Unnatural History of Tetralogy of Fallot
Propective Follow-Up of 40 Years After Surgical Correction

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Background—Prospective data on long-term survival and clinical outcome beyond 30 years after surgical correction of tetralogy of Fallot are nonexistent.

Methods and Results—This longitudinal cohort study consists of the 144 patients with tetralogy of Fallot who underwent surgical repair at <15 years of age between 1968 and 1980 in our center. They are investigated every 10 years. Cumulative survival (data available for 136 patients) was 72% after 40 years. Late mortality was due to heart failure and ventricular fibrillation. Seventy-two of 80 eligible survivors (90%) participated in the third in-hospital investigation, consisting of ECG, Holter, echocardiography, cardiopulmonary exercise testing, N-terminal pro-brain natriuretic peptide measurement, cardiac magnetic resonance (including dobutamine stress testing), and the Short Form-36 questionnaire. Median follow-up was 36 years (range, 31–43 years). Cumulative event-free survival was 25% after 40 years. Subjective health status was comparable to that in the normal Dutch population. Although systolic right and left ventricular function declined, peak exercise capacity remained stable. There was no progression of aortic root dilation. A previous shunt operation, low temperature during surgery, and early postoperative arrhythmias were found to predict late mortality (hazard ratio, 2.9, 1.1, and 2.5, respectively). An increase in QRS duration and a deterioration of exercise tolerance and ventricular dysfunction did not predict mortality. Insertion of a transannular patch was a predictor for late arrhythmias (hazard ratio, 4.0; 95% confidence interval, 1.2–13.4). An increase in QRS duration and a deterioration of exercise tolerance and ventricular dysfunction did not predict mortality. Insertion of a transannular patch was a predictor for late arrhythmias (hazard ratio, 4.0; 95% confidence interval, 1.2–13.4).

Conclusions—Although many patients needed a reoperation or developed arrhythmias, late mortality was low, and the clinical condition and subjective health status of most patients remained good. Previous shunt, low temperature during surgery, and early postoperative arrhythmias were found to predict late mortality. (Circulation. 2014;130:1944-1953.)

Key Words: arrhythmias, cardiac follow-up studies morbidity survival tetralogy of Fallot

Tetralogy of Fallot (ToF) is the most prevalent form of cyanotic congenital heart diseases.1 Although mortality was substantial in the earliest era of surgical correction,2 survival has improved dramatically over the years: 90% of patients are currently alive 30 years after successful surgical correction at a young age.3–6 Despite these satisfactory results, survival up to 30 years is lower than in the normal population, and little is known about long-term functional outcome and life expectancy beyond 30 years.5,7

Editorial see p 1931
Clinical Perspective on p 1953

Although anatomic correction and physiological correction have been achieved, complications such as pulmonary regurgitation leading to right ventricular (RV) dysfunction, recurrent obstruction of the RV outflow tract, arrhythmias, sudden death, and aortic dilation and regurgitation are found in late survivors.1,8,9

Information on outcome after correction beyond 30 years is limited and has mostly been collected retrospectively. Most previous studies focused on a selection of patients regularly seen at the outpatient clinic, which may lead to selection bias. Our study is part of a unique ongoing longitudinal follow-up that started in 1990. The patients are investigated in hospital every 10 years.10,11 The aim of the present study is to provide data on survival and clinical course, including late sequelae, in survivors up to 40 years after initial correction and to detect predictors for outcome.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

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Methods

Study Patients
All consecutive patients who underwent surgical correction for ToF (excluding pulmonary atresia) in our institution between 1968 and 1980 at <15 years of age were included in this longitudinal study. The cohort was first studied in 1990, and the second follow-up was performed in 2001. For the current third follow-up, survival status of the patients was obtained from the Dutch National Population Registry. All patients who were alive and had participated in 1 or both of the earlier follow-up studies were invited for the third in-hospital investigation in 2011 to 2012. Detailed information describing the baseline characteristics, surgical procedure, and 10- and 20-year follow-up results has been reported previously.10,11 The study protocol was approved by the institutional Medical Ethics Committee (2010-015). Written informed consent was obtained from all study participants.

Survival and Adverse Events
Survival was compared with the survival of the reference, age-matched Dutch population. Adverse events were defined as all-cause mortality, cardiac reinterventions (both percutaneous and surgical), symptomatic arrhythmias (needing medication or an intervention), stroke, heart failure (needing medication or hospital admission), and endocarditis.

Clinical Assessment
Medical examination included history, physical examination, subjective health status assessment (Short Form-36), standard 12-lead ECG, 24-hour ambulatory Holter monitoring, 2-dimensional echocardiography, cardiopulmonary exercise testing, N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement, and cardiac magnetic resonance (CMR) imaging with dobutamine stress testing unless contraindicated.

