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REVIEW

Editor's Choice — Aortic Re-operation After Replacement of the Proximal Aorta: A Systematic Review and Meta-Analysis

Mario Gaudino [a,*], Leonard N. Girardi [a], Mohamed Rahouma [a], Jeremy R. Leonard [a], Antonino Di Franco [a], Christopher Lau [a], Neil Mehta [b], Ahmed Abouarab [a], Alexandra N. Schwann [a], Gaetano Scuderi [a], Michelle Demetres [c], Richard B. Devereux [b], Umberto Benedetto [a], Jonathan W. Weinsaft [b]

[a] Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, NY, USA
[b] Department of Medicine (Cardiology), Weill Cornell Medicine, New York, NY, USA
[c] Samuel J. Wood Library and C.V. Starr Biomedical Information Centre, Weill Cornell Medicine, New York, NY, USA

WHAT THIS PAPER ADDS

To the best of the authors' knowledge, this is the first meta-analysis to examine risk of recurrent aortic surgery after proximal aortic grafting, as well as to differentiate risk in relation to initial surgical indication (dissection, aneurysm) and presence of Marfan syndrome. Data provide clear evidence that aortic re-operation occurs in a sizable proportion of patients, for which risk is greatest among patients with aortic dissection.

Objective/background: The aim was to estimate risk of aortic re-operation, and re-operative morbidity and mortality, following replacement of the proximal aorta for aneurysm or dissection.
Methods: A meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Meta-Analysis of Observational Studies in Epidemiology guidelines. A comprehensive literature review was performed to identify all articles reporting aortic re-operation after proximal aortic replacement. The proximal aorta was defined as extending to the origin of the brachiocephalic trunk. The incidence rate for aortic re-operation (IRAR) was calculated, and stratified based on presence/absence of connective tissue disorders, as well as initial surgical indication. Pooled in hospital mortality and post-operative complication rates were estimated.
Results: In total, 7821 patients who underwent proximal aortic replacement from 47 studies were included: 8.3% ($n = 649$) had Marfan syndrome (MS). During a weighted mean follow up of 4.7 $\pm$ 0.3 years, 11.5% ($n = 903$) underwent aortic re-operation. Mean weighted time between initial surgery and re-operation was 5.2 $\pm$ 0.2 years. IRAR was 2.4% per person-year (PPY) (confidence interval [CI] 2.1—2.8%). Patients with MFS had a threefold higher IRAR (6.0% PPY, CI 4.1—8.8%) than did patients without a connective tissue disorders (2.3% PPY, CI 1.9—2.7%; $p < .001$). IRAR was 2.5% PPY (CI 2.1—3.0%) after operation for dissection and 1.3% PPY (CI 0.9—2.0%) after operation for aneurysm ($p = .004$ for subgroup differences). IRAR proximal and distal to the left subclavian artery was 1.2% PPY (CI 1.0—1.5%) and 1.3% PPY (CI 1.1—1.6%), respectively. The pooled in hospital mortality and complication rates after re-operation were 14.31% (CI 11.28—17.99%) and 18.08% (CI 10.54—29.25%), respectively. On meta-regression, initial operation for dissection was the only significant predictor of aortic re-operation (beta = .030, $p = .001$).
Conclusion: Aortic re-operation occurs at a mean rate of 2.4% per person-year in the five years after proximal aortic replacement and is strongly associated with initial operation for dissection.

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INTRODUCTION

Prosthetic replacement of the proximal aorta provides life-saving benefits for patients with aortic dissection (AoD), as well as for those with aortic aneurysms (AA). Despite the known benefits of surgery, long-term risks of re-operation remain. Prosthetic grafting entails localised resection of aortic tissue but does not address alterations in aortic tissue

* Corresponding author. Department of Cardiothoracic Surgery, Weill Cornell Medicine, 525 East 68th Street, New York, NY 10065, USA.
E-mail address: mfg9004@med.cornell.edu (Mario Gaudino).

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substrate in non-grafted segments. In addition, grafting alters aortic geometry and entails implantation of prosthetic material with different material properties compared with native aortic tissue. These factors can potentially increase pulse wave energy transmission to distal aortic segments, and thereby contribute to the risk of recurrent AoD or AA. In this context, systematic data regarding residual risk following initial proximal aortic repair are necessary to tailor surveillance and prognostic assessment of at risk cohorts.

