Long-term follow-up after transatrial–transpulmonary repair of tetralogy of Fallot: influence of timing on outcome

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Abstract

OBJECTIVES: Our goal was to report the long-term serial follow-up after transatrial–transpulmonary repair of tetralogy of Fallot (TOF) and to describe the influence of the timing of the repair on outcome.

METHODS: We included all patients with TOF who had undergone transatrial–transpulmonary repair between 1970 and 2012. Records were reviewed for patient demographics, operative details and events during the follow-up period (death, pulmonary valve replacement,

Key question
Do long-term outcomes differ between patients in whom repair of TOF was performed early (≤6 months) or late (>6 months)?

Key findings
Patients in whom early repair was elected experienced a worse event-free survival and developed events earlier during follow-up.

Take-home message
After long-term follow-up, we observed a worse event-free survival rate in patients with elective early repair of TOF (≤6 months).

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cardiac reinterventions and hospitalization/intervention for arrhythmias). In patients with elective early primary repair of TOF after 1990, a subanalysis of the optimal timing of TOF repair was performed.

**RESULTS:** A total of 453 patients were included (63% male patients; 65% had transannular patch); 261 patients underwent primary elective repair after 1990. The median age at TOF repair was 0.7 years (25th–75th percentile 0.3–1.3) and decreased from 1.7 to 0.4 years from before 1990 to after 2000, respectively ($P < 0.001$). The median follow-up duration after TOF repair was 16.8 years (9.6–24.7). Events develop in 182 (40%) patients. In multivariable analysis, early repair of TOF (<6 months) [hazard ratio (HR) 3.06; $P < 0.001$] and complications after TOF repair (HR 2.18; $P = 0.006$) were found to be predictive for an event. In a subanalysis of the primary repair of TOF after 1990, the patients ($n = 125$) with elective early repair (<6 months) experienced significantly worse event-free survival compared to patients who had elective repair later ($n = 136$). In multivariable analysis, early repair (HR 3.00; $P = 0.001$) and postoperative complications (HR 2.12; $P = 0.010$) were associated with events in electively repaired patients with TOF.

**CONCLUSIONS:** Transatrial–transpulmonary repair of TOF before the age of 6 months may be associated with more events during the long-term follow-up period.

**Keywords:** Tetralogy of Fallot · Long-term outcome · Transannular patch · Timing of tetralogy of Fallot repair

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**ABBREVIATIONS**

- CI: Confidence interval
- HR: Hazard ratio
- PS: Pulmonary stenosis
- PVR: Pulmonary valve replacement
- RV: Right ventricular
- RVOT: RV outflow tract
- RVOTO: RVOT obstruction
- SE: Standard error
- TOF: Tetralogy of Fallot
- TP: Transannular patch

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**INTRODUCTION**

Since the first repair of tetralogy of Fallot (TOF) in 1954, the surgical approach and the timing of the operation have changed. Initially, a right ventricular (RV) incision with a patch across the RV outflow tract (RVOT) was performed. In the current era, the primary transatrial–transpulmonary approach with the intention to minimize the use of a transannular patch (TP) is commonly used [1–3]. The goal of this transatrial–transpulmonary approach is to preserve the integrity of the pulmonary annulus and to avoid a ventriculotomy. This approach potentially reduces myocardial scarring and ventricular dilatation [1, 2]. These changes in surgical techniques together with improvements in cardiopulmonary bypass techniques and perioperative management have been associated with increased survival rates [1, 2].

The age at which TOF is repaired has decreased over time [2–5]. However, there is no consensus regarding the optimal timing of the primary repair of TOF [2, 4, 6, 7]. Early primary repair of TOF is advocated by some because it minimizes the time at risk for cyanotic spells, hypoxia and RV pressure overload [6, 8]. The potential disadvantages of early repair of TOF are a longer stay in the intensive care unit, increased risk of reinterventions and more frequent use of a TP [7, 9–12].

We previously published results of a relatively large TOF cohort operated on by the transatrial–transpulmonary approach [2].

Considering the ongoing discussion on the timing of primary repair of TOF [2, 13], the current updated serial analysis of this identical cohort had 2 objectives: first, to investigate the current freedom from events and second, to investigate the potential influence of the timing of primary TOF repair on long-term outcomes.

**METHODS**

**Patients**

All included patients had undergone transatrial–transpulmonary repair of TOF before June 2012 and were born after 1 January 1970 [2]. We excluded patients with pulmonary atresia, absent pulmonary valve syndrome, double outlet RV and atrioventricular septal defect, with missing surgical reports or in whom a primarily transventricular approach was used. The local ethics committees approved this retrospective study and waived informed consent.