If a patient was unwilling or unable to visit the outpatient clinic, a questionnaire was sent to obtain information on morbidity and subjective health status and to receive permission for the use of information from medical records.

Subjective Health Status Assessment
The scores on the 36-item short-form healthy survey (Short Form-36) of all study participants were compared with results of the normative Dutch population12 and with their own results from 2001.

ECG and Holter Monitoring
Standard 12-lead surface ECGs were analyzed for rhythm, PR interval, and QRS duration. ECGs with pacemaker rhythm were excluded from comparison of conduction times. A 24-hour Holter monitoring was performed with a Cardio Perfect Holter DR180+ 3-channel recorder (Welch Allyn Cardio Control, NorthEast Monitoring, Maynard, MA).

Echocardiography
A complete 2-dimensional transthoracic Doppler echocardiography was performed with the iE33 xMATRIX X5-1 system (Philips Medical Systems, Best, the Netherlands). Cardiac dimensions and function were measured according to the current guidelines.13,14 RV function was assessed visually to allow comparison with the 2 previous studies. Additionally, more objective measures, including fractional area change and tricuspid annular plane systolic excursion, were measured to quantify RV function.

Cardiopulmonary Exercise Testing
Maximal workload and oxygen consumption (\( \dot{V}_O_{max} \)) were assessed by cardiopulmonary exercise testing using a bicycle ergometer with gradual workload increments of 20 W/min (ramp protocol) and compared with the values of normal individuals corrected for age, sex, height, and weight. The ratio of minute ventilation to carbon dioxide production (\( Ve/VCO_2 \)) was assessed at the anaerobic threshold and at maximum workload. Performance was considered maximal when a respiratory quotient of \( \geq 1.1 \) was reached.

NT-proBNP Measurement
Peripheral venous blood samples were collected after 30 minutes of rest. Plasma NT-proBNP levels were determined with the use of the commercially available electrochemiluminescence immunoassay Elecsys (Roche Diagnostics, Basel, Switzerland). The normal value for NT-proBNP in our hospital is \(<14\) pmol/L.

CMR Imaging With Dobutamine
CMR imaging was performed with a Signa 1.5-T whole-body scanner (GE Medical Systems, Milwaukee, WI) with dedicated phased-array cardiac surface coils. Details of the MR sequence used have been reported previously.15 Images were collected at rest and after low-dose (7.5 µg·kg\(^{-1}\)·min\(^{-1}\)) and high-dose (20 µg·kg\(^{-1}\)·min\(^{-1}\)) dobutamine administration. Contraindications for the use of dobutamine were previous sustained ventricular tachycardia (VT), frequently recurrent supraventricular tachycardia, and inflow or outflow obstruction of the ventricles. For CMR analyses, a commercially available Advanced Windows workstation (GE Medical Systems) was used, equipped with Q-mass (version 5.2, Medis Medical Imaging Systems, Leiden, the Netherlands). The ventricular volumetric data set was quantitatively analyzed by a single investigator (J.A.A.E.C.) using manual outlining of endocardial borders in end systole and end diastole, excluding large trabeculae (visible on 3 subsequent slices) and the papillary muscles from the blood volume. Biventricular end-diastolic volume, end-systolic volume, ejection fraction (EF), and valvular regurgitation fractions were calculated and compared with reference values.16

Statistical Analysis
For the descriptive data analyses, we used the Statistical Package for Social Sciences (version 20.0, SPSS, Inc, Chicago, IL). Continuous data are presented as mean with standard deviation or median with interquartile range. Categorical variables are presented as frequencies and percentages. For comparison of continuous variables between independent groups, the Student unpaired \( t \) test was used; for repeated measures, the paired \( t \) test or Wilcoxon signed-rank test were performed. Frequencies of unpaired data were compared by use of the \( \chi^2 \) test or Fisher exact test when applicable, and for paired data, the McNemar test was used. To quantify correlations between 2 variables, we used the Pearson correlation test or Spearman correlation test. For advanced statistical analyses of the longitudinal and survival data, the \( R \) software version 3.0.1 package was used (www.r-project.org). Univariable and multivariable Cox proportional hazard regression analyses were used to identify predictors for the predefined events: all-cause mortality, arrhythmias or pacemaker implantation, and pulmonary valve replacement (PVR). The following covariates were included in the models: early postoperative arrhythmias, temperature during surgery, palliative shunt before corrective surgery, insertion of a transannular patch, age at operation, and era of operation (before or after 1975). Because of the low frequencies for the aforementioned events, we used a penalized likelihood approach for estimating the Cox model.17 To account for missing covariate data, we used a multiple imputation approach.18 Wald tests were used to assess which covariates were most associated with the risk of each event. Time-dependent Cox regression analysis was used to assess the effects of the time-dependent covariates: QRS duration, VT on Holter, exercise capacity, and left ventricular (LV) fractional shortening on outcome.

