The Impact of Degenerative Connective Tissue Disorders on Outcomes Following Endovascular Aortic Intervention in the Global Registry for Endovascular Aortic Treatment

Christopher L Delaney,1 Ross Milner,2 and Jack Loa,3 Adelaide, Australia; Chicago, Illinois; Sydney, Australia, on behalf of the Global Registry for Endovascular Aortic Treatment (GREAT) Investigators

ABSTRACT: OBJECTIVE: Endovascular therapy for the management of aortic pathology in patients with degenerative connective tissue disorder (DCTD) is controversial. Current guidelines are based on a paucity of literature and registry data are lacking. This study reports on medium term outcomes of patients with diagnosed DCTD compared to those without DCTD who were included in the W.L. Gore Global Registry for Endovascular Aortic Treatment (GREAT).

METHODS: Patients included in the GREAT registry who underwent treatment for any thoracic or abdominal aortic pathology were included and grouped according to the presence or absence of a DCTD. Baseline demographic and procedural data were collected as well as data relating to key outcomes within 5 years follow-up, including all-cause mortality, aortic-related mortality, reinterventions and serious adverse events (SAE). Multivariable Cox proportional hazards models were built to determine if any association existed between the presence of DCTD and any key outcomes.

RESULTS: The analysis included 92 (1.9%) with DCTD and 4741 (98.1%) without DCTD. Patients with DCTD were more likely to be female (34.8% vs. 18.5%, P < .0001) and younger (66.8 [15.1] vs. 71.7 [10.3] years, P = .013) than those without DCTD. They were also more likely to have had prior aortic intervention (22.8% vs. 13.9%, P = .015) and an associated branch vessel procedure with the index operation (30.3% vs. 18.6%, P = .005). The majority of reinterventions in both groups occurred within the first 2 years and multivariable models demonstrated that the presence of DCTD was not predictive of all-cause mortality, aortic-related mortality, reinterventions or SAE within 5 years.

CONCLUSIONS: Within the limitations of registry data, this work demonstrates the medium term safety and durability of endovascular stent-grafts across a spectrum of aortic pathology in some patients with DCTD. More work is required to determine the applicability of these findings to specific sub-types of DCTD and aortic pathology.
INTRODUCTION

The management of aortic pathology has evolved greatly over recent years, owing largely to the ongoing advances in endovascular technology. There are however, still areas of controversy, for which consensus has not been reached to guide the most effective management strategies. Patients with degenerative connective tissue disorder (DCTD) and associated aortic involvement are an important example.

The DCTD’s commonly associated with aortic pathology are Marfan Syndrome (MFS), Loeys-Dietz Syndrome (LDS), Ehlers-Danlos Syndrome (EDS) and Familial Thoracic Aortic Aneurysm and Dissection (FTAAD). The fragile nature of aortic tissue in these patients combined with the outward radial force and fixation requirements of aortic stent-grafts have led many to believe that endovascular intervention for these patients is likely to be associated with a significant risk of early to mid-term complications\(^1\,^2\) and is not deemed to be a durable long-term option. Indeed, based on a relative paucity of data, comprising mainly of small series with limited follow-up, current European guidelines suggest that endovascular repair should be considered only for complex redo surgery or as bridging procedures in the event of emergency.\(^3\)

In contrast, acceptable mid to long-term results have been reported for open surgical reconstruction of such pathology\(^4\,^5\) and this is, therefore, currently considered the gold-standard of care. Despite this, the challenges associated with surgical reconstruction are formidable. In patients without a diagnosed DCTD, even in the most experienced of hands, open repair of the thoraco-abdominal aorta is associated with a 7.5% operative mortality and 5.3% and 5.7% with spinal cord pathology and permanent renal failure, respectively.\(^6\) The level of complexity increases in the setting of a connective tissue disorder, with a recent case series of 65 patients reporting a 14% in hospital mortality.\(^7\)

Challenging the acceptability of such a high rate of peri-operative complication is recent data from the Society of Vascular Surgery Vascular Quality Initiative Registry. In the largest series of thoracic endovascular aortic repair in patients with DCTD reported to date, 102 patients demonstrated a peri-operative mortality of 2.9% with 2% experiencing spinal cord complications.\(^8\) Over an average of 15.6 months follow-up, the mortality was 5.3% and of the 26.7% of patients with a diagnosed endoleak, all had resolved with appropriate reintervention. In light of these acceptable outcomes and the expected faster recovery time and reduced hospital length of stay associated with endovascular surgery, it may be that the role of endovascular repair as a first line treatment for patients with DCTD and aortic pathology warrants further consideration.

