Mutations in TGFBR2, encoding the transforming growth factor (TGF)-β type II receptor, were first described in 2004 in patients with thoracic aortic root aneurysms and skeletal features of the Marfan syndrome (MFS).\(^1\) Subsequently, mutations in both TGFBR2 and TGFBR1 (TGF-β type I receptor) were described to be associated with early onset and aggressive thoracic aortic disease with MFS-like skeletal features, but also hypertelorism, craniosynostosis, developmental delay, cleft palate and bifid uvula, congenital heart disease and aneurysms, and dissections throughout the arterial tree with marked arterial tortuosity; this condition was termed Loeys-Dietz syndrome (LDS).\(^2\) Since then, phenotypes associated with TGFBR1 and TGFBR2 mutations have been shown to encompass milder forms of LDS, as well as autosomal dominant forms of thoracic aortic aneurysm and aortic dissection associated with no syndromic features and decreased penetrance.\(^3-5\)

Clinical Perspective on p 558

Similar to the wide range of phenotypes associated with TGFBR1 and TGFBR2 mutations, the natural history of the thoracic aortic disease has been reported to have a wide spectrum, from cases of aggressive aortic disease with onset at an early age and a risk of dissection, despite no or little enlargement of the aortic root,\(^6\) to cases with a better prognosis close
to that of classical MFS because of FBN1 mutations. The current recommendations for management of patients with TGFBR1 and TGFBR2 mutations are based on limited data, which are possibly skewed toward the early onset, severe end of the spectrum.7,8

Although clinical data from patients with either TGFBR1 or TGFBR2 mutations are typically aggregated in reporting presentation and natural history, data from one center found significant differences in aortic disease presentation in TGFBR1 versus TGFBR2 mutant patients.9

Importantly, ascending aortic dissections with minimal enlargement of the aortic root were identified with TGFBR2 mutations, whereas dissections in patients with TGFBR1 mutations were only reported in association with significant enlargement of the aorta, suggesting that recommendations for aortic management should be based also on the specific mutation.

The MAC (Montalcino Aortic Consortium; http://www.montalcinoaorticconsortium.org/), an international scientific group associating numerous centers with expertise in heritable thoracic aortic disease, was formed in 2013 to setup a multicenter retrospective registry of patients with genetically triggered thoracic aortic disease with a mission to define the optimal gene-based clinical management for these patients. MAC includes pediatricians, cardiologists, geneticists, and cardiovascular surgeons. Here we report data on 441 patients with TGFBR1 or TGFBR2 mutations followed up in participating centers.

Materials and Methods

Population

All patients with TGFBR1 or TGFBR2 mutations from the participating centers were included in the registry. Data forms with key demographic, genotypic, phenotypic, and outcome variables based on current knowledge were defined to record relevant data in a standardized manner. The form was shared digitally with all centers in the MAC consortium. For each patient, investigators filled in the data fields and returned the form to the coordinating center. When uncertainties were noted, clarification was requested from the site investigator.

Clinical data for all individuals were obtained with informed consent of the patients’ parents/legal guardians (for children) or the patients themselves in accordance with the Declaration of Helsinki and national legal regulations.

The majority of the centers participating in the registry provide care for both children and adults; one center is a provider of healthcare for children only and one is for adults only. One center is a surgery referral center, whereas the others are either genetic referral centers or referral centers that provide multidisciplinary care of heritable thoracic aortic disease. Familial screening is actively pursued by all centers.

The data collection period was from December 2014 to August 2015.

Mutation Analysis

TGFBR1 and TGFBR2 mutations were identified in clinical diagnostic laboratories or research laboratories with verification by a clinical laboratory. Blood samples were obtained after informed consent was provided by patients or parents, in agreement with local bioethics regulations. Mutation pathogenicity was evaluated with UMD-Predictor and Human Splicing Finder and confirmed in many cases by segregation with thoracic aortic disease in the family.

FBN1 mutation screening was performed either before or at the time of TGFBR1/2 sequencing (aortopathy panel), in almost all patients. In <10 patients, FBN1 screening was not performed after TGFBR1/2 sequencing had revealed a pathogenic mutation.