**Events**

The medical records of all patients were reviewed through December 2017. Cardiac events during the follow-up period were recorded until the patient’s latest visit to the outpatient clinic. All patients were followed up according to regular follow-up protocols. The latest information for these follow-up visits was obtained for >85% of patients within 4 years before data acquisition.

For mortality rate analysis, each patient’s status was checked in municipal administrative records. Early complications after TOF repair were defined as complications within 30 days or during the hospital stay [14]. After TOF repair, the following early postoperative complications were recorded: infection, arrhythmia, chylothorax, post-pericardiotomy syndrome, fluid retention, prolonged use of inotropic drugs (>48 h), early reoperation and early death. Long-term events were defined as all-cause mortality, pulmonary valve replacement (PVR), cardiac reoperations, catheter-based reinterventions and arrhythmias that required intervention and/or hospitalization. Patients lost to follow-up were censored at the last known follow-up date.

**Elective repair of tetralogy of Fallot**

A subgroup analysis was performed regarding the optimal timing of primary TOF repair in electively repaired patients. TOF repair before the age of 6 months was considered early; repair when
the patient was older than 6 months was considered late. For this analysis, patients with a palliative shunt, a duct-dependent circulation and a balloon pulmonary valvuloplasty or RV outflow stent prior to TOF repair were excluded. Also, patients who had a non-elective operation, defined as a TOF repair within 72 h of worsening cyanosis or cyanotic spells, were excluded.

Prior to the year 2000, the 2 centres in this study had the same surgical practice regarding the timing of TOF repair, and the age at TOF repair did not differ between the centres. After the year 2000, one of the centres opted for earlier primary TOF repair—around the age of 3 months. This practice resulted in a difference in median age at TOF repair in the cohort after 2000. In the Netherlands, referral to a specific centre is based mainly on where the patient lives.

Statistical analyses

Continuous variables with a normal distribution were summarized as the mean (standard deviation). Variables with a non-normal distribution were presented as the median (25th–75th percentiles). Differences between groups were analysed using the Student’s t-test or the Mann–Whitney U-test. Categorical variables were presented as numbers and percentages and were evaluated by the χ² test.

The incidence of the events over time was evaluated according to the Kaplan–Meier method; differences between groups were evaluated using the log-rank test. The Cox proportional hazard analysis was used to determine whether factors had an influence on the probability of the event. We found no deviations of the proportional hazards assumption by inspecting the plots of log minus log survival functions. Potential factors associated with events—selected from the literature—were explored in univariable Cox regression models. All factors from the univariable analyses were included in the multivariable backwards model in which a P-value of <0.157 was required for the factor to be retained in the model. All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Two-sided P-values <0.05 were considered statistically significant.

RESULTS

We included 453 patients. The median age at TOF repair was 0.7 (0.3–1.3) years [2]. A TP was used in 294 (65%) patients (Table 1). The total analysis comprised 7505 patient-years (5118 TP; 2387 non-TP). The maximum follow-up after TOF repair was 40.6 years, with a median follow-up of 16.2 (9.2–22.8) years.

Mortality rate

The overall mortality rate was 4% (14 TP; 5 non-TP); the early mortality rate was 2%; late deaths occurred in 10 patients. For
the entire cohort, the overall survival rate was 97% at 10 years (standard error (SE) 1%); 96% at 20 years (SE 1%); 95% at 25 years (SE 1%) and 93% at 30 years (SE 2%), with no significant differences in survival between patients who had a TP and those who did not (Fig. 1).

Eleven patients died of cardiac causes; 6 patients, of non-cardiac causes; and in 2 patients, the cause of death was unknown. Since our previous analysis, 3 patients died, 1 of a cardiac cause [2].

Events during the follow-up period

After TOF repair, 270 events developed in 182 (40%) patients; 55 (12%) patients developed 2 or more events. The event-free survival rate was 74% at 10 years (SE 2%), 62% at 20 years (SE 3%) and 34% at 30 years (SE 4%). Non-TP patients experienced a better event-free survival rate ($P<0.001$) (Fig. 1). However, events developed earlier in the non-TP group at a median of 2.9 (0.5–7.6) versus 6.9 (2.1–19.9) years after TOF repair ($P=0.02$) (Table 1).