Before any significant conclusions can be made however, longer term follow-up data in large cohorts of patients is required. The Global Registry for Endovascular Aortic treatment (GREAT) recruited over 5000 patients between 2010 and 2016. Many patients now have 5 year follow up outcomes. The purpose of this study is to report on medium term outcomes of patients with diagnosed DCTD compared to those without DCTD who were included in GREAT following endovascular treatment of aortic pathology.

METHODS

The Global Registry for Endovascular Aortic Treatment (Clinicaltrials.gov identifier: NCT01658787) provides a pragmatic perspective on the use and durability of all commercially available Gore thoracic and abdominal aortic endografts, including the iliac branched excluder (W.L. Gore Associates, Flagstaff, AZ) across the spectrum of acute and chronic aortic pathology. The registry includes both on-label and off-label use of any of these devices. Its broad inclusion criteria and prospective, observational, multi-centre design has facilitated data collection from 114 centres across four continents. Further information on independent data assessment and the technical and methodological aspects of GREAT has been previously published.\(^9\) All participating sites were awarded institutional ethics approval before recruitment began and all patients provided written, informed consent.

Study Design

This study is a retrospective data analysis of data from GREAT which allows for a comparison of outcomes for patients with and without DCTD who underwent initial treatment of any thoracic or abdominal aortic pathology using any W.L. Gore sponsored device. Patients within the registry were excluded if data identifying the presence or not of DCTD were missing. For the purpose of GREAT, a definition of DCTD was not provided and such a diagnosis was at the discretion of the investigators at each site.

Study Outcomes

In addition to baseline demographic data and anatomic and procedural characteristics, data were
provided on all-cause mortality, aortic-related mortality, reinterventions (overall and device related) and serious adverse events (SAE) within 5 year follow-up.

Specifically, a reintervention was defined as any invasive or minimally invasive measure related to the initial aortic procedure at any time following the initial procedure. Device-related reinterventions were any reintervention related to a deficiency of the device(s) implanted into the aorta performed at any time following the initial procedure (these include reinterventions for endoleaks, device migration, device fracture and limb stenosis or occlusion.)

An outcome was defined as meeting the SAE criteria of the International Organisation of Standardisation if it was associated with death, reintervention or deterioration of clinical state requiring hospital readmission or prolongation of existing hospital admission.

Aortic-related mortality was defined as a death that occurred in hospital or within 30 d of the index procedure or subsequent reintervention as well as deaths with associated SAE's related to the aorta (including, but not limited to, aortic rupture, aortic dissection, aortic occlusion and stent-graft complication).

Statistical Analysis

Cox proportional hazards regression analysis was performed to assess the relationship between DCTD and all-cause mortality, aortic-related mortality, any reintervention and any SAE within 5 years. To start, all patients without an event by 5 years were censored at 5 years. Separate univariable Cox proportional hazards models were then built for history of DCTD and a list of potential co-variates.

The potential co-variates tested were: gender, age, body mass index, hypercholesterolaemia, tobacco use, coronary artery disease, branch vessel procedure, aneurysm diameter, neck length, neck angle, access method and site. These were selected based on expert knowledge and utilized in previous studies on risk factors.

To address the proportional hazards assumption, an interaction with time was provided for covariates and was kept in the model if $P < .1$. All significant interactions with time were also provided as options to forward selection.

For descriptive tables, categorical variables were listed as numbers and percentages and assessed using Chi-square or Fisher's exact test. Continuous variables were reported as mean and standard deviation and assessed using Kruskall-Wallis tests. $P$-values < .05 were considered significant.

RESULTS

Baseline Characteristics

There were 4833 patients identified as being suitable for inclusion in this analysis. Of these, 92 (1.9%) were documented as having a history of DCTD, while 4741 (98.1%) had no recorded history of DCTD. Baseline demographics and procedural characteristics are presented in Table I. Those with a history of DCTD had an average age that was about 5 years younger [66.8 (15.1) vs. 71.7 (10.3) years, $P = .013$] and were more likely to be female (34.8% vs. 18.5%, $P < .0001$). They were also more likely to have had previous aortic intervention (22.8% vs. 13.9%, $P = .015$), with the site of prior intervention being the thoracic aorta 77% of the time in DCTD patients and 55% of the time in non-DCTD patients. In addition, those with DCTD were more likely to have had an associated aortic branch vessel procedure with the index operation (30.3% vs. 18.6%, $P = .005$). Of these branch vessel procedures, 26% of DCTD and 25% of non-DCTD procedures were surgically debranched arch vessel procedures to facilitate thoracic aortic repair. Overall, the majority of patients in both groups underwent index intervention for abdominal aortic aneurysms (AAA).

