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Long Term Outcomes and Durability of Fenestrated Endovascular Aneurysm Repair: A Meta-analysis of Time to Event Data

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Short title: Durability of FEVAR: A Meta-Analysis of Time to Event Data

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WHAT THIS PAPER ADDS

This meta-analysis, which approached the literature with a broad search strategy, delivers robust long term estimates for survival, freedom from re-intervention, target vessel patency, and one year sac regression after fenestrated endovascular aneurysm repair (FEVAR). These are important to inform contemporary discussions around durability of FEVAR and may influence future practice when counselling patients on FEVAR during the consent process. The meta-analytical technique of pooling raw, patient level time to event data, directly extracted from Kaplan–Meier curves, is novel to the field of vascular surgery and to an extent enables this study to overcome challenges with study heterogeneity.

Objective: Despite widespread use, long term outcomes for fenestrated endovascular aneurysm repair (FEVAR) are uncertain. This meta-analysis reports long term survival, freedom from re-intervention, target vessel patency, and one year sac regression after FEVAR.

Data Sources: Systematic review and meta-analysis to pool time to event data according to PRISMA guidelines. The study was registered with the international prospective register of systematic reviews (PROSPERO) (ID: CRD42023401468).

Review Methods: Medline, Embase, and Cochrane databases were searched 1992 – 2023; articles were independently screened by two authors. Publication of complete time to event data for any outcome of interest was an inclusion criterion. Raw Kaplan–Meier probabilities were directly extracted from published curves and pooled by random effects. Risk of bias was assessed using ROBINSI and certainty with GRADE.

Results: A total of 3 569 records were retrieved, 2 869 screened after duplicate removal, yielding 37 included studies (*n* = 4 371). Pooled mean age was 73.2 years (interquartile range [IQR] 72.2, 73.7) and 87.4% male (95% confidence interval [CI] 85.8 – 88.9). Pooled Kaplan–Meier estimated probabilities of survival (*n* = 34 studies, *n* = 4 192 patients) at one, three, and five years were 91.6% (95% CI 90.2 – 92.9), 80.8% (95% CI 78.0 – 83.2), and 65.1% (95% CI 60.9 – 69.1). For freedom from re-intervention (*n* = 24, *n* = 3 211 patients) at one, three, and five years these were 90.2% (95% CI 87.3 – 92.7), 80.9% (95% CI 76.5 – 84.9), and 73.8% (95% CI 67.1 – 79.6). For target vessel patency (*n* = 13, *n* = 5805 target vessels) at one, three, and five years, these were 96.6% (95% CI 94.9 – 98.0), 94.5% (95% CI 91.7 – 96.7), and 93.1% (95% CI 89.3 – 96.0). Pooled estimate of sac regression (*n* = 8, *n* = 560) at one year was 40.2% (95% CI 28.9 – 52.7). Risk of bias was judged as moderate in 11 studies and low for the remaining 26.

Conclusion: There are moderate to low certainty data supporting reasonable long term outcome estimates following fenestrated endovascular aneurysm repair. Beyond five years there is a lack of data in the literature.

Key words: Abdominal aortic aneurysm, Complex endovascular aneurysm repair, Endovascular procedures, Endovascular aneurysm repair, Fenestrated endovascular aneurysm repair, Juxtarenal abdominal aortic aneurysm

<H1>INTRODUCTION

The 2020 UK National Institute for Health and Care Excellence (NICE) guidelines for abdominal aortic aneurysms[1] sparked a polemic in recommending open surgical repair (OSR) over endovascular aneurysm repair (EVAR) for infrarenal abdominal aortic aneurysms (AAAs) in the majority of eligible patients. This is at odds with the European Society for Vascular Society (ESVS) guidelines,[2] which suggest infrarenal EVAR "should be considered as the preferred treatment modality" "in most patients with a reasonable life expectancy" (recommendation 60).[2] For complex aneurysm repair including juxtarenal AAAs, comparatively new endovascular therapies such as fenestrated EVAR (FEVAR) have been rapidly adopted.[3] This phenomenon will have been partly due to the significant advantage FEVAR confers over OSR in terms of early morbidity, especially renal insufficiency secondary to suprarenal clamping.[4] In spite of its rapid uptake, the evidence for FEVAR is limited.[1] As a result, both NICE and ESVS guidelines treat FEVAR cautiously: the former stipulates "special arrangements… for research" (recommendation 1.5.6) as a condition for complex EVAR.[1] The current long term outcomes research for FEVAR falls foul of small sample sizes, heterogeneous populations, immature data, and non-standardised outcome reporting. By using a meta-analytical technique to pool raw Kaplan–Meier estimates for outcomes of interest, this study aims to overcome some of the issues related to variability and report robust estimates for long term outcomes for FEVAR. It is hoped these results will go towards informing the discussion around the durability of FEVAR.

<H1>MATERIALS AND METHODS

<H2>***Search methodology***

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5] It was also registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42023401468). Medline, Embase, and Cochrane databases were interrogated for records published from 1992 to 2023 on 29/10/2022 (updated 5 June 2023); full search strings are available in the Supplementary material. References of relevant articles were also screened and included if meeting inclusion criteria.

<H2>***Screening, inclusion, and exclusion criteria***

All articles were screened by two independent reviewers, and discrepancies were resolved after discussion between reviewers. Quality assessment was also performed by two independent reviewers.

All adults with AAAs of all subtypes who underwent aneurysm repair with custom made fenestrated stent grafts were included. Outcomes of interest were survival, freedom from re-intervention, target vessel patency (by number of vessels not patients), sac behaviour (freedom from sac expansion/ incidence rate of sac shrinkage). Only studies with ≥ 15 patients enrolled, median/mean follow up ≥ 12 months, and complete Kaplan–Meier analysis/time to event data of at least one outcome of interest were included.

Exclusion criteria were thoracic and thoraco-abdominal aortic aneurysm types I – III, non-aneurysmal aortic pathology (dissection, penetrating aortic ulcers), and when the majority of the study population had undergone previous aneurysm repair.

Branched endografts (BEVAR), chimney/snorkel EVAR (ChEVAR), physician modified endografts, and hybrid techniques were also excluded. This exclusion also applied to studies that merged data from FEVAR/BEVAR/ChEVAR/physician modified endograft patients; thus, only those studies with exclusively custom made FEVAR populations were included. Studies which presented erroneous, incomplete, or no Kaplan–Meier analysis/time to event data of at least one outcome of interest were excluded, as were any duplicate or metachronous publications from the same centre (longest follow up study included). Case reports, conference abstracts, and review articles were excluded.