Statistical Analysis

Statistical analyses were performed in an exploratory manner. Descriptive analyses used means and standard deviations and contingency tables as appropriate. Wilcoxon rank-sum tests were used to compare continuous variables between groups and Fisher exact tests for categorical distributions. Survival curves were estimated using the Kaplan–Meier method and compared by means of log-rank tests. Multinomial logistic regression was used to assess the association between the odds of undergoing preventive surgery or aortic dissection and aortic tortuosity and extra-aortic features. Model selection was performed using backward stepwise elimination using the Akaike information criterion. Cox modeling was also used as a way to assess whether conclusions were sensitive to the choice of the model and strengthen the results. In both cases, a Generalized Estimating Equations approach was used to account for the within-family correlation arising from patients belonging to the same family.

P values <0.05 were considered as statistically significant. All calculations were performed using the R software.10

Results

Study Cohort

A total of 441 patients in 228 families from 15 centers from around the world (Europe, United States, Australia, and Japan) were included in this study. General characteristics are reported in Table 1; the population of the surgical center differed from the population of other centers only in the fact that all the patients from the surgical center underwent surgery. Mutations in TGFBR2 were 50% more frequent than those in TGFBR1 (Table I in the Data Supplement). The 2 populations were similar in terms of the probands/nonprobands ratio, sex distribution, and age at last follow-up. Of note, the systemic score required for the diagnosis of MFS (11) was ≥7 in 20% of both populations (Figure I in the Data Supplement). This underlines the phenotypic overlap between MFS because of mutations in the FBN1 gene and clinical phenotype in patients with TGFBR1 or TGFBR2 mutations.

Probands Versus Nonprobands

The feature leading to discovery of the genotype differed between probands and nonprobands, with probands more frequently being diagnosed based on the finding of an aneurysm, dissection, facial appearance, and less frequently presenting with family history as a reason for evaluation. Comparison of the 2 populations is provided in Table II in the Data Supplement; probands show more aortic and extra-aortic features. Similar differences were observed between probands and nonprobands when patients with either TGFBR1 or TGFBR2 mutations were analyzed separately.

TGFBR1 Versus TGFBR2

Patients with either TGFBR1 or TGFBR2 mutations were similar in most phenotypic features (Table 1). This was also true when only probands were considered (data not shown). Congenital heart defects were reported more frequently in cases with a TGFBR2 mutation than with a TGFBR1 mutation (ventricular septal defect: 6 TGFBR2 versus 2 TGFBR1; atrial septal defect: 11 versus 4; bicuspid aortic valve: 11 versus 3; persistent ductus arteriosus: 25 versus 3).
Survival did not differ between patients with a TGFBR1 or a TGFBR2 mutation (Figure 1). Forty-six deaths were recorded (19 TGFBR1 and 27 TGFBR2) and occurred in 33 patients because of an aortic event (Table III in the Data Supplement). Median age of death was 28.4 years for TGFBR1 mutation patients and 34.8 years for TGFBR2 (P=0.2). Survival free of any vascular event (ie, lethal or not) is shown in Figure 2, and it did not differ between populations with either a TGFBR1 or a TGFBR2 mutation.

However, a event-free survival differed significantly between men and women in the cohort of TGFBR1 mutation cases, whereas there was no such differences in men and women in the cohort with TGFBR2 mutation (Figure 3). The proportion of patients with a type A aortic dissection was also greater in males than in females in the cohort with a TGFBR1 mutation (30% versus 12%; P=0.004), as was the proportion of patients with any aortic event (defined as surgery, dissection, or rupture) (52% versus 30%; P=0.005) or just an aortic dissection (33% versus 15%; P=0.01). These differences were not observed in the TGFBR2 mutation cohort. Aortic root diameters obtained <1 year prior to a dissection or at the time of surgical repair of an aneurysm were variable (Figure 4).