For description of survival of the total cohort and the Dutch reference population, the Kaplan–Meier method was used. Cumulative event incidences were computed with the use of a nonparametric estimator of cumulative incidence functions. All statistical tests were 2 sided, and the level of significance was at \( P<0.05 \).

Results

Study Patients
The original study cohort consisted of 144 consecutive patients who underwent surgical correction of ToF between 1968 and 1980. Baseline characteristics are presented in Table 1. Further baseline and surgical details have been reported previously.10,11
For the present study 36 years (range, 31–43 years) after correction, 80 patients were eligible. Of them, 72 (90%) were included: 53 (66%) participated in-hospital and 19 (24%) gave permission to use the hospital records of their regular clinical follow-up. There were no differences in baseline characteristics between the participating and non-participating patients.

Survival
Survival status was obtained in 136 patients (94%). Eight patients moved abroad and were untraceable. Cumulative survival after surgical correction was 83% after 10 years, 81% after 20 years, 78% after 30 years, and 72% after 40 years (Figure 1). In total, 35 of the 144 patients died, 23 within 30 days after surgery. Of the hospital survivors, cumulative survival was 98% after 10 years, 96% after 20 years, 92% after 30 years, and 86% after 40 years. In patients who survived 30 days postoperatively, incident mortality rate was 0.29 per 100 patient-years.

In the last 10 years, 6 patients died. Three patients died of end-stage heart failure 26, 28, and 38 years after surgery at 31, 32, and 51 years of age, respectively. Two of them had nonsustained VTs on Holter in 1990 or 2001. In 1 of these patients, death was triggered by an infection.

Two other patients died of ventricular fibrillation 24 and 34 years after surgery at 28 and 41 years of age, respectively. One patient died after a shooting incident.

Adverse Events
Cumulative event-free survival after 40 years was 25% (Figure 2). In the last 10 years, 35 patients (49% of the participants) were hospitalized at least once.

Reinterventions
The cumulative incidence of reinterventions after 35 years of follow-up was 44% (Figure 3). In the last decade, 32 patients required ≥1 reinterventions: PVR (n=20); closure of a ventricular septal defect (n=8); balloon dilation of the pulmonary artery or branch (n=6); aorta-related reoperation (n=3), including 1 elective aortic arch replacement because of an aneurysm (aortic diameter, 57 mm); and infundibulectomy (n=1).

Pulmonary Valve Replacement
Despite a rather conservative approach to PVR in our center,11 the cumulative incidence of PVR was 40% at 35 years (Figure 3). Of the participating patients, 35 underwent PVR at a median of 24 years (interquartile range, 16–29 years) after the initial correction. In the last decade, surgical PVR was performed in 19 patients for the first time, 2 of whom underwent transcatheter PVR later. One patient underwent transcatheter PVR after receiving a surgical homograft in 2000.

Arrhythmias
The cumulative incidence of symptomatic arrhythmias was 17% at 35 years (Figure 4). In the last decade, 5 patients had new symptomatic arrhythmias; 3 patients had atrial fibrillation and needed electric cardioversion. One of them underwent catheter ablation afterward. One patient had atrial flutter, and 1 patient was treated for arrhythmias of unknown origin in another hospital. In the last decade, 2 patients received a pacemaker and 2 received an implantable cardioverter-defibrillator (ICD). Both ICDs were implanted for secondary prevention after the patients experienced sustained VTs. One other patient had an ICD indication because of recurrent VTs but has refused implantation. Thirty-five years after surgical correction, the cumulative incidences of pacemaker and ICD implantation were 10% and 5% respectively.