<H2>***Study quality assessment***

Study quality and risk of bias assessment was conducted using the ROBINS I tool;[6] certainty assessment for each meta-analysed result was conducted using the GRADE tool.[7]

<H2>***Data extraction***

Basic data were extracted from included studies such as name, years of data collection, number of patients enrolled, number of target vessels, mean/median follow up, types of aneurysms included, and types of grafts used. Demographic/pre-operative data such as age, gender, comorbidities, and maximal aneurysm diameter; intra-operative data such as procedural time, fluoroscopy time, and contrast volume were also collected.

Raw patient data were directly extracted from Kaplan–Meier curves using the "digitize" *R* package using a methodology put forward by Guyot *et al*.[8] Estimated Kaplan–Meier probabilities of survival, freedom from re-intervention, target vessel patency, freedom from sac expansion ≥ 5 mm, and incidence rate of sac shrinkage

≥ 5 mm were tabulated in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, USA) for each study for each available time point (range 1 – 12 years). In addition, numbers at risk for each outcome for each time point were collected.

<H2**>*Statistical analysis***

Basic study, pre-operative, and intra-operative data were analysed by simple summary statistical methods in Microsoft Excel to calculate the median, interquartile range (IQR), and crude proportions with 95% confidence interval (CI). Pre-operative data were further analysed by meta-analytical methods using the *R* package “meta”:[9] means were pooled by a DerSimonian Laird random effects model; proportions were logit transformed before pooling by a generalised linear mixed effects model.

Applying a methodology described by Combescure *et al.*,[10] a meta-analysis of Kaplan–Meier estimated probabilities was undertaken. An arcsine transformation with continuity correction of 0.25 was applied to probabilities before pooling by a DerSimonian Laird random effects model; 95% CI for pooled Kaplan–Meier estimated probabilities were obtained by a bootstrapping procedure.[10] These operations were completed using the “metasurvival” *R* package,[11] also yielding mean/median survival times and heterogeneity statistics (Q, H^2, and I^2). Summary curves for survival, freedom from re-intervention, and target vessel patency were plotted from pooled probabilities and their 95% CIs in *R* (v4. 1. 2, R Foundation for Statistical Computing, Vienna, Austria). Data maturity was assessed by applying a 10% Pocock threshold (the period of follow up achieved by 10% of participants).[12] Sensitivity analyses were performed for study size by excluding studies with ≤ 50 patients and ≤ 150 target vessels at risk at the start of the study period.

Study subgroups were created by (1) aneurysm type: only juxtarenal/pararenal/short necked aneurysms were included; suprarenal and limited type IV thoracoabdominal aneurysms (TAAAs) were also included; (2) graft type: Zenith fenestrated endograft (Cook, Brisbane, Australia) only studies; Anaconda fenestrated endograft (Terumo, Tokyo, Japan) only studies; (3) graft complexity: three or more target vessels per patient; fewer than three target vessels per patient; and (4) study recency: median data collection year > 2009; median data collection year ≤ 2009.

Pooled Kaplan–Meier estimated probabilities for subgroups were calculated and summary probability curves plotted by the same method described above. Statistical difference between cognate subgroups was investigated by Logrank test and Hazard functions were calculated. This required raw event data were calculated from numbers at risk and estimated probabilities of survival using the equation:

$$e_j = n_j - \left(\frac{S(T_j)}{S(T_{j-1})} \times n_j\right),$$

where *e* = events, T_j= time$_{year}$, $S(T)$ = estimated survival probability at *T*, *n* = number at risk.

Cumulative raw event data were also used to calculate pooled rates of events per 1 000 patient years. Total patient years were approximated by multiplying reported follow up durations by total numbers at risk. For sac shrinkage, cumulative incidence proportions were logit transformed, and pooled using a generalised linear mixed effects model; this was performed using the *R* package “metafor”.[13]

<H1>RESULTS

<H2>***Search results***

A total of 3 569 records were retrieved from the database searches; after the removal of 700 duplicates, 2 869 records underwent title and abstract screening. In total, 240 records underwent full text screening, and from these, 37 studies met criteria for inclusion in this meta-analysis (Fig. 1).

<H2>***Study quality assessment***

Eleven studies (*n* = 37) were considered to have a moderate risk of bias, all other studies a low risk of bias (Supplementary Table S2).

<H2>***Meta-analysis population***

The 37 studies included for meta-analysis reported data for 4 371 patients who underwent FEVAR. Basic study data including outcomes of interest reported by each study are available in Supplementary Table S1. Pooled mean age was 73.2 years (95% CI 72.7 – 73.7) and pooled male proportion was 87.4% (95% CI 85.8 – 88.9) (Table 1). This population demonstrated significant comorbidity with high pooled proportions for ischaemic heart disease at 49.9% (95% CI 45.6 – 53.8) and hypertension at 82.2% (95% CI 78.2 – 85.6). The majority of the included population received treatment for juxtarenal/pararenal/short necked aneurysms (crude proportion 92.5%; 95% CI 91.6 – 93.3) and were treated with a Zenith fenestrated graft (81.1%; 95% CI 80.0 – 82.3).

<H2>***Survival***

Thirty-four studies (*n* = 4 192) reported complete Kaplan–Meier analyses for all cause mortality post-FEVAR. The pooled Kaplan–Meier estimated probabilities of survival at one, three, and five years were 91.6% (95% CI 90.2 – 92.9), 80.8% (95% CI 78.0 – 83.2), and 65.1% (95% CI 60.9 – 69.2) (Fig. 2), all moderate GRADE certainty. Pooled death rate at five years was estimated as 93.8 deaths per 1 000 patient years (95% CI 90.3 – 97.3) (Table 2).

In terms of subgroup analyses for survival, no subgroups reached a statistically significant hazard ratio (HR) on logrank test between survival curves curtailed to a 10% Pocock threshold. For the studies that only included juxtarenal/pararenal/ short necked aneurysms (*n* = 20 studies, 1 920 patients), data were mature up to six years and pooled survival estimates at one, three, and five years were 92.0% (95% CI 89.8 – 93.9), 81.4% (95% CI 77.0 – 85.2), and 66.1% (95% CI 59.6 – 72.1) (Supplementary Figure S1). 7.34 years (95% CI 5.96 – 8.45), mean survival time as 7.27 years (95% CI 6.68 – 7.77), and I^2 = 50.4%. For the subgroup of studies that also included suprarenal/limited T4 TAAAs (*n* = 11 studies, 1 712 patients), these aneurysms made up 12.5% (95% CI 10.9 – 14.2) of the aggregated study population for which this raw data were available (*n* = 9 studies, 1558 patients). Pooled Kaplan–Meier estimates of survival for this subgroup at one, three, and five years were 91.5% (95% CI 89.3 – 93.4), 80.8% (95% CI 76.3 – 84.4), and 67.4% (95% CI 61.9 – 72.1). Data were mature up to five years for this subgroup, median survival time was estimated at 8.0 years (95% CI 6.9 – 8.6), and I^2 = 44.7%.

