The Impact of Changing Medical Therapy on Transplantation-Free Survival in Pediatric Dilated Cardiomyopathy

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Objectives
We sought to determine whether the introduction of these agents had altered the outcome of dilated cardiomyopathy (DC) in childhood.

Background
Pediatric DC has a poor prognosis. Angiotensin-converting enzyme inhibitors (ACEIs) and beta-adrenergic receptor blockers (BBs) improve survival in adults with DC, but their effectiveness in children has not been confirmed.

Methods
We performed a single-institution retrospective review of all diagnosed cases of DC and related phenotypic variants between 1976 and 2005, with multivariate analysis of risk factors for the end point of death or cardiac transplantation.

Results
A total of 189 patients presented between January 1, 1976, and March 31, 2005. Forty-four patients died, 34 underwent cardiac transplantation, and 10 were lost to follow-up during this period. The 2- and 5-year transplantation-free survival rates for all patients were 63.6% (95% confidence interval [CI]: 56.4% to 70.8%) and 56.3% (95% CI: 48.5% to 64.1%), respectively. For patients treated with digoxin but neither an ACEI nor a BB (n = 110), the 5-year transplantation free survival rate was 67.5% (95% CI: 53.5% to 82.0%) and for those treated with the addition of an ACEI but no BB (n = 65), the rate was 57.2% (95% CI: 43.6% to 69.4%) (p = NS). Combination therapy with an ACEI and a BB (n = 57) was not associated with an improvement in 5-year transplantation-free survival (58.5%; 95% CI: 42.5% to 72.0%, p = NS). In multivariable analysis, presentation with a low left ventricular ejection fraction increased the risk of death or transplantation, but the end point was not influenced by time era or treatment strategy.

Conclusions
DC in childhood has a high risk of death or the need for transplantation. Medical treatment has shifted toward combination ACEI and BB therapy in the current era. Our retrospective data, however, suggest only a transient survival advantage associated with the combined use of ACEI and BB over ACEI alone and no obvious or sustained improvement in transplantation-free survival accompanying the change from digoxin-based medical therapy. (J Am Coll Cardiol 2010;55:1377–84) © 2010 by the American College of Cardiology Foundation

Dilated cardiomyopathies (DCs) are a heterogeneous group of diseases linked by a common phenotype of cardiac chamber dilation and impaired myocardial contractility (1). Although this phenotype is shared by children and adults, the underlying etiologies and their outcomes differ. Ischemic DC is rare in children, whereas DC as part of a generalized myopathy is more common in children than in adults. Overall, approximately two-thirds of childhood DC is idiopathic in origin (2), although, increasingly, specific abnormalities of sarcomeric, cytoskeletal, and sarcolemmal linkage proteins are being identified (3). The prognosis of pediatric DC also differs from that of DC presenting in adults. Survival in some subgroups seems to be better than that in adult cohorts (4), whereas in others, survival beyond childhood is rare. Importantly, and in contradistinction to adult populations, there has been no clear trend toward improvement in survival over time (4–7). In general, pharmacotherapy of pediatric DC has mirrored that of adult DC, with a transition from the almost exclusive use of digoxin and diuretics to widespread use of angiotensin-converting enzyme inhibitors (ACEIs) in the 1980s (8,9) and second- and third-generation beta-adrenergic receptor blockers (BBs) in the 1990s. Although there is compelling evidence supporting the use of both ACEIs and BBs in adults with heart failure of either ischemic or nonischemic origin (9,10), it is not clear whether adopting the
use of these agents has improved the prognosis of pediatric DC (11). We therefore sought to assess the impact of changing medical therapy from a digoxin-based regimen to a BB/ACEI-based regimen on the transplantation-free survival of patients with DC in the context of single-institution experience accumulated between 1976 and 2005.

**Methods**

Institutional research ethics board approval was obtained.

