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SYSTEMATIC REVIEW

Editor's Choice – Extending Aortic Replacement Beyond the Proximal Arch in Acute Type A Aortic Dissection: A Meta-Analysis of Short Term Outcomes and Long Term Actuarial Survival

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WHAT THIS PAPER ADDS

The extent of aortic replacement in acute type A dissection is an important matter of debate. Although a "less is more" approach (i.e., a proximal repair), is widely adopted, many patients require re-operative surgery. This meta-analysis demonstrates that an aggressive approach, involving total arch replacement during initial surgery, has the potential to improve long term survival *vs.* a proximal repair in selected patients.

Objective: The extent of aortic replacement during surgery for acute type A aortic dissection (ATAAD) is an important matter of debate. This meta-analysis aimed to evaluate the short and long term outcomes of a proximal aortic repair (PAR) *vs.* total arch replacement (TAR) in the treatment of ATAAD.

Data Sources: A systematic search of PubMed and Embase was performed. Studies comparing PAR to TAR for ATAAD were included.

Review methods: The primary outcomes were early death and long term actuarial survival at one, five, and 10 years. Random effects models in conjunction with relative risks (RRs) were used for meta-analyses.

Results: Nineteen studies were included, comprising 5 744 patients (proximal: $n = 4\ 208$; total arch: $n = 1\ 536$). PAR was associated with reduced early mortality (10.8% [95% confidence interval (CI) 8.4 — 13.7] *vs.* 14.0% [95% CI 10.4 — 18.7]; RR 0.73 [95% CI 0.63 — 0.85]) and reduced post-operative renal failure (10.4% [95% CI 7.2 — 14.8] *vs.* 11.1% [95% CI 6.7 — 17.5]; RR 0.77 [95% CI 0.66 — 0.90]), but there was no difference in stroke (8.0% [95% CI 5.9 — 10.7] *vs.* 7.3% [95% CI 4.6 — 11.3]; RR 0.87 [95% CI 0.69 — 1.10]). No statistically significant difference was found for survival after one year (83.2% [95% CI 77.5 — 87.7] *vs.* 78.6% [95% CI 69.7 — 85.5]; RR 1.05 [95% CI 0.99 — 1.11]), which persisted after five years (75.4% [95% CI 71.2 — 79.2] *vs.* 74.5% [95% CI 64.7 — 82.3]; RR 1.02 [95% CI 0.91 — 1.14]). After 10 years, there was a significant survival benefit for patients who underwent TAR (64.7% [95% CI 61.1 — 68.1] *vs.* 72.4% [95% CI 67.5 — 76.7]; RR 0.91 [95% CI 0.84 — 0.99]).

Conclusion: PAR appears to lead to an improved early mortality rate and a reduced complication rate. In the current meta-analysis, the suggestion of an improved 10 year survival benefit of TAR was found, which should be interpreted in the context of potential confounders such as age at presentation, comorbidities, and haemodynamic stability. In any case, PAR seems to be intuitive in older patients with limited dissections, and in those presenting in less stable conditions.

Keywords: Aortic dissection, Aortic replacement, Total arch replacement, Type A dissection
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INTRODUCTION

Acute type A aortic dissection (ATAAD) is a catastrophic disease that has high morbidity and mortality rates, and an incidence of 6 per 100 000 population per year.[1] More than half of patients die before arrival at hospital;[1] survivors require high risk emergency surgery. Although peri-operative mortality has declined over past decades, in hospital mortality remains high, ranging from 5% to 20% in relatively stable patients to 35% in unstable patients.[2,3] In addition, devastating complications such as peri-operative ischaemic stroke remain prevalent in up to 15% of patients.[4]

There has been ongoing debate about which surgical strategy provides the optimal outcome. A proximal aortic repair (PAR; i.e. surgery restricted to the ascending aorta or a hemi-arch replacement) has been the most widely adopted surgical approach. However, total aortic arch replacement (TAR) might reduce the risk of distal aneurysm formation and late complication rate.[5] Indeed, long term survival after surgery for ATAAD ranges from 80% at five years to 60% at 10 years,[6] and is influenced by false lumen patency and distal aortic events such as extension of dissection, aortic rupture, or visceral malperfusion.[7] However, TAR can be a more challenging procedure and is associated with increased early morbidity and mortality compared with PAR.[8]

Several studies of both techniques, mostly single centre, with mid and long term results have been published, but a potential survival benefit for either one approach has not yet been confirmed.[8,9] Therefore, the aim of this systematic review and meta-analysis was to address this competing risks dilemma by evaluating the short, mid, and long term outcomes of PAR *vs.* TAR in ATAAD, with emphasis on long term actuarial survival rates at pre-specified timepoints.

MATERIALS AND METHODS

Protocol

This systematic review and meta-analysis was conducted in accordance with the Preferred reporting items for Systematic Reviews and Meta-Analysis (PRISMA) statement.

Eligibility criteria

Types of participants. All adult patients undergoing urgent or emergency surgery for acute Stanford type A aortic dissection were eligible. Studies including patients operated on electively were excluded.

Types of interventions. Studies comparing PAR with TAR were included. PAR was defined as ascending aortic repair with or without hemi-arch replacement. Hemi-arch replacement was defined as lesser curvature replacement without debranching or island replacement of the supra-aortic vessels. TAR was defined as aortic arch replacement using supra-aortic debranching, selective re-implantation, or re-implantation as an island. Studies describing fully endovascular or hybrid procedures (i.e., combined surgical and endovascular approaches in the same setting) were excluded. Studies describing aortic arch replacement using fenestrated stent grafts were also excluded, as were studies describing the proximal group as a hemi-arch replacement with descending aortic stent implantation.

Outcome measures. The primary outcomes of the current study were early death (defined as in hospital or 30 day mortality) and long term survival defined as one, five, and 10 year actuarial survival. Studies were excluded if they did not report on any of these given timepoints. Secondary outcomes were peri-operative complications such as stroke and renal failure, and long term aortic events and/or aortic re-operation. As studies reported aortic events and re-operations differently, and aortic events are definition dependent, aortic events and re-operations were also combined as a single outcome.

Types of studies. All comparative studies were eligible for inclusion.

Search and study selection

A comprehensive search query was applied to the PubMed (i.e., PubMed Central and MEDLINE) and Embase databases using a combination of terms, including “acute type A aortic dissection” AND “arch repair” OR “hemi-arch repair” OR “ascending aortic repair”, and alternative spellings (Supplementary Table S1A,B). The search was performed by an author trained in systematic literature searches (J.D.). The last search was performed on 26 February 2021.

Data extraction and outcomes

All data were extracted by the first two authors (S.H. and B.P.A.) using a pre-defined worksheet. All data were reported as means $\pm$ SD. If reported differently, data were converted to means and SD using the method of Wan *et al.*[10] When studies reported ascending aortic repair and hemi-arch replacement separately, data from these groups were combined in one PAR group. When studies reported on hemi-arch and total arch replacement, both as a TAR procedure, data were only used if actual TAR was reported separately.