<H2>***Freedom from re-intervention***

Twenty-four studies (*n* = 3 211) reported complete Kaplan–Meier analyses for freedom from re-intervention post-FEVAR. The pooled Kaplan–Meier estimated probabilities of freedom from re-intervention at one, three, and five years were 90.2% (95% CI 87.3 – 92.7), 80.9% (95% CI 76.5 – 84.9), and 73.8% (95% CI 67.1 – 79.6) (Fig. 3), all moderate GRADE certainty. Pooled re-intervention rate at five years was estimated as 61.8 re-interventions per 1 000 patient years (95% CI 58.5 – 65.2).

In terms of subgroup analyses for freedom from re-intervention, three or more target vessels per patient reached a statistically significant HR when comparing curves to 10 years (HR 0.52; 95% CI 0.44 – 0.61, $p < 1 \times 10^{-12}$); and to five years (curtailed to a 10% Pocock threshold) (HR 0.51; 95% CI 0.50 – 0.84, $p < 1 \times 10^{-12}$). This was also observed when comparing studies that only included juxtarenal/pararenal aneurysms with those that also included suprarenal and limited type IV TAAAs to 10 years (HR 1.41; 95% CI 1.18 – 1.68, $p < .0001$); and to five years (curtailed to a 10% Pocock threshold) (HR 1.41; 95% CI 1.18 – 1.68, $p < .001$). However, these relationships were replicated in the recency subgroup, with more recent studies (median data collection year > 2009) reaching statistically significant HRs at 10 years (HR 0.75; 95% CI 0.63 – 0.90, $p = .001$); and at five years (curtailed to a 10% Pocock threshold) (HR 0.75; 95% CI 0.63 – 0.91, $p = .002$). Graft type was not found to have any material effect on freedom from re-intervention.

<H2>***Target Vessel Patency***

Thirteen studies (*n* = 5 805 target vessels) reported complete Kaplan–Meier analyses for target vessel patency post-FEVAR. The pooled Kaplan–Meier estimated probabilities of target vessel patency at one, three, and five years were 96.6% (95% CI 94.9 – 98.0), 94.5% (95% CI 91.7 – 96.7), and 93.1% (95% CI 89.3 – 96.0) (Fig. 4), all moderate GRADE certainty. Pooled loss of target vessel patency rate at five years was estimated as 50.0 losses per 1 000 target vessel years (95% CI 45.5 – 54.5).

In terms of subgroup analyses for target vessel patency, three or more target vessels per patient reached a statistically significant HR when comparing curves to 10 years (HR 0.38; 95% CI 0.30 – 0.48, $p < 1 \times 10^{-13}$); and to five years (curtailed to a 10% Pocock threshold) (HR 0.38; 95% CI 0.30 – 0.49, $p < 1 \times 10^{-12}$). This was also observed when comparing studies that only included juxtarenal/pararenal aneurysms to those that also included suprarenal and limited type IV TAAAs to 10 years (HR 1.69; 95% CI 1.28 – 2.24, $p < .0001$); and to five years (curtailed to a 10% Pocock threshold) HR 1.65; 95% CI 1.24 – 2.19, $p < .001$). However, this relationship was replicated in the recency subgroup, with more recent studies (median data collection year >2009) reaching statistically significant HRs to 10 years (HR 0.33; 95% CI 0.26 – 0.42, $p < 1 \times 10^{-22}$); and to five years (curtailed to a 10% Pocock threshold) (HR 0.34; 95% CI 0.27 – 0.44, $p < 1 \times 10^{-21}$). Graft type was not found to have any material effect on target vessel patency.

<H2>***Aneurysm sac behaviour***

Eight studies ($n = 863$) reported complete incidence data for freedom from sac expansion (≥ 5 mm) and eight studies ($n = 560$) reported complete incidence data for incidence of sac shrinkage (≥ 5 mm). Freedom from sac expansion at one, three, and four years (longest data maturity timepoint) was 97.8% (95% CI 92.4 – 99.9), 91.5% (95% CI 88.8 – 96.7), and 86.1% (95% CI 74.6 – 93.0), one and three years moderate GRADE certainty, four years low certainty. Cumulative incidence of sac shrinkage at one year was 40.2% (95% CI 28.9 – 52.7), (Supplementary Figure S2); and at two years was 59.0% (95% CI 36.9 – 77.9), very low GRADE certainty for these results. Pooled occurrence of sac regression at one year was estimated as 134.2 sac regressions per 1 000 patient years (95% CI 126.1 – 142.2).

<H2>*Sensitivity analyses*

Sensitivity analyses with the exclusion of small studies ≤ 50 patients and ≤ 150 target vessels at risk at the start of the study period demonstrated no significant difference in results for any outcome reported (Supplementary Table S3).

<H3>DISCUSSION

In the current meta-analysis of individual patient data, estimated event rates at five years were observed for mortality as 93.8 deaths per 1 000 patient years (95% CI 90.3 – 97.3); re-intervention as 61.8 re-interventions per 1 000 patient years (95% CI 58.5 – 65.2); and loss of target vessel patency as 50.0 losses per 1000 target vessel years (95% CI 45.5 – 54.5). At one year, the rate of aneurysm sac regression was estimated as 134.2 events per 1 000 patient years (95% CI 126.1 – 142.2). Despite some limitations this suggests that FEVAR is a useful and durable option for treatment of patients with complex AAAs.

<H2>***Survival, re-intervention, and target vessel patency***

Survival, re-intervention, and target vessel patency rates reported in this article are comparable to previously published meta-analyses.[14,15] Compared with the meta-analysis of Rao *et al.*,[14] long term survival rates for FEVAR at one, three, and five years reported here are comparable at 91.6% (c.f.[14]: 93%), 80.8% (c.f. 74%), and 65.1% (c.f. 55%), even compared with survival rates for open surgical repair up to three years:[14] 91.6% (c.f. 89%), 80.8% (c.f. 80%), and 65.1% (c.f. 73%). The higher survival rates reported here are likely attributable to an operator learning curve and the recent procedural and technological advancements in FEVAR.[16] Further, likely dependent on these same effects,[16] are the statistically significant HRs at five years found to favour more recent studies for freedom from re-intervention (HR 0.75; 95% CI 0.61 – 0.91, $p < .01$) and target vessel patency (HR 0.34; 95% CI 0.27 – 0.44, $p < 1 \times 10^{-21}$). Significant HRs were also observed in the aneurysm type and graft complexity subgroup analyses for freedom from re-intervention and target vessel patency, favouring studies that included suprarenal/limited type IV TAAAs and more complex grafts. However, this is suspected not to be a real effect and likely confounded by recency of data collection. For the aneurysm type subgroups, all studies including suprarenal/ limited type IV TAAA for re-intervention and target vessel patency analyses collected data beyond 2009 apart from two studies and one study, respectively. For the graft complexity subgroups, more recent studies are likely to have implanted more complex grafts; this is confirmed by several studies reporting an increase in graft complexity with time.[16,17]