A total of 88 (19%) patients received a PVR: 29% in the TP group versus 1% in the non-TP group ($P<0.001$). The PVR-free survival rate was 96% at 10 years (SE 1%), 83% at 20 years (SE 2%) and 48% at 30 years (SE 5%) after TOF repair. Since our previous analysis, 36 patients received a first PVR.

Excluding PVR, other late reoperations were performed in 58 (13%) patients, 6 more since the previous analysis. The main indication for late reoperations was residual RVOT obstruction (RVOTO) and trunk or branch pulmonary stenosis (PS) in 47 patients. Other reoperations were for a ventricular septal defect ($n=4$), a ventricular septal defect and RVOTO or PS ($n=5$) and other causes ($n=2$).

A total of 23 percutaneous interventions for valvular PS and 33 for branch PS were performed in 38 (8%) patients. Eighteen (4%) patients needed percutaneous interventions for valvular PS; 18, for branch PS (4%); and 2 patients needed both. In 3 patients a stent was implanted in the RVOT prior to PVR and an aorta-pulmonary collateral was closed in 1 patient.

Late after TOF repair, 5 patients received a pacemaker and 1 patient, an implantable cardioverter-defibrillator due to heart failure. Two patients needed a catheter ablation for ventricular arrhythmias; 2 patients needed a catheter ablation for atrial flutter; and 1 patient needed an ablation for Wolff-Parkinson-White syndrome. One patient was hospitalized due to a self-limiting arrhythmia.

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Early versus late primary repair of tetralogy of Fallot

Figure 2 and Table 2 show the decrease in age at TOF repair. Before 1990, the median age at TOF repair was 19.5 (9.1–48.4) months compared to 6.5 (3.5–11.5) months after 1990 ($P<0.001$). Likewise, patients in the 1990–1999 cohort were significantly older at TOF repair compared to those in the 2000–2012 cohort: 9.9 (5.3–15.7) versus 4.2 (3.0–10.1) months ($P<0.001$). Patients in the youngest cohort at TOF repair (2000–2012) experienced the worst event-free survival rate (Fig. 3). There is a strong, significant correlation between weight and age at TOF repair ($r=0.924$; $P<0.001$).

To explore the potential influence of timing of TOF repair on outcomes, we performed a subanalysis of patients who underwent primary elective TOF repair after 1990 ($n=261$). The patient characteristics and outcomes of the primary elective TOF repair group are shown in Table 3. A TP occurred significantly more often in the early repair group compared to the late repair group: 64.0% versus 51.5% ($P=0.046$).

Prior to TOF repair, no differences in oxygen saturation were observed between the total early repair and late repair groups. The median echocardiographic RVOT velocity, indicating the gradient, was slightly higher in the early repair group compared to the late repair group: 4.6 (4.0–5.0) versus 4.3 (4.0–4.7) m/s ($P=0.047$). A shorter interval between the echocardiogram
before surgery and the TOF repair was observed in the early repair group compared to the late repair group: 33 (17–48) versus 67 (35–110) days (\(P < 0.001\)).

Despite a significantly shorter median follow-up period in the early repair group, significantly more events developed in the early repair group (37% vs 20%; \(P = 0.003\)). A total of 30 patients received a PVR: 8.8% in the early repair group versus 13.9% in the late repair group (\(P = 0.24\)). The overall PVR-free survival rate in the primary elective TOF repair group was 97% at 10 years (SE 1%), 85% at 20 years (SE 3%) and 66% at 25 years (SE 6%). The reported difference in events was mainly driven by late reoperations other than PVR (\(n = 27\)), 22 (17.6%) in the early repair group versus 5 (3.7%) in the late repair group (\(P < 0.001\)). The main reason for late reoperation other than PVR was residual RVOTO and trunk or branch PS in 24 patients. In 1 patient, a residual VSD was closed and the trunk PS was relieved; in 1 patient a VSD was closed and in 1 patient the patent ductus arteriosus was closed. Figure 4 shows that patients in the late repair group had a significantly better event-free survival rate (\(P < 0.001\)).

Predictors for events

In Table 4, the Cox proportional hazard analysis is shown for all patients (\(n = 453\)). In univariable analysis, TP, postoperative complications, early TOF repair and year of TOF repair were found to be predictive for events. Multivariable analysis showed that patients were significantly more likely to experience an event if they had an early TOF repair [hazard ratio (HR) 3.06, 95% confidence interval (CI) 1.67–5.61] or a postoperative complication (HR 2.18, 95% CI 1.25–3.83).