Risk of bias in individual studies

Risk of bias was independently assessed by the first two authors independently (S.H. and B.P.A.) using the ROBINS-I tool for risk of bias assessment for non-randomised intervention studies.

Statistical analysis

Relative risks (RRs) with their corresponding 95% confidence intervals (CIs) were used as outcomes of the meta-analyses, as analyses were performed at pre-specified actuarial timepoints. Actuarial survival (in which survival is measured at pre-defined timepoints, as opposed to Kaplan—Meier survival analysis in which time to event analysis is used)[11] was performed in order to ensure homogeneous pooled follow up rates at one, five, and 10 years, instead of mixing different follow up periods, enabling the identification of a potential late survival benefit. This long term survival was reported for the whole cohort (not just limited to patients surviving hospitalisation). Random effects models were used for meta-analyses, which were presented in forest plots. Potential heterogeneity was assessed using the I^2 test, in which a cut off p value of $< .10$ was applied in conjunction with an I^2 test result of $> 50\%$ to be indicative of significant heterogeneity. Post hoc analyses on subgroups of studies reporting on very long term survival were performed, as well as subgroup analyses of studies reporting exclusively on DeBakey type I patients. Sensitivity analyses were performed to evaluate the effect of a tear oriented strategy. Meta-regression analyses were performed to evaluate the influence of age on long term treatment effects, the effect of cerebral perfusion (CP) time on stroke, and effect of circulatory arrest (CA) time on renal failure as a complication, of which the latter two were non-adjusted for operation type. Meta-regression data were presented graphically as bubble plots and as transformed odds ratios (ORs), derived from log odds ratios (beta coefficients). Of note, as complications such as renal failure and stroke are definition dependent, only RRs, instead of absolute pooled percentages, were reported. It was hypothesised that the relative effect would be consistent between studies, regardless of definition. All analyses were performed in open source software, namely Rstudio, using the "meta" and "dmetar" software packages (R Foundation for Statistical Analysis, Vienna, Austria).

Risk of bias across studies

Publication bias was assessed visually using funnel plots of the primary outcomes (early death and long term survival). Additionally, statistical assessment was performed using Egger's test. These statistical assessments were performed using the "meta" and "dmetar" packages in Rstudio.

RESULTS

Study selection

The search strategy was applied to the electronic databases and generated 4 561 hits in PubMed and 2 654 hits in Embase. After the exclusion of duplicates, 6 099 records were screened based on titles and abstracts. Subsequently, the full texts of 35 studies were evaluated, of which 16 were excluded. Reasons for exclusion were as follows: non-comparative studies ($n = 7$); no actual TAR ($n = 4$); no actual PAR ($n = 3$); hybrid repair ($n = 1$); and insufficient patient characteristics (hospital survivors only, $n = 1$). Eventually, 19 studies were included for meta-analysis (Fig. 1).[12–30]

Study characteristics

The 19 included studies were published between 2003 and 2020, describing patients treated for ATAAD between 1986 and 2018.[25,27] All studies were retrospective. One study was a report of an international registry,[16] one a study of a national registry,[14] and all other studies were single centre experiences. The 19 studies comprised a total of 5 744 patients, of whom 4 208 underwent PAR (73.3%) and 1 536 underwent TAR (26.7%). Total mean follow up was 47 $\pm$ 41 months. The mean age of the total cohort was 60.0 $\pm$ 14.1 years and 64.0% of patients were male (PAR: 61.2 $\pm$ 14.2 years, 61.4% males; TAR: 57.1$\pm$13.3 years, 70.6% males). Furthermore, 4.1% of patients had confirmed connective tissue disease (PAR: 3.3%; TAR: 6.1%). Table 1 describes the study and baseline characteristics.

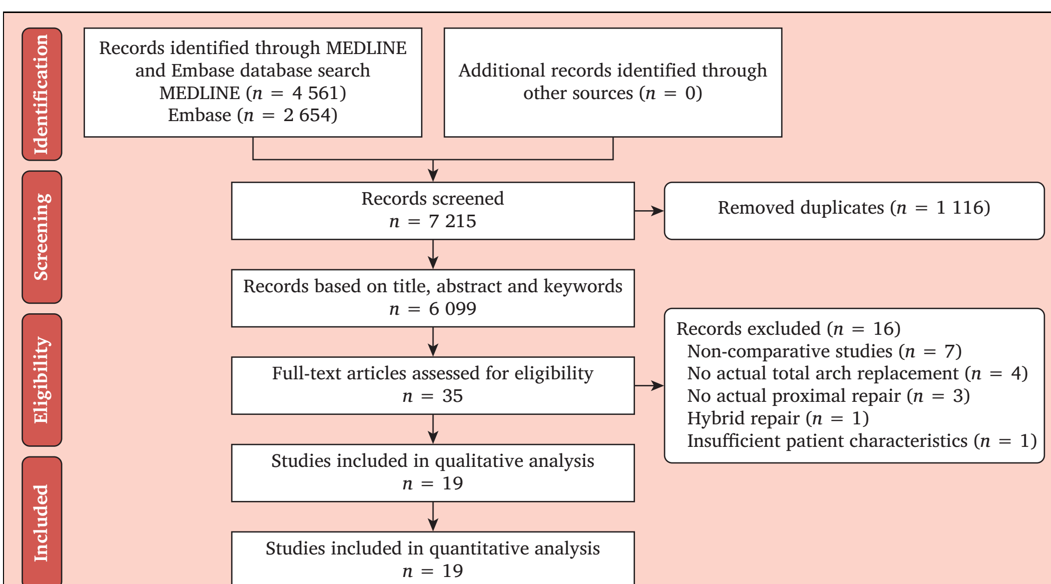

Figure 1. Preferred reporting items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram demonstrating the selection process of studies comparing proximal aortic repair with total arch replacement for type A aortic dissection.