Key Outcomes

A summary of key outcomes within 5 years of follow-up is presented for each group in Table II. There is no significant difference detected between DCTD and non-DCTD patients in any of these outcomes. To demonstrate the chronological occurrences of these outcomes, Table III is descriptive and display the frequencies of these outcomes at relevant peri-procedural and post-procedural time points (1, 6 and 12 months, then 2, 3, 4, 5 and 6 years) for those with and without DCTD respectively.

Mean (SD) follow-up duration was 2.72 (1.60) years for patients with DCTD with 12 of 92 (13%) patients recording follow-up outcomes for 5 years or more. In patients without DCTD, Mean (SD) follow-up was 2.96 (1.73) years with 814 of 4741 (17.2%)
Table I. Baseline demographic and procedural characteristics (* = chi-square test; ** = Fishers exact test; *** = Kruskal wallis test)

|                     | DCDT          | No DCDT        | P-value |
|---------------------|---------------|----------------|---------|
| Age (years)         | 66.8 (15.1)   | 71.7 (10.3)    | .013*** |
| Gender (F)          | 32 (34.8%)    | 875 (18.5%)    | <.0001* |
| BMI                 | 28.4 (6.8)    | 27.5 (5.3)     | .56***  |
| Prior aortic repair | 21 (22.8%)    | 660 (13.9%)    | .015*   |
| Branch vessel procedures done | 27(30.3%) | 808(18.6%) | .005*  |
| Indication for index procedure | | | |
| Thoracic Aneurysm   | 12 (13.0%)    | 381 (8.0%)     | .08*    |
| Abdominal Aneurysm  | 64 (69.6%)    | 363 (76.6%)    | .12*    |
| Thoraco-Abdominal Aneurysm | 3 (3.3%) | 91 (1.9%) | .36*  |
| Dissection          | 8 (8.7%)      | 270 (5.7%)     | .22*    |
| Other               | 5 (5.4%)      | 367 (7.7%)     | .41*    |
| Hospital length of stay (days) | 4.0 (7.43) | 4.1 (6.28) | .04*** |
| Follow-up duration (years) | 2.72 (1.60) | 2.96 (1.73) | .26*** |

Table II. Summary of key outcomes from the time of index procedure to 5 years follow-up for patients with and without DCDT (* = chi-square test; ** = Fishers exact test)

|                     | DCDT Total (Procedure-5 Years) | No history DCDT Total (Procedure-5 Years) | P-value |
|---------------------|-------------------------------|------------------------------------------|---------|
| Number of Subjects With Any Follow-Up | 92                            | 4741                                    |         |
| Subjects With Any Event Below | 30(32.6%)                      | 1438 (30.3%)                            | .64*    |
| Mortality           | 23 (25.0%)                    | 977 (20.6%)                             | .30*    |
| Stroke/TIA          | 5 (5.4%)                      | 150 (3.2%)                              | .22**   |
| Spinal Cord Ischemia| 0 (0.0%)                      | 18 (0.4%)                               | 1.00**  |
| All Reinterventions | 12 (13.04%)                   | 523 (11.03%)                            | .54*    |
| Device Related      | 7 (7.6%)                      | 359 (7.6%)                              | .99*    |

recording follow-up outcomes for 5 years or more. Mortality rate appeared to peak between 12 months and 2 years post-procedure for both DCTD and non-DCTD patients but otherwise occurred at fairly similar frequency across each time period in both groups. Peri-operative mortality was 3 of 92 (3.3%) for the DCTD group and 54 of 4741 (1.1%) for the non-DCTD group (P = .09). There were no cases of spinal cord ischaemia in the DCTD groups and 18 (0.4%) cases reported in the non-DCTD group.

There were 13 (14.1%) reinterventions in the DCTD group, of which 8 of 13 (61.5%) were device related and only 1 of 13 (7.7%) occurred beyond 2 years of follow-up. In the non-DCTD group, 546 (11.5%) reinterventions occurred. Of these, 375 of 546 (68.6%) were device related and only 86 of 546 (15.8%) were reported after 2 years of follow-up.

Given that the majority of patients in each group were treated for AAA, a sub-group analysis of 30-d outcomes was performed. Of the DCTD AAA patients, 4 of 64 (6.25%) compared to 130 of 3631 (3.6%) in the non-DCTD AAA group, had a documented key outcome. This was not statistically significant (P = .20). The sample size of DCTD patients in other groups of aortic pathology meant that statistical analysis was not performed on further sub-groups due to the likelihood of being underpowered.