Long term re-intervention rate was found to be quite high: 22.4% at four years (c.f. Spanos *et al*.: 24%,[15]) which is expected for EVAR.[18] However, long term target vessel patency was excellent: 93.1% at five years (c.f. 86.8%),[15] which may suggest that most re-interventions are not related to loss of target vessel patency. Re-intervention rates are more likely to be due to endoleaks: a recent review reports a 7.60% (95% CI 2.52 – 14.6) pooled rate of type I endoleak for FEVAR.[19]

<H2>*Aneurysm sac behaviour*

Over the last decade, post-operative aneurysm sac behaviour has been proposed as a potential metric for successful EVAR and a positive predictor for survival and freedom from re-intervention.[20–22] The incidence of sac shrinkage ≥5 mm at one year reported here: 40.2% (95% CI 28.9 – 52.7) is highly comparable with the 40% incidence of sac shrinkage ≥5 mm at one year reported for a large infrarenal EVAR cohort (n = 14 817).[22] In this infrarenal EVAR study, sac shrinkage ≥5 mm compared with sac stability and expansion was associated with 16.7% and 37.5% less risk of long term mortality, respectively.[22] For the incidence of late re-interventions in infrarenal EVAR, no shrinkage was an independent risk factor for late complications compared with shrinkage ≥ 10 mm (HR 3.11, $p < .001$).[20] Although these associations cannot be demonstrated in the present study, it is a promising prospect for FEVAR durability that the incidence of sac shrinkage should be comparable to infrarenal EVAR. Further, in one recent but small scale study, FEVAR was even shown to be associated with a greater proportion of sac shrinkage compared to infrarenal EVAR.[23]

<H2>*This meta-analysis in context*

The somewhat controversial NICE guidelines for the management of AAAs describe the evidence for FEVAR as "limited in quantity and quality".[1] The ESVS guidelines make the recommendation (no. 96) that for juxtarenal aneurysms FEVAR should be the preferred complex EVAR option if feasible;[2] however, the cited literature to support this recommendation were systematic reviews[14] and a multicentre study (n = 318), for which the median follow up was only six months.[24]

High level evidence in the form of a randomised controlled trial (RCT) does not currently exist for FEVAR; this is in contrast to EVAR for infrarenal AAAs, which has been the subject of several key RCTs.[25] A FEVAR RCT will be challenging to deliver: currently, there is insufficient equipoise on treatment among specialists;[26] aneurysms suitable for FEVAR are relatively rare and heterogeneous, not to mention practical implications related to the cost of custom made grafts and time delay to implantation required for manufacture.[27] Relatively small and heterogeneous study populations combined with significant variation in outcome reporting also create challenges for meaningful meta-analysis. This present study aimed to overcome these issues by collecting raw pooled patient data from published survival curves.[10] In this respect it has been successful in pooling thousands of patients' survival, re-intervention, and target vessel patency data, delivering robust estimates for these outcomes up to the furthest point of data maturity. Arguably, this article should have curtailed presented pooled Kaplan–Meier curves at this point;[12] however, these have been purposefully presented in their entirety to highlight how few studies report on outcomes post-FEVAR beyond five years, and how few patients are still included in follow-up for these time-points. Take for example survival: only one study[28] reported complete Kaplan–Meier data for 38 patients at 12 years.

This concentration of the current literature on short-term outcomes is unsurprising with the emergence of large registry data that often find collecting long-term follow-up data challenging. The Society of Vascular Surgery Vascular Quality Initiative (VQI) is an undoubtedly valuable resource for researchers.[29] However, it only requires contributors to record follow up at one year [29] and long term follow up rates for EVAR patients have recently been reported as 64% (0 – 100% range).[30] No studies of VQI data met inclusion criteria for this present meta-analysis. Several VQI studies were included in full text screening and excluded due to the inseparable inclusion of branched EVAR[31] and physician modified endografts.[32] The former study reported Kaplan–Meier analyses of survival up to three years, which was reportedly well captured by linkage with the Social Security Death Index.[31] However, by its authors' own admission, low follow up rates precluded the reporting of re-intervention data. This issue was replicated in another VQI study which included 5507 FEVAR patients over a nine year period, but by one year follow up only included 55 patients (<1%) at risk of re-intervention.[32]

Looking to the future, preliminary results of the UK COMPlex AneurySm Study (UK-COMPASS)[26] have been recently presented and their publication is imminent. UK-COMPASS is a risk adjusted and anatomically stratified cohort comparison study of OSR, FEVAR and infrarenal EVAR for juxtarenal AAAs. Its results will provoke discussion around FEVAR mid and long term outcomes.

<H2>*Limitations*

The limitations of this study are related to features of the studies meta-analysed, namely a preponderance of retrospective study designs and lack of standardised definitions for aneurysm types (juxtarenal/ pararenal/suprarenal). It is certain that the lack of standardised criteria for patient inclusion and reporting outcomes significantly impacted the statistical measures of heterogeneity calculated in this meta-analysis. Heterogeneity ranged between “moderate” and “substantial” by Cochrane criteria[33] for survival, re-intervention, target vessel patency and sac behaviour (> 30%). These results were also reflected in the GRADE certainty assessment completed. Further, eleven studies (*n* = 37) were considered to have a moderate risk of bias by ROBINS-I analysis.[6] This is a significant proportion (29.7%); the most common domains identified as potential sources of bias were “due to confounding”, “selection of participants”, and “due to missing data”. With the aim of including as many studies as possible in this analysis, a decision was made to include studies with small cohorts and studies with two arms for which it was possible to separate custom made FEVAR results. Small study cohorts may have fallen victim to selection bias and comparative studies to morphological confounding factors if patients were deemed eligible for more than one type of repair. However, these types of studies were relatively rare and despite their inclusion, median study size was 96 patients (IQR 57, 147). Further, sensitivity analyses demonstrated no significant difference in results with the exclusion of these smaller studies. Some studies lost a significant proportion of patients to follow-up. It is believed that the meta-analytical method used to pool time to event *probabilities* will have corrected for these issues, especially with the use of a Pocock data maturity threshold which takes into account censored patients. In terms of subgroup meta-analyses, the absence of sex based analyses may be noted. These are important, as demonstrated in a recent meta-analysis which observed a significant increase in the risk of peri-operative mortality and major adverse events for women following elective infrarenal EVAR.[34] For this present study, subgroups for this meta-analysis could only be created at a study level. An attempt was made to perform sex-based meta-analyses from studies which directly compared sexes, but these were insufficient to make the results meaningful. Addressing this topic will be a key aim for future studies in complex EVAR.