Table 1. Study and baseline characteristics of 19 studies comparing proximal aortic repair with total arch replacement for type A aortic dissection

Study (year), country	Study period	Patients – n	Mean FU time ± SD – mo	Group	Patients – n	Mean age ± SD – y	Male sex – n	Marfan syndrome – n	Hypertension – n
Aizawa (2016),[12] Japan	2003–2014	267	57 ± 32	Proximal	225	66 ± 12	103	3	NR
				Extensive	42	59 ± 12	31	0	NR
di Eusanio (2015),[13] Italy	1997–2012	240	57.6 ± 46.8	Proximal	187	64.4 ± 11.2	125	5	138
				Extensive	53	59.2 ± 12.3	41	3	40
Easo (2012),[14] Germany	2006–2010	658	30 d/1 mo	Proximal	518	59.1 ± 13.3	324	NR	283
				Extensive	140	58.3 ± 11.9	86	NR	88
Kim (2011),[15] South Korea	1999–2009	188	48	Proximal	144	57.6 ± 11.5	69	7	92
				Extensive	44	55.0 ± 12.1	26	1	24
Larsen (2017),[16] IRAD	1996–2015	1 241	NR	Proximal	907	60.8 ± 14.1	584	24	674
				Extensive	334	59.1 ± 13.6	253	13	218
Lio (2016),[17] Italy	2006–2013	92	30.5 ± 29.8	Proximal	59	66 ± 10	43	NR	51
				Extensive	33	61 ± 12	28	NR	30
Merkle (2018),[18] Germany	2006–2015	240	NR	Proximal	198	62.2 ± 18.6	126	3	150
				Extensive	42	62.3 ± 14.6	27	1	31
Ohtsubo (2002),[19] Japan	1989–2001	88	42 ± 36	Proximal	64	68	19	NR	NR
				Extensive	24	68	13	NR	NR
Omura (2016),[20] Japan	1999–2014	197	60 ± 48	Proximal	109	70 ± 11	50	0	NR
				Extensive	88	61 ± 13	62	0	NR
Rice (2015),[21] USA	1999–2014	489	52 ± 67	Proximal	440	57.9 ± 14.8	313	9	370
				Extensive	49	62.4 ± 13.4	38	1	44
Rylski (2014),[22] Germany	2001–2013	153	62 ± 41	Proximal	139	61.0 ± 14.7	95	7	106
				Extensive	14	54.7 ± 14.0	8	0	13
Shiono (2006),[23] Japan	1995–2005	134	120	Proximal	105	66.9 ± 13.0	46	5	NR
				Extensive	29	59.5 ± 14.9	15	3	NR
Sun (2011),[24] China	2003–2008	214	44 ± 18	Proximal	66	46 ± 13	36	5	36
				Extensive	148	45 ± 11	126	19	107
Tan (2003),[25] the Netherlands	1986–2001	277	31.2	Proximal	260	NR	NR	NR	NR
				Extensive	17	NR	NR	NR	NR
Trivedi (2016),[26] USA	2007–2014	259	NR	Proximal	167	63.3 ± 13.3	92	NR	128
				Extensive	92	58.9 ± 11.2	58	NR	73
Uchida (2020),[27] Japan	2006–2018	253	52 ± 2	Proximal	169	63.3 ± 12.7	95	6	NR
				Extensive	84	57.3 ± 10.6	54	4	NR
Uchida (2009),[28] Japan	1997–2008	120	67	Proximal	55	72.3	25	NR	NR
				Extensive	65	64.4	28	NR	NR
Yang (2019),[29] USA	1996–2017	472	64	Proximal	322	60.3 ± 14.9	226	16	230
				Extensive	150	56.7 ± 12.7	104	5	107
Zhang (2014),[30] China	2002–2010	162	56 ± 33	Proximal	74	49.1 ± 12.6	55	12	47
				Extensive	88	45.5 ± 13.6	74	21	64

FU = follow up; NR = not reported; SD = standard deviation.

Risk of bias within studies

The risk of bias assessment was performed using the ROBINS-I tool. Supplementary Figures S2 and S3 show the risk of bias assessment. In general, risk of bias was assessed to be moderate to low, although a potential risk of confounding was seen, potentially introduced by the patients' presenting status, entry tear location, and surgical expertise.

Qualitative synthesis

Of the 19 studies, seven described a purely tear oriented strategy,[12,18,19,22,23,25,27] while the strategy was not purely tear oriented in 10 studies,[14,15,17,20,21,24,26,28–30] and another two studies did not report on the strategy.[13,16] A purely tear oriented strategy comprised the mere exclusion of the entry tear without additional procedures. A non-exclusively tear oriented strategy was aimed at resection of the entry tear in conjunction with a more aggressive approach in case of a combination of concomitant arch aneurysms,[15,17,20,21,24,26,29] dissected arch vessels,[20,24,26,29] or evidence of connective tissue disease.[17,24] In the PAR group, DeBakey type I dissection was present in 89.0% of cases, DeBakey type II in 7.8% of cases, and DeBakey type III in 3.2%. In the TAR group, DeBakey type I was prevalent in 97.0% of cases, while only 2.4% of patients had DeBakey type II dissection and 0.6% retrograde type III (dissection type was reported in 14 studies, $n = 4\,678$ patients). The entry tear was located in the ascending aorta in 84.3% of cases in the PAR group and in the aortic arch in 10.0% of cases. In the remaining cases, no specific tear was found. In the TAR group, the entry tear was located in the ascending aorta in 64.6% of patients and in the arch in 32.1% (tear location was reported by six studies, $n = 1\,685$ patients). Seventeen studies ($n = 5\,371$ patients) reported the use hypothermic CA. A variety of arterial cannulation sites were used, of which femoral cannulation was most prevalent (reported by 16 studies, $n = 4\,819$ patients). In the PAR group, CP was used in 91.1% of patients, while CP was used in 97.9% of TAR patients (reported by 18 studies, $n = 4\,503$ patients).

Regarding TAR technique, in 614 of 1 536 patients (40.0%) a conventional elephant trunk or frozen elephant trunk was employed (FET), ranging from 9.6% to 100% (reported by 19 studies, $n = 1\,536$). These operative variables are presented in Table 2.

Quantitative synthesis

Short term outcomess. A significantly reduced early mortality rate was observed in the PAR group (PAR: 10.8% [95% CI 8.4 − 13.7]; TAR: 14.0% [95% CI 10.4 − 18.7]; RR 0.73 [95% CI 0.63 − 0.85]; Fig. 2A). Early mortality was reported by all studies, $n = 5\,744$ patients). No significant differences were seen in PAR or TAR surgery with regard to stroke rates (reported by 18 studies, $n = 5\,467$ patients [PAR: 8.0% (95% CI 5.9 − 10.7); TAR: 7.3% (95% CI 4.6 − 11.3); RR 0.87 (95% CI 0.69 − 1.10)]; Fig. 2B), but a reduced post-operative renal failure rate was found in the PAR group (reported by 15 studies, $n = 4\,568$ patients [PAR: 10.4% (95% CI 7.2 − 14.8); TAR: 11.1% (95% CI 6.7 − 17.5); RR 0.77 (95% CI 0.66 − 0.90)]; Fig. 2C).

Long term outcomes. Pooled actuarial survival rates are presented at one (seven studies), five (12 studies), and 10 year (five studies) follow ups. At one year, no statistically significant differences were found in survival between PAR and TAR (reported by seven studies, $n = 1\,538$ patients [PAR: 83.2% (95% CI 77.5 − 87.7); TAR: 78.6% (95% CI 69.7 − 85.5); RR 1.05 (95% CI 0.99 − 1.11)]; Fig. 3A), which persisted at five years (reported by 12 studies, $n = 3\,012$ patients [PAR: 75.4% (95% CI 71.2 − 79.2); TAR: 74.5% (95% CI 64.7 − 82.3); RR 1.02 (95% CI 0.91 − 1.14)]; Fig. 3B). Importantly, a long term treatment effect was noted, as a significant survival benefit in favour of TAR was seen at the 10 year follow up (reported by five studies, $n = 1\,559$ patients [PAR: $n = 1\,201$ patients; TAR: $n = 358$ patients]; PAR: 64.7% [95% CI 61.1 − 68.1]; TAR 72.4% [95% CI 67.5 − 76.7]; RR 0.91 [95% CI 0.84 − 0.99]; Fig. 3C). Of note, there was a non-statistically significant difference in age between PAR and TAR patients (TAR patients mean difference [MD] 4.43 years younger than PAR patients [95% CI −0.10 − 8.97; $p = .060$]).