**Case ascertainment.** All patients in our institutional database diagnosed between January 1, 1976, and March 31, 2005, with a recorded diagnosis compatible with DC based on echocardiographic, angiographic, or radionuclide imaging criteria were retrospectively identified. All diagnostic terms representative of the primary cardiomyopathies (as defined by the World Health Organization classification [1]), except for hypertrophic cardiomyopathy, were included as search terms. Patients younger than 18 years of age and meeting phenotypic criteria of left ventricular (LV) chamber dilation with an LV basal short-axis dimension at end-diastole greater than body surface area–defined upper normal limits (12) and in later years institutional normative z-scores, and having a left ventricular ejection fraction (LVEF) of <50% were included. When clinical or tissue diagnosis had been made, this was noted. Examination of all available clinical records was performed, and cases were assigned to 1 of 6 etiologic groups: post-myocarditis, neuromuscular disease, metabolic disease, post-anthracycline exposure, idiopathic dilated, and unclassified. The latter included those with LV noncompaction, phenotypic restrictive cardiomyopathy with either coexisting LV dilation or decreased systolic function, and endocardial fibroelastosis in which LV dilation was part of the phenotype.

In the special case of myocarditis, the diagnosis was verified to have been made on the basis of any 1 of 3 retrospective criteria: 1) histopathologic findings at endomyocardial biopsy using the Dallas criteria (13) when applicable; 2) marginal histopathologic evidence of lymphocytic infiltrate with necrosis and/or fibrosis when the preponderance of clinical evidence supported this diagnosis; and 3) a suggestive clinical picture with decreased LVEF and associated viral pathogen isolation from blood or myocardial tissue by polymerase chain reaction or virus isolation. Because LV dilation is not seen universally at the onset of myocarditis, the presence of an LVEF within normal range at diagnosis was not considered an exclusionary criterion when there was independent evidence of myocarditis, but an abnormal LVEF was nevertheless required for these cases to be included.

Phenotypic hypertrophic cardiomyopathies were excluded from this analysis. Also excluded were DCs in association with congenital structural heart disease, primary arrhythmogenic cardiomyopathies, and tachycardia-induced cardiomyopathies.

**Medical management.** Because survival time was our primary end point, we defined the onset of disease for each patient as being the day on which a verifiable diagnostic study (usually an echocardiogram) with criteria fulfilled was demonstrated. We did not include the reported duration of symptoms in establishing disease onset. Cardiac medications prescribed after diagnosis were recorded in the following agent-defined classes: digoxin, ACEIs, and BBs. The use of these medications was confirmed throughout the course of follow-up by review of the clinical records at each follow-up contact. Maintenance of a particular agent class for at least 2 months of continuous therapy or until death or transplantation was required to enter a treatment group. Patients treated with combination medical therapies or serial addition of medications were classified according to the medications used at their most recent recorded follow-up, provided that at least 1 month of treatment was completed on the respective regimen (destination treatment). We prospectively designated 3 mutually exclusive destination treatment subgroups: digoxin but no ACEI or BB, ACEI with or without digoxin, and BB and ACEI with or without digoxin. Diuretics were not regarded as a definitive therapy class for the purpose of this analysis.

Our medication dosing guidelines during the study period were as follows: digoxin 5 to 10 μg/kg/day with intermittent levels required for a target of 1.2 to 2.5 ng/l; captopril target dose between 2 and 3 mg/kg/day divided every 8 h; enalapril target dose 0.3 to 0.6 mg/kg/day divided every 12 h; carvedilol target dose 1 mg/kg/day divided every 12 h; metoprolol target dose 2 to 4 mg/kg/day divided every 12 h. Medications were routinely up-titrated over a period of 2 to 4 weeks, with subsequent dose adjustment made on the basis of hemodynamic tolerance and weight gain.

Once a treatment group was entered, continuation of medical therapy and LVEF were ascertained through serial clinical follow-up, and the occurrence of death or cardiac transplantation was determined. Patients were censored from further survival analysis when or if they were lost to clinical follow-up or at age 18 years of age. Medication withdrawal for reasons of either intolerance or clinical improvement did not result in a patient being censored from a treatment group or survival analysis. In such cases, treatment group was defined according to the medication last received.

**Assessment of outcome.** Follow-up data were attained up to age 18 if this occurred at our institution or until August 1, 2005, for the end point of death, transplantation, or continued clinical follow-up, regardless of transplantation listing. We did not determine the outcome of patients lost to follow-up by our institution. To identify any possible time era–related effect that was independent of patient
characteristics, we conducted analyses of the cohort divided into time quartiles of 7 years (9.7 years for the most recent period) as well as an analysis of survival probability, comparing the time era of 1976 to 1989 with that of 1990 to 2005.