Heart Failure
The cumulative incidence of heart failure at 35 years of follow-up was 3%.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=144)</th>
<th>1990 (n=79)</th>
<th>2001 (n=79)</th>
<th>2012 (n=72)</th>
<th>No Third Study* (n=72)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>87 (60)</td>
<td>46 (58)</td>
<td>44 (56)</td>
<td>42 (58)</td>
<td>45 (63)</td>
<td>0.609</td>
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<tr>
<td>Age at study (IQR), y</td>
<td>...</td>
<td>18.5 (15.1–23.2)</td>
<td>30.4 (26.3–35.6)</td>
<td>39.8 (36.1–45.5)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age at operation (IQR), y</td>
<td>4.6 (1.7–6.6)</td>
<td>4.3 (1.4–6.5)</td>
<td>4.3 (1.4–6.6)</td>
<td>4.3 (1.4–6.6)</td>
<td>3.8 (1.4–7.2)</td>
<td>0.163</td>
</tr>
<tr>
<td>Previous palliation, n (%)</td>
<td>50 (35)</td>
<td>25 (32)</td>
<td>25 (32)</td>
<td>20 (28)</td>
<td>30 (42)</td>
<td>0.080</td>
</tr>
<tr>
<td>Transannular patch, n (%)</td>
<td>87 (60)</td>
<td>48 (55)</td>
<td>47 (54)</td>
<td>48 (67)</td>
<td>44 (51)</td>
<td>0.488</td>
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<td>Hypothermia, n (%)</td>
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<tr>
<td>Temperature &lt;20°C</td>
<td>43 (30)</td>
<td>25 (32)</td>
<td>27 (34)</td>
<td>24 (33)</td>
<td>19 (26)</td>
<td>0.746</td>
</tr>
<tr>
<td>Temperature 20°C–35°C</td>
<td>89 (62)</td>
<td>52 (66)</td>
<td>50 (63)</td>
<td>47 (65)</td>
<td>42 (58)</td>
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<tr>
<td>Temperature unknown</td>
<td>12 (8)</td>
<td>2 (2)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>11 (15)</td>
<td></td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.
*Including deceased and emigrated patients.
†2012 vs no third study.
Stroke
In the last decade, 4 patients had a transient ischemic attack. Two of them had an open foramen ovale.

Endocarditis
Two patients were diagnosed with endocarditis: 1 had bacteremia with *Streptococcus oralis* 5 years after ICD implantation, which resolved on antibiotics only after the ICD had been removed. The other had bacteremia with *Streptococcus sanguis* 21 years after pulmonary homograft implantation. The patient was treated with antibiotics and remained free of recurrent bacteremia afterward.

Subjective Health Status Assessment
Patients scored significantly better on the domains of role limitations resulting from physical or emotional problems, bodily pain, and social functioning compared with normative data (Figure 5). In direct comparison with their own previous results, patients showed a less favorable general health perception (*P* = 0.042) than 10 years ago.

ECG and Holter Monitoring
The ECG and Holter findings are summarized in Table 2. None of the patients had ventricular pauses >3 seconds.

Echocardiography
Echocardiographic findings are summarized in Tables 2 through 4. The systolic function of both ventricles diminished in the last 10 years. In 21 patients (40%), the estimated RV pressure was >40 mm Hg, but in all but 3 patients, this was completely attributable to residual pulmonary stenosis. Normal diastolic LV function was observed in 35 patients (55%), impaired relaxation in 13 (20%), pseudonormal diastolic filling in 2 (3%), and restrictive relaxation pattern in 14 (22%).

There was no progression of aortic root dilation in the last decade. No correlations were found between pulmonary regurgitation or tricuspid regurgitation and right atrial dilation, RV dilation, or RV function.

Cardiopulmonary Exercise Testing
Table 2 shows the results of bicycle ergometry. Forty percent of the patients had a reduced exercise capacity (<85% of expected workload). These patients did not significantly differ from those with a normal test result with regard to age at the time of operation, current age, or findings at echocardiography and CMR (dimensions and ventricular function).
NT-proBNP Measurement
Median NT-proBNP level was 16.4 pmol/L (interquartile range, 6.7–32.0 pmol/L). An elevated NT-proBNP level (>14.0 pmol/L) was measured in 58% of the patients. NT-proBNP (logarithmic) correlated modestly with echocardiography-derived LV end-systolic dimension ($r=0.31, P=0.03$) and CMR-derived LV end-diastolic volume ($r=0.36, P=0.01$). No correlations were found with age at operation, current age, exercise capacity, or RV dimensions.

CMR Imaging
CMR was performed in 49 of the 72 patients (68%). Contraindications for CMR were either the presence of a pacemaker or ICD or claustrophobia. The results of CMR are summarized in Table 5. RV and LV end-diastolic dilation was observed in 15 patients (31%) and 2 patients (4%), respectively. In 23 patients (47%), RV EF was diminished, and in 14 (29%) patients, LV EF was diminished. RV EF correlated with LV EF ($r=0.54, P<0.001$).

Thirty patients consented to dobutamine stress. In 5 of them, dobutamine administration was terminated before the dose was increased because of adverse effects: increase in ventricular extrasystoles, ventricular bigeminy, nonsustained VT, symptomatic blood pressure drop, and anxiety. All of these effects recovered spontaneously. LV EF and RV EF increased significantly after administration of 7.5 μg·kg⁻¹·min⁻¹ dobutamine ($P<0.001$ for both), but after a dose of 20 μg·kg⁻¹·min⁻¹, there was no further increase ($P=0.4$ and $P=0.9$, respectively).