Significant heterogeneity for the pooled five year actuarial survival data was noted ($I^2 = 74\%$, $p < .001$) but not for one year ($I^2 = 0\%$, $p = .64$) and 10 year actuarial survival ($I^2 = 26\%$, $p = .25$). For aortic re-operations and re-operations or events, at long term follow up (which differed between studies), a non-significant reduction in events in favour of the TAR group was found (Supplementary Fig. S4).

Surgical times. Surgical times were submitted to meta-analysis and presented as absolute MDs. All surgical times were reduced in favour of the PAR group (Supplementary Fig. S5). CA time was 20.72 minutes shorter in the PAR group (reported by nine studies, $n = 3\,630$ patients [95% CI 15.0 − 26.4]), CP time was 28.17 minutes shorter in the PAR group (reported by eight studies, $n = 1\,760$ patients [95% CI 7.2 − 49.1]), cardiopulmonary bypass time was 55.43 minutes shorter in the PAR group (reported by 15 studies, $n = 4\,422$ patients [95% CI 34.4 − 76.4]), and aortic cross clamping time was 28.44 minutes shorter in the PAR group (reported by 11 studies, $n = 2\,706$ patients [95% CI 18.9 − 38.0]). However, significant heterogeneity was noted (I^2 range 83% − 97%; all $p < .001$).

Subgroup and sensitivity analysis. For studies describing ATAAD patients exclusively with DeBakey type I dissection, a subgroup analysis was performed for early mortality (nine studies, $n = 2\,537$ patients). In this analysis, no significant difference was found between a PAR and TAR strategy in terms of early mortality, when specified for patients with DeBakey type I dissection (RR 0.83 [95% CI 0.67 − 1.04]; Supplementary Fig. S6).

In order to evaluate the robustness of the pooled 10 year actuarial survival rates, the studies reporting on 10 years,

Table 2. Dissection and procedural characteristics during the index operation in 19 studies comparing proximal aortic repair to total arch replacement for type A aortic dissection

Study	Year	Exclusively tear oriented strategy	Group	De-Bakey I − *n*	De-Bakey II − *n*	Entry tear Asc − *n*	Entry tear Arch − *n*	Use of HCA	Temperature − °C (*n*)	Arterial cannulation	Use of CP − *n*	Antegrade/retrograde CP (*n*)	Use of (F)ET (*n*)
Aizawa[12]	2016	Yes	Proximal	146	40	NR	NR	Yes	26–28	NR	225	Antegrade or retrograde	NA
			Extensive	34	1	NR	NR	Yes	26–28	NR	42	Antegrade or retrograde	No
di Eusanio[13]	2015	NR	Proximal	187	0	130	35	Yes	26	Various	187	Antegrade (187)	NA
			Extensive	53	0	16	31	Yes	26	Various	53	Antegrade (53)	Yes (25)
Easo[14]	2012	No	Proximal	518	0	518	0	Yes	23	NR	347	NR	NA
			Extensive	140	0	140	0	Yes	23	NR	118	NR	Yes (48)
Kim[15]	2011	No	Proximal	144	0	86	35	Yes	Deep (110) Moderate (34)	Femoral or axillary or both	141	Antegrade (42) or retrograde (99)	NA
			Extensive	44	0	7	33	Yes	Deep (31) Moderate (13)	Femoral or axillary or both	44	Antegrade (27) or retrograde (17)	Yes (5)
Larsen[16]	2017	NR	Proximal	808	99	NR	NR	Yes	22	Various	NR	NR	NA
			Extensive	316	18	NR	NR	Yes	20	Various	NR	NR	Yes (29)
Lio[17]	2016	No	Proximal	NR	NR	NR	NR	Yes	27	Femoral or axillary or asc	59	Antegrade	NA
			Extensive	NR	NR	NR	NR	Yes	27	Femoral or axillary or asc	33	Antegrade	No
Merkle[18]	2018	Yes	Proximal	98	37	156	26	Yes	NR	Femoral or axillary or asc	148	NR	NA
			Extensive	38	5	22	29	Yes	NR	Femoral or axillary or asc	42	NR	No
Ohtsubo[19]	2002	Yes	Proximal	NR	NR	NR	NR	Yes	Profound	Femoral + axillary	5	Antegrade	NA
			Extensive	NR	NR	NR	NR	Yes	Profound	Femoral + axillary	21	Antegrade	No
Omura[20]	2016	No	Proximal	109	0	73	27	Yes	NR	Femoral or asc	109	Antegrade (61) or retrograde	NA
			Extensive	88	0	21	53	Yes	23	Femoral or asc	88	Antegrade (86) or retrograde	Yes (88)
Rice[21]	2015	No	Proximal	NR	NR	NR	NR	Yes	Profound	Femoral or axillary or asc	433	Retrograde (433)	NA
			Extensive	NR	NR	NR	NR	Yes	Profound	Femoral or axillary or asc	49	Retrograde (49)	No
Rylski[22]	2014	Yes	Proximal	139	0	NR	NR	Yes	Deep	Axillary	139	Antegrade	NA
			Extensive	14	0	NR	NR	Yes	Deep	Axillary	14	Antegrade	No
Shiono[23]	2006	Yes	Proximal	72	28	NR	NR	Yes	Deep, 20	Femoral	105	Antegrade	NA
			Extensive	24	3	NR	NR	Yes	Deep, 20	Femoral	29	Antegrade	No
Sun[24]	2011	No	Proximal	66	0	NR	NR	Yes	18–22	Axillary	66	Antegrade (66)	NA
			Extensive	148	0	NR	NR	Yes	18–22	Axillary	148	Antegrade (148)	Yes (148)