**Data analysis.** Analysis was performed using commercially available software (SAS Institute, Cary, North Carolina; Prism 4, GraphPad Corp., San Diego, California). Comparisons among groups for normally distributed parametric data used the Student t test. For skewed data, the Kruskal-Wallis test was used. Nonparametric data were analyzed using the chi-square test. Survival analysis was performed using the Kaplan-Meier method, with post hoc testing using the Scheffé test when a specific hypothesis existed. For between-group analysis in the survival probability distributions, we did not adjust the p value when performing multiple comparisons. Cox proportional hazard analysis was performed to assess independent predictors of outcome in a multivariable model. Data are expressed as mean ± SD or median with interquartile range, and 95% confidence interval (CIs) are given where appropriate.

**Assumptions.** Our analysis makes certain statistical assumptions, for example, that there was an equivalent propensity to treat any given etiologic group with any and all combinations of medical therapy available at the time, and general assumptions regarding survival analysis also pertain, including that the presence of a proportional hazard remains constant throughout the survival analysis.

**Results**

Characteristics of the patients identified are listed in Table 1. There were 189 patients included in this analysis from 1976 to March 31, 2005. By the conclusion of the study period, 44 patients (23%) were verified to have died without undergoing transplantation, and 34 (18%) underwent transplantation. All of the remaining 111 patients were censored at their last documented follow-up visit at our institution, with 15 (8%) patients transferred to an adult cardiologist at age 18. Another 36 (19%) patients were discharged from follow-up with complete clinical and echocardiographic recovery. Of the remainder, 6 (3%) were followed at other centers, 43 (23%) were currently in active follow-up at our center, and 10 (5%) were censored without information regarding further care (lost to follow-up).

The median age at presentation was 1.0 years (interquartile range 0.5 to 8.0 years) and did not differ significantly between time quartiles (Fig. 1B). The overall male-to-female ratio was 1.2:1. Cardiac transplantation as an outcome became more common in the latter period of study (after 1989), with 26% of patients from that time onward receiving a transplant until August 2005. Death after cardiac transplantation occurred in 6 (17.6%) of these patients.

Disease groups identified are shown in Table 1. As expected, idiopathic DC was the largest of these. The prevalence of each of the diagnoses showed no significant

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**Table 1** Diagnosis and Outcomes in 189 Patients

<table>
<thead>
<tr>
<th>Disease Group</th>
<th>All Patients (N = 189)</th>
<th>Unclassified (N = 24)</th>
<th>Idiopathic DC (N = 98)</th>
<th>Neuromuscular Disorders (N = 14)</th>
<th>Inborn Errors of Metabolism (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at diagnosis, yrs (IQR)</td>
<td>1.0 (0.5–8.0)</td>
<td>1.0 (0.3–4.5)</td>
<td>1.0 (0.3–6.5)</td>
<td>2.0 (0.8–6.0)</td>
<td>3.0 (1.1–4.5)</td>
</tr>
<tr>
<td>Male/female</td>
<td>103/86</td>
<td>23/14</td>
<td>45/15</td>
<td>47/13</td>
<td>51/14</td>
</tr>
<tr>
<td>EF at presentation, % (mean ± SD)</td>
<td>29 ± 14</td>
<td>25 ± 15</td>
<td>27 ± 12</td>
<td>22 ± 10</td>
<td>29 ± 4.0</td>
</tr>
<tr>
<td>Follow-up, months (mean ± SD)</td>
<td>43 ± 5.4</td>
<td>43 ± 5.4</td>
<td>33 ± 5.4</td>
<td>43 ± 5.4</td>
<td>14.0 ± 16.0</td>
</tr>
<tr>
<td>No. lost to follow-up</td>
<td>10</td>
<td>6</td>
<td>22</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>No. of deaths (pre-transplantation)*</td>
<td>44</td>
<td>6</td>
<td>23</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>No. of cardiac transplantations</td>
<td>34</td>
<td>2</td>
<td>22</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*No. of deaths does not include patients who underwent transplantation and later died (n = 6). CI — confidence interval; EF — ejection fraction; IQR — interquartile range.
difference between time quartiles by chi-square analysis (Fig. 1B), suggesting that newer molecular diagnostic techniques did not have a significant impact on the diagnostic categorization in our recent institutional experience.