Cox Proportional Hazards Regression Analysis

Cox proportional hazards regression modelling demonstrated that in multivariable models the presence of DCTD was not predictive of all-cause mortality, aortic-related mortality, all reinterventions and SAE’s within 5 years. The multivariable models for each of these key outcomes are shown in Table IV(A–D). In each case, the
Table III. (a): Key outcomes over time for patients (A with DCTD and (B) with no history of DCTD

| Procedure | 1 Month | 6 Months | 1 Year | 2 Years | Total (Procedure-2 Years) |
|-----------|---------|----------|--------|---------|--------------------------|
| Number of Subjects With Any Follow-Up | 92 | 90 | 85 | 81 | 71 | 92 |
| Subjects With Any Event Below | 3(3.3%) | 8(8.9%) | 3(3.5%) | 6(7.4%) | 11(15.5%) | 26(28.3%) |
| Mortality | 1(1.1%) | 3(3.3%) | 1(1.2%) | 3(3.7%) | 9(12.7%) | 17(18.5%) |
| Stroke/TIA | 0(0%) | 2(2.2%) | 0(0%) | 1(1.2%) | 1(1.4%) | 4(4.3%) |
| Spinal Cord Ischemia | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) |
| All Reinterventions | 2(2.2%) | 4(4.4%) | 2(2.4%) | 2(2.5%) | 2(2.8%) | 12(13.0%) |
| Device Related Reinterventions | 0(0%) | 2(2.2%) | 1(1.2%) | 2(2.5%) | 2(2.8%) | 7(7.6%) |

(b): Procedure | 1 Month | 6 Months | 1 Year | 2 Years | Total (Procedure-6 Years) |
|-----------|---------|----------|--------|---------|--------------------------|
| Number of Subjects With Any Follow-Up | 49 | 30 | 12 | 4 | 49 | 92 |
| Subjects With Any Event Below | 3(6.1%) | 2(6.7%) | 1(8.3%) | 1(25.0%) | 7(14.3%) | 31(33.7%) |
| Mortality | 3(6.1%) | 2(6.7%) | 1(8.3%) | 1(25.0%) | 7(14.3%) | 24(26.1%) |
| Stroke/TIA | 1(2.0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) |
| Spinal Cord Ischemia | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) |
| All Reinterventions | 0(0%) | 1(3.3%) | 0(0%) | 0(0%) | 0(0%) | 12(13.0%) |
| Device Related Reinterventions | 0(0%) | 1(3.3%) | 0(0%) | 0(0%) | 1(2.0%) | 7(7.6%) |

| Procedure | 1 Month | 6 Months | 1 Year | 2 Years | Total (Procedure-2 Years) |
|-----------|---------|----------|--------|---------|--------------------------|
| Number of Subjects With Any Follow-Up | 4741 | 4738 | 4467 | 4146 | 3646 | 4741 |
| Subjects With Any Event Below | 58(1.2%) | 274(5.8%) | 286(6.4%) | 286(6.9%) | 326(8.9%) | 1106(23.3%) |
| Mortality | 2(0.0%) | 91(1.9%) | 163(3.6%) | 194(4.7%) | 225(6.2%) | 675(14.2%) |
| Stroke/TIA | 5(0.1%) | 31(0.7%) | 32(0.7%) | 30(0.7%) | 20(0.5%) | 112(2.4%) |
| Spinal Cord Ischemia | 7(0.1%) | 8(0.2%) | 1(0.0%) | 1(0.0%) | 1(0.0%) | 18(0.4%) |
| All Reinterventions | 47(1.0%) | 178(3.8%) | 109(2.4%) | 82(2.0%) | 90(2.5%) | 460(9.7%) |
| Device Related Reinterventions | 14(0.3%) | 73(1.5%) | 89(2.0%) | 71(1.7%) | 80(2.2%) | 296(6.2%) |

Number of Subjects With Any Follow-Up | 2755 | 1632 | 814 | 342 | 2755 |
| Subjects With Any Event Below | 223(8.1%) | 133(8.1%) | 63(7.7%) | 40(11.7%) | 438(15.9%) | 1470(31.0%) |
| Mortality | 161(5.8%) | 90(5.5%) | 51(6.3%) | 36(10.5%) | 338(12.3%) | 1013(21.4%) |
| Stroke/TIA | 19(0.7%) | 21(1.3%) | 4(0.5%) | 1(0.3%) | 44(1.6%) | 151(3.2%) |
| Spinal Cord Ischemia | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 0(0%) | 18(0.4%) |
| All Reinterventions | 56(2.0%) | 32(2.0%) | 11(1.4%) | 4(1.2%) | 90(3.3%) | 523(11.0%) |
| Device Related Reinterventions | 48(1.7%) | 32(2.0%) | 10(1.2%) | 3(0.9%) | 82(3.0%) | 360(7.6%) |
Table IV. (a): Multivariable models of 5 year outcomes for (A) all-cause mortality; (B) aortic related mortality; (C) reinterventions and (D) serious adverse events. (* = an interaction between two variables)