Continued

Table 2-*continued*

Study	Year	Exclusively tear oriented strategy	Group	De-Bakey I – *n*	De-Bakey II – *n*	Entry tear Asc – *n*	Entry tear Arch – *n*	Use of HCA	Temperature – °C (*n*)	Arterial cannulation	Use of CP – *n*	Antegrade/ retrograde CP (*n*)	Use of (F)ET (*n*)
Tan[25]	2003	Yes	Proximal	NR	NR	NR	NR	Yes	NR	Femoral	260	Antegrade (260)	NA
			Extensive	NR	NR	NR	NR	Yes	NR	Femoral	17	Antegrade (17)	No
Trivedi[26]	2016	No	Proximal	112	55	NR	NR	Yes	Deep	Asc or femoral or subclavian	167	Antegrade or retrograde or both	NA
			Extensive	87	5	NR	NR	Yes	Deep	Asc or femoral or subclavian	92	Antegrade or retrograde or both	Yes (26)
Uchida[27]	2020	Yes	Proximal	169	0	NR	NR	NR	NR	Femoral + axillary	169	Antegrade	NA
			Extensive	84	0	NR	NR	NR	NR	Femoral + axillary	84	Antegrade	Yes (84)
Uchida[28]	2009	No	Proximal	NR	NR	NR	NR	NR	NR	NR	55	NR	NA
			Extensive	NR	NR	NR	NR	NR	NR	NR	65	NR	Yes (65)
Yang[29]	2019	No	Proximal	322	0	NR	NR	Yes	25	Various	317	Antegrade (91) or retrograde (194) or both (32)	NA
			Extensive	150	0	NR	NR	Yes	26	Various	150	Antegrade (54) or retrograde (5) or both (91)	Yes (18)
Zhang[30]	2014	No	Proximal	74	0	74	0	Yes	26–28	Femoral + axillary	74	Antegrade (66) or retrograde (8)	NA
			Extensive	88	0	88	0	Yes	26–28	Femoral + axillary	88	Antegrade (81) or retrograde (7)	Yes (88)

Asc = ascending aorta; HCA = hypothermic circulatory arrest; CP = cerebral perfusion; (F)ET = (frozen) elephant trunk; NR = not reported; NA = not applicable.

were re-evaluated at the five year actuarial timepoint in subgroup analysis (five studies, $n = 1\,087$ patients). Supplementary Fig. S7 shows that, at five years, the later survival benefit for the TAR group was not yet observed (RR 0.88; 95% CI 0.96 – 1.05). As two studies reported long term actuarial survival rates beyond five years, but before 10 years (namely at seven and eight years, respectively),[13,30] an additional analysis was performed for all studies reporting actuarial survival rates beyond five years (seven studies, $n = 1\,961$ patients; Supplementary Fig. S8), confirming the long term results (RR 0.91; 95% CI 0.85 – 0.98). As a difference in strategy (i.e., purely tear oriented *vs*. non-exclusively tear oriented) has the potential to bias outcome, sensitivity analyses were performed to evaluate its influence (Supplementary Table S9, which also presents the number of analysed studies and corresponding patient numbers), which demonstrated consistent results across all primary outcomes, regardless of strategy.

Meta-regression analyses. For meta-regression analysis of age and long term treatment effect (i.e., 10 year survival), the five studies reporting on 10 year survival were included ($n = 1\,559$ patients). Meta-regression revealed that the treatment effect of TAR was attenuated with increasing age, implying that the treatment effect of more extensive surgery (TAR) on 10 year survival modestly decreases with increasing age (transformed OR of 0.997 [95% CI 0.990 – 0.999] per patient year or OR 0.97 per 10 years [$p = .048$]; Fig. 4A). Eight studies were included for meta-regression of CP duration on stroke ($n = 1\,760$ patients). Figure 4(B) shows that increased CP duration was associated with an increased risk of stroke. This result implies that with every minute increase in the duration of CP, the risk of stroke increases significantly (transformed OR 1.349 [95% CI 1.020 – 1.786]; $p = .034$). Unfortunately, significant heterogeneity was noted ($I^2 = 99\%$; $p < .001$). Furthermore, a significant effect of CA time duration on renal failure was

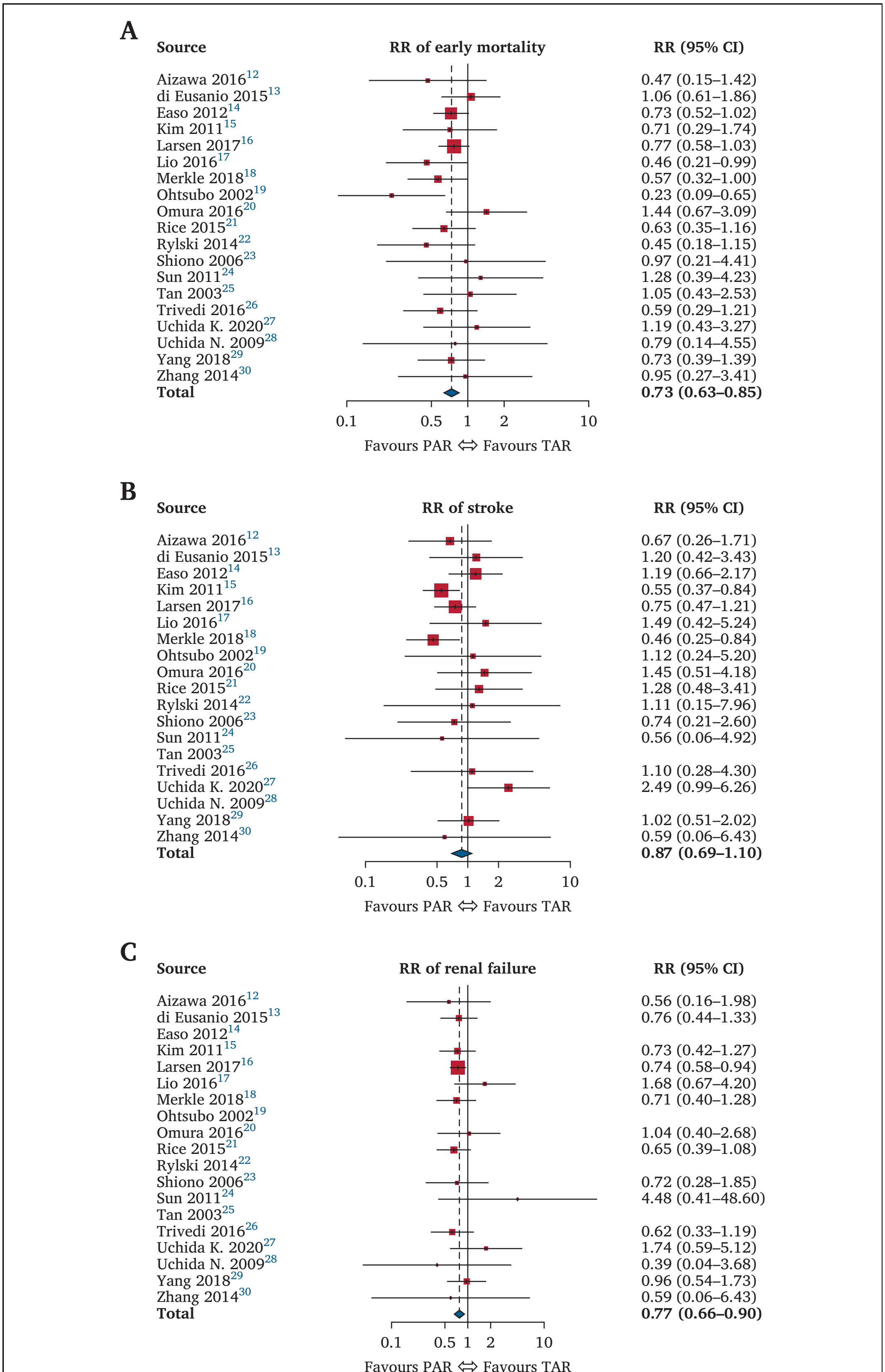

Figure 2. Forest plots demonstrating outcomes of proximal aortic repair (PAR) *vs.* total arch replacement (TAR) for (A) early mortality, (B) stroke, and (C) renal failure, where $I^2 = 0\%$ ($p = .54$), $I^2 = 19\%$ ($p = .24$), and $I^2 = 0\%$ ($p = .78$), respectively. CI = confidence interval; RR = relative risk.