To investigate whether prognosis information could be derived from molecular biology data, the survival of subgroups with at least 10 patients sharing the same altered amino acid were compared with survival of patients with a mutation affecting other amino acids of the same protein. This was possible for 2 amino acid substitutions from the protein kinase domain of the TGFBR1 protein and 4 amino acid substitutions from the protein kinase domain of the TGFBR2 protein (Figure II and III in the Data Supplement).

### Relation Between Aortic Disease Severity and Other Phenotypic Features

We evaluated the risk for aortic root surgery or aortic dissection in the TGFBR1 and TGFBR2 cohorts as a function of the presence or absence of aortic tortuosity and extravascular features. In univariate analyses, all features were significantly associated with preventive surgery or dissection, except craniosynostosis (Table 2).
In a first multivariate model (Table 3), we tested the craniofacial features previously reported to impact aortic outcome, specifically hypertelorism, bifid or broad uvula, craniosynostosis, and arched palate. This was possible on 223 patients for whom these 4 characteristics were known. Hypertelorism was the only parameter that was found to be significantly associated with preventive surgery (odds ratio 2.35; \( P=0.04 \)) and tended to be associated with aortic dissection (odds ratio 2.1, \( P=0.07 \)). In a second multivariate model (Table 4), aortic tortuosity and all extra-arterial features were added as potential predictors (ie, hypertelorism, broad or bifid uvula, craniosynostosis, arched palate, aortic tortuosity, tortuosity of the cervical arteries, wide scar, and translucent skin). This analysis was possible on 145 patients. In adjusted analysis, the odds ratio for surgical repair of an aneurysm was >2 for hypertelorism (2.6), aortic tortuosity (3.7), and translucent skin (3.0). Similarly, the odds ratio for dissection was >2 for hypertelorism (2.1), aortic tortuosity (3.9), and wide scars (4.0). Using Akaike stepwise descending selection, the previous criteria and the cervical artery tortuosity were selected; these criteria were then tested again in the 185 patients with complete data for these features (Table IV in the Data Supplement). Akaike stepwise descending selection selected hypertelorism, aortic tortuosity, and wide scars. Fitting the model on the data set with complete data on these 3 features (n=214 patients) confirmed the previous results (Table 5). Analysis using Cox model provided similar results (Table V and VI in the Data Supplement).

The occurrence of an extra-aortic event (vascular repair, dissection, or rupture) tended to be more frequent in the...
patients who had an aortic dissection (15% versus 9%; P=0.09) with no difference between sex. In contrast, the proportion of patients with an elevated systemic score ≥ 7 was identical in patients with or without previous aortic dissection (19% versus 22%; P=0.6).

Presentations With Acute Aortic Dissections
Type A aortic dissection was the first aortic event in 71 patients, 32 in TGFBR1 carriers and 39 in TGFBR2 carriers. Type B dissection was the first aortic event in 19 patients, 3 TGFBR1 carriers (1.7% of the population) and 16 TGFBR2 carriers (6% of the population; P=0.03).

A measure of the aorta before or at the time of the type A aortic dissection was available in 31 patients, 22 of whom had these measurements within 1 year or at the time of dissection (Figure 4B). This diameter was smaller in patients with a TGFBR2 mutation than in those with a TGFBR1 mutation (TGFBR2, 51.8±13.4 mm versus TGFBR1, 68.3±23.0 mm; P=0.06).

The diameter of the aortic root measured within 1 year of the aortic event was ≤45 mm in 7 patients. Interestingly, all these patients were women, and 6 had TGFBR2 mutations, with extra-aortic features. A brief summary of presentation of these cases is provided in the Data Supplement.

Of note, among the 98 patients who had aortic root repair initially (63 TFB2 and 35 TGFBR1), dissection of the ascending aorta was subsequently observed in 10 patients (4 TGFBR1 and 6 TGFBR2).