Table 4 shows the Cox proportional hazard analysis for the patients who underwent primary elective TOF repair after 1990 (\(n = 261\)). Multivariable analysis showed that patients were significantly more likely to experience an event if they had an early TOF repair (HR 3.06, 95% CI 1.67–5.61) or postoperative complications (HR 2.18, 95% CI 1.25–3.83).

In the primary elective repair group, female patients experienced a worse event-free survival rate (\(P = 0.010\)). No gender differences were observed in the median age at TOF repair, degree of RVOTO before TOF repair or the use of a TP. There was also no significant difference in weight at TOF repair in male versus female patients. In the overall patient group, no difference in the event-free survival rate between gender was observed.

**DISCUSSION**

This study is one of the largest describing several decades of serial follow-up in transatrial–transpulmonary repair in patients with TOF. Our main findings are that survival is good, but long-term...
Table 3: Patient, surgical and outcome characteristics for primary elective repair of TOF after 1990

<table>
<thead>
<tr>
<th>Patient and surgical characteristics</th>
<th>Early TOF repair (n = 125)</th>
<th>Late TOF repair (n = 136)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOF repair after 2000</td>
<td>94 (75.2)</td>
<td>54 (39.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>76 (60.8)</td>
<td>90 (66.2)</td>
<td>0.37</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.2 (2.6–3.7) (n = 80)</td>
<td>2.9 (2.5–3.5) (n = 67)</td>
<td>0.094</td>
</tr>
<tr>
<td>22q11 deletion</td>
<td>14 (11.2)</td>
<td>8 (6.9)</td>
<td>0.18</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>4 (3.2)</td>
<td>11 (8.1)</td>
<td>0.075</td>
</tr>
<tr>
<td>Age TOF repair (years)</td>
<td>0.29 (0.23–0.39)</td>
<td>0.95 (0.68–1.43)</td>
<td>&lt;0.001</td>
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<td>RVOT gradient before TOF repair (m/s)</td>
<td>4.6 (4.0–5.0) (n = 116)</td>
<td>4.3 (4.0–4.7) (n = 105)</td>
<td>0.047</td>
</tr>
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<td>Time between repair and presurgical echocardiogram (days)</td>
<td>33 (17–46) (n = 16)</td>
<td>67 (35–110) (n = 105)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxygen saturation at TOF repair (%)</td>
<td>95 (85–99) (n = 73)</td>
<td>91 (85–98) (n = 54)</td>
<td>0.80</td>
</tr>
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<td>Age at TOF repair (years)</td>
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<td>0.80</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>66 (47–90) (n = 65)</td>
<td>90 (61–115) (n = 109)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TP</td>
<td>80 (64.0)</td>
<td>70 (51.5)</td>
<td>0.046</td>
</tr>
<tr>
<td>Valvulotomy</td>
<td>33 (26.4)</td>
<td>70 (51.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>3.0 (2.0–4.0) (n = 20)</td>
<td>3.0 (2.0–3.0) (n = 117)</td>
<td>0.85</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>28 (22.4)</td>
<td>19 (14.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Early reoperation</td>
<td>4 (3.2)</td>
<td>2 (1.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>Early death</td>
<td>4 (3.2)</td>
<td>1 (0.7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gradient RVOT after TOF repair (m/s)</td>
<td>2.7 (2.0–3.3) (n = 99)</td>
<td>2.5 (2.2–3.2) (n = 99)</td>
<td>0.71</td>
</tr>
<tr>
<td>Time between TOF repair and post-surgical echocardiogram (days)</td>
<td>7 (6–8) (n = 99)</td>
<td>7 (6.5–9) (n = 99)</td>
<td>0.058</td>
</tr>
<tr>
<td>Outcomes during follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at end of follow-up (years)</td>
<td>12.5 (7.1–17.2)</td>
<td>18.8 (11.8–23.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with events</td>
<td>46 (36.8)</td>
<td>28 (20.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Time after TOF repair (years)</td>
<td>12.1 (6.8–16.8)</td>
<td>18.0 (10.6–22.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deaths</td>
<td>5 (4.0)</td>
<td>1 (0.7)</td>
<td>0.107</td>
</tr>
<tr>
<td>PVR</td>
<td>11 (8.8)</td>
<td>19 (13.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>Time after TOF repair (years)</td>
<td>15.8 (12.2–19.5)</td>
<td>14.6 (12.7–22.0)</td>
<td>0.97</td>
</tr>
<tr>
<td>Other late reoperations</td>
<td>22 (17.6)</td>
<td>5 (3.7)</td>
<td>&lt;0.001</td>
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<td>3.1 (1.2–5.8)</td>
<td>0.98</td>
</tr>
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<td>HC intervention for PS</td>
<td>12 (9.6)</td>
<td>7 (5.1)</td>
<td>0.23</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0.48</td>
</tr>
<tr>
<td>ICD</td>
<td>0 (0)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Results are given as median (25th–75th percentile) or as counts (percentages).
HC: heart catheterization; ICD: implantable cardioverter defibrillator; ICU: intensive care unit; PS: pulmonary stenosis; PVR: pulmonary valve replacement; RVOT: right ventricular outflow tract; TOF: tetralogy of Fallot; TP: transannular patch.
morbidly may increase in patients who have an early repair. Furthermore, long-term morbidity after transatrial-transpulmonary TOF repair remains high. Compared to our previous analysis of the same cohort (2015), longitudinal follow-up showed an increase of 0.7% (n = 3) in the mortality rate and 7.9% (n = 36) of PVR over a 3.5-year period.