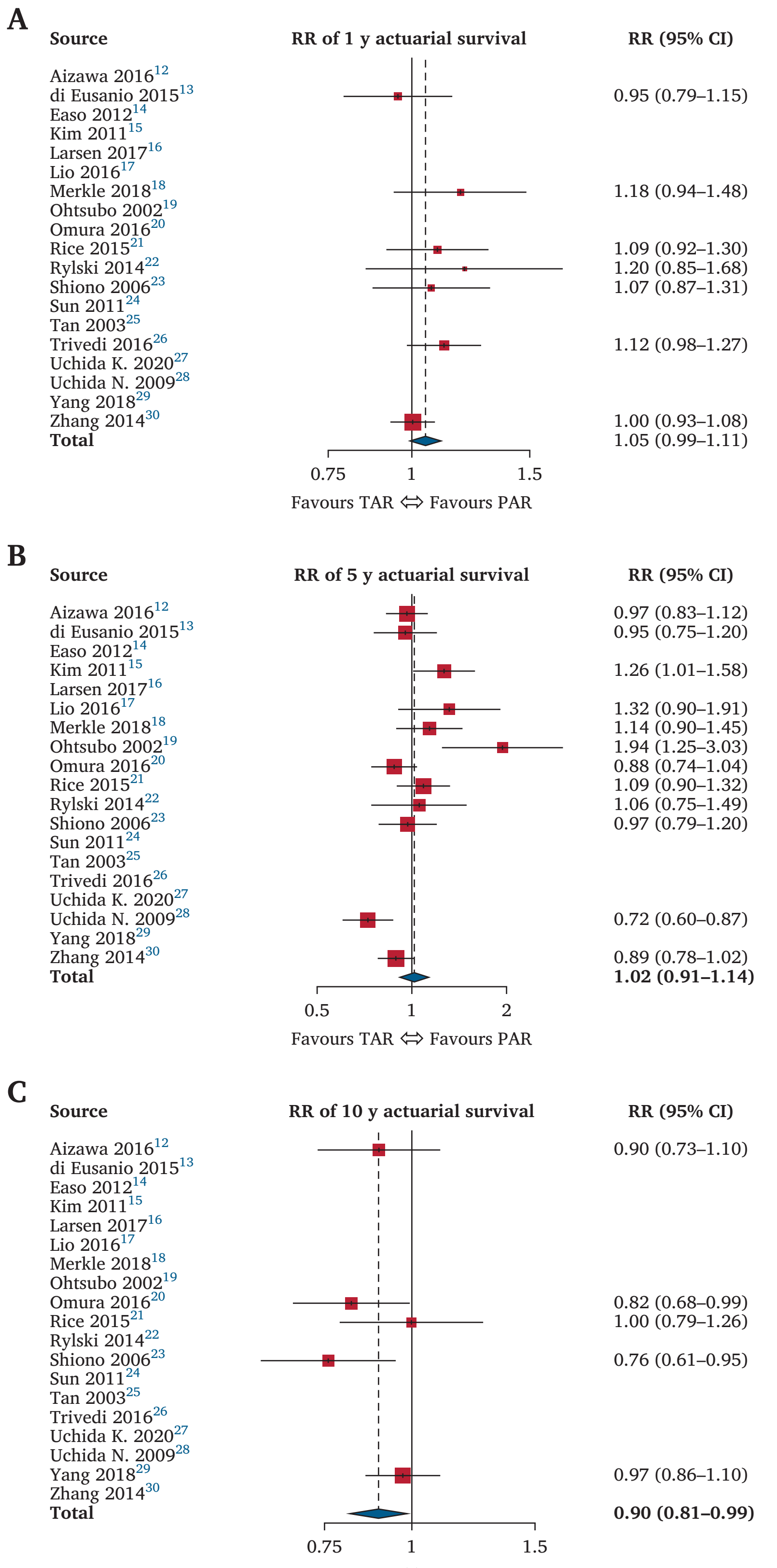

Figure 3. Forest plots demonstrating long term outcomes of proximal aortic repair (PAR) *vs.* total arch replacement (TAR) for (A) one year actuarial survival, (B) five year actuarial survival, and (C) 10 year actuarial survival, with $I^2 = 0\%$ ($p = .64$), $I^2 = 69\%$ ($p < .001$), and $I^2 = 26\%$ ($p = .25$), respectively. CI = confidence interval; RR = relative risk.

found as a measure of end organ damage (seven studies, $n = 2\,884$ patients [Supplementary Fig. S10]; transformed OR 3.158 [95% CI 1.391 − 7.243]; $p = .006$). Finally, the influence of the use of (F)ET on 10 year survival and aortic events and re-operations was evaluated but no significant effect was found ($p = .51$ and $p = .99$, respectively).

Risk of bias across studies. Supplementary Fig. S11 presents the funnel plots for the primary outcomes of early death and long term survival. Publication bias was assessed to be unlikely ($p = .79$ and $p = .15$, respectively).

DISCUSSION

The aortic arch is the anatomical crossroad between the brain and the body, which makes surgical replacement of this aortic region complex, resulting in high morbidity and mortality rates. Surgical correction of ATAAD is one of the most challenging and risk carrying procedures in the field of cardiac surgery, especially in an emergency setting. Whether extension of aortic replacement to, and beyond, the arch has a beneficial effect is one of the most important knowledge gaps in surgical treatment of ATAAD, as outlined in the important consensus statement by Czerny *et al.*,[31] on behalf of the joint European cardiothoracic surgery and vascular surgery societies. Of note, in this consensus statement, in the absence of comparative evidence, no recommendation for the extent of surgery in ATAAD has been proposed, other than exclusion of the primary entry tear. In the current meta-analysis, it was demonstrated that, although a PAR strategy might result in beneficial peri-operative and early post-operative outcomes, a TAR strategy is associated with a significant survival benefit at the 10 year follow up.

In the PAR *vs.* TAR debate, the competing risks dilemma plays a central role.[32] The potential advantages of a TAR strategy are expected to surface gradually during long term follow up. Two previous meta-analyses failed to demonstrate a survival benefit for TAR in the longer term,[8,9] but these analyses had the drawback of pooling studies with follow up periods ranging from 44 to 67 months,[8] potentially obscuring the results. In this setting, it seems more appropriate to pool actuarial survival rates at pre-specified timepoints.[33] By analysing pre-specified actuarial survival timepoints, it is appreciable that the inferior outcome in the short term is gradually attenuated over time, eventually revealing the improved long term survival in TAR (Fig. 3).

Tear driven strategy

A tear driven strategy in DeBakey type I dissection (i.e., aimed at resection of the primary entry, irrespective of more distal aortic pathology) usually results in PAR and has been widely adopted for ATAAD treatment in the acute setting. The patient's survival (in adequate neurological condition) of the index operation should be the surgical team's primary objective in the treatment of ATAAD.[32] It was found that the PAR strategy was associated with shorter CA, CP, and aortic cross clamping times compared with TAR. In addition, reduced CP duration was associated with improved neurological outcomes (i.e., a reduction in stroke rate) in the current analysis, and the duration of CP should therefore be as short as possible.

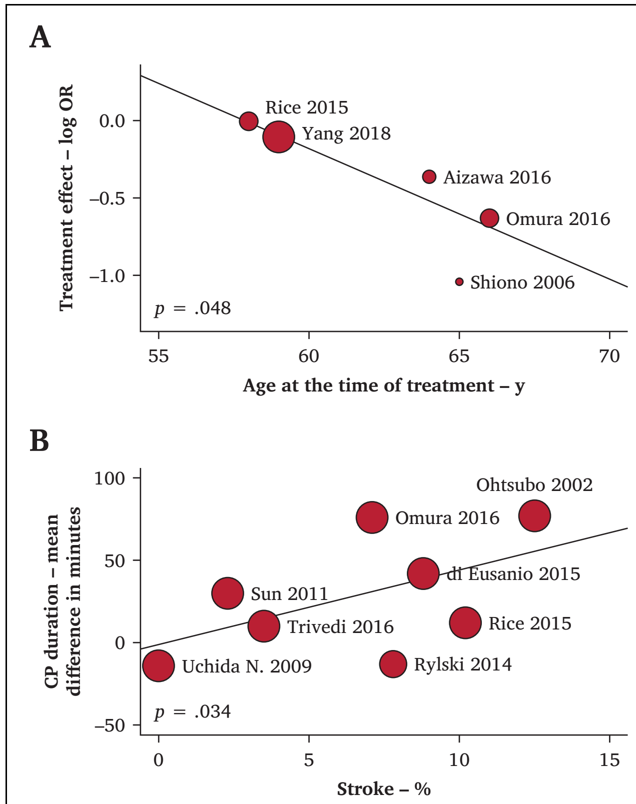

Figure 4. Meta-regression analyses for (A) influence of age on long term (i.e., 10 year survival) treatment effect of total aortic replacement (TAR) and (B) effect of duration of cerebral perfusion on the risk of stroke, with $I^2 = 0\%$ ($p = .81$) and $I^2 = 99\%$ ($p < .001$), respectively.

Therefore, the choice to follow a tear oriented strategy should be influenced by the patient's haemodynamic status at presentation and risk profile (in terms of haemodynamic compromise, neurological impairment, end organ malperfusion, and comorbidities). Indeed, several reports have demonstrated that patients presenting in a critical condition have significantly increased peri-operative mortality rates, of up to 40%, compared with 3% in patients without any form of ischaemia.[34] Furthermore, patients with extensive atherosclerotic disease, especially involving the carotid arteries, might not respond well to longer periods of CA or selective CP, potentially favouring PAR. Another important factor to take into consideration, is the patient's age. Inherently, long term survival is determined by age at presentation. Nevertheless, several studies have identified age (especially > 70 years)[35] to be associated with early morbidity and mortality, advocating a less aggressive approach in patients older than this. In line with these findings, a modestly diminished treatment effect of TAR *vs.* PAR (OR 0.97 per 10 year age increase) when patient age increased was found (Fig. 4A).

In ATAAD patients with a DeBakey type II dissection, the risk of future distal complications is much lower than in those with DeBakey type I dissection.[36] As the false lumen is obliterated completely during PAR in patients with DeBakey type II dissections, such an approach might be advocated in these anatomical dissection types, when seen in the absence of distal aortic pathology (i.e., absence of arch or descending aortic aneurysms). Finally, TAR is a highly specialised operation involving a significant and steep learning curve, for which mortality is reported to be increased in less experienced hands.[37] Therefore, in such cases, PAR, with reduced operative complexity, could still be the preferred approach.

When to extend aortic replacement

An important finding of this meta-analysis is an increased treatment effect of TAR in younger patients. Indeed, young patients in particular have an increased risk of late distal aortic events and require late re-operation more often.[38] Hypothetically, the beneficial treatment effect of TAR can either be triggered by a reduction in late aortic events or by the capacity of certain TAR strategies such as FET to facilitate a future endovascular approach to address residual distal aortic pathology. Additionally, several reports have demonstrated younger age to be associated with more favourable peri-operative mortality in the setting of TAR in ATAAD.[13] Also in patients with connective tissue disease, such as Marfan syndrome presenting with ATAAD, the benefit of both a proximal extension (i.e., aortic root replacement),[39] and a distal extension (i.e., TAR), has been demonstrated, which resulted in a reduced re-operation rate and improved long term survival.[39] Furthermore, when the supra-aortic vessels are involved, in conjunction with neurological symptoms at presentation, a more aggressive approach is justified,[26,29] as restoration of brain perfusion is imperative for survival in adequate neurological condition. Additionally, false lumen patency and the presence of arch or descending aortic aneurysms extending beyond Ishimaru zone 3[31] enhance the probability of distal aortic events and influence long term survival.[7]

Although the current data support an all in one TAR strategy during the initial procedure, previous studies have demonstrated planned distal open aortic re-operation (i.e., a deferred TAR strategy within six months of the event) to be a feasible option as well.[40] These procedures carry mortality rates of around 7% when performed electively.[22,40] Alternatively, a hybrid strategy, including a second stage thoracic endovascular aortic repair (TEVAR) procedure, may be valid in selected patients. TEVAR is used increasingly for treatment of descending aortic aneurysms and carries a class IIa indication for treatment of type B dissection in most recent guidelines.[41] With the advent of fenestrated grafts, TEVAR has also been applied to aortic arch pathology, which is also advocated in specific instances by most recent recommendations.[31] However, TEVAR for arch disease is challenging and technically complex, and it requires a stable proximal landing zone in a non-dilated part of the ascending aorta to avoid endoleak. Nevertheless, in this setting, stroke is also prevalent in up to 14% of patients undergoing branched TEVAR, the most important drawback of this procedure.[31]