Pregnancies
One hundred and twenty-two women had 316 pregnancies (Table 6). The diagnosis was not known in 103 of these women (84%); aortic dissection occurred during 5 (1.6%)

Figure 2. Survival free of vascular features. A, Survival free of any vascular feature (including discovery of arterial or aortic aneurysm, surgery, or dissection). B, Survival free of vascular or aortic event (including surgery or dissection).
pregnancies. Three dissections were type A aortic dissections: a TGFBR1 had preventive surgery and was receiving a β-blocker; 1 TGFBR2 mutation had preventive aortic surgery (aortic diameter 48 mm) and dissected above the graft (aortic diameter 31 mm); and the aortic root diameter was 35 mm at the time of type A aortic dissection in the last TGFBR2 woman.

The 2 type B aortic dissections were observed in women with a TGFBR2 mutation during their first pregnancy (aged 34 years) and third pregnancy (aged 30 years), respectively.

Interestingly, the prevalence of extra-aortic features was higher in women when pregnancy was complicated by an aortic dissection: vertebral artery tortuosity (100% [4/4] versus 46% [22/48]), hypertelorism (100% [4/4] versus 23% [16/69]), translucent skin (75% [3/4] versus 56% [58/86]), bifid or broad-based uvula (75% [3/4] versus 22% [17/79]), and arched palate (100% [4/4] versus 44% [34/78]). The systemic score for MFS was 5 in 2 women with aortic dissection during pregnancy and 9 in 1, whereas it was ≥7 in 8/73 women with pregnancies without aortic dissection. No uterine rupture was reported.

**Discussion**

We report here the largest cohort of patients with mutations in either the TGFBR1 or TGFBR2 gene. Although TGFBR1 and TGFBR2 proteins cooperate to initiate signaling after binding to the TGF-β ligand, the clinical features associated with a
mutation in the TGFBR1 gene differ from those associated with
a mutation in TGFBR2 gene. The prevalence of aortic events
(surgery or dissection) was lower in females than in males
with a TGFBR1 mutation, whereas no similar sex effect was
observed in those with a TGFBR2 mutation. In fact, in female
patients harboring a TGFBR2 mutation, type A dissections of
moderately dilated ascending aorta appeared more frequently
than in males, which was not the case with TGFBR1. This sug-
gests that the aortic features may differ between the 2 popu-
lations, with more aggressive aortic disease in patients with
TGFBR2 mutations, especially for women. Such specificity
has previously been suggested in a population by Tran-Fadulu
et al.9 The reason for this observation remains unknown. Addi-
tionally, type B aortic dissections tend to be more frequent as
the presenting feature in patients with a TGFBR2 mutation
compared with those with a TGFBR1 mutation. It is notable
that the nonaortic systemic phenotypic features were similar
between TGFBR1 and TGFBR2 mutation patients, with both
groups also having similar MFS systemic scores and similar
prevalence of features of LDS, such as hypertelorism, broad or
bifid uvula, wide scars, and translucent skin.

The observation of different event-free survivals according
to the affected amino acid within the protein kinase domain
also illustrates the importance of genetic prognostic factors
(Figures II and III in the Data Supplement) and heterogeneity
of these pathologies.

The second striking observation in our cohort is that the
observed survival is much better than was initially reported.6
The improved survival in this population as compared with
this initial report may be because of several factors. First,
an ascertainment bias often exists when new pathologies are identified, with the most severe forms initially being recognized and milder phenotypes only reported later. This was the case with MFS. In addition, the initial report of patients with $TGFBR1$ and $TGFBR2$ gene mutations was limited to patients with marked and severe aortic disease and significant features of MFS and LDS, which is in distinct contrast to the population reported here. The fact that the presence of these features was associated with a higher likelihood of an aortic event, such as aortic dissection, supports the hypothesis that the initial cohort reported was particularly severely affected. This underscores the variability of the phenotype and the spectrum of disease severity that can be associated with a mutation in these genes. Second, the benefits of better diagnosis and care of patients with these mutations may be contributing to their improved survival. Early diagnosis before the advent of a catastrophic event allows for prophylactic aortic surgery and a reduced risk of aortic dissection, a benefit previously emphasized in this population. The results of aortic surgery in this group of patients seem to be similar to those observed in patients with MFS, that is, a decreased risk with or without surgery and underscores the benefit of an early diagnosis.

