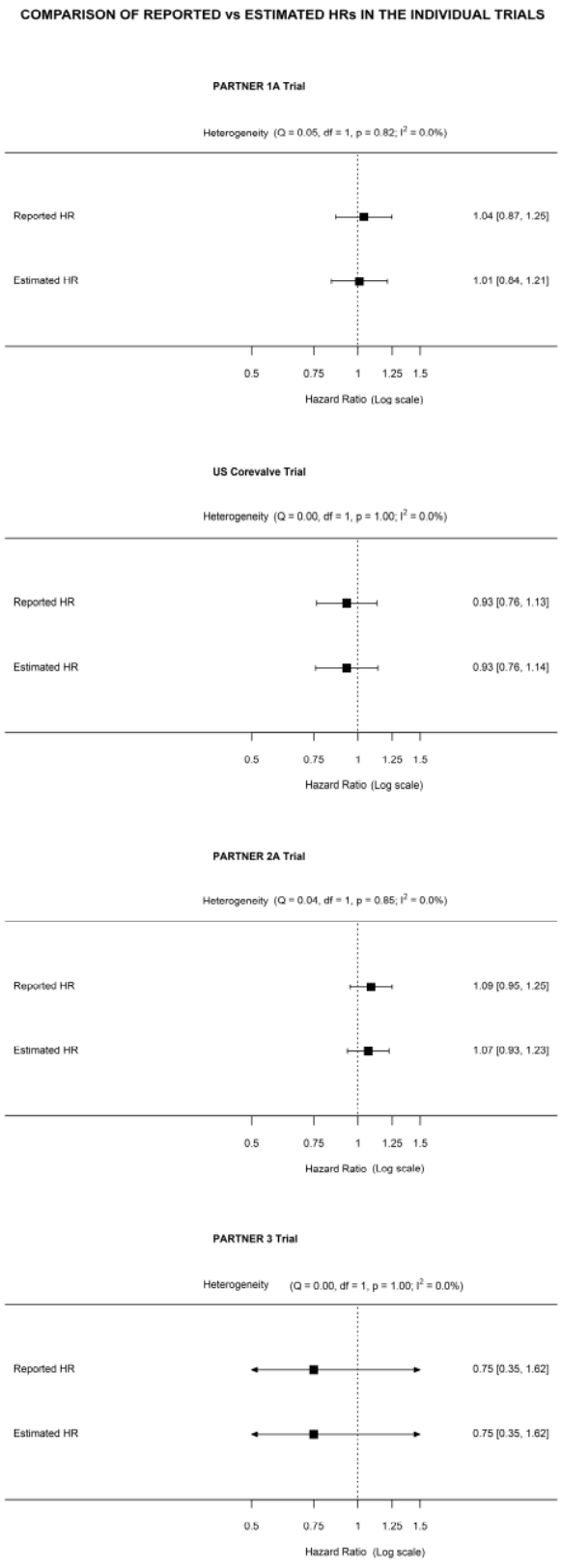
Trial	Randomization Process	Deviations from intended interventions	Missing Outcome Data	Measurement of Outcome	Selection of reported result	Overall Bias Assessment
PARTNER 1A	Some concerns	Major concerns	Major concerns	Major concerns	No concerns	Major concerns
CORE VALVE	Some concerns	Major concerns	Major concerns	Major concerns	No concerns	Major concerns
NOTION	Some concerns	No concerns	No concerns	No concerns	No concerns	Some concerns
PARTNER 2A	Some concerns	Some concerns	No concerns	No concerns	No concerns	Some concerns
SURTAVI	Some concerns	Some concerns	No concerns	No concerns	No concerns	Some concerns
PARTNER 3	Some concerns	Some concerns	Major Concerns	Major concerns	No concerns	Major concerns
EVOLUT Low Risk	Some concerns	Some concerns	No concerns	No concerns	No concerns	Some concerns

NOTION = Nordic Aortic Valve Intervention, PARTNER = Placement of Aortic Transcatheter Valves, SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation.