|                                      | Number of Observations Used | Coefficient | Pr > ChiSq | Hazard Ratio |
|--------------------------------------|-----------------------------|-------------|------------|--------------|
| Degenerative Connective Tissue Disease | 4087(815)                   | 0.09440     | .6853      | 1.099        |
| Gender                               | .                           | 0.20874     | .0146      | 1.232        |
| BMI                                  | .                           | -0.04512    | <.0001     | 0.956        |
| Maximum Diameter of Aortic Aneurysm/Lesion (mm) | .                           | 0.01419     | <.0001     | 1.014        |
| Aortic Branch Vessel Procedure       | .                           | 0.16647     | .0689      | 1.181        |
| Cut-down access method               | .                           | 0.12516     | .0850      | 1.133        |
| Brachial access site                 | .                           | 1.88073     | .0005      | 6.558        |
| Brachial access site*Time            | .                           | -0.26016    | .0061      | 0.771        |
| Other access site                    | .                           | 2.55173     | <.0001     | 12.829       |
| Other access site*Time              | .                           | -0.37852    | .0004      | 0.685        |

(b):

|                                      | Number of Observations Used | Coefficient | Pr > ChiSq | Hazard Ratio |
|--------------------------------------|-----------------------------|-------------|------------|--------------|
| Degenerative Connective Tissue Disease | 4087(84)                   | -4.89090    | .9859      | 0.008        |
| Degenerative Connective Tissue Disease*Time | .                           | -11.69274  | .9766      | 0.000        |
| Gender                               | .                           | 0.44293     | .0684      | 1.557        |
| BMI                                  | .                           | -0.05004    | .0214      | 0.951        |
| Maximum Diameter of Aortic Aneurysm/Lesion (mm) | .                           | 0.01483     | .0210      | 1.015        |
| Aortic Branch Vessel Procedures      | .                           | 0.80155     | .0010      | 2.229        |
| Cut-down access method               | .                           | 0.62015     | .0121      | 1.859        |
| Brachial access site                 | .                           | 1.34168     | <.0001     | 3.825        |
| Other access site                    | .                           | 1.52963     | <.0001     | 4.616        |

(c):

|                                      | Number of Observations Used | Coefficient | Pr > ChiSq | Hazard Ratio |
|--------------------------------------|-----------------------------|-------------|------------|--------------|
| Degenerative Connective Tissue Disease | 4087 (419)                 | 0.03977     | .9016      | 1.041        |
| Degenerative Connective Tissue Disease*Time | .                           | -0.56178    | .0001      | 0.570        |
| Gender                               | .                           | 0.28947     | .0123      | 1.336        |
| Maximum Diameter of Aortic Aneurysm/Lesion (mm) | .                           | 0.01175     | <.0001     | 1.012        |
| Aortic Branch Vessel Procedure       | .                           | 1.14100     | <.0001     | 3.130        |
| Aortic Branch Vessel Procedure*Time  | .                           | -0.14132    | .0009      | 0.868        |
| Percutaneous access method           | .                           | -0.25550    | .0102      | 0.775        |
| Brachial access site                 | .                           | 0.68897     | .0009      | 1.992        |
| Other access site                    | .                           | 0.73418     | .0036      | 2.084        |

(continued on next page)
univariable models for all potential covariates can be found in Supplementary Tables I–IV. The univariable model for aortic-related mortality (Supplementary Table II) did find a history of DCTD predictive, however, this association did not hold once controlling for risk factors in the multivariable model.

Although a history of DCTD was not predictive of any of the key outcomes, in each case, there were some covariates that were found to be predictive. Table IV demonstrates that female sex, BMI, maximum aortic diameter and an access site other than the femoral artery were predictive of all-cause mortality. Similarly, aorta-related mortality could be predicted by the same covariates with the exception of gender and the addition of concurrent aortic branch vessel procedures and the requirement for open access (See Table IV(B)). The need for reintervention and SAE’s were predicted by female sex, maximum aortic diameter, concurrent aortic branch vessel procedures and alternative access sites (see Table IV(C and D)).

**DISCUSSION**

This medium term registry data from nearly 5000 patients has allowed comparison of major outcomes between those with and without a diagnosis of DCTD. The results demonstrate that endovascular repair across the spectrum of thoracic and abdominal aortic pathology in DCTD patients is safe and durable with outcomes that are equivalent to those in non-DCTD patients.