The data reported here indicates that surgical repair that is limited to the aortic root may be inefficient in individuals with either $TGFBR1$ or $TGFBR2$ gene mutations. Ten percent of the patients who had surgery for an aortic root aneurysm subsequently presented with dissections of the ascending aorta. This observation suggests that aortic replacement should include the entire ascending aorta when possible. Additionally, limiting the risk for dissection after surgical repair of the aortic

Table 2. Patients With Mutation Either in $TGFBR1$ or $TGFBR2$: Prognostic Value of Aortic Tortuosity and Extra-Aortic Features on Aortic Risk (Preventive Surgery or Dissection) Univariate Analysis

| Features on Aortic Risk (Preventive Surgery or Dissection) | No Event, N=258 | Preventive Surgery, N=80 | Dissection, N=103 | $P$ Value |
|------------------------------------------------------------|-----------------|--------------------------|------------------|-----------|
| Hypertelorism                                               | 41/201 (20.4%)  | 28/66 (42.4%)            | 29/70 (41.4%)    | <0.001    |
| Bifid or broad uvula                                        | 54/215 (25.1%)  | 26/69 (37.7%)            | 28/74 (37.8%)    | 0.037     |
| Craniosynostosis                                           | 14/172 (8.1%)   | 10/60 (16.7%)            | 7/78 (9.2%)      | 0.169     |
| Arched palate                                              | 84/217 (38.7%)  | 42/70 (60.0%)            | 31/78 (39.7%)    | 0.006     |
| Aortic tortuosity                                          | 16/137 (11.7%)  | 18/66 (27.3%)            | 23/69 (33.3%)    | <0.001    |
| Head and neck arterial tortuosity                          | 57/125 (45.6%)  | 33/62 (53.2%)            | 35/50 (70.0%)    | 0.013     |
| Wide scars                                                 | 48/220 (21.8%)  | 15/64 (23.4%)            | 33/76 (43.4%)    | 0.001     |
| Translucent skin                                           | 73/226 (32.3%)  | 35/70 (50.0%)            | 33/75 (44.0%)    | 0.014     |

Patients with dissection (type A or B) despite prior preventive surgery were classified as dissection.

Table 3. Patients With Mutation Either in $TGFBR1$ or $TGFBR2$: Prognostic Value of Aortic Tortuosity and Extra-Aortic Features on Aortic Risk (Preventive Surgery or Dissection)

| Features on Aortic Risk (Preventive Surgery or Dissection) | Preventive Surgery; OR (95% CI), $P$ Value | Dissection; OR (95% CI), $P$ Value |
|------------------------------------------------------------|-------------------------------------------|-----------------------------------|
| Hypertelorism                                               | OR=2.11 (0.99–4.53), $P$=0.05             | OR=2.05 (0.90–4.67), $P$=0.09     |
| Broad or bifid uvula                                        | OR=1.12 (0.51–2.50), $P$=0.77            | OR=1.42 (0.67–3.04), $P$=0.36     |
| Craniosynostosis                                           | OR=1.23 (0.42–3.64), $P$=0.70            | OR=1.11 (0.33–3.76), $P$=0.87     |
| Arched palate                                              | OR=1.27 (0.66–2.45), $P$=0.47            | OR=0.90 (0.43–1.87), $P$=0.77     |

Multinomial logistic model: prognostic value of features of the craniofacial index in the population of 223 patients with all the data. CI indicates confidence interval; and OR, odds ratio.

Table 4. Patients With Mutation Either in $TGFBR1$ or $TGFBR2$: Prognostic Value of Aortic Tortuosity and Extra-Aortic Features on Aortic Risk (Preventive Surgery or Dissection)

| Features on Aortic Risk (Preventive Surgery or Dissection) | Preventive Surgery; OR (95% CI), $P$ Value | Dissection; OR (95% CI), $P$ Value |
|------------------------------------------------------------|-------------------------------------------|-----------------------------------|
| Hypertelorism                                               | OR=3.41 (0.75–15.52), $P$=0.11           | OR=3.50 (0.89–13.86), $P$=0.07    |
| Broad or bifid uvula                                        | OR=0.43 (0.12–1.57), $P$=0.20            | OR=1.49 (0.52–4.30), $P$=0.46     |
| Craniosynostosis                                           | OR=0.35 (0.08–1.46), $P$=0.15            | OR=4.04 (1.18–13.86), $P$=0.03    |
| Arched palate                                              | OR=2.64 (0.85–8.19), $P$=0.09            | OR=1.06 (0.31–3.59), $P$=0.92     |