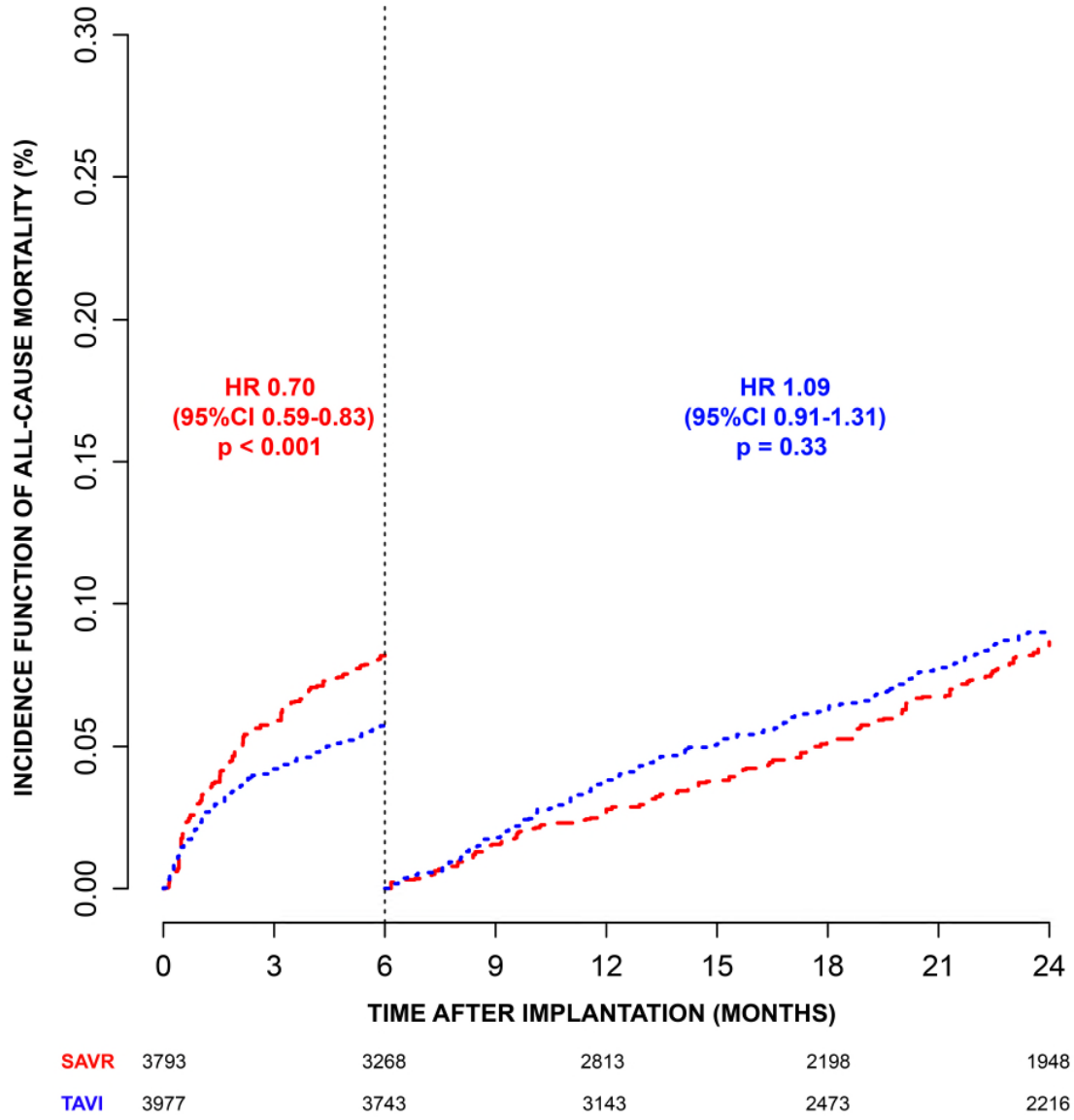
eFigure1. Flow diagram for the identification and selection of trials comparing TAVI and SAVR.