Among patients with sporadic AoD, several population based studies have shown that mortality is elevated after aortic replacement,[1–3] and that residual false lumen patency impairs long-term prognosis.[4,5] Among patients with genetically mediated AA, data from the authors' group reported that >50% of AoD occurred in patients with Marfan syndrome (MS) who had previously undergone aortic surgery—supporting the notion that surgical risk persists despite adequate initial repair.[6] Despite this, longitudinal data regarding re-operation following initial aortic surgery have been largely derived from single centre studies of variable size and follow up duration, prohibiting objective cross sectional assessment of the aortic re-intervention risk.

This meta-analysis was designed to (i) estimate the risk of aortic re-operation after proximal aortic replacement; (ii) determine the temporal and anatomical distribution of the aortic re-intervention; (iii) assess differential post-operative risk factors for aortic re-intervention; and (iv) estimate the risk of the aortic re-intervention.

METHODS

The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Table S1; see Supplementary Material).[7,8]

Search strategy

A medical librarian (M.D.) performed comprehensive searches to identify studies that evaluated re-operation on the aorta following initial operation on the proximal aorta. For study purposes, the proximal aorta was defined as extending to the origin of the brachiocephalic trunk. Full details of the search strategy are provided in Table S2 (see Supplementary Material).

Study selection and inclusion criteria

Database searches were conducted, de-duplicated, and screened by four preliminary reviewers (A.D.F., J.L., G.S., and J.W.W): a fourth independent reviewer (M.G.) confirmed adequacy of studies based on predefined inclusion and exclusion criteria for titles and abstracts. Articles considered for inclusion included studies in which adults (≥18 years old) underwent open or endovascular re-operation on the aorta following initial surgery for AA or AoD on the proximal aorta, as defined above. Studies including patients undergoing initial operation on other aortic segments were excluded. Studies reporting re-operation on the aortic valve were also excluded. The full text of initially screened studies was then retrieved for a second round of eligibility screening. Reference lists of articles selected for inclusion in the study were also searched and additional studies included (i.e., backward snowballing). The full PRISMA flow diagram outlining the study selection process is shown in Fig. S1 (see Supplementary Material). The Newcastle–Ottawa Quality Assessment Scale for Cohort Studies for Critical appraisal of eligible studies was used (Table S3; see Supplementary Material). Studies with scores of six or more were included.[9]

Clinical outcomes/definitions

The primary outcome was the incidence rate of aortic re-operation (IRAR; open or endovascular). Aortic re-operation rates were further stratified based on (i) clinical history of connective tissue disorder; (ii) indication for initial surgery (AA repair or AoD); and (iii) location (proximal vs. distal to the left subclavian artery). The pooled rates of in hospital mortality and morbidity after re-operation were also calculated.

Morbidity was defined as the incidence of at least one of the following: post-operative myocardial infarction, stroke, need for tracheostomy, and renal failure requiring dialysis. Diagnosis and definition of connective tissue disorders were those used in the original papers (see Table 1).

Data extraction and statistical analysis

Extracted variables included the following: study name, publication year, study design, age, surgical procedure, prevalence and type of connective tissue disorders (using definitions applied in source papers), number of initial operations for AA/AoD, number/type of aortic re-operation, in hospital mortality, and morbidity after re-operation.

Measurement data are reported as mean ± SD. For aortic re-operation, IRAR with underlying Poisson process with a constant event rate was used to account for different follow up times of the various studies with the total number of events observed within a treatment group out of the total person-time of follow up for that treatment group calculated from study follow up. Pooled event rates with 95% confidence interval (CI) were calculated for the binary outcomes. Uni- and multivariable meta-regression was used to assess the effect of age, initial operation for aneurysm or dissection, and MS on the incidence and time of aortic re-operation. Subgroup analyses were conducted to compare IRAR in (i) Marfan versus non-connective cohorts; (ii) AoD versus AA cohorts; and (iii) proximal versus distal to the left subclavian artery.

The Cochran Q statistic and the I^2 test were used to assess studies' heterogeneity. For the primary outcome, if heterogeneity was significant ($I^2 > 75\%$), a leave-one-out sensitivity analysis was performed.[10] Funnel plot and Egger's regression test were used to assess for potential publication bias. A random effect model (inverse variance method) was used for the whole analysis. Hypothesis testing for equivalence was set at the two tailed .05 level.

Table 1. Characteristics of individual studies (references listed in Appendix).