Historically, there has been limited literature to support the use of endovascular technology in patients with DCTD. This is probably due to the relative infrequency of patients presenting with such pathology and the reluctance of surgeons to challenge the dogma that a stent-graft in the perceived fragile aorta of a patient with DCTD is best avoided.\(^\text{10}\)

More recently, the evolution of stent-graft technology and improvements in endovascular procedural skills, coupled with the challenges associated with training in complex aortic reconstructive procedures,\(^\text{11}\) has resulted in the publication of more data exploring the role of endovascular surgery for the treatment of aortic pathology in DCTD patients.\(^\text{12-15}\)

The majority of these have focused on thoracic endovascular repair (TEVAR) of acute or chronic Type B Aortic Dissection (TBAD) in patients with MFS. Systematic reviews of this data have

| (d): | Number of Observations Used | Coefficient | Pr > ChiSq | Hazard Ratio |
|---|---|---|---|---|
| Degenerative Connective Tissue Disease | 4109 (2093) | 0.07569 | .5985 | 1.079 |
| Degenerative Connective Tissue Disease*Time | . | -0.24541 | .0021 | 0.782 |
| Gender | . | 0.28006 | <.0001 | 1.323 |
| Hypertension | . | 0.00835 | .0128 | 1.008 |
| Maximum Diameter of Aortic Aneurysm/Lesion (mm) | . | 0.01193 | <.0001 | 1.012 |
| Maximum Diameter of Aortic Aneurysm/Lesion*Time | . | -0.00120 | .0332 | 0.999 |
| Aortic Branch Vessel Procedures | . | 0.60896 | <.0001 | 1.839 |
| Aortic Branch Vessel Procedures*Time | . | -0.08398 | <.0001 | 0.919 |
| Endovascular conduit access method | . | 0.37006 | .0793 | 1.448 |
| Other access site | . | 0.92435 | <.0001 | 2.520 |
| Other access site*Time | . | -0.11067 | .0374 | 0.895 |
demonstrated high technical success and perioperative safety profile associated with such treatment but have raised concerns about the high reintervention rate required to treat endoleak in the medium to long-term. This likely reflects the fact that independent of the presence of a DCTD, repair of TBAD is more complex than that of other aortic pathology and has a greater risk profile. Such a concept is supported by the current data, which, although not specific to thoracic aortic pathology in patients with MFS, suggests that the presence of DCTD is not an independent predictor of a higher reintervention rate in the medium term.

The current work also demonstrates that the majority of reinterventions required are within 2 years of the index procedure. This was the same for both DCTD and non-DCTD patients and as was shown in the Vascular Quality Initiative Registry data, is likely an indication that endoleaks requiring reintervention tend to occur early and resolve following appropriate further treatment.

These findings challenge the concept that endovascular intervention for aortic pathology in DCTD patients is not a durable option in the medium term. In fact, when compared to open surgery, the current gold-standard for such complex aortic pathology, it seems that both the peri-operative mortality rate and early to medium-term reintervention rates are comparable, if not better, with endovascular intervention. The peri-operative mortality of DCTD patients in this registry was 3.3% with a 5 year mortality of 25%. Perioperative reintervention rate was 5.4% and 5 year reintervention rate was 13%. In a series of 658 non-DCTD patients who underwent open AAA repair from American College of Surgeons data, the peri-operative reintervention rate was 7.1%. Furthermore, in 68 non-DCTD patients aged <65 years, the peri-operative mortality rate was 5.9%, while 47% of patients had died and 13% of patients required a reintervention in a median follow-up period of 6.4 years. In the more complex group with thoracic aortic involvement, the outcomes for open surgery in non-DCTD patients range from 3.4% to 12.3% in published series reporting in-hospital mortality. A peri-operative reintervention rate for bleeding was reported as 5.8% in one large series of >800 patients undergoing open thoracoabdominal aortic surgery.

Specific to those with DTCD who underwent open thoracic or thoraco-abdominal aortic intervention, a single centre reported outcomes on 65 patients, including a 14% in-hospital mortality and 31% peri-operative reintervention rate. Over a median 3.5 year follow-up, overall mortality was 25% and a further 11% required reintervention. Given the fragile abnormal tissue handling characteristics associated with DCTD, it is not surprising that these outcomes in DCTD patients undergoing open aortic surgery are not as good when compared to those in non-DCTD patients. Despite this, from an endovascular perspective, the GREAT registry data demonstrates a significantly higher number of branch vessel procedures were performed concurrent with the index aortic procedure in patients with DCTD. This is likely reflective of more complex endovascular procedures in this patient cohort with more overlap and seal zones able to give rise to a higher reintervention rate. The fact that this was not the case in the current registry, in combination with mortality and reintervention outcomes that are at least comparable with those of open surgery for non-DCTD patients, further enhances the safety profile of such endovascular intervention.