### Timing of repair of tetralogy of Fallot

The debate regarding the optimal timing of primary TOF repair is ongoing, and the data on this topic with sufficient follow-up duration are relatively scarce [4, 6, 7, 15].

Our study stands out because of the relatively long follow-up period [12, 16–20]. In agreement with much of the literature, we observed a significant decrease in the median age at TOF repair over time [2–5]. Remarkably, patients in our 2000–2012 cohort with the lowest age at TOF repair (4.2 months) experienced the worst event-free survival.

We analysed the whole group (n = 453) and the electively repaired patients after 1990 (n = 261) separately. For this analysis we excluded patients with previous palliation or with non-elective surgery, because they probably reflect the more severe spectrum of TOF. In the subanalyses of elective primary TOF repair, patients with early repair received more TPs and experienced significantly worse event-free survival rates compared to patients with late primary TOF repair. We assessed relevant preoperative clinical parameters that might have affected this outcome. The degree of RVOTO was slightly higher in the early repair group. Cunningham et al. [18] also observed that, despite similar residual RVOTO of <20 mmHg after TOF repair, reinterventions were more common when the TOF repair was performed before 55 days of age. Possibly there is a difference in growth of the (branch) pulmonary artery(ies) between patients operated on early or later in life [18] or a patient-size difference in the size of the TP, resulting in more pulmonary regurgitation/PS and the subsequent need for reinterventions.

Some researchers observed that repair before the age of 28 days is associated with more TPs, longer hospital stay and increased mortality rate [7, 17, 19, 20]. Studies in patients beyond the neonatal age found that an older age at complete TOF repair is associated with shorter hospital stays and lower mortality rates [16, 17, 20–22]. Dorobantu et al. [16] observed, in a large (n = 1662) study with a median follow-up of 4.7 years, that at 12 years the mortality rate was higher when repair was performed before the age of 60 days. However, these studies often have limited follow-up duration. In our electively repaired cohort, the median follow-up after TOF repair was 13.9 years.

It is hard to determine whether our findings relate to more severe anatomical defects and therefore the need for the earlier TOF repair. However, the combined findings from the literature may indicate that it might be better to postpone primary elective TOF repair in asymptomatic patients with TOF until at least 6 months of age. Recently, interest has increased in transcatheter RVOT palliation prior to primary repair, potentially postponing repair in symptomatic patients with TOF [16, 17, 20].

### Survival

Recent observations point towards increased survival after TOF repair performed in past decades, which is mainly driven by the decrease in early mortality rates [2, 5, 11, 23]. We observed an overall survival rate of 96% at 20 years and of 93% at 30 years. Relatively few studies have reported the 25- to 30-year survival rates of contemporary surgical approaches. d’Udekem et al. [11] described a 97% 25-year survival rate in a large cohort operated

### Table 4: Predictors for the composite end point for all patients and for patients with an elective primary TOF repair after 1990