First author (year)	Study type	No. of patients	Mean ± SD age (y)	MS/ other CTD[a]	FU time (mo)	Mean ± SD time to re-operation (mo)	Re-operation	Re-operated patients	MS re-operated patients	CTD re-operated patients	Proximal aorta re-operation	Distal aorta re-operation	Unspecified re-operation	Number of isolated root procedures
Bachet (1990)	Prospective	105	51	22	51	8–120	12	11	NR	NR	7	2	3	NA
Bekkers (2012)	Retrospective	232	58 ± 13	16	86.4	NR	47	43	NR	NR	30	17	0	NA
Casselman (2000)	Retrospective	121	59 ± 11	2	43 ± 46	55.2 ± 33.6	24	24	NR	NR	15	8	1	NA
Cho (2016)	Retrospective	142	56 ± 11.4 (ascending aorta) 53.3 ± 10.7 (arch)	8	79.2 ± 55.2	59.3 ± 34.6	15	13	4	4	3	10	2	NA
Concistre (2012)	Retrospective	250	62.5 ± 12.4	12	56.4 ± 67.2	56.4 ± 30	25	25	NR	NR	24	1	0	NA
Dohmen (2001)	Retrospective	62	56	NR	NR	NR	8	8	NR	NR	7	1	0	NA
Fattouch (2009)	Retrospective	189	52 ± 11	49	88 ± 44	NR	28	28	NR	NR	9	19	0	NA
Fukunaga (1999)	Retrospective	148	55.4	10	NR	22.6	22	20	0	0	15	7	0	NA
Galloway (1993)	Retrospective	66	59 ± 14	2	32 ± 26	48	3	3	1	1	2	1	0	NA
Gambardella (2017)	Retrospective	426	68.3 ± 12.3	NR	60	NR	32	32	NR	NR	2	30	0	NA
Gariboldi (2006)	Retrospective	147	60.6 ± 13	6	53.4	56.4 ± 33.6	10	8	2	2	3	7	0	NA
Geirsson (2007)	Retrospective	221	61.6	10/1	39.7	Proximal: 52.59; distal: 40.35	24	24	NR	NR	11	13	0	NA
Girdauskas (2008)	Retrospective	58	34.5 ± 10.9	58	36.2 ± 25.5	45.1 ± 32.3	18	15	15	15	4	14	0	31
Glauber (2011)	Prospective	23	62 ± 13	1	22 ± 10	13.5	2	2	1	1	0	2	0	NA
Hagl (2003)	Retrospective	142	46	10	42	NR	4	4	NR	NR	0	4	0	94
Halstead (2007)	Retrospective	179	60.4 ± 14.5	15	61	NR	30	16	4	4	15	15	0	NA
Hata (2004)	Retrospective	84	64.5 ± 14.6	7	33.2	NR	5	5	1	1	4	1	0	NA
Heinemann (1990)	Prospective	86	48.3	NR	38.4	18.4	11	8	NR	NR	3	8	0	NA
Iribarne (2017)	Prospective	869	61	65	50.4 ± 30	33.8	37	37	2	2	17	19	1	NA
Kan (2006)	Retrospective	23	61.0 ± 12.3	NR	36.5 ± 17.3	NR	1	1	NR	NR	0	1	0	NA
Kari (2014)	Retrospective	122	33 ± 12	122	156 ± 91.2	111.6 ± 80.4	44	40	40	40	22	22	0	16
Kazui (2002)	Retrospective	105	58.1 ± 13.3	11	64.8	NR	25	21	NR	NR	9	7	9	NA