Another concept that warrants discussion is the notion that to achieve a durable outcome using endovascular technology in DCTD patients, the stent graft should have a seal zone in non-aortic tissue. This is in order to alleviate the risk of vessel degeneration due to the outward radial force of the stent graft and subsequent stent graft failure. The systematic review from Pacini et al. noted that no endoleaks were identified in patients with MFS and TBAD when the stent graft was deployed with seal zones overlapping previous surgical grafts. Although such a hybrid approach may be preferable, in the clinical setting it is not always possible and may not be necessary. Data from the current study show a significantly higher proportion of patients within the DCTD group have undergone prior aortic intervention (open or endovascular) than within the non-DCTD group. Although the procedural details specific to seal zones within native aortic tissue or prosthetic were not available from this registry database, it is possible that results could be skewed if the DCTD group had a greater proportion of cases in which a stent graft was sealed in a prior surgical graft. There were, however, still 77% of DCTD patients who had not previously undergone an aortic intervention, in whom, seal zones must have been native aorta. Given that the presence of DCTD was not an independent predictor of reintervention, it may be that sealing in non-aortic tissue could be considered desirable rather than essential. While this cannot yet be recommended, it should be the focus of longer term data analysis across the spectrum of DCTD disorders.

Of course, in drawing conclusions from this registry data, it must be acknowledged that a
possible selection bias exists given that many patients with DCTD at the institutions involved with the GREAT registry were likely to have been treated with open surgery based on historic standards of care. It is possible therefore, that many of the DCTD patients included in this registry of endovascular aortic intervention were chosen due to ease of repair or other confounding variables. It must also be considered that within the constraints of the GREAT registry, the definition of DCTD was left to the discretion of individual sites and investigators. It is assumed that the DCTD group is comprised of patients with a diagnosis of either MFS, LDS, EDS or FTAAD, however, some patients may only have a presumed diagnosis which has not been confirmed and others may not fit diagnostic criteria. There are also many sub-types of EDS and while only those with Vascular type EDS should have been included, it is not possible to confirm this.

Based on the average age of patients in the DCTD group at the time of index surgery (66.8 years), it is likely that the majority of patients in this cohort have MFS or FTAAD. Alternatively, younger patients may have been treated with open surgery and this registry may represent a bias towards older patients with DCTD. Vascular EDS and LDS have a median survival of 48 and 37 years respectively and are far less common than MFS and FTAAD in which patients typically present later and live well into their 7th and 8th decade.21 This is consistent with the fact that data regarding outcomes of aortic treatment for patients with EDS and LDS are scarce and this registry data may not be truly representative of this sub-group of DCTD patients. Given the extreme fragility of vascular tissue that has been reported in the management of vascular type EDS and LDS patients, it is possible that endovascular technology does not behave the same way in these patients as it does in other DCTD patients and the recommendations arising from this work may not hold true for this small proportion of DCTD patients.

The same consideration applies to the type of aortic pathology. This work presents data across the spectrum of aortic pathology, including thoracic and abdominal and thoraco-abdominal aortic aneurysms, type A and B aortic dissection and others such as aortic coarctation and penetrating aortic ulcer. Nearly 70% of patients in the DCTD group underwent repair of their AAA. Sub-group analysis of this cohort of patients compared to those in the non-DCTD group who underwent AAA repair did not reveal any difference in 30 day event rate. Further sub-group analysis of other pathologies was not performed due to the small sample size of DCTD patients meaning that the analyses would likely be underpowered to detect a statistical difference.

Such pragmatic and real-world data is one of the strengths of the GREAT registry, however, in this case, it does limit the conclusions that can be made regarding the use of endovascular technology in DCTD patients with specific aortic pathologies.

It must also be mentioned that data from this registry represents outcomes from endovascular technology arising from a single manufacturer only. While it is likely that the findings from this work will hold true for devices from other manufacturers, such a statement cannot be made with any certainty. Furthermore, while the GREAT registry has been subject to rigorous validation and verification of data integrity, there is no formal core-lab accreditation of the registry data. Also, as with all registries, data collection and analysis is limited by losses to follow-up and presentations to non-tertiary regional hospitals with unrecognized complications with a subsequent risk of data inaccuracy and under-reporting outcomes.

In summary, these findings from the GREAT registry data challenge current guidelines suggesting that the use of endovascular technology in patients with DCTD and aortic pathology should be reserved for use only in an emergency situation or in the event that complex redo surgery is required. This work demonstrates the medium term safety and durability of endovascular stent-grafts across a spectrum of aortic pathology in patients with DCTD. It is not yet reasonable to suggest that such technology should replace open surgery as the gold-standard for aortic treatment in DCTD patients and it may be that in select groups, such as those with vascular-type EDS, this is never the case. Patients with DCTD should therefore be evaluated on a case by case basis based on their underlying pathology, family history and age of presentation and a decision on choice of intervention made accordingly. Careful, long-term follow-up is required to confirm the suitability of such treatment in specific sub-types of both DCTD and aortic pathology.