<H2>*Conclusions*

There are moderate to low certainty data supporting reasonable long term outcome estimates following fenestrated endovascular aneurysm repair. This systematic review has also demonstrated a paucity of mature long term data for patients undergoing fenestrated aortic aneurysm repair. There is a need for more evidence, ideally from a randomised control trial but pragmatically from larger retrospective series with complete long term follow up.

CONFLICTS OF INTEREST

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram for article selection of studies reporting long term outcomes for custom made fenestrated endovascular aneurysm repair (FEVAR) of complex abdominal aortic aneurysms (AAAs).

Figure 2. Cumulative Kaplan–Meier estimate of survival probabilities for all studies reporting long term outcomes for custom made fenestrated endovascular aneurysm repair (FEVAR) of complex abdominal aortic aneurysms (AAA). Grey line = individual study; black square = end of single study follow up; red line = pooled random effects survival probability; dashed red line = 95% confidence interval. Data maturity analysis (Pocock threshold= 10%) suggests maturity up to five years.

Figure 3. Pooled Kaplan–Meier estimated freedom from re-intervention probabilities for all studies reporting long-term outcomes for custom-made fenestrated endovascular aneurysm repair (FEVAR) of complex abdominal aortic aneurysms (AAA). Grey line = individual study; black square = end of single study follow up; red line = pooled random effects survival probability; dashed red line= 95% confidence interval. Data maturity analysis (Pocock threshold = 10%) suggests data maturity up to five years.

Figure 4. Pooled Kaplan–Meier estimated target vessel patency for all studies reporting long term outcomes for custom made fenestrated endovascular aneurysm repair (FEVAR) of complex abdominal aortic aneurysms (AAAs). Grey line = individual study; black square = end of single study follow up; red line = pooled

Table 1. Summary statistics for basic study data, pre-operative data and procedural data for studies reporting long term outcomes for custom made fenestrated endovascular aneurysm repair (FEVAR) of complex abdominal aortic aneurysms (AAA).

Variable	Number of studies combined		Simple summary statistic	Pooled, weighted random effects estimate
	Summary	**Meta-analysis**	**Median/crude proportion**	**Pooled mean/proportion**
Basic study data				
Study size, patients	37	–	96 (57, 147)	–
Median year of data collection	37	–	2010.5 (2008.5, 2013.5)	–
Follow up – mo	37	–	26 (21, 36)	–
Pre-operative data				
Age – y	37	23	73.4 (72.2–74.1)	73.2 (72.7–73.7)
AAA diameter – mm	31	19	60.0 (58.7–61.9)	60.2 (58.9–61.5)
Male – %	34	34	87.2 (86.2–88.3)	87.4 (85.8–88.9)
IHD/CAD – %	34	34	52.1 (50.6–53.7)	49.9 (45.6–53.8)
HTN (%)	33	33	79.5 (78.2–80.8)	82.2 (78.2–85.6)
COPD/respiratory disease –%	31	31	39.3 (37.7–40.9)	37.4 (33.2–41.7)
DM – %	33	33	16.3 (15.1–17.5)	16.2 (14.9–17.6)
Juxtarenal/pararenal/short necked aneurysms – %	30	30	92.5 (91.6–93.3)	99.6 (97.3–99.9)
Suprarenal/limited type IV thoracoabdominal aneurysms – %	30	30	5.5 (4.8–6.3)	0.2 (0.02–1.6)
Procedural data				
Z-fen graft – %	36	36	81.1 (80.0–82.3)	1.0 (99.96–1.0)
Anaconda graft – %	36	36	18.7 (17.5–19.8)	0.0 (0.0–0.0004)
Target vessels per patient	32	–	2.75 (2.46–3.19)	–
Procedural time – min	24	11	240 (198.5–270)	240.4 (203.8–277.0)
Fluoroscopy time – min	22	8	64.5 (50–78)	65.6 (52.0–79.2)
Contrast volume – mL	25	11	164.5 (133.25–190)	151.5 (116.8–186.1)

random effects survival probability; dashed red line = 95% confidence interval. Data

maturity analysis (Pocock threshold = 10%) suggests data maturity up to six years.

Data are presented as median (interquartile range); raw proportion (95% CI); pooled mean (95% CI); pooled proportion (95% CI). CI= confidence interval; IHD = ischaemic heart disease; CAD = coronary artery disease; HTN = hypertension; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; Z-fen graft = Zenith fenestrated graft.

Table 2. Summary of findings table including GRADE assessment for meta-analyses of time to event data fo of custom made fenestrated endovascular aneurysm repair of complex abdominal aortic aneurysms.

GRADE certainty assessment								
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No. of patients/target vessels at start of the time interval/T_0**	**Effe pro eve eve pati (95**
Survival at 1, 3, and 5 years, data maturity = 5 years; I^2 = 52.0%, mean survival time = 7.2 years (95% CI 6.8–7.5)								
34	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	4 192 patients	91.(

Table 2. Summary of findings table including GRADE assessment for meta-analyses of time to event data fo of custom made fenestrated endovascular aneurysm repair of complex abdominal aortic aneurysms.

GRADE certainty assessment								
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No. of patients/target vessels at start of the time interval/T_0**	**Effe pro eve eve pati (95**
								35. 1 0 yea
28	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	2 133 patients	80.
							3 638 patients	69. 10 (66
15	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	833 patients	65.
							2 262 patients	93. 1 0 yea

Freedom from re-intervention at 1, 3, and 5 years; data maturity = 5 years; I^2 = 71.5%, mean time to re-intervention = 9.0 years (95% CI 8.3–9.5)

24	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	3211 patients	90.
								39. inte 1 0 yea
20	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	1357 patients	80.
							2789 patients	64. inte 1 0 yea
9	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	461 patients	73.
							1 453 patients	61. inte 1 0 yea

Target vessel patency at 1, 3, and 5 years; data maturity = 6 years; I^2 = 66.3%, mean time to loss of target vessel patency= 11.1 years (95% CI 10.6–11.5)

Table 2. Summary of findings table including GRADE assessment for meta-analyses of time to event data fo of custom made fenestrated endovascular aneurysm repair of complex abdominal aortic aneurysms.