Prognostic value of aortic tortuosity and extra-aortic features in the population of 145 patients with all the data. CI indicates confidence interval; and OR, odds ratio.
root is important, leading to advise (1) avoidance of strenuous exercise and (2) use of β-blockade.16,17

We also found an association between risk for either aortic surgery or dissection and the presence of either aortic tortuosity or extra-aortic features (Table 2). A similar association was previously reported.4,6 When multivariate analysis was performed in our population, hypertelorism, aortic tortuosity, and wide scars were the 3 factors that remained significantly associated with aortic dissection. The interpretation of this last result is not straightforward, and some limitations have to be underlined, such as the limited size of the population in which numerous factors have been investigated and the incomplete evaluation of some of the patients, which may have led to an assessment biased (biased subgroup). Additionally, the population is being medically managed, and hopefully, this management has changed the spontaneous natural history into a better medical history, in which the prognostic factors are less easy to detect. It is striking that the arterial tortuosity and extra-aortic features were present in almost all the women who presented type A aortic dissection with little to minimal aortic root enlargement and in the women who experienced dissections associated with pregnancy. In fact, presence of these features may assist in defining the optimal timing of surgery in this population because it is suggested that syndromic patients, specifically those patients with features of LDS, should be managed more aggressively than patients lacking these syndromic features.

It is notable that a maximal diameter of the aorta <45 mm on measurements <1 year prior to dissection or at the time of an ascending aortic dissection was found only in women with a TGFBR2 mutation. In contrast, no dissection was observed <45 mm in men with either TGFBR1 or TGFBR2 mutations or in women with TGFBR1 mutations.

It is true that optimal diameter for surgery can only be derived from systematic prospective follow-up18 and should also depend on the risk associated with aortic root surgery in this population. There is also a discussion that aortic diameter should be normalized by body surface area, including a proposal by Svensson et al.,19 but the seminal paper from Coady uses non-normalized diameter.20 The recent study in MFS also does not support the use of normalized aortic diameter to decide on the timing of surgery.18 Considering the available data, including the data reported here, a recommendation could be made to consider surgery usually in adults at a diameter of 45 mm (absolute value), which is lower than that recommended for patients with FBN1 gene mutations (MFS patients).14 This threshold could be lowered toward 40 mm for females with TGFBR2 gene mutations and severe phenotypic features associated with aortic dissection in our population, such as aortic tortuosity, hypertelorism, and wide scars and low body surface areas. A less aggressive surgical management strategy could be pursued in the absence of any familial event or rapid increase in aortic diameter, especially in women harboring TGFBR1 mutations. This scheme would take into account the great variability of the vasculopathy associated with mutations in TGFBR1 or TGFBR2 and its relation with the extra-aortic features. However, defining an aortic diameter for surgery from our population with no or incomplete follow-up, often no therapy, and no education at the time of the aortic event (an aortic event was the trigger for diagnosis in more than 50% of the patients) may not be perfectly relevant for an educated patient with a clear diagnosis who is receiving β-blocker therapy. Then, the risk for aortic dissection may be lowered, therefore, delaying optimal timing for aortic surgery, including possibly waiting for a larger diameter. Besides, the prognostic information associated with the affected amino acid within the protein may become also useful to define optimal surgical timing in coming years (Figure II and III in the Data Supplement).