Continued

Table 1-*continued*

First author (year)	Study type	No. of patients	Mean ± SD age (y)	MS/ other CTD[a]	FU time (mo)	Mean ± SD time to re-operation (mo)	Re-operation	Re-operated patients	MS re-operated patients	CTD re-operated patients	Proximal aorta re-operation	Distal aorta re-operation	Unspecified re-operation	Number of isolated root procedures
Kim (2012)	Retrospective	129	55.9 ± 11.4	6	29.5	NR	9	9	NR	NR	0	9	0	NA
Kimura (2015)	Retrospective	451	63.5 ± 12.2	12	81.6 ± 58.8	67.2 ± 46.8	43	37	5	5	13	30	0	NA
Kirsch (2001)	Retrospective	160	57.5 ± 13.3	13	54.1 ± 67.2	68.4 ± 54	37	30	NR	NR	25	7	5	NA
Lewis (1992)	Retrospective	280	47.1	NR	46	NR	20	20	NR	NR	NR	NR	20	280
Long (2003)	Retrospective	70	59 ± 2	8	46 ± 6	50.3 ± 2.3	14	14	NR	NR	3	9	2	NA
Malvindi (2012)	Retrospective	592	61 ± 12	NR	78	62.4 ± 63.6	104	104	8	8	67	34	3	NA
Moon (2001)	Retrospective	119	62 ± 15	8	57 ± 43	NR	11	9	NR	NR	1	5	5	NA
Nguyen (1997)	Retrospective	56	32	18	NR	NR	6	6	4	4	2	4	0	56
Nguyen (1999)	Retrospective	65	NR	NR	62 ± 16	54	10	10	NR	NR	6	4	0	NA
Ochiai (2005)	Retrospective	46	61.8 ± 9.9	0	64.8 ± 40.8	NR	3	3	NR	NR	0	3	0	NA
Ohtsubo (2002)	Retrospective	88	66.2 ± 11.1	4	42 ± 36.3	NR	7	7	3	3	0	7	0	NA
Olsson (2007)	Retrospective	291	59	7	66	28.8	46	34	3	3	30	15	1	NA
Omura (2016)	Retrospective	172	66 ± 13	7	60 ± 48	NR	21	21	NR	NR	17	4	0	NA
Rizzoli (1990)	Retrospective	119	53	20	67.2	NR	13	12	NR	NR	5	4	4	NA
Sabik (2000)	Retrospective	208	NR	NR	56.4 ± 45.6	NR	13	13	NR	NR	5	8	0	NA
Shimizu (2012)	Retrospective	50	32.2	50	NR	65	36	22	22	22	14	22	0	50
Shiono (2006)	Retrospective	134	65.3	8	NR	NR	12	12	3	3	8	4	0	NA
Song (2010)	Retrospective	118	60	10	42 ± 39.6	NR	13	13	0	0	0	13	0	NA
Suehiro (2006)	Retrospective	246	59	9	56.4 ± 63.6	NR	41	41	NR	NR	11	26	4	NA
Tan (2005)	Retrospective	243	58 ± 12	10	54	NR	86	58	3	3	35	13	38	NA
Tanaka (2005)	Retrospective	18	69.7 ± 10.9	0	28 ± 14	NR	0	0	0	0	0	0	0	NA
Taniguchi (1991)	Retrospective	44	42 ± 10	20	69.6	NR	7	6	NR	NR	0	6	0	44
Westaby (1997)	Retrospective	64	63 ± 9	3	NR	NR	4	4	NR	NR	3	1	0	NA
Yamashiro (2009)	Retrospective	90	67.8 ± 4.6	NR	NR	76.8 ± 51.6	4	4	NR	NR	0	4	0	NA
Zierer (2007)	Retrospective	168	61 ± 16	10	78 ± 66	60 ± 50	28	26	NR	NR	12	16	0	NA

Note. MS = Marfan syndrome; CTD = connective tissue disease; FU = follow up; NR = not reported; NA = not available.
[a] Other CTDs included Ehlers Danlos syndrome.

Excel 2010 (Microsoft, Redmond, WA, USA) was used for initial data extraction. Analyses were performed using R (version 3.3.3 R Project for Statistical Computing) using the following statistical packages: “meta” and “metafor” within RStudio (0.99.489; http://www.rstudio.com) and Comprehensive Meta-Analysis (CMA) version 3.0 (2006; Biostat, Englewood, NJ, USA).

RESULTS

Characteristics of eligible studies

Of 646 retrieved articles and an additional 21 articles identified by backward snowballing, 47 met the inclusion criteria for this meta-analysis (detailed references are listed in Appendix S1; see Supplementary Material). Forty-six studies (97.9%) were single institution series. Mean sample size was 166.4 (range 18—869) and mean follow up time was 4.93 years (range 1.83—13 years).

A total of 7821 patients comprised the study population, the baseline characteristics of whom are reported in Table 1. Mean age was 56.5 years; connective tissue disorders occurred in 8.3% ($n = 650$), among whom nearly all (99.8%; $n = 649$) had MS.

Meta-analysis

During a weighted mean follow up of 4.7 ± 0.3 years, 11.5% of patients in the study cohort ($n = 903$) underwent re-operation on the aorta. Overall IRAR was 2.4% per person-year (95% CI 2.11—2.8; Fig. 1, Table S4 [see Supplementary Material]). The weighted mean time from