GRADE certainty assessment								
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients/target vessels at start of the time interval/T_0	Effe pro eve eve pati (95
13	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	5 805 target vessels	96.0
								21.0 ves 1 00 ves (19
11	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	2 769 target vessels	94.5
							5 369 target vessels	33.0 ves 1 00 ves (31
6	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	1 106 target vessels	93.1
							2 661 target vessels	50.0 ves 1 00 ves (45

Aneurysm sac regression at 1 and 2 years; $I^2 =$ 80.9% for 1 year, $I^2 =$ 0% for 2 years

8	Observational studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	560 patients	40.2
								134 reg 1 00 yea 142
3	Observational studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	95 patients	59.0
								159 reg 1 00 yea 178

Freedom from aneurysm sac expansion at 1, 3, and 4 years; data maturity= 4 years; I^2= 72.8%, mean time to sac expansion= 8.6 years (7.3–9.1)

Table 2. Summary of findings table including GRADE assessment for meta-analyses of time to event data fo of custom made fenestrated endovascular aneurysm repair of complex abdominal aortic aneurysms.

GRADE certainty assessment								
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**No. of patients/target vessels at start of the time interval/T_0**	**Effe pro eve eve pati (95**
8	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	863 patients	97.
								18. exp 1 0 yea
4	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	257 patients	91.
							595 patients	47. exp 1 0 yea
2	Non-randomised studies	Not serious	Serious*	Not serious	Not serious	Moderate risk of publication bias†	92 patients	86.
							240 patients	51. exp 1 0 yea

Data are presented as pooled proportion (95% CI) or pooled rate of event (95% CI).

Abbreviations: CI = confidence interval.

*High/moderate heterogeneity (I^2 statistic).

†Retrospective study designs.

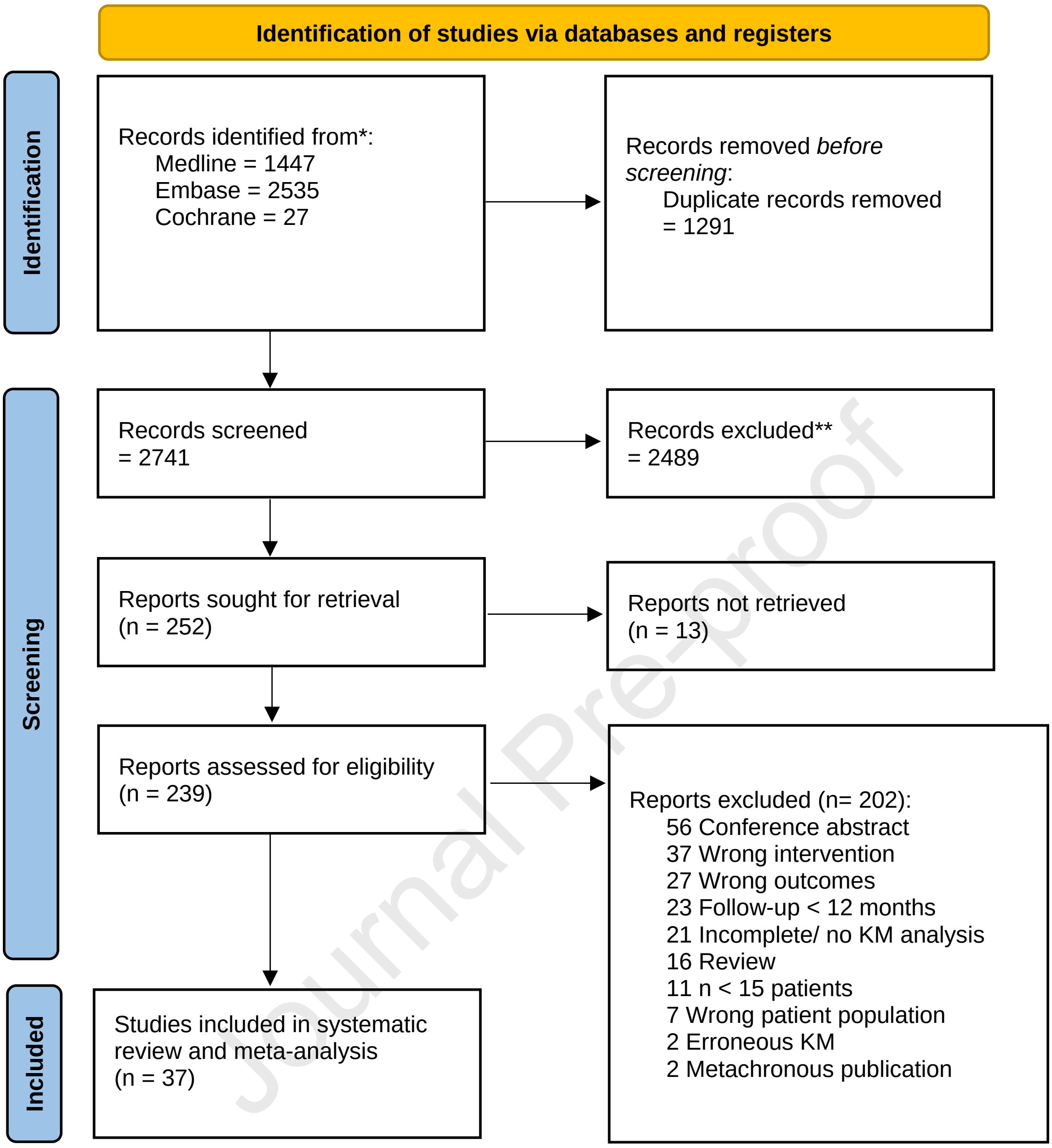
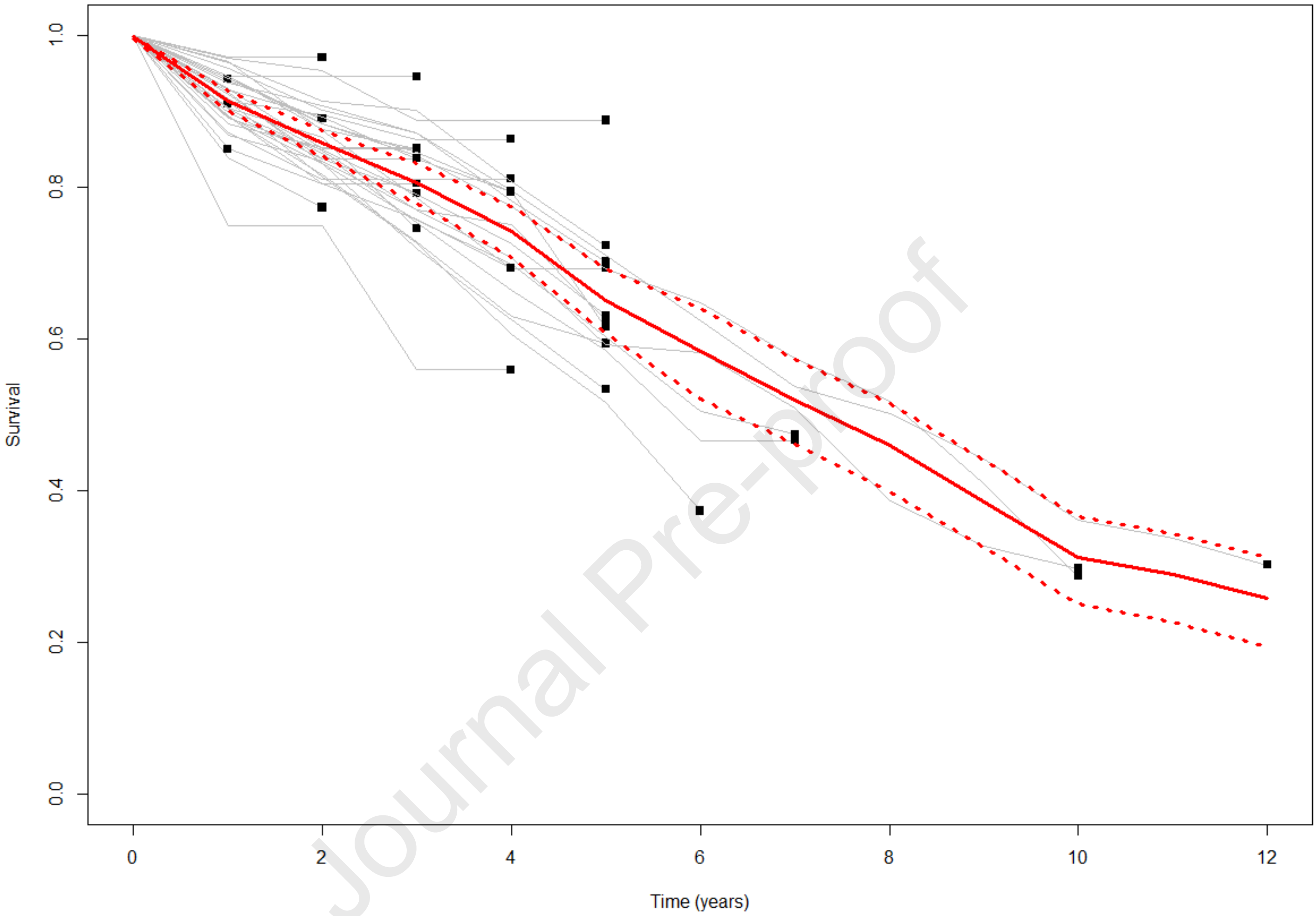