Predictor Analyses
Results of the baseline parameters Cox regression analysis are presented in Table 5. Early postoperative arrhythmias, a palliative shunt before initial correction, and lower temperature during surgery were predictive of mortality. In the time-dependent Cox regression analyses, no predictors for mortality were found. Increase in QRS duration and decrease in maximally achieved workload during cardiopulmonary exercise testing over time were predictive for PVR (hazard ratio, 1.14 per 10-millisecond increase, $P=0.023$; and hazard ratio, 0.961, $P=0.001$, respectively) but not for mortality. Ventricular dysfunction on echocardiogram or arrhythmias on Holter in 1990 or 2001 did not predict adverse outcome. After adjustment for changes in QRS duration, exercise capacity, VTs on Holter, and LV fractional shortening, patients without a previous palliative shunt still showed a trend toward lower all-cause mortality (hazard ratio, 0.22; $P=0.064$).

The presence of a supraventricular arrhythmia on ECG in 1990 or 2001 predicted mortality (hazard ratio, 13.9, $P=0.016$; and hazard ratio, 14.5, $P=0.004$, respectively).

Discussion
In this unique prospective, longitudinal cohort study of an unselected cohort of ToF patients with detailed clinical evaluation and analysis of predictors for outcome, we found that late mortality up to 40 years was low. Early postoperative

![Figure 4. Cumulative incidences of supraventricular tachycardia (SVT), ventricular tachycardia (VT), and all arrhythmias, including implantation of pacemakers and cardioverter-defibrillators.](image)

![Figure 5. Results of Short Form-36 for patients with tetralogy of Fallot (ToF) and the normal Dutch population. Higher scores indicate more favorable subjective health status. *$P<0.001$.](image)
Table 2. Diagnostic Measurements