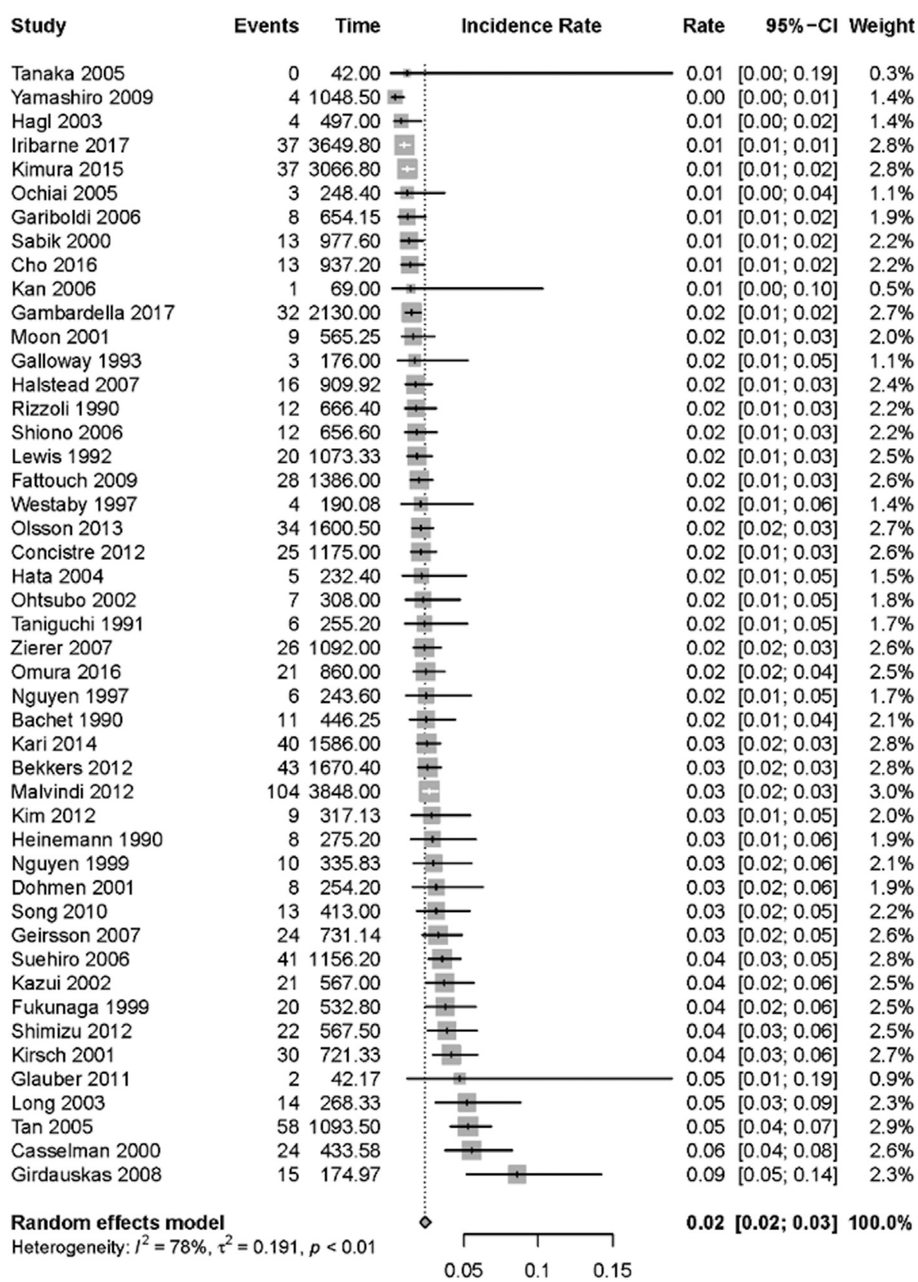


Figure 1. Pooled events rate for aortic re-operation in the overall population. *Note*. CI = confidence interval.