Figure 1. PRISMA diagram for article selection of studies reporting long-term outcomes for custom-made fenestrated endovascular aneurysm repair (FEVAR) of complex abdominal aortic aneurysms (AAA).



Year	0	1	2	3	4	5	*6*	*7*	*8*	*9*	*10*	*11*	*12*
N.studies	34	34	31	28	20	15	*6*	*5*	*3*	*3*	*3*	*1*	*1*
N.risk	4192	4192	2955	2133	1287	833	*310*	*221*	*145*	*109*	*76*	*39*	*38*

Figure 2. Pooled Kaplan Meier Estimated Survival probabilities for all studies reporting long-term outcomes for custom-made fenestrated endovascular aneurysm repair (FEVAR) of complex abdominal aortic aneurysms (AAA).

Grey line= individual study, black square= end of single study follow-up, red line= pooled random-effects survival probability, dashed red line= 95% confidence interval.

NB: Data maturity analysis (Pocock threshold= 10%) suggests maturity up to 5 years.

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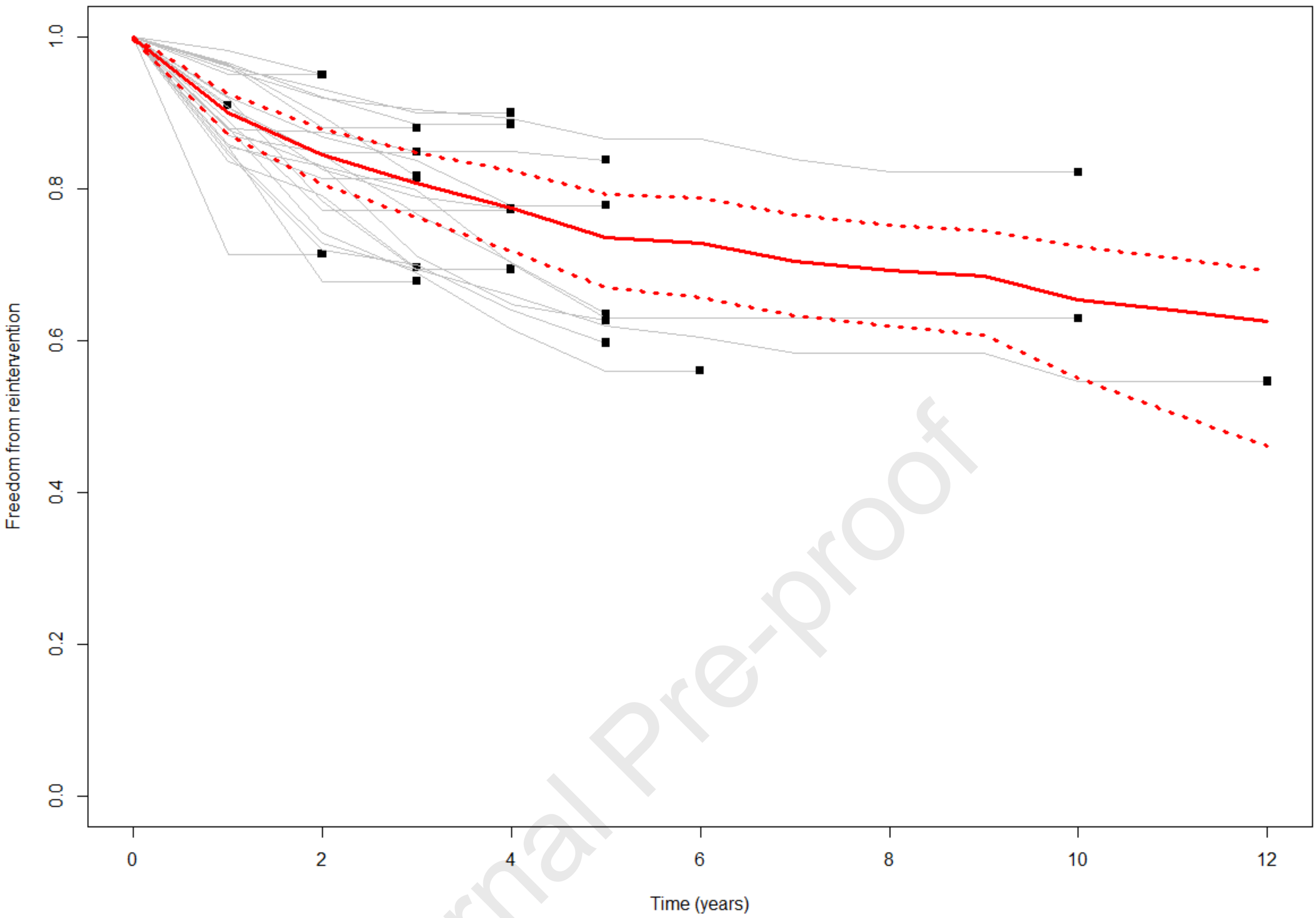
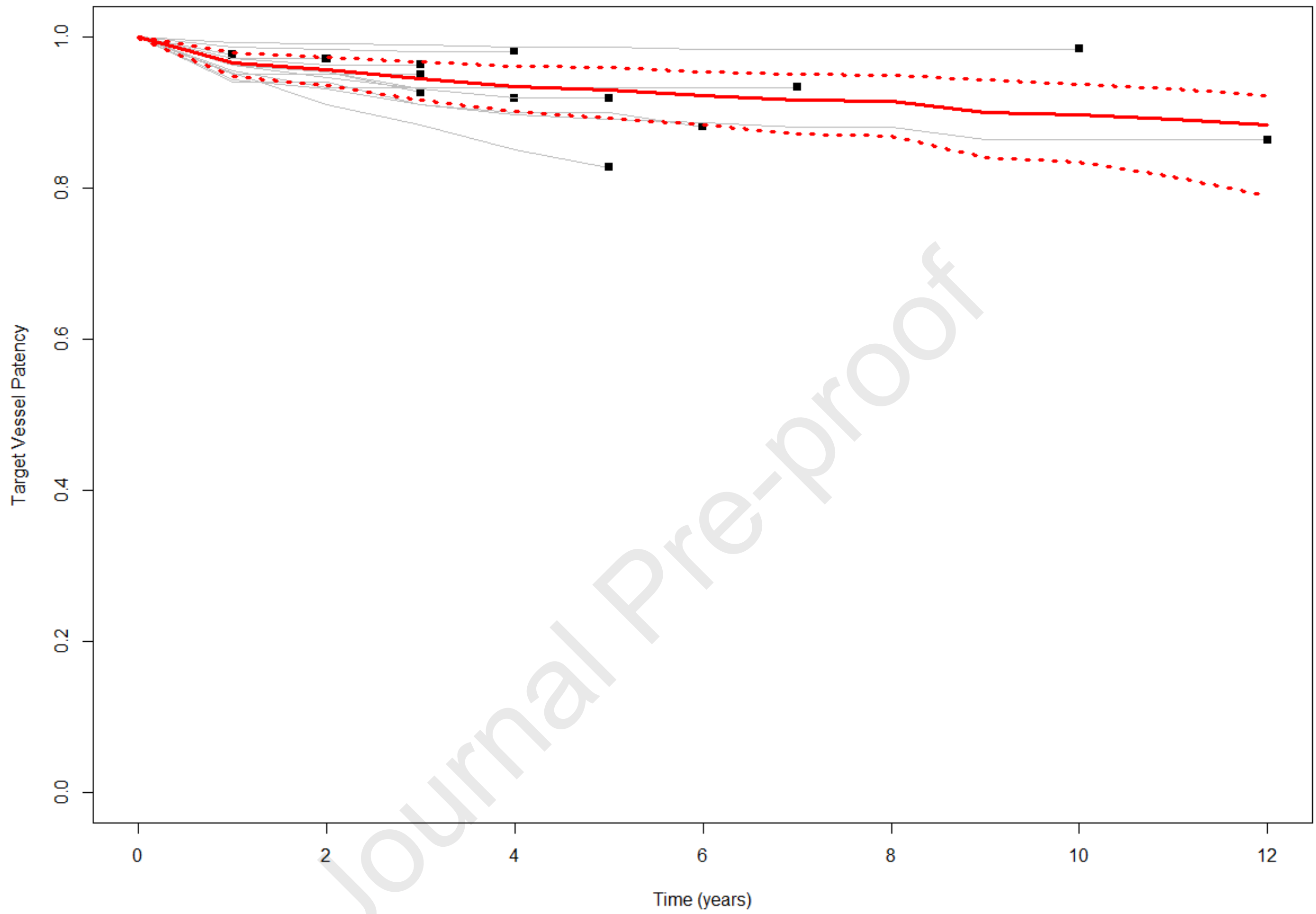


Year	0	1	2	3	4	5	*6*	*7*	*8*	*9*	*10*	*11*	*12*
N.studies	24	24	23	20	14	9	*4*	*3*	*3*	*3*	*3*	*1*	*1*
N.risk	3211	3211	2123	1357	748	461	*183*	*131*	*94*	*64*	*32*	*12*	*10*

Figure 3. Pooled Kaplan Meier Estimated probabilities for Freedom from Re-intervention for all studies reporting long-term outcomes for custom-made fenestrated endovascular aneurysm repair (FEVAR) of complex abdominal aortic aneurysms (AAA).