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>All patients (n = 453)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>1.22</td>
<td>0.90–1.64</td>
</tr>
<tr>
<td>Centre</td>
<td>1.27</td>
<td>0.91–1.79</td>
</tr>
<tr>
<td>22q11 deletion</td>
<td>0.82</td>
<td>0.40–1.67</td>
</tr>
<tr>
<td>Year of TOF repair</td>
<td>1.02</td>
<td>1.00–1.05</td>
</tr>
<tr>
<td>TOF repair &lt;6 months</td>
<td>1.87</td>
<td>1.37–2.54</td>
</tr>
<tr>
<td>RVOT obstruction at TOF repair (m/s)</td>
<td>2.18</td>
<td>1.52–3.13</td>
</tr>
<tr>
<td>Complications after TOF repair</td>
<td>2.18</td>
<td>1.25–3.83</td>
</tr>
<tr>
<td>Elective primary repair patients (n = 261)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>1.81</td>
<td>1.15–2.87</td>
</tr>
<tr>
<td>Centre</td>
<td>1.55</td>
<td>0.94–2.56</td>
</tr>
<tr>
<td>22q11 deletion</td>
<td>1.39</td>
<td>0.66–2.89</td>
</tr>
<tr>
<td>Year of TOF repair</td>
<td>1.08</td>
<td>1.03–1.13</td>
</tr>
<tr>
<td>TOF repair &lt;6 months</td>
<td>2.85</td>
<td>1.76–4.64</td>
</tr>
<tr>
<td>RVOT obstruction at TOF repair (m/s)</td>
<td>1.26</td>
<td>0.96–1.76</td>
</tr>
<tr>
<td>Complications after TOF repair</td>
<td>1.86</td>
<td>1.12–3.10</td>
</tr>
</tbody>
</table>

CI: confidence interval; RVOT: right ventricular outflow tract; TOF: tetralogy of Fallot; TP: transannular patch.
on after 1980, with only 16 patients followed up 25 years after TOF repair. Park et al. [5] described, in a cohort operated on after 1986, a 25-year survival rate of 93%. In our study, the overall survival rate was higher, which may relate in part to differences in the composition of the diagnoses of the populations [5].

Morbidity
Morbidity remains high after TOF repair, with worse survival in patients who have a TP. The use of a TP damages the integrity of the pulmonary valve and the RVOT, causing pulmonary regurgitation [13, 23]. Long-term exposure to moderate to severe pulmonary regurgitation causes RV dilatation, impaired ventricular function and arrhythmias that often require reinterventions [1, 13, 23]. Over time, attempts were made by surgeons to avoid or minimize the use of a TP, and new valve-sparing techniques were developed [3]. In patients with narrow RVOTs, a TP might be necessary and cannot be avoided, but TP use also differs among surgeons [24].

Gender
In patients who had elective primary repair after 1990, we observed a significantly better event-free survival in male compared to female patients. The reason for this is not entirely clear. We did not observe this difference in the overall cohort. Gender differences in PS or valve sizes have not been reported. In older patients with TOF, male gender was associated with ventricular tachyarrhythmias, a larger cardiac mass, biventricular volumes and peak VO₂, but a lower ejection fraction [25, 26]. These factors may affect long-term morbidity and survival rates [13].

Limitations
Due to the retrospective nature of this study, we had missing values. Our study represents the experience of 2 centres. After the year 2000 there was a difference in age of TOF repair between the 2 centres, which could have influenced our results. We also did not perform a competing risk analysis.

Likewise, our study shows the experience after TOF repair over multiple decades. During this time, the availability of diagnostic methods, indications for and timing of (re)interventions have changed, which could have influenced our results and could therefore be a bias.

CONCLUSIONS
The transatlanto-transpulmonary repair of TOF before the age of 6 months is associated with more events during long-term follow-up, mainly due to an increase in interventions for RVOTO. We noted a trend towards a decrease in age at TOF repair. These findings suggest that, if clinically feasible, it may be better to delay primary TOF repair for as long as possible. Further prospective studies are needed to determine the optimal timing for primary repair of TOF.

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Author contributions
Eva van den Bosch: Conceptualization, Data curation, Formal analysis; Investigation; Methodology; Project administration; Writing—original draft. Ad J.J.C. Bogers: Supervision; Writing—review & editing. Jolien W. Roos-Hesseling: Writing—review & editing. Arie P.J. van Dijl: Writing—review & editing. Marie H.E.J. van Wijngaarden: Data curation; Writing—review & editing. Eric Boersma: Formal analysis; Methodology; Supervision. Aagje Nijveld: Writing—review & editing. Linda W.G. Luijten: Conceptualization; Data curation; Writing—review & editing. Ronan Talke: Writing—review & editing. Laurens P. Koopman: Conceptualization; Methodology; Supervision; Writing—original draft; Writing—review & editing. Willem A. Helbing: Conceptualization, Funding acquisition; Methodology; Supervision; Writing—original draft; Writing—review & editing.

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