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<td><strong>ECG</strong></td>
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<tr>
<td>Rhythm, n (%)</td>
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<td></td>
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<tr>
<td>Sinus</td>
<td>66 (84)</td>
<td>69 (87)</td>
<td>58 (83)</td>
<td>0.7</td>
<td>0.3</td>
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<tr>
<td>Atrial</td>
<td>6 (8)</td>
<td>5 (6)</td>
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<tr>
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<td>3 (4)</td>
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<tr>
<td>Atrial fibrillation</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
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<tr>
<td>Nodal</td>
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<tr>
<td>Pacemaker</td>
<td>5 (6)</td>
<td>2 (3)</td>
<td>7 (10)</td>
<td>1.0</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>PR interval (mean±SD), ms</td>
<td>159±32</td>
<td>162±27</td>
<td>173±41</td>
<td>0.008†</td>
<td>0.02†</td>
<td></td>
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<tr>
<td>PR &gt;200 ms, n (%)</td>
<td>3 (4)</td>
<td>4 (6)</td>
<td>11 (18)</td>
<td>0.02</td>
<td>0.1</td>
<td></td>
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<tr>
<td>QRS duration (mean±SD), ms</td>
<td>120±29</td>
<td>135±32</td>
<td>144±32</td>
<td>&lt;0.001†</td>
<td></td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>QRS duration &gt;120 ms, n (%)</td>
<td>27 (39)</td>
<td>46 (62)</td>
<td>46 (72)</td>
<td>&lt;0.001†</td>
<td>0.1</td>
<td></td>
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<tr>
<td>QRS duration &gt;180 ms, n (%)</td>
<td>1 (1)</td>
<td>6 (8)</td>
<td>8 (13)</td>
<td>0.1</td>
<td>0.2</td>
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<tr>
<td>24-h Holter, n</td>
<td>70</td>
<td>76</td>
<td>56</td>
<td></td>
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</tr>
<tr>
<td>Supraventricular arrhythmias, n (%)</td>
<td>15 (21)</td>
<td>44 (59)</td>
<td>29 (52)</td>
<td>0.03†</td>
<td>1.0</td>
<td></td>
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<tr>
<td>Sinus node disease</td>
<td>12 (17)</td>
<td>20 (27)</td>
<td>14 (25)</td>
<td>0.5</td>
<td>1.0</td>
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<tr>
<td>VT</td>
<td>7 (10)</td>
<td>27 (36)</td>
<td>19 (34)</td>
<td>0.3</td>
<td>0.8</td>
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<td>Paroxysmal atrial fibrillation</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (2)</td>
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<tr>
<td>Paroxysmal atrial flutter</td>
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<td>1 (1)</td>
<td>0</td>
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<tr>
<td>VT 3–10 complexes, n (%)</td>
<td>7 (10)</td>
<td>9 (12)</td>
<td>10 (18)</td>
<td>1.0</td>
<td>0.4</td>
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<tr>
<td>VT &gt;10 complexes, n (%)</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td></td>
<td></td>
<td>1.0</td>
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<tr>
<td>Bicycle ergometry, n</td>
<td>73</td>
<td>71</td>
<td>52</td>
<td></td>
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<tr>
<td>Maximal heart rate</td>
<td>86±11</td>
<td>89±10</td>
<td>86±12</td>
<td>0.7</td>
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<td>0.04†</td>
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<td>(mean±SD), %</td>
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<tr>
<td>Maximal exercise capacity</td>
<td>88±17</td>
<td>83±16</td>
<td>89±18</td>
<td>0.6</td>
<td>0.02†</td>
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<tr>
<td>(mean±SD), %</td>
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</tr>
<tr>
<td>Exercise capacity &lt;85%, n (%)</td>
<td>26 (36)</td>
<td>39 (55)</td>
<td>21 (40)</td>
<td>1.0</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Arrhythmias, n (%)</td>
<td>14 (19)</td>
<td>17 (24)</td>
<td>12 (23)</td>
<td>0.2</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>VO₂ max, %</td>
<td>...</td>
<td>...</td>
<td>81±17</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REmax</td>
<td>...</td>
<td>...</td>
<td>1.4±0.2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ve/Vco₂, anaerobic threshold</td>
<td>...</td>
<td>...</td>
<td>27.0±4.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ve/Vco₂, maximum workload</td>
<td>...</td>
<td>...</td>
<td>29.5±4.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Echocardiographic parameters, n</strong></td>
<td>79</td>
<td>79</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA dilation, n (%)</td>
<td>35 (44)</td>
<td>65 (82)</td>
<td>59 (86)</td>
<td>&lt;0.001†</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>RV dilation, n (%)</td>
<td>72 (91)</td>
<td>56 (71)</td>
<td>62 (89)</td>
<td>0.7</td>
<td>0.01†</td>
<td></td>
</tr>
<tr>
<td>LA dilation, n (%)</td>
<td>3 (4)</td>
<td>12 (15)</td>
<td>23 (34)</td>
<td>&lt;0.001†</td>
<td></td>
<td>0.01†</td>
</tr>
<tr>
<td>LV dilation, n (%)</td>
<td>1 (1)</td>
<td>7 (9)</td>
<td>7 (10)</td>
<td>0.4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>RV systolic function normal, n (%)</td>
<td>...</td>
<td>54 (78)</td>
<td>19 (28)</td>
<td></td>
<td>&lt;0.001†</td>
<td></td>
</tr>
<tr>
<td>LV systolic function normal</td>
<td>76 (96)</td>
<td>70 (90)</td>
<td>34 (50)</td>
<td>&lt;0.001†</td>
<td></td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>FS &lt;20%, n (%)</td>
<td>3 (4)</td>
<td>7 (10)</td>
<td>6 (9)</td>
<td>0.6</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Valve regurgitation (more than trace), n (%)</td>
<td>4 (5)</td>
<td>15 (19)</td>
<td>19 (28)</td>
<td>&lt;0.001†</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>AR</td>
<td>0</td>
<td>6 (8)</td>
<td>13 (19)</td>
<td>0.004†</td>
<td>0.004†</td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td>65 (82)</td>
<td>62 (79)</td>
<td>43 (62)</td>
<td>0.002†</td>
<td>0.001†</td>
<td></td>
</tr>
<tr>
<td>TR</td>
<td>45 (57)</td>
<td>49 (62)</td>
<td>49 (71)</td>
<td>0.1</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Arrhythmias were found to be a new predictor for late mortality. Although morbidity was substantial, the subjective health status was excellent, and objective exercise capacity remained stable.

Mortality and Major Events
In the total cohort, cumulative survival 40 years after surgical correction was 72%, with one fifth of deaths occurring within 30 days after surgery. In the hospital survivors, cumulative survival was 86% after 40 years of follow-up. This is only slightly lower than survival in the general Dutch population. The causes of late death in our cohort were heart failure and arrhythmia, which is in accordance with the literature.

Morbidity was substantial in our population; only one quarter of the patients were free from events after 40 years. Reinterventions were required in nearly half of the patients, mostly PVR. This is considerably more than reported in other studies, probably reflecting the earlier era of initial operation and longer duration of follow-up in our study.