Grey line= individual study, black square= end of single study follow-up, red line= pooled random-effects survival probability, dashed red line= 95% confidence interval.

NB: Data maturity analysis (Pocock threshold= 10%) suggests data maturity up to 5 years.



Year	0	1	2	3	4	5	6	*7*	*8*	*9*	*10*	*11*	*12*
N.studies	13	13	12	11	8	6	4	*3*	*2*	*2*	*2*	*1*	*1*
N.risk	5805	5805	3898	2769	1637	1106	656	*440*	*315*	*224*	*109*	*40*	*29*

Figure 4. Pooled Kaplan Meier Estimated Target Vessel Patency for all studies reporting long-term outcomes for custom-made fenestrated endovascular aneurysm repair (FEVAR) of complex abdominal aortic aneurysms (AAA).

Grey line= individual study, black square= end of single study follow-up, red line= pooled random-effects survival probability, dashed red line= 95% confidence interval.

NB: Data maturity analysis (Pocock threshold= 10%) suggests data maturity up to 6 years.

Short title: Durability of FEVAR: a meta-analysis of time-to-event data

Figure 1: follow page D

Figure 2: follow H1 and H2

Figure 3: follow H1 and H2

Figure 4: follow H1 and H2

Supplementary figures and tables.

Supplementary data PRISMA_2020_checklist

Supplementary data PRISMA_2020