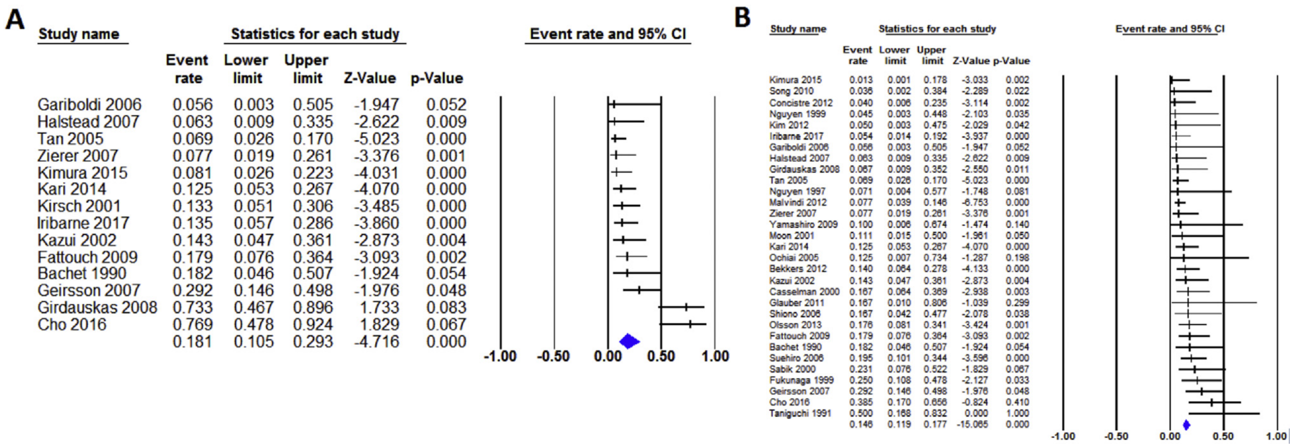


Figure 2. Forest plots of pooled events rates for (A) complications after aortic re-operation and (B) peri-operative mortality after aortic re-operation. *Note*. CI = confidence interval.

initial surgery to re-operation was 5.2 ± 0.2 years. Mean time to re-operation in the individual studies is shown in Fig. S2 (see Supplementary Material) (range: 8—192 months).

Patients with MS had a higher IRAR than patients without connective tissue disorders (6.0% [95% CI 4.1—8.8] vs. 2.3 [95% CI 1.9—2.7] per person-year [$p < .001$ for subgroup differences]) (Fig. S3; see Supplementary Material). IRAR after initial operation for AoD was nearly twofold higher than after initial operation for AA (2.5% [95% CI 2.1—3.0] vs. 1.3% per person-year [95% CI 0.9—2.0]; $p = .004$ for subgroup differences) (Fig. S4; see Supplementary Material). IRAR proximal to the left subclavian artery was 1.2% per person-year (95% CI 1.0—1.5), whereas IRAR distal to the left subclavian artery was 1.3% per person-year (95% CI 1.1—1.6; $p = .585$ for subgroup differences).