Survival with cardiomyopathy. Overall, we observed an important early risk of death or transplantation in our patient population, with actuarial freedom from this composite outcome of 71.3% (95% CI: 64.6% to 77.9%) at 12 months post-diagnosis and a further steady decrease to 56% at 5 years post-diagnosis (Table 1). The importance of the date of diagnosis was assessed by survival analysis using the Kaplan-Meier method for cohorts segregated by time era. These were designated as diagnosis occurring between 1976 and 1989 (n = 60) and 1990 and 2005 (n = 129), corresponding roughly to the pre- and post-transplantation era at our institution. Survival curves for these time eras were very similar, with no statistical difference for transplantation-free survival (log-rank test: p = 0.65, data not shown).

**Survival by treatment strategy.** All but 13 patients in the cohort had received oral maintenance therapy with ≥1 of the agents in question. Treatment was maintained in all patients until the defined end point of death or transplantation was reached. Treatment was discontinued in 6 patients while in follow-up because of improved or normalized systolic function. For the remaining 170 patients (96.5% of whom commenced oral maintenance therapy), medication use continued until death, transplantation, or the last recorded follow-up assessment. **Figure 1** demonstrates the frequency of medication choices according to year of diagnosis. An ACEI as a therapy was introduced in this institution in the early 1980s and became more prevalent in the 1990s. Of those receiving an ACEI, captopril was used in 47% (n = 55), enalapril in 37% (n = 43), and
ramipril in 6% (n = 8). BBs were not used in our experience until 1991, and then their use became more frequent. Of those patients receiving a BB, metoprolol (33%, n = 19) and carvedilol (61%, n = 35) were used in the majority. We noted only 1 patient who was treated with a BB while not being treated concurrently with an ACEI.

With regard to changes in patient characteristics with time (Fig. 1), we did note some variance in the echocardiographic severity at presentation, with those in time quartile 2 (1983 to 1989) having a somewhat higher LVEF at presentation than those in quartile 4 (1996 to 2005) (p = 0.03; 1-way analysis of variance, Bonferroni post-test). We did not find any interquartile differences in the LVEF at the last recorded follow-up visit (including that before death or transplantation); this LVEF was significantly higher than the LVEF at presentation in every quartile (data not shown). The prevalence ratio of the diagnoses of myocarditis to idiopathic DC showed no significant trend with time by chi-square analysis (Fig. 1).

By comparing the transplantation-free survival course of all patients as a function of destination treatment strategy (Fig. 2), we were unable to demonstrate any survival advantage at 60 months for those treated with an ACEI or a combination of an ACEI and BB over treatment with digoxin alone. Careful inspection of the early hazard phase for mortality or transplantation did, however, demonstrate a 9% survival advantage with the combination of ACEI and BB over ACEI alone by 11 months of therapy, and a 14% advantage at 21 months (hazard ratio: 1.49). Thereafter, however, the survival curves converged, so that by 60 months, no advantage was evident.

We did note a group of 13 patients in whom no oral maintenance therapy was attained. For the most part, as plotted in Figure 2, these 13 patients progressed to death or transplantation quite rapidly, with only 30.5% (95% CI: 5% to 56%) surviving longer than 12 months. We found that for all treatment groups, the predominant hazard phase was evident in the first 24 months after clinical detection and that there was relatively less attrition after 24 months of follow-up.

SURVIVAL BY DISEASE ETIOLOGY/PHENOTYPE AND EF AT DIAGNOSIS. There was a significant difference in survival between the 6 etiologic groups (Fig. 3). Patients with a diagnosis of myocarditis had a 5-year survival probability of 78% versus 52% for those with idiopathic DC (p = 0.03; Scheffé test). Patients with either neuromuscular or metabolic diseases fared the worst (5-year survival rate of 26% and 33%, respectively). Although all patients with anthracycline-induced cardiomyopathy survived, the numbers were too small to draw any conclusion. Interestingly, comparing the initial and last recorded LVEF in all patient groups other than those with neuromuscular/metabolic disease (Table 1), an overall improvement was noted, including for those patients who died or required a heart transplantation.

ECHOCARDIOGRAPHIC SEVERITY AT PRESