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# Impact of reimplantation technique of supra-aortic branches in total arch replacement on stroke rate and survival: results from the ARCH registry†

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## Abstract

**OBJECTIVES:** Our objective was to evaluate the impact of reimplantation techniques of the supra-aortic branches in total arch replacement on the rates of permanent neurological deficit (PND) and survival.

**METHODS:** We identified patients enrolled in the ARCH registry who underwent total arch replacement between 2000 and 2015 with either *en bloc* or separate reimplantation of the supra-aortic branches.

**RESULTS:** A total of 3345 patients were included in the present analysis. From this cohort, 686 patients underwent *en bloc* and 2659 patients had separate reimplantation of the supra-aortic branches. Propensity score analysis identified 461 matched patient pairs. In the matched cohort, there were no differences regarding the mortality rate (15.6% vs 15.7%,  $P = 0.710$ ) or PND (9.2% vs 12.1%,  $P = 0.231$ ). Although separate reimplantation of the supra-aortic branches was not associated with an increased mortality rate on multivariable logistic regression, it increased the risk of PND [odds ratio (OR) 1.56, 95% confidence interval (CI) 1.06–2.29;  $P = 0.023$ ]. Propensity-adjusted regression confirmed these findings and found a similar risk for PND with separate reimplantation of the supra-aortic branches (OR 1.50, 95% CI 1.01–2.23;  $P = 0.047$ ), although this significance was not found with conditional logistic regression ( $P = 0.20$ ). No significant differences between survival were seen between the 2 matched cohorts (stratified log rank  $P = 0.35$ ).

**CONCLUSIONS:** Separate reimplantation of the supra-aortic branches in total arch replacement is a significant predictor of stroke in the overall group, although comparable stroke rates were observed in the matched cohort. The current trend towards separate reimplantation of supra-aortic branches may expose certain subgroups of patients to an increased risk of stroke, e.g. those with a high atherosclerotic burden.

**Keywords:** Aortic arch • Aortic dissection • Aortic arch aneurysm • Aortic arch replacement

## INTRODUCTION

Stroke has emerged as the single most important factor influencing outcome after aortic surgery. Advances in perioperative management over the past decade have lowered the incidence of other complications traditionally associated with large cardiac procedures such as myocardial failure and bleeding [1]. Moreover, the incidence and extent of perioperative stroke in aortic surgery have a large

impact on the patient's quality of life once the aneurysm has been successfully repaired [2]. Results after open surgical replacement of the entire aortic arch are greatly influenced by the underlying disease, whether the patient shows a dilatative form of aneurysmal disease as seen in connective tissue disorders or if the underlying disease is mostly atherosclerotic. In a series focusing on arch surgery in patients with Marfan disease, the rate of permanent neurological deficit (PND) for those undergoing total arch replacement after previous aortic surgery was zero despite the complexity of patients [3]. Whereas intraoperative adjuncts such as hypothermic circulatory

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arrest (HCA) and selective antegrade perfusion have certainly improved outcomes after open arch replacement, a substantial risk for perioperative stroke remains [4]. An isolated aneurysm of the aortic arch is rare, and most arch aneurysms that ultimately lead to surgical intervention are caused by aneurysms or dissections of either the ascending or the descending aorta that at some point extend into the arch. Therefore, arch replacement is usually only part of the treatment of complex, multisegmental aortic disease [5].

Replacement of the entire aortic arch can either be performed by reanastomosing the supra-aortic branches *en bloc* as an 'island' or the branches can be reimplanted separately, either directly or using an interposition graft. In recent years, the trend has been towards replacing the entire aortic arch during an initial procedure using the frozen elephant trunk (FET) technique to facilitate further interventions on the downstream aorta. The fact that some devices are only available with a quadrifurcated graft [6] has again fuelled the discussion about which technique is preferable. Data from patients with connective tissue disorders have shown that the residual aortic tissue left during *en bloc* reimplantation of the supra-aortic branches will dilate over time and may result in the need for reintervention [3]. Nevertheless, selective reimplantation of the supra-aortic branches necessitates more extensive manipulation of these vessels; it has been suggested that the additional manipulation is associated with a higher stroke rate.

Therefore, the purpose of this study was to evaluate the impact of the reimplantation technique of supra-aortic branches in total arch replacement on the rates of stroke and survival.

## METHODS

### Study cohort

Patients who underwent total arch replacement between 2000 and 2015 who were registered in the ARCH Multi-institutional Database [7], with either *en bloc* replacement of the supra-aortic vessels as an island patch or separate reimplantation of these vessels, were included in the analysis. Thirty-seven centres contributed to the database prospectively collected institutional data on patients who underwent aortic arch surgery. The data were cleaned and aggregated; institutional definitions of variables were retained. Follow-up data were collected by each centre separately per local protocols. Record linkage was not available. Neuroprotection strategies included HCA alone, HCA with antegrade cerebral perfusion, HCA with retrograde cerebral perfusion, or HCA with antegrade and retrograde cerebral perfusion, with varying circulatory arrest temperatures. Elective, urgent and emergent cases were included. From this cohort, 686 patients received *en bloc* reimplantation, and 2659 patients received branched replacement.

### Operative methods

Institutional variations existed with regards to operative approach and neuroprotection strategies. Generally, following the establishment of cardiopulmonary bypass, the body is cooled to a targeted hypothermic temperature, after which whole-body circulation is arrested and the aortic arch is replaced. Adjunct antegrade or retrograde cerebral perfusion was used during this period. Descending endoprostheses were deployed as per clinical applicability or institutional preference.

## Clinical end points

Mortality and PNDs were the primary outcomes of interest. Mortality was defined as all-cause mortality that occurred intraoperatively, within the same admission postoperatively, or within 30 days postoperatively. Institution-specific definitions of other outcomes were retained. The circulatory arrest temperature was categorized according to definitions previously established by the International Aortic Arch Surgery Study Group [8].

## Statistical analysis

Results are presented as number (%), mean  $\pm$  standard deviation, or median (interquartile range), depending on the type of data and normality. Percentages were calculated as the proportion of available data. Statistical analyses were conducted with the  $\chi^2$  test for categorical variables and with the Student's *t*-test or Mann-Whitney test for continuous variables. The McNemar and Wilcoxon signed-rank tests were used for paired data.

Missing data were managed through multiple imputations, which replaced missing values based on a predictor matrix of non-outcome variables. Twenty multiple-imputed datasets were created to complete non-outcome variables that had at least 70% data available. Each dataset underwent 200 iterative cycles to generate missing values, with predictive mean matching, logistic regression, or multinomial or ordered logit regression used as appropriate for varying data types. All subsequent analyses of imputed datasets followed the application of Rubin's rules [9].

Propensity score matching was used to balance covariates between the 2 cohorts. A logistic regression model, incorporating age, gender, year and continent of operation, coronary artery disease, peripheral vascular disease, previous cardiac operation, cerebrovascular disease, lung disease, renal dysfunction, Marfan syndrome, urgency of operation, concomitant procedures, use of a descending endoprosthesis, neuroprotection approach, circulatory arrest temperature and arterial cannulation. Patients were then matched one to one using a greedy algorithm and caliper width of 0.2 of the standard deviation of the logit of the propensity score. Balance of covariates was assessed with standardized mean differences. Paired statistical tests were used to analyse outcomes. Matching was performed separately in each imputed dataset, with descriptive results averaged and significance values aggregated according to Rubin's rules. Propensity score-adjusted regression of the complete dataset, using the propensity score as a covariate, was also performed on the complete dataset. Post hoc conditional logistic regression analysis, with patient pairs as clusters, was performed to reconcile differences between matched and regression results. Event-free survival was calculated by Kaplan-Meier methods with the stratified log-rank test used to calculate differences in survival with patient pairs entered as strata. All *P*-values less than 0.05 were deemed to be significant. All statistical analyses were performed using R (version 3.2.5, R Core Team, Vienna, Austria) or SPSS (version 23, SPSS Inc., IBM Corp., Armonk, NY, USA).

## RESULTS

### Preoperative and intraoperative data

Overall, 3345 patients were included in the present analysis. Significant variations in temporal and geographical practice

**Table 1:** Baseline and procedural characteristics of patients undergoing total arch replacement, comparing *en bloc* versus separate replacement of supra-aortic vessels

|                                   | Overall cohort              |  |         | Matched cohort              |   |                  |      |
|-----------------------------------|-----------------------------|--|---------|-----------------------------|---|------------------|------|
|                                   | <i>En bloc</i><br>(n = 686) | Separate<br>reimplantation<br>(n = 2659) | P-value | <i>En bloc</i><br>(n = 461) | Separate<br>reimplantation<br>(n = 461) | SMD (%)          |      |
| <b>Baseline characteristics</b>   |                             |  |         |                             |   |                  |      |
| Year of surgery                   | 2007 (2004–2010)            | 2010 (2008–2012)                         | <0.001  | 61%                         | 2008 (2006–2011)                        | 2008 (2006–2011) | 2.2  |
| Continent                         |                             |  | <0.001  | 214%                        |   |                  | 7.2  |
| North America                     | 100 (14.6)                  | 278 (10.5)                               |         |                             | 82 (17.8)                               | 85 (18.4)        |      |
| Europe                            | 572 (83.4)                  | 496 (18.7)                               |         |                             | 365 (79.2)                              | 357 (77.4)       |      |
| Asia-Pacific                      | 14 (2.0)                    | 1885 (70.9)                              |         |                             | 14 (3.0)                                | 19 (4.1)         |      |
| Age (years)                       | 63 (52–70)                  | 67 (54–75)                               | <0.001  | 24%                         | 63 (52–70)                              | 63 (51–71)       | 3.1  |
| Men                               | 462 (67.3)                  | 1895 (71.3)                              | 0.050   | 8%                          | 313 (67.9)                              | 316 (68.4)       | 2.9  |
| CAD                               | 144 (21)                    | 623 (23.4)                               | 0.10    | 6%                          | 103 (22.3)                              | 106 (22.9)       | 2.4  |
| PVD                               | 134 (19.5)                  | 499 (18.8)                               | 0.61    | 10%                         | 85 (18.4)                               | 86 (18.7)        | 3.2  |
| Previous cardiac operation        | 160 (23.3)                  | 484 (18.2)                               | 0.005   | 14%                         | 131 (28.4)                              | 135 (29.2)       | 3.0  |
| CVA                               | 66 (9.6)                    | 260 (9.8)                                | 0.75    | 1%                          | 46 (10.0)                               | 46 (10.0)        | 2.8  |
| Lung disease                      | 116 (16.9)                  | 403 (15.2)                               | 0.24    | 5%                          | 82 (17.7)                               | 80 (17.4)        | 2.3  |
| Renal dysfunction                 | 86 (12.5)                   | 264 (9.9)                                | 0.083   | 4%                          | 58 (12.6)                               | 58 (12.6)        | 1.9  |
| Marfan syndrome                   | 45 (6.6)                    | 144 (5.4)                                | 0.24    | 5%                          | 35 (7.6)                                | 36 (7.8)         | 2.8  |
| Aneurysm                          | 356 (52.3)                  | 1403 (53)                                | 0.74    | 2%                          | 232 (50.5)                              | 247 (54.8)       | 8.4  |
| Dissection                        | 407 (59.9)                  | 1301 (49.4)                              | <0.001  | 21%                         | 275 (60.2)                              | 250 (55.8)       | 8.8  |
| Urgency                           |                             |  | <0.001  | 17%                         |   |                  | 4.9  |
| Elective                          | 366 (53.4)                  | 1538 (57.8)                              |         |                             | 256 (55.4)                              | 260 (56.3)       |      |
| Urgent                            | 66 (9.6)                    | 143 (5.4)                                |         |                             | 36 (7.8)                                | 37 (8.0)         |      |
| Emergent                          | 254 (37)                    | 978 (36.8)                               |         |                             | 170 (36.8)                              | 165 (35.7)       |      |
| <b>Procedural characteristics</b> |                             |  |         |                             |   |                  |      |
| Coronary artery bypass grafting   | 125 (18.2)                  | 464 (17.5)                               | 0.64    | 2%                          | 77 (16.7)                               | 82 (17.7)        | 3.5  |
| Mitral procedure                  | 20 (2.9)                    | 47 (1.8)                                 | 0.087   | 7%                          | 14 (3.0)                                | 13 (2.8)         | 3.1  |
| Aortic procedure                  | 335 (48.8)                  | 620 (23.3)                               | <0.001  | 55%                         | 198 (42.9)                              | 198 (43.0)       | 1.8  |
| No ET/FET                         | 216 (31.5)                  | 1345 (50.6)                              | <0.001  | 41%                         | 170 (36.8)                              | 174 (37.7)       | 4.3  |
| ET                                | 243 (35.4)                  | 753 (28.3)                               |         |                             | 134 (29.0)                              | 132 (28.6)       |      |
| FET                               | 227 (33.1)                  | 561 (21.1)                               |         |                             | 158 (34.2)                              | 156 (33.8)       |      |
| Arterial cannulation              |                             |  | <0.001  | 44%                         |   |                  | 4.4  |
| Central                           | 259 (37.8)                  | 1498 (56.3)                              |         |                             | 187 (40.6)                              | 187 (40.7)       |      |
| Peripheral-antegrade              | 318 (46.4)                  | 659 (24.8)                               |         |                             | 196 (42.5)                              | 194 (42.2)       |      |
| Peripheral-retrograde             | 87 (12.7)                   | 413 (15.5)                               |         |                             | 61 (13.2)                               | 61 (13.3)        |      |
| Other                             | 22 (3.2)                    | 89 (3.3)                                 |         |                             | 17 (3.7)                                | 18 (3.9)         |      |
| Brain perfusion strategy          |                             |  | <0.001  | 90%                         |   |                  | 14.9 |
| HCA                               | 142 (20.7)                  | 103 (3.9)                                |         |                             | 66 (14.3)                               | 60 (13.0)        |      |
| HCA + ACP                         | 535 (78)                    | 1931 (72.6)                              |         |                             | 389 (84.4)                              | 390 (84.4)       |      |
| HCA + RCP                         | 9 (1.3)                     | 47 (1.8)                                 |         |                             | 6 (1.3)                                 | 8 (1.7)          |      |
| HCA + ACP + RCP                   | 0 (0)                       | 578 (21.7)                               |         |                             | 0 (0.0)                                 | 4 (0.9)          |      |
| Lowest temperature (°C)           | 24 (20–25)                  | 24 (22–25)                               | <0.001  | 23%                         | 24 (20–25)                              | 24 (20–25)       | 1.8  |
| Hypothermia                       |                             |  | <0.001  | 40%                         |   |                  | 7.4  |
| Profound                          | 1 (0.1)                     | 9 (0.3)                                  |         |                             | 1 (0.2)                                 | 1 (0.2)          |      |
| Deep                              | 196 (28.6)                  | 420 (15.8)                               |         |                             | 119 (25.8)                              | 116 (25.2)       |      |
| Moderate                          | 475 (69.2)                  | 2041 (76.8)                              |         |                             | 333 (72.2)                              | 335 (72.7)       |      |
| Mild                              | 15 (2.2)                    | 186 (7)                                  |         |                             | 8 (1.7)                                 | 9 (2.0)          |      |

Data are presented as number (%) or median (interquartile range).

ACP: antegrade cerebral perfusion; CAD: coronary artery disease; CVA: cerebrovascular disease; ET: elephant trunk; FET: frozen elephant trunk; HCA: hypothermic circulatory arrest; PVD: peripheral vascular disease; RCP: retrograde cerebral perfusion; SMD: standardized mean difference.

existed between both cohorts, with the *en bloc* group typically operated on in earlier years and more frequently in Europe. The *en bloc* cohort was also slightly younger and had a greater proportion of aortic dissections. Similar proportions of emergent and elective procedures were seen in both groups, though a statistical difference existed. Differences in perfusion and neuroprotection strategies were also seen between the 2 groups (Table 1, Supplementary Material, Table S1). Durations of cardiopulmonary bypass time and lower body circulatory arrest time were similar in both cohorts, although brain circulatory arrest time was reduced in the separate reimplantation group.

## Overall and propensity matched outcomes

The unadjusted mortality rate was significantly higher for the *en bloc* cohort compared to those who received separate reimplantation (15.5% vs 9.8%,  $P < 0.001$ ), as well as for low cardiac output syndrome and bleeding. There were no significant differences in temporary neurological deficit or spinal cord injuries.

Propensity score analysis, also balanced for year and continent of operation, identified 461 matched patient pairs. Although neuroprotection strategy was included as a balancing covariate, its standardized mean difference was 14.9% despite similar aggregated frequencies. The standardized mean difference for the

**Table 2:** Treatment duration and outcomes of patients undergoing total arch replacement, comparing *en bloc* versus separate reimplantation of supra-aortic vessels

|                                    | Overall cohort              |  |                    | Matched cohort              |   |                    |
|------------------------------------|-----------------------------|--|--------------------|-----------------------------|---|--------------------|
|                                    | <i>En bloc</i><br>(n = 686) | Separate<br>reimplantation<br>(n = 2659) | P-value            | <i>En bloc</i><br>(n = 461) | Separate<br>reimplantation<br>(n = 461) | P-value            |
| Treatment times (mins)             |                             |  |                    |                             |   |                    |
| CPB time                           | 203 (162–252)               | 207 (167–252)                            | 0.58 <sup>a</sup>  | 203 (162–258)               | 224 (186–275)                           | 0.004 <sup>b</sup> |
| Cross-clamp time                   | 126 (96–160)                | 124 (91–163)                             | 0.70 <sup>a</sup>  | 123 (93–161)                | 135 (100–171)                           | 0.014 <sup>b</sup> |
| Lower body circulatory arrest time | 51 (40–70)                  | 53 (38–76)                               | 0.12 <sup>a</sup>  | 52 (40–71)                  | 54 (37–76)                              | 0.57 <sup>b</sup>  |
| Brain circulatory arrest time      | 5 (2–24)                    | 3 (1–8)                                  | 0.001 <sup>a</sup> | 4 (2–18)                    | 4 (2–13)                                | 0.20 <sup>b</sup>  |
| Clinical outcomes, n (%)           |                             |  |                    |                             |   |                    |
| Mortality                          | 106 (15.5)                  | 259 (9.8)                                | <0.001             | 72 (15.6)                   | 72 (15.7)                               | 0.71 <sup>c</sup>  |
| PND                                | 60 (8.8)                    | 187 (7.1)                                | 0.12               | 42 (9.2)                    | 55 (12.1)                               | 0.23 <sup>c</sup>  |
| TND                                | 44 (6.6)                    | 137 (5.8)                                | 0.47               | 30 (6.7)                    | 30 (6.6)                                | 0.76 <sup>c</sup>  |
| SCI                                | 18 (3.4)                    | 57 (2.2)                                 | 0.12               | 14 (3.7)                    | 19 (4.6)                                | 0.56 <sup>c</sup>  |
| LCOS                               | 43 (9)                      | 102 (4.2)                                | <0.001             | 26 (8)                      | 24 (8.1)                                | 0.61 <sup>c</sup>  |
| Bleeding                           | 92 (14.1)                   | 215 (8.1)                                | <0.001             | 63 (14.2)                   | 69 (15.4)                               | 0.61 <sup>c</sup>  |
| ICU LOS (days)                     | 3 (1–9)                     | 3 (2–6)                                  | 0.78               | 3 (2–9)                     | 5 (2–13)                                | 0.18 <sup>c</sup>  |
| Hospital LOS (days)                | 13 (8–21)                   | 20 (11–30)                               | <0.001             | 13 (8–21)                   | 14 (8–27)                               | 0.087 <sup>c</sup> |

LOS was reported for less than 80% of all patients but was included due to clinical relevance. Data are presented as number (%) or median (interquartile range).

<sup>a</sup>Mann-Whitney *U*-test.

<sup>b</sup>Wilcoxon signed-rank test.

<sup>c</sup>McNemar test.

CPB: cardiopulmonary bypass; ICU: intensive care unit; LCOS: low cardiac output syndrome; LOS: length of stay; PND: permanent neurological deficit; SCI: spinal cord injury; TND: temporary neurological deficit.

covariates ranged from 1.8% to 7.4%, demonstrating appropriate balance. No significant differences in clinical outcomes were seen between the 2 matched cohorts, with comparable rates of mortality ( $P = 0.710$ ) and PND ( $P = 0.231$ ) (Table 2).

Separate reimplantation was not associated with death on multivariable logistic regression, but it was associated with an increased risk of PND [odds ratio (OR) 1.56, 95% confidence interval (CI) 1.06–2.29;  $P = 0.023$ ] (Table 3). Propensity-adjusted regression identified a similar risk for PND with separate reimplantation (OR 1.50, 95% CI 1.01–2.23;  $P = 0.047$ ), although subsequent conditional logistic regression, stratified by matched pairs, did not indicate any significance (OR 1.37, 95% CI 0.83–2.24;  $P = 0.20$ ).

### Long-term outcomes

Survival data were available for 85% of patients, with 497 patients either lost to follow-up or missing data for long-term survival. Overall survival rates at 1, 2, 3 and 5 years were 78.5%, 75.6%, 73.5% and 67.0%, respectively (Fig. 1). No significant differences between survival were seen between the 2 matched cohorts (stratified log rank  $P = 0.35$ ).

## DISCUSSION

Although the additional burden of replacing the entire aortic arch as an adjunct to elective or emergent proximal repair is not well defined, more recent data suggest that total arch replacement can be performed with moderate additional risk. In 2009, Uchida *et al.* [10] published one of the few reports comparing hemiarch replacement with an open distal anastomosis to total arch replacement with implantation of a FET. In 120 patients presenting with acute Type A dissection, mortality was only 4% with

**Table 3:** Risk-adjusted outcomes for separate supra-aortic vessel replacement in total arch replacement

|  | Odds ratio<br>(95% CI) | P-value |
|--|------------------------|---------|
| <b>Mortality</b>                                     |                        |         |
| Unadjusted regression                                | 0.60 (0.47–0.76)       | <0.001  |
| Logistic regression <sup>a</sup>                     | 1.08 (0.78–1.50)       | 0.64    |
| Propensity-adjusted logistic regression <sup>b</sup> | 1.01 (0.73–1.40)       | 0.95    |
| Conditional logistic regression <sup>c</sup>         | 1.01 (0.68–1.53)       | 0.68    |
| <b>Permanent neurological deficit</b>                |                        |         |
| Unadjusted regression                                | 0.79 (0.58–1.07)       | 0.12    |
| Logistic regression <sup>a</sup>                     | 1.56 (1.06–2.29)       | 0.023   |
| Propensity-adjusted logistic regression <sup>b</sup> | 1.50 (1.01–2.23)       | 0.047   |
| Conditional logistic regression <sup>c</sup>         | 1.37 (0.84–2.24)       | 0.20    |

<sup>a</sup>Logistic regression against 19 covariates including type of supra-aortic vessel replacement.