Health Status Assessment
Exercise capacity was clearly impaired in our ToF patients but remained stable in the last 10 years. The lowest \( V_{\text{O}_{2}\text{max}} \) in our study population was 51% of the predicted value. This is still considerably higher than the 36% described by Giardini et al.24 Over time, our patients showed a decrease in general health perception scores, which can be related to age because this effect also is seen in the general population.

Arrhythmias
Arrhythmias and sudden death are important late complications.4,8,25 We found a lower prevalence of arrhythmias than described by Khairy et al.25 In our study, supraventricular arrhythmias were common on Holter, but only 5 patients had symptomatic arrhythmias. The prevalence of SVT on Holter did not increase in the last decade and did not predict outcome. In addition, an increase in QRS duration did not predict arrhythmias or mortality. However, strikingly, 2 of the 3 patients with an atrial arrhythmia (atrial flutter) on ECG in 2001 died during the last 10 years. Their atrial arrhythmia could have been an indicator of worsening hemodynamics, but none of these patients had more than mild RV dysfunction, and only 1 had LV dysfunction in 2001. It seems that these supraventricular arrhythmias should not be considered insignificant.

Ventricular Function
Late deterioration of RV and LV function has been an increasing concern.26,27 Indeed, this was found in our study because systolic RV function was impaired in >75% and systolic LV function in 50% of the patients. Moreover, diastolic LV dysfunction was found often. The deterioration of LV function could be explained by adverse ventricular-ventricular interaction associated with RV dilation, which influences LV twist.28

We found a significant association between RV and LV dysfunction. In addition, we found a modest but significant correlation between LV dimensions and NT-proBNP levels. In other studies, NT-proBNP levels correlated with both LV and RV dimensions and LV function.29 Whether NT-proBNP predicts clinical outcome remains to be established.

Administration of dobutamine during CMR led to an increase in RV EF and LV EF at a low dose, but no further increase was

Table 2. Continued

<table>
<thead>
<tr>
<th></th>
<th>1990 (n=79)</th>
<th>2001 (n=79)</th>
<th>2012 (n=70)</th>
<th>2012 vs 1990</th>
<th>2012 vs 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vmax PR, m/s</td>
<td>1.8</td>
<td>1.8</td>
<td>2.0</td>
<td>0.007†</td>
<td>0.1</td>
</tr>
<tr>
<td>Vmax TR, m/s</td>
<td>2.7</td>
<td>2.8</td>
<td>2.7</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>32±4</td>
<td>37±4</td>
<td>39±6</td>
<td>&lt;0.001†</td>
<td>0.001†</td>
</tr>
<tr>
<td>LV diameter, mm</td>
<td>44±6</td>
<td>49±6</td>
<td>48±7</td>
<td>&lt;0.001†</td>
<td>0.7</td>
</tr>
<tr>
<td>Aortic diameter, mm</td>
<td>32±4</td>
<td>37±4</td>
<td>36±5</td>
<td>0.002†</td>
<td>0.08</td>
</tr>
</tbody>
</table>

AR indicates aortic regurgitation; FS, fractional shortening; LA, left atrial; LV, left ventricular; MR, mitral regurgitation; PR, pulmonary regurgitation; RA, right atrial; RERmax, maximum respiratory exchange ratio; RV, right ventricular; SVT, supraventricular tachycardia; TR, tricuspid regurgitation; Vmax, maximal velocity found with Doppler echocardiography; and VT, ventricular tachycardia.

*p values are displayed only for measures performed in 2 or all 3 studies.
†Significant.
observed at a high dose. As described by Parish et al., who found a similar stress response, this is caused mainly by the lack in further decrease of RV end-systolic volume, indicating diminished contractile reserve. Because this is not apparent at rest, dobutamine stress CMR may contribute to the decision making in terms of intervention such as timing of PVR in these patients.

**Aortic Dilation**

Dilation of the ascending aorta is found in 15% to 87% of the ToF patients, presumably inherent to volume overload resulting from the original overriding position of the aorta. Additionally, intrinsic vascular wall properties could play a role. We found aortic root dilation (>40 mm) in 24% of our patients at the last follow-up. The long-term risk of aortic dilation in ToF patients has not been clarified yet. In our longitudinal follow-up, the aortic diameter did not increase over time, and until now, no aortic dissection occurred. However, in 1 patient, the aortic arch was electively replaced because of an aortic diameter of 57 mm.

**Predictors for Late Events**

Patients with a palliative shunt before initial correction, that is, Waterston shunt, Blalock-Taussig shunt, or Potts anastomosis,
were more at risk of dying or needing PVR than patients without them. Because in our cohort the use of a palliative shunt was related to the era of surgery rather than to anatomy, selection bias regarding more or less favorable anatomy is very unlikely. Therefore, our study supports early initial correction without previous shunt if the patient’s condition tolerates.

Mortality was higher in patients who experienced early postoperative arrhythmias. In addition, these patients had a higher risk of late arrhythmias or pacemaker implantation. The occurrence of early arrhythmias and their relation to the increased risk of death and permanent pacing have previously been described in small series and, on the basis of our results, seem to have clinical relevance. More attention for these early postoperative arrhythmias and their underlying mechanism is needed and may attribute to risk stratification for preventive interventions such as ICD implantation.

A QRS duration >180 milliseconds and an increase in QRS duration over time have been recognized as predictors for VT and late sudden death. Our study showed a steady increase in QRS duration over time. However, all patients with a QRS duration >180 milliseconds in 1990 or 2001 are still alive, and QRS duration could not be identified as predictor for mortality in our study.

Although the numbers in our study are small, supraventricular arrhythmias on ECG in 1990 or 2001 seem to be predictive of mortality. The importance of atrial arrhythmias as a predictor for outcome has been suggested before. However, the exact mechanism remains to be elucidated.

The insertion of a transannular patch has received much attention as a possible cause of pulmonary regurgitation and long-term morbidity. Our results confirm the association of a transannular patch with PVR but not with mortality. These results are similar to the results of the study by Lindberg et al. Furthermore, we found an association between the use of a transannular patch and the occurrence of late arrhythmias. Nowadays, surgeons tend to use smaller transannular patches to minimize pulmonary regurgitation and its long-term sequelae. Whether this will result in better outcome has to be established.

Study Limitations
Although the number of patients in this study is relatively small, we report the results of a longitudinal follow-up of consecutive patients without selection bias related to disease severity. After a median follow-up of 36 years, we gathered medical information on 72 of the approached patients (90%). We found no significant differences in baseline characteristics between participating and nonparticipating patients; therefore, we believe that we have minimized selection bias.

From 1968 to 1980, the era in which our cohort was operated on, the standard surgical policy gradually changed from secondary correction after previous shunting, use of a large transannular patch, and surgery at very low temperature to primary correction at higher temperatures. These factors were accounted for in our analyses of predictors for outcome. We believe that there is no bias concerning temperature during surgery, but we cannot completely exclude that the use of a previous shunt was related to more complex anatomy.

Diagnostic methods have been changed during the last 36 years. For comparing echocardiography data of the present study with the previous studies, we had to use the same methods used in the past. Some of these techniques are not seen as being up-to-date. However, we also performed and reported innovative diagnostic methods available in 2012.

Conclusions
Long-term survival after successful surgical correction of ToF in childhood is good. Morbidity, however, is substantial, with almost half of the patients needing at least 1 reintervention. There is concern about the deterioration of both RV and LV function. Nevertheless, the clinical condition and subjective health status of most patients remain good, and aortic dimensions did not increase over time.

Acknowledgments
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Disclosures
None.

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Surgical correction of tetralogy of Fallot has been possible for only ≈50 years. Information on long-term outcome is virtually absent in the literature. This information, however, is of major importance for clinicians involved in the care of these patients and for the patients themselves. Both clinicians and patients would like to know what they can expect and of which late complications they should be aware. Our study provides unbiased information on survival, morbidity, and cardiac function in patients up to 43 years after surgical Fallot correction. Although not normal, survival is quite good, with 86% of the patients who survived the operation alive after 40 years. Ventricular function, both right and left sided, has decreased over time in many patients. There is a gradual increase in tricuspid regurgitation. Functional capacity of the patients is good; the mean maximum workload on bicycle ergometry is 89% of expected, and on the Short Form-36 questionnaire, a tool to measure health perception, patients score equal to or even better than the normal population. However, almost half of the patients have had at least 1 reintervention, mainly pulmonary valve replacement (40%). Patients who had a palliative shunt before correction were more at risk of dying or needing pulmonary valve replacement. Those who had early postoperative arrhythmias were not only more likely to develop late arrhythmias but also had a higher risk for mortality. These new data may contribute to risk stratification and decision making on, for example, prophylactic implantation of a cardioverter-defibrillator.
Unnatural History of Tetralogy of Fallot: Prospective Follow-Up of 40 Years After Surgical Correction
Judith A.A.E. Cuypers, Myrthe E. Menting, Elisabeth E.M. Konings, Petra Opic, Elisabeth M.W.J. Utens, Willem A. Helbing, Maarten Witsenburg, Annemien E. van den Bosch, Mohamed Ouhlous, Ron T. van Domburg, Dimitris Rizopoulos, Folkert J. Meijboom, Eric Boersma, Ad J.J.C. Bogers and Jolien W. Roos-Hesselink

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