**AUTHOR CONTRIBUTIONS**

The authors certify that all authors have made a direct and substantial contribution to the research

**DECLARATION OF COMPETING INTEREST**

RM is a paid consultant for WL Gore
SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.avsg.2021.07.013.

REFERENCES

1. Gagne-Loranger M, Voisine P, Dagenais F. Should endovascular therapy be considered for patients with connective tissue disorder? Can J Cardiol 2016;32(1):1–3.
2. Van de Luijigaaarden KM, Goncalves FB, Hoeks SE. Familial abdominal aortic aneurysm is associated with more complications after endovascular aneurysm repair. J Vasc Surg 2014;59:275–82.
3. Riambau V, Bockler D, Brunkwall J, et al. Management of descending thoracic aorta diseases: Clinical practice guidelines of the European Society for Vascular Surgery. Eur J Vasc Endovasc Surg 2017;53(1):4–52.
4. Dardik A, Krosnick T, Perler BA. Durability of thoracoabdominal aortic aneurysm repair in patients with connective tissue disorders. J Vasc Surg 2002;36(4):696–703.
5. Niinami H, Aomi S, Tagusari O. Extensive aortic reconstruction for aortic aneurysms in Marfan syndrome. Ann Thorac Surg 1999;67:1864–7.
6. Coselli JS, LeMaire SA, Preventza O, et al. Outcomes of 3309 thoracoabdominal aortic aneurysm repairs. J Thorac Cardiovasc Surg 2016;151:1323–38.
7. Keschenau PR, Kotelis D, Bisschop J, et al. Open thoracic and thoraco-abdominal aortic repair in patients with connective tissue disease. Eur J Vasc Endovasc Surg 2017;54:588–96.
8. Qato K, Conway AM, Nguyen NT. Outcomes of thoracic endovascular repair in patients with connective tissue disorders. J Vasc Surg 2019;69(6):e84–5.
9. Loa J, Dubencic S, Cao P, et al. The gore global registry for endovascular aortic treatment: objectives and design. Ann Vasc Surg 2016;31:70–6.
10. Harky A, Iqbal R, Giordano V. Aortic endovascular stenting in patients with systemic connective tissue disorders: does the prohibitive dogma still stand tall? [published online ahead of print, 2019 Jul 29]. J Int Med Res 2019;30060519863963. doi:10.1177/0300060519863963.
11. Smith ME, Andraska EA, Sutzko DC. The decline of open abdominal aortic aneurysm surgery among individual training programs and vascular surgery trainees. J Vasc Surg 2020;71(4):1371–7.
12. Waterman AL, Feezor RJ, Lee WA, et al. Endovascular treatment of acute and chronic aortic pathology in patients with Marfan syndrome. J Vasc Surg 2012;55:1234–41.
13. Nordon IM, Hinchliffe RJ, Holt PJ. Endovascular management of chronic aortic dissection in patients with Marfan syndrome. J Vasc Surg 2009;50:987–91.
14. Geibusch P, Kotelis D, von Tengg-Kobligk H. Thoracic aortic endografting in patients with connective tissue diseases. J Endovasc Ther 2008;15:144–9.
15. Bockler D, Meisenbacher K, Peters AS. Endovascular treatment of genetically linked aortic diseases. Gefasschirurgie 2017;22(suppl 1):S1–7.
16. Pacini D, Parolari A, Berretta P. Endovascular treatment for type B dissection in Marfan syndrome: is it worthwhile? Ann Thorac Surg 2013;95:737–49.
17. Altab M, Songdechakraiwut T, Green SY, et al. Contemporary outcomes in open thoracoabdominal aortic aneurysm repair in octogenarians. J Thorac Cardiovasc Surg 2015;149(2 suppl):S134–41.
18. Deery SE, O’Donnell TF, Bodewes TC, et al. Early reintervention following open and endovascular aortic aneurysm repair is associated with high mortality. J Vasc Surg 2018;67(2):433–40.
19. Altab N, Abisi S, Yong Y. Mid-term results of endovascular aortic aneurysm repair in the young. Eur J Vasc Endovasc Surg 2013;46(3):315–19.
20. LeMaire SA, Price MD, Green SY. Results of open thoracoabdominal aortic aneurysm repair. Ann Cardiothorac Surg 2012;1(3):286–92.
21. Cury M, Zeidan F, Lobato AC. Aortic disease in the young: Genetic aneurysm syndromes, connective tissue disorders and familial aortic aneurysms and dissections. Int J Vasc Med 2013;2013:267215. doi:10.1155/2013/267215.