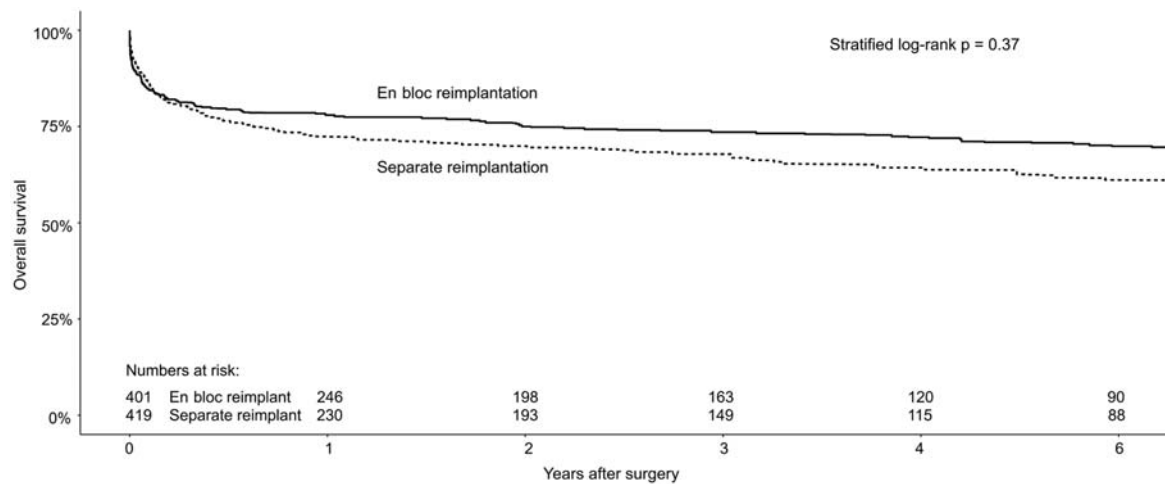
<sup>b</sup>Logistic regression with propensity score as covariate.

<sup>c</sup>Conditional logistic regression fitted on the propensity matched model.

CI: confidence interval.

no new cerebral events and 95% survival at 5 years in the FET and 69% in the hemiarch group.

A Chinese-American collaboration focusing specifically on patients with Type A dissection and an entry tear in the arch analysed 104 patients who underwent the FET technique and total arch replacement and compared them with 728 patients undergoing surgery for Type A dissection with entry tears elsewhere. Operative mortality was 8.6% with a 2.9% paraplegia rate. The stroke rate was surprisingly low at 1.9%. In this series, survival and freedom from late adverse events were 89% and 85% at 8 years, respectively, after a mean follow-up of  $5.6 \pm 2.6$  years. Compared to other series, the time from onset of symptoms to



**Figure 1:** Long-term survival for propensity matched patients undergoing total arch replacement, comparing separate reimplantation of supra-aortic vessels with *en bloc* island patch.

surgery was long at  $4.7 \pm 3.5$  days. Furthermore, computed tomographic results after a mean of  $4.6 \pm 2.9$  years postoperatively were available only for 65 patients but showed complete obliteration of the false lumen in 63 patients. The authors concluded that Type A dissection with entry in the arch can be treated safely by the FET procedure and total arch replacement and provides durable results [11].

Unfortunately, detailed data comparing outcome variables in *en bloc* reimplantation and branched reimplantation of the supra-aortic branches are not available. Techniques to replace the aortic arch vary widely and have changed considerably over time in each institution. These changes are reflected in the data submitted to the ARCH registry and represent the weaknesses and the strengths of this database. Obviously, not every patient has a stroke after arch surgery, and large numbers are needed to find differences in outcomes with different techniques. It is only in a database with many different approaches used that we can tease out differences between 2 distinct technical approaches. One centre would never be able to find differences between these 2 approaches, even if they existed. In a large Japanese series with 423 patients undergoing total arch replacement using a 4-branched graft, PND occurred in 3.3% of patients, whereas the mortality rate was 4.8% [12]. These results are in line with data from other Asian groups, such as a series from the Okita group with 1007 patients, 3.5% PND and 4.5% overall mortality rate (9.6% in emergency and 2.1% in elective patients) [13]. As has been reported previously, Asian groups tend to advocate a more aggressive approach and mostly recommend total arch replacement during initial surgery for Type A dissection. Whether this approach is also due to a more favourable anatomy in the Asian population and a more pronounced atherosclerotic burden in Western countries that increases the risk for stroke during total arch replacement is under discussion. In the current analysis, where the surgery was performed emerged as a risk factor for death, indicating different patient populations. In the current study, when normalized to the mortality rate in patients undergoing surgery in Asian-Pacific centres, the odds-ratio for patients undergoing surgery in European centres was 2.5 times higher (OR 1.0 vs Europe, OR 2.5;  $P < 0.001$ ). Even results from experienced centres varied widely depending on the patient population and the actual extent of aortic arch replacement. In a series from the United States that included 733 patients undergoing arch