The fourth conclusion that can be derived from our cohort is that pregnancy is associated with an increased risk of aortic dissection compared with the general population. This risk is moderate, however (5 dissections among 316 pregnancies in 122 women), and the underlying genetic disease was not recognized before dissection in 4 of the 5 pregnant women who dissected. In 2 patients, a previous prophylactic valve-sparing aortic surgery did not prevent the occurrence of dissection, which highlights the fact that the entire aorta is abnormal and

### Table 5. Patients With Mutation Either in TGFBR1 or TGFBR2: Prognostic Value of Aortic Tortuosity and Extra-Aortic Features on Aortic Risk (Preventive Surgery or Dissection)

| Feature                                | Preventive Surgery; OR (95% CI), P Value | Dissection; OR (95% CI), P Value |
|----------------------------------------|----------------------------------------|----------------------------------|
| Hypertelorism                          | OR=2.27 (1.08–5.18), P=0.03           | OR=2.21 (0.97–5.04), P=0.06     |
| Aortic tortuosity                      | OR=2.04 (0.78–5.36), P=0.15           | OR=3.80 (1.64–8.79), P<0.01     |
| Wide scars                             | OR=0.73 (0.30–1.81), P=0.50           | OR=2.99 (1.42–6.28), P<0.01     |

Prognostic value of selected features in the population of 214 patients with all the data, after model selection based on the Akaike criterion. CI indicates confidence interval; and OR, odds ratio.

### Table 6. Pregnancies and Dissections in Women Harboring a Mutation in TGFBR1 or TGFBR2

|                | TGFBR1 | TGFBR2 | Total |
|----------------|--------|--------|-------|
| No. of pregnancy | 138    | 178    | 316   |
| 0              | 33     | 60     | 93    |
| 1              | 14     | 10     | 24    |
| 2              | 19     | 28     | 47    |
| 3              | 18     | 19     | 27    |
| 4              | 7      | 7      | 14    |
| 5              | 3      | 3      | 6     |
| 6              | 1      | 2      | 3     |
| 13             | 1      | 0      | 1     |
| Aortic dissection during pregnancy | 1 (0.7%) | 4 (2.2%) | 5 (1.6%) |
| 1st pregnancy  | 1      | 1      | 2     |
| 2nd pregnancy  | 2      | 2      |       |
| 3rd pregnancy  | 1      | 1      |       |
that surgery is not a definitive cure in these diseases. (In fact, early surgery for early aortic dilatation may actually be a risk factor for a distal aortic event, and 10% of our patients with prophylactic aortic root surgery presented with subsequent dissection of the ascending aorta.) The low incidence of complications during pregnancies was reported previously in other smaller series of patients with a TGFBR2 mutation, and this study extends the results to patients with a TGFBR1 mutation. Of note, no uterine rupture was reported in the cohort used in this study.

Finally, our series again underscores the overlap observed between the clinical features observed in patients with classical MFS because of FBN1 mutations, LDS as initially described because of TGFBR1 and TGFBR2 mutations, and an inherited risk for thoracic aortic disease in the absence of syndromic features because of mutations in these same genes. In the cohort reported here, 20% of the population demonstrated multiple phenotypic features found in MFS with an elevated systemic score ≥7.

There are some limitations to this study. The retrospective nature of the data may have introduced a bias, although the centers reported all the patients seen with a TGFBR1 or a TGFBR2 mutation in this registry. The multicenter nature of this report makes it less prone to selection bias, which is also minimized by inclusion of different centers driven by different specialties (pediatricians, geneticists, cardiologists, and cardiovascular surgeons). On the other hand, the centers that participated in this survey are all secondary or tertiary reference centers, so that the more severe forms may be over-represented. It also cannot be excluded the possibility that chance may have played a role in some of the significant associations that we found. This could not be avoided because we performed the statistical analyses in an exploratory manner and, thus, performed a substantial number of statistical tests; however, 2 different models (ie, multinomial and Cox modeling) were used that led to similar results and, thus, strengthen the findings. Our results should nevertheless be taken cautiously, and future confirmation of our findings will be needed before final conclusions can be drawn.

Finally, and most importantly, many of the phenotypic features are subjective, so that the presence of hypertelorism, wide scars, broad uvula, and arterial tortuosity may not reflect identical entities within the different centers and throughout the literature. However, imprecise definition of clinical features is also a limit of all the previous reports on the topic. It is one of the aims of the MAC to propose consensus definitions for all these features. This work is already ongoing through assessing tortuosity by a defined vertebral artery tortuosity index and similar assessments for aortic tortuosity.

In conclusion, the survival of patients with a TGFBR1 or a TGFBR2 gene mutation seems to be better than initially reported. The presence of a TGFBR2 mutation, female sex, aortic tortuosity, hypertelorism, and translucent skin is associated with an increased aortic dissection risk and may help to determine the optimal surgical timing (45 mm in the general population, lowered toward 40 in females with low body surface area, harboring a TGFBR2 mutation and presenting extra-aortic features could be proposed). In future, the prognostic value of specific mutations may also become useful for further individualization of surgical threshold. Finally, pregnancy seems not to have the ominous prognosis that was initially reported.

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Disclosures

None.

Appendix

From the CNMR Syndrome de Marfan et apparentés (G.J., O.M., M.L., M.S., M.A., C.B.) and Département de Génétique (C.B.), AP-HP Hôpital Bichat; INSERM U1148, LVTS (G.J., M.A., C.B.); Université Denis Diderot Paris 7, Paris (G.J., C.B.); Unité de Recherche Clinique HU Paris Île-de-France Ouest, Boulogne, France (J.R.); Division of Medical Genetics, University of Texas at Houston Health Science Centre (E.R., D.M.M.); Department of Medicine, Washington University School of Medicine, St. Louis, MO (A.B.); Servei de Cardiologia, Hospital Universitari Vall d’Hebron, Barcelona, Spain (A.E., G.T.); Department of Cardiology & Center for Medical Genetics, University Hospital Ghent, Belgium (J.D.B., L.M.-M.); Service de Génétique Médicale, Hôpital Pellegrin, Bordeaux, France (S.N., C.Z.); Department of Bioscience & Genetics, National Cerebral and Cardiovascular Center Research Institute, Suita, Osaka, Japan (T.M., H.M.); German Aorta Centre Hamburg at the Centre of Cardiology & Cardiovascular Surgery, University Medical Centre Hamburg-Eppendorf, Germany (Y.V.K.); Service de Génétique, Hôpital Femme-Mère-Enfant, Bron, France (S.D.-G.); Department of Pediatrics-Cardiology, Texas Children’s Hospital/Baylor College of Medicine, Houston (S.A.M.); Marfan and Aortic Disease Clinic, Royal Prince Alfred Hospital, University of Sydney, Australia (R.J.); Service de Génétique Clinique, CHU de Rennes, France (S.O.); Department of Clinical Genetics (L.C.A., M.B.) and Department of Molecular Genetics (L.C.A., K.H.), The Children’s Hospital at Westmead; Discipline of Pediatrics & Child Health, The University of Sydney, Australia (L.C.A., M.B.); Division of Cardiothoracic Surgery, Baylor College of Medicine and Department of Cardiovascular Surgery, Texas Heart Institute, Houston (S.L.); and Perelman School of Medicine, University of Pennsylvania. Smilow Center for Translational Research, Philadelphia (R.P.).
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CLINICAL PERSPECTIVE

The general prognosis of patients with a TGFBR2 or a TGFBR1 mutation has been reported to be poor. This large multicenter, international study demonstrates that the prognosis is actually much better than initially reported (with ≈75% survival at 75 years), similar in men and women with a TGFBR1 mutation and with earlier aortic outcomes in men than in women with a TGFBR2 mutation. However, the phenotype and the disease severity are variable between patients. Some phenotypic factors are associated with more aggressive vascular disease: the presence of a TGFBR2 mutation, female sex, presence of aortic tortuosity, hypertelorism, or translucent skin are associated with an increased risk of aortic dissection. Based on our data, preventive aortic root replacement could be proposed at 45 mm, a threshold that could be lowered toward 40 mm in females with low body surface area harboring a TGFBR2 mutation and presenting with extra-aortic features. Some mutations seem to be associated with earlier surgery for aortic disease.