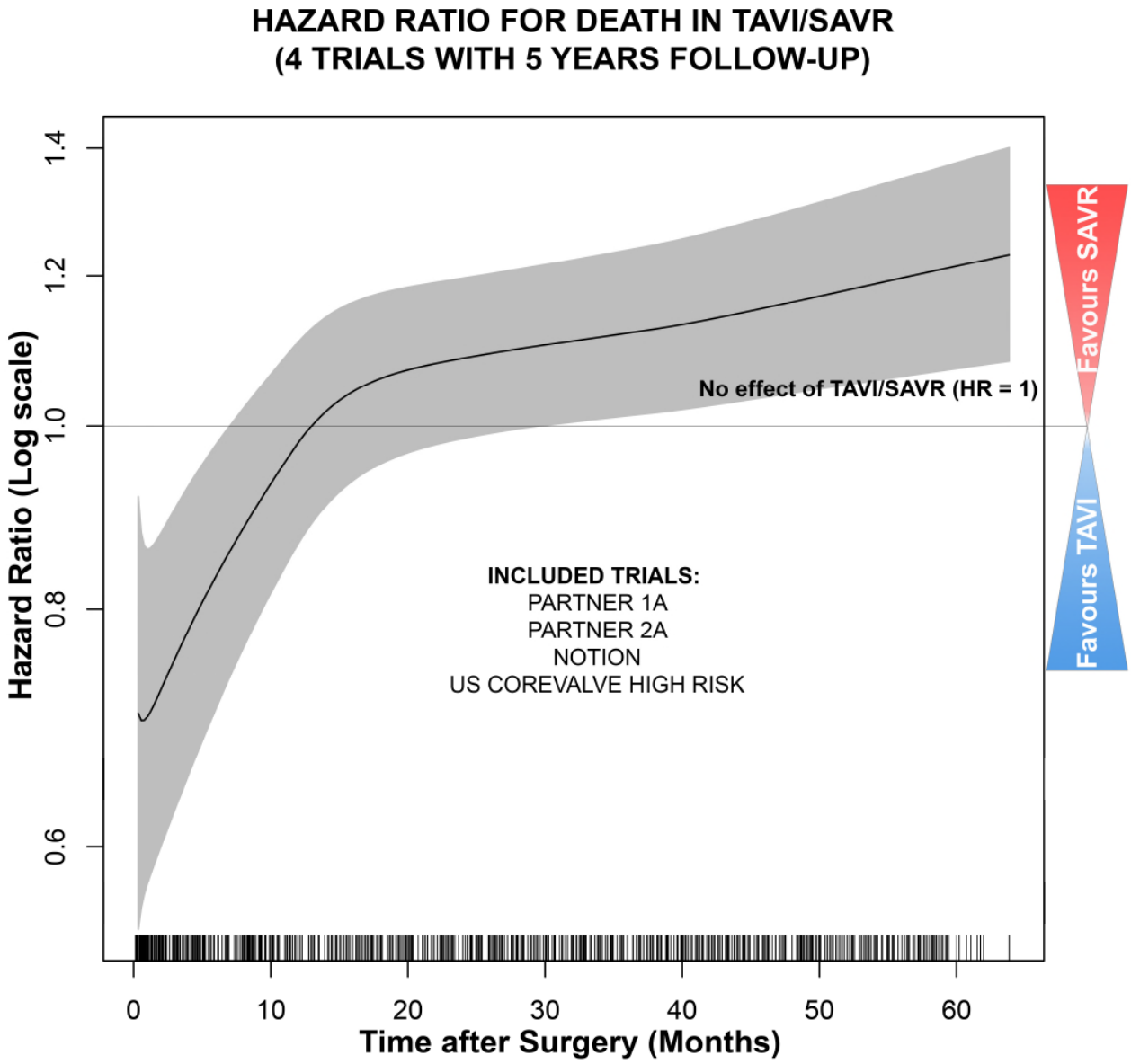
eFigure2. Quality assessment of estimated IPD data.



eFigure3. Landmark analysis with a cut-off at 6 months to analyze mortality up to 2 years.



eFigure4. Hazard ratio trend including only trials with 5 years follow-up.



eFigure 5. Funnel plot of 1-year HR.