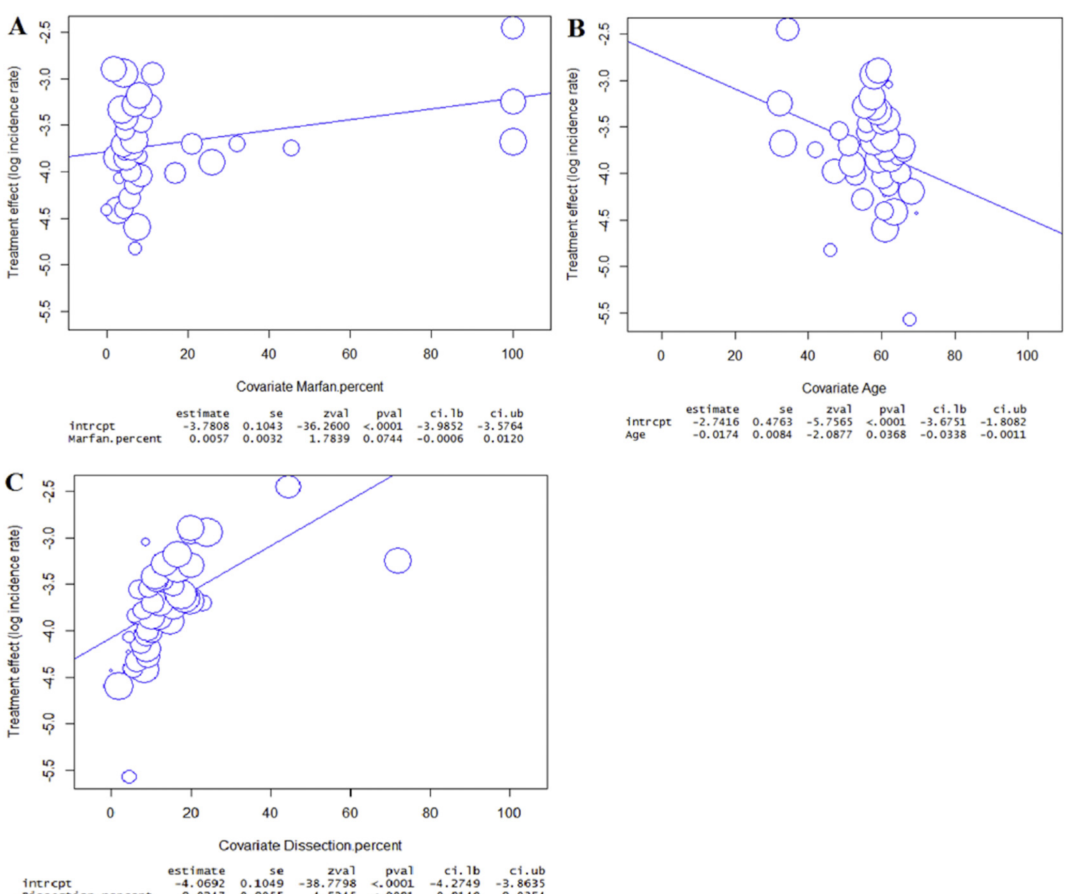


Figure 3. Results of the univariable meta-regression analysis for aortic re-operation rate: (A) percentage of patients with Marfan syndrome; (B) mean age at initial operation; (C) percentage of initial operation for aortic dissection (size of the circle is proportional to the weight of each study).

The pooled in hospital mortality after re-operation was 14.31% (95% CI 11.28—17.99) and the pooled complication rate after re-operation was 18.08% (95% CI 10.54—29.25; Fig. 2). Details of indication for re-operation and post-operative complications are given in Tables S5 and S6 (see Supplementary Material). Heterogeneity for the primary outcome was 78%. The funnel plot of and leave-one-out analysis confirmed the solidity of the results (Fig. S5; see Supplementary Material). The cumulative analysis for the primary outcome is shown in Fig. S6 (see Supplementary Material). The number of studies used for each outcome analysis is reported in Table S4 (see Supplementary Material). No effect of publication year on the primary outcome was found at subgroup analysis ($p = .39$; see Fig. S7 [Supplementary Material]) and meta-regression ($p = .24$; see Fig. S8 [Supplementary Material]).

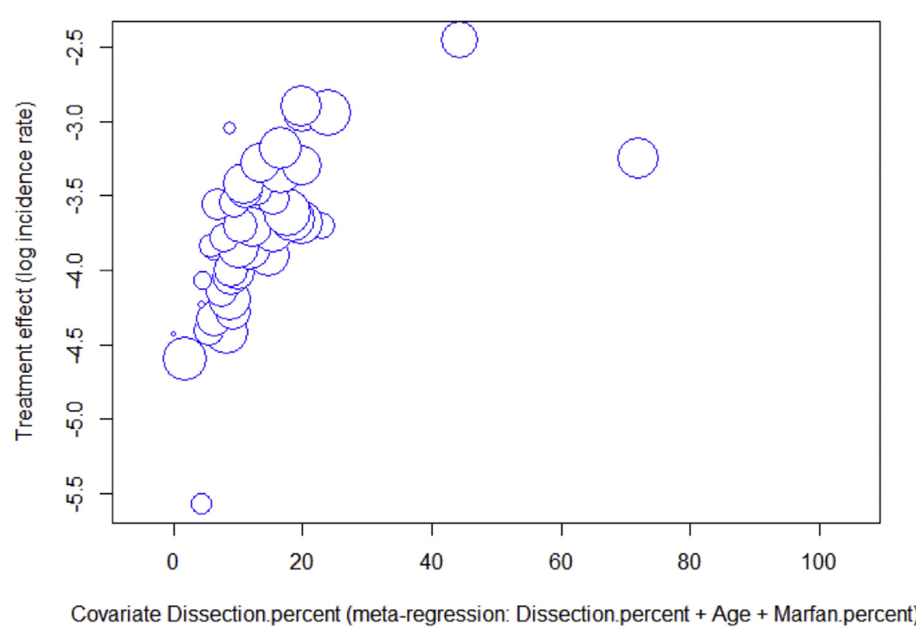
Meta-regression

Initial operation for the aortic dissection was the only variable associated with the rate of aortic re-operation on univariable and multivariable meta-regression (beta = .025, $p < .001$ at univariable; beta = .030, $p = .001$ at multivariable [Figs. 3 and 4]).

DISCUSSION

Given that prior research has been performed in single centre cohorts and entailed variable follow up durations, currently a general and objective estimate of the recurrent aortic risk after proximal aortic replacement is difficult to ascertain. This meta-analysis provides new insights. Key findings are as follows. First, the need for aortic re-operation (open or endovascular) occurred in 11.5% of patients at a rate of 2.4% per year during a weighted mean follow up of 4.7 ± 0.3 years. Second, initial operation for AoD was the most important predictor of re-operation: initial operation for AoD was the only variable associated with aortic re-operation in meta-regression. Third, likelihood of aortic re-intervention varied also based on pre-operative aortic substrate, as evidenced by an almost threefold increase in re-operation rate in patients with MS. Fourth, re-operation location was similarly distributed between aortic segments proximal and distal to the left subclavian artery.