Although the retrospective nature of the included studies in this meta-analysis might pose a limitation, the data are a relevant and realistic reflection of common clinical practice. By convention, surgery for ATAAD is performed by cardiac surgeons on call, and not exclusively by specialised aortic surgeons, who are trained in the TAR procedure. As TAR seems to have a beneficial effect in a selected group of patients in the long term, these findings also advocate concentration and centralisation of ATAAD procedures in specialised aortic centres, in close collaboration with vascular surgeons. In summary, Figure 5 presents a

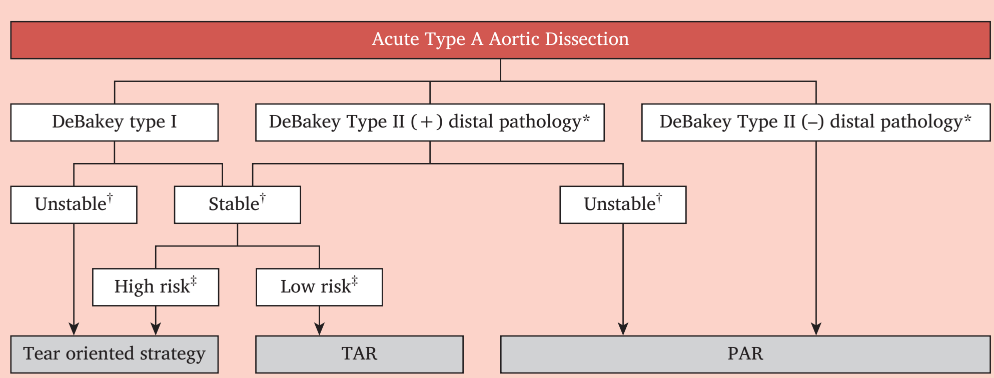

Figure 5. Flowchart presenting a proposal to determine surgical strategy for acute type A aortic dissection patients, based on the current findings and available literature, where *distal aortic pathology is defined as arch or descending aortic aneurysm or known connective tissue disease; †stability is defined as absence of neurological impairment, end organ malperfusion, or tamponade, and ‡increased risk is defined as patients with excessive comorbidities or aged > 70 years. Note that "deferred total arch replacement (TAR)" might be an option for tear oriented or proximal aortic repair (PAR) patients in a later stage, either performed with an open surgical or endovascular approach.

potential surgical strategy plan, partly based on the findings of the current meta-analysis, and partly based on existing literature and incorporated references.

Circulatory arrest and cerebral protection

The pathophysiology and the prevention of peri-operative stroke in patients with ATAAD has been identified as the most important topic of future clinical research by experts in the field.[31] In the current meta-analysis, it was found that TAR is associated with a prolonged duration of CA (Supplementary Fig. S4) *vs.* PAR. Using meta-regression analysis it was found that longer CP and CA times are related to increased rates of stroke and renal failure, which serve as a marker of end organ damage (Fig. 4B, Supplementary Fig. S10), potentially influencing early mortality. As such, early morbidity and mortality rates might be reduced with the optimisation of CA and cerebral protection strategies. Firstly, TAR is increasingly performed using the FET technique (only 40% in the current meta-analysis). These four branched prostheses facilitate early re-initiation of systemic perfusion through one of the branches, after completion of the distal anastomosis.[42] Some authors have even suggested nearly eliminating CA, as they either clamp the stent graft distally after insertion,[43] or occlude the distal stent using a balloon,[44] leading to significantly fewer renal complications.[45] Moreover, another meta-analysis has suggested axillary artery cannulation to be superior to femoral cannulation, in terms of mortality and neurological complications.[46] Then, selective CP during hypothermic CA (HCA) is recommended in all patients undergoing arch surgery by most recent guidelines.[31] Theoretically, a combination of strategies, during which retrograde perfusion is used at the end of HCA to flush out air and embolic debris, could reduce the likelihood of stroke.[47] Also, the importance of patent left subclavian artery (LSA) flow should not be underestimated, as the LSA perfuses the posterior cerebellum and anterior spinal artery.

Limitations

The meta-analysis comprised 19 retrospective studies, potentially susceptible to bias. Considering the low incidence of ATAAD, the acute setting, and the complexity of these procedures, the realisation of a prospective randomised study is extremely challenging, making meta-analysis of retrospective studies the most reliable alternative. Although risk of bias was assessed to be moderate to low, the patients' presenting status, tear location, extent of dissection (DeBakey type I or II), use of FET, and surgeons' expertise might still have led to confounding. Unfortunately, none of the studies performed a competing risks analysis, potentially underestimating the incidence of aortic events and re-operations. As single centre, multicentre, and international registries were included in this meta-analysis, there is a potential of duplicate patient inclusion in the analyses. Also, only 14 studies reported long term outcomes beyond one year. The pooling of long term data from different follow up periods may obscure actual long term results. Therefore, reported actuarial survival rates were chosen to be pooled. A disadvantage of such an approach is that the different points in time (i.e., one, five, and 10 years) do not incorporate all reporting studies. Ten year actuarial survival was only reported by five studies, potentially making these results prone to biased reporting. Therefore, in a retrospective sensitivity analysis, the results of these studies at five years were evaluated, which confirmed the results. Of note, although non-statistically significant, TAR patients analysed at the 10 year follow up tended to be of younger age at presentation, potentially influencing long term survival. Additionally, it was noted that nine of 19 studies were conducted in Asian centres (mainly Japan), potentially leading to a relative over representation of their results, which have been reported to be superior to those of European centres.[48] These results were potentially explained by a more favourable anatomy and reduced arteriosclerotic burden in the Asian population.[31] In a *post hoc* analysis, this finding was confirmed in the meta-analysis, where early mortality in Asian studies was 7.3%compared with 16.5% in non-Asian studies. However, as the current study aimed to evaluate the potential long term benefit of TAR over PAR, it is hypothesised that the relative benefit itself was not affected by the geographical distribution of the included studies and centres. Finally, not all studies reported on the location of the primary entry tear. Proximal and distal arch tears, especially in the aortic arch, influence operative strategy, as primary entry tear resection is imperative.

Conclusion

This meta-analysis has demonstrated that PAR leads to improved early mortality and reduced complication rates in patients undergoing emergency surgery for ATAAD. Despite its increased surgical complexity and associated peri-operative morbidity and mortality, the suggestion of a 10 year survival benefit of TAR was found, which should be interpreted in the light of potential confounders, such as age at presentation, comorbidities, and haemodynamic stability. However, in the context of the current findings, a tear oriented strategy is indicated in older patients with limited dissections, and those presenting in less stable clinical conditions. If patients are younger, present as relatively stable, and there is sufficient surgical expertise, TAR could have a long term benefit. Future research should focus on the realisation of aortic teams specialised in aortic arch surgery and surgical techniques that reduce surgical complexity on the one hand, while facilitating replacement of the entire dissected aorta on the other hand, albeit in a two staged or hybrid fashion.

CONFLICT OF INTEREST STATEMENT AND FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.12.045.

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