surgery, 16% of patients had acute dissection and 20% had total arch replacement. The stroke rate was 2.8% and the mortality rate was 9.7% [14]. In the Houston experience with 489 patients, which compared total arch replacement with limited proximal arch repair, the stroke rate was 8.2% vs 10.5% in the acute setting [15]. In the latter series, the supra-aortic vessels were implanted *en bloc*. In a series from the Coselli group with 119 patients, looking at arch reinterventions only, the permanent stroke rate was 5.9% and the mortality rate was 8.4% [16]. This series exemplifies the difficulties in analysing the specific outcome depending on the mode of reimplantation of the supra-aortic branches; the authors described their technique in detail, but a multitude of different approaches were used depending on the underlying disease and the surgeon's preference. Nevertheless, the overall results are comparable with other series from the United States such as the Mayo Clinic experience with 168 patients undergoing total arch replacement after previous cardiac surgery, a permanent stroke rate of 5.4% and a mortality rate of 8.3% [17]. European groups, such as that from Bologna, Italy, reported permanent stroke rates from total arch replacement for acute dissection of 7.5% with a 22.6% mortality rate [18]. Interestingly, in this series, the rate of strokes was higher in patients in whom only the proximal arch was treated (9.1%). The same group also reported on aortic arch reinterventions in 154 patients with a permanent stroke rate of 4.5% and a mortality rate of 11.7% [19]. Unfortunately, the authors did not elaborate on how the supra-aortic branches were reimplanted. The Hannover group was instrumental in developing an FET prosthesis with a branched graft. In their series with 100 patients using the Thoraflex device (Vascutek, Renfrewshire, Scotland), the overall stroke rate was 9%, whereas it was 14% in patients with acute dissection, 10% in patients with chronic dissection and 3% in patients presenting with aneurysms [20]. The overall mortality rate was 7%. Because severe stroke or intracranial bleeding is a major contributor to in-hospital deaths, it is difficult to compare stroke rates between centres without knowing how many deaths were due to neurological events.

Considering the above-mentioned results, it seems that permanent stroke rates in patients undergoing total arch replacement range from about 3% in elective patients, 5% in redo cases and up to 15% in patients with acute dissection. Whereas 56.9% of patients in the current study underwent elective surgery, the rate of PND is at the upper limit of what could be expected, with

8.8% in patients with *en bloc* reimplantation and 7.1% in patients with separate reimplantation of the supra-aortic branches in the overall cohort and 9.2% and 12.1% in the matched-pairs group. To reconcile differences between the propensity matched and logistic regression analyses with the conflicting findings regarding the influence of separate reimplantation on stroke rates, we performed a subsequent conditional logistic regression analysis within the propensity matched cohort. No significant difference was found with this post hoc analysis. Several factors may explain this discrepancy. First, even though propensity score methods purport to have several statistical advantages over multivariable regression, the former approach produces slightly more conservative measures of association [21]. Second, it is important to note that, due to imbalances in cohort numbers, over 70% of patients could not be matched and therefore were discarded from the analysis, resulting in reduced statistical power. In a systematic review of 43 studies that described associations between exposure and outcome, 10% of analyses had discrepancies of significance between regression techniques and propensity score techniques [21]. At present, there are no standards to determine which of these 2 approaches offers the true results.

The mortality rate is also in the upper range of what has been recently reported in the literature: 15.5% of patients died after *en bloc* reimplantation, 9.8% of patients with separate reimplantation of the supra-aortic branches in the overall cohort and 15.6% and 15.7% in the matched-pairs group. Following matching, we noted an increase in the proportion of redo operations, the use of FET procedures and other factors that increased the risk profile of patients in the matched cohort, therefore increasing the mortality rate.

The differences in results before and after propensity-score matching show the extent to which the rates of mortality and stroke depend on patient characteristics. The current report of the ARCH registry is certainly not perfect regarding the heterogeneity of the techniques used, but it is probably the best evidence currently available concerning an important topic in aortic surgery that is notoriously difficult to evaluate.

## Limitations

This study has some key limitations. Firstly, the ARCH Multi-institutional Database is limited by the inherent drawbacks of any retrospective database, including heterogeneities in key clinical definitions, patient selection, presence of missing data and quality of data. Although we have attempted to account for some of these limitations through statistical means, a robust analysis with prospectively collected data, ideally in a randomized design, is required to corroborate these findings. Secondly, several key variables have not been captured within this database, such as key technical steps and brain perfusion parameters, which limit the robustness of the analysis. Finally, many centres often preferentially have a single operative approach, in terms of either neuroprotection or technical approach, with skills refined through years of experience. Such experience adds a significant confounder to interpreting clinical outcomes that is difficult to isolate.

## CONCLUSION

Although the current study is limited by the inherent shortcomings of retrospective registry data analysis, we were able to

perform extensive propensity score matching due to the large number of patients enrolled in the registry. The current data suggest that the choice of reimplantation technique does not affect the 30-day mortality rate or the long-term survival rate. Nevertheless, separate reimplantation of the supra-aortic branches is a significant predictor of stroke in logistic regression analyses based on the entire cohort, although comparable stroke rates were observed in the matched cohort. The current trend towards separate reimplantation of supra-aortic branches may expose certain subgroups of patients to increased risk of stroke, e.g. those with a high atherosclerotic burden.

## SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

**Conflict of interest:** none declared.

## REFERENCES

- [1] Higgins J, Lee MK, Co C, Janusz MT. Long-term outcomes after thoracic aortic surgery: a population-based study. *J Thorac Cardiovasc Surg* 2014; 148:47-52.
- [2] Okada N, Oshima H, Narita Y, Abe T, Araki Y, Mutsuga M *et al.* Impact of surgical stroke on the early and late outcomes after thoracic aortic operations. *Ann Thorac Surg* 2015;99:2017-23.
- [3] Schoenhoff FS, Kadner A, Czerny M, Jungi S, Meszaros K, Schmidli J *et al.* Should aortic arch replacement be performed during initial surgery for aortic root aneurysm in patients with Marfan syndrome? *Eur J Cardiothorac Surg* 2013;44:346-51.
- [4] Thomas M, Li Z, Cook DJ, Greason KL, Sundt TM. Contemporary results of open aortic arch surgery. *J Thorac Cardiovasc Surg* 2012;144:838-44.
- [5] Czerny M, König T, Reineke D, Sodeck GH, Rieger M, Schoenhoff F *et al.* Total surgical aortic arch replacement as a safe strategy to treat complex multisegmental proximal thoracic aortic pathology. *Interact CardioVasc Thorac Surg* 2013;17:532-6.
- [6] Shrestha M, Beckmann E, Krueger H, Fleissner F, Kaufeld T, Koigeldiyev N *et al.* The elephant trunk is freezing: the Hannover experience. *J Thorac Cardiovasc Surg* 2015;149:1286-93.
- [7] Yan TD, Tian DH, LeMaire SA, Misfeld M, Elefteriades JA, Chen EP *et al.* The ARCH Projects: design and rationale (IAASSG). *Eur J Cardiothorac Surg* 2014;45:10-16.
- [8] Yan TD, Bannon PG, Bavaria J, Coselli JS, Elefteriades JA, Griep RB *et al.* Consensus on hypothermia in aortic arch surgery. *Ann Cardiothorac Surg* 2013;2:163-8.
- [9] Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New Jersey, USA: John Wiley & Sons, 1987.
- [10] Uchida N, Shibamura H, Katayama A, Shimada N, Sutoh M, Ishihara H. Operative strategy for acute type A aortic dissection: ascending aortic or hemiarch versus total arch replacement with frozen elephant trunk. *Ann Thorac Surg* 2009;87:773-7.
- [11] Ma WG, Zhang W, Wang LF, Zheng J, Ziganshin BA, Charilaou P *et al.* Type A aortic dissection with arch entry tear: surgical experience in 104 patients over a 12-year period. *J Thorac Cardiovasc Surg* 2016;151: 1581-92.
- [12] Tanaka Y, Mikamo A, Suzuki R, Kurazumi H, Kudo T, Takahashi M *et al.* Mortality and morbidity after total aortic arch replacement. *Ann Thorac Surg* 2014;97:1569-75.
- [13] Okita Y, Okada K, Omura A, Kano H, Minami H, Inoue T *et al.* Total arch replacement using antegrade cerebral perfusion. *J Thorac Cardiovasc Surg* 2013;145:563-71.
- [14] Leshnower BG, Kilgo PD, Chen EP. Total arch replacement using moderate hypothermic circulatory arrest and unilateral selective antegrade cerebral perfusion. *J Thorac Cardiovasc Surg* 2014;147:1488-92.
- [15] Rice RD, Sandhu HK, Leake SS, Afifi RO, Azizzadeh A, Charlton-Ouw KM *et al.* Is total arch replacement associated with worse outcomes during repair of acute type A aortic dissection? *Ann Thorac Surg* 2015;100: 2159-65.

- [16] Preventza O, Garcia A, Cooley DA, Tuluca A, Simpson KH, Bakaeen FG *et al.* Reprint of: Reoperations on the total aortic arch in 119 patients: short- and mid-term outcomes, focusing on composite adverse outcomes and survival analysis. *J Thorac Cardiovasc Surg* 2015;149:S59-64.
- [17] Quintana E, Bajona P, Schaff HV, Dearani JA, Daly RC, Greason KL *et al.* Open aortic arch reconstruction after previous cardiac surgery: outcomes of 168 consecutive operations. *J Thorac Cardiovasc Surg* 2014; 148:2944-50.
- [18] Di Eusano M, Berretta P, Cefarelli M, Jacopo A, Murana G, Castrovinci S *et al.* Total arch replacement versus more conservative management in type A acute aortic dissection. *Ann Thorac Surg* 2015;100:88-94.
- [19] Di Bartolomeo R, Berretta P, Pantaleo A, Murana G, Cefarelli M, Alfonsi J *et al.* Long-term outcomes of open arch repair after a prior aortic operation: our experience in 154 patients. *Ann Thorac Surg* 2017;103: 1406-12.
- [20] Shrestha M, Kaufeld T, Beckmann E, Fleissner F, Umminger J, Abd Alhadi F *et al.* Total aortic arch replacement with a novel 4-branched frozen elephant trunk prosthesis: single-center results of the first 100 patients. *J Thorac Cardiovasc Surg* 2016;152:148-59.
- [21] Shah BR, Laupacis A, Hux JE, Austin PC. Propensity score methods gave similar results to traditional regression modeling in observational studies: a systematic review. *J Clin Epidemiol* 2005;58:550.