Regarding mechanism, the observed association between AoD and increased risk of re-operation following proximal aortic grafting is consistent with established concepts regarding surgical AoD repair. When grafting is performed for type A AoD, conventional surgical approaches usually entail repair of a limited portion of the diseased aorta and dissected native segments commonly persist. Prior studies have shown frequent extension of the dissection to the non-resected aortic segment and false lumen perfusion in approximately half of cases.[5,11,12] Imaging studies have shown that AoD true and false lumens differ with respect to flow and energy propagation pattern.[13] Communication between true and false lumen predisposes to progressive aortic expansion and increases the risk of recurrent surgery.[11,12] Consistent with this, false lumen patency after AoD has been linked to mortality risk in both single centre studies and meta-analyses.[4,5] False lumen patency has also been linked to risk of aortic re-operation.[5] In this context, the observed association between AoD and recurrent aortic



	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-3.7226	1.1662	-3.1920	0.0014	-6.0084	-1.4368
Dissection.percent	0.0296	0.0085	3.4937	0.0005	0.0130	0.0462
Age	-0.0051	0.0187	-0.2747	0.7836	-0.0418	0.0315
Marfan.percent	-0.0061	0.0064	-0.9628	0.3357	-0.0186	0.0064

Figure 4. Results of the multivariable meta-regression model, including age, percentage of patients with Marfan syndrome, and percentage of initial operation for aortic dissection (size of the circle is proportional to the weight of each study).

risk is probably at least in part, attributable to aortic derangements not resolved by the initial operation. The observation that the IRAR was slightly higher for the portion of the aorta distal to the left subclavian artery (where the chance that the false lumen is still perfused after repair are higher) also supports the concept that anatomical derangement of the aortic wall is the most important determinant of aortic re-operation.

It should also be noted that MS and initial operation for AoD are closely linked, and that AoD can occur in these patients, despite minimal aortic dilation.[6,14,15] The finding of increased risk of recurrent aortic surgery among patients with MS adds to the growing literature documenting increased recurrent aortic risk among patients with genetically mediated aortopathies. Among post-dissection patients enrolled in the IRAD registry, MS independently conferred risk of recurrent AoD.[16] However, in the present analysis, multivariable regression, including both MS and initial surgical indication, demonstrated AoD to be the sole independent predictor of aortic re-operation. These data suggest that, irrespective of genetic alterations in aortic substrate, the disruption of the anatomical integrity of the aorta and probably the consequent modification of the mechanical properties of the vascular wall are the strongest determinants of the need for recurrent aortic surgery.

Current European Society of Cardiology Guidelines state that if stable results are documented over the first year after aortic surgery the follow up imaging can be less strict than after thoracic endovascular aneurysm repair,[17] and the European Society of Vascular Surgery Guidelines recommend annual follow up for the first three years followed by imaging every 2—3 years.[18] The finding of a mean interval from index surgery to aortic re-operation of 5.2 years (range: 8—192 months) suggests that rigorous surveillance should be continued even after the early time interval after proximal aortic surgery. Also, the re-operation rate in the present analysis is lower than that reported in many single centre studies and must be balanced against the risk of more extensive aortic replacement at the time of the initial procedure.

Several limitations should be noted. It is possible that ascertainment bias may have affected the results, whereby some patients with recurrent AoD or AA died prior to medical evaluation or were declined procedures owing to high risk. Also, clinical classifications of connective tissue disorders and location of the re-operation may have differed or been imprecise in the included studies. Finally, published data may reflect experienced aortic centres, at which rates of medical complexity and re-intervention may be higher than that in the general community. Future prospective studies, entailing standardised clinical classification and dedicated imaging are needed to further assess incidence and mechanisms of recurrent aortic events following proximal aortic grafting.

In conclusion, the results of this meta-analysis demonstrate aortic re-operations after proximal aortic repair occur at a rate of 2.4% per person-year in the first five years after surgery. Initial operation for aortic dissection is the strongest independent predictor of aortic re-operation. Efforts to reduce the number of initial operations for dissection by early prophylactic treatment of proximal aortic diseases (in particular, in high risk populations) and close post-operative follow up are key to improving patient outcomes.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejvs.2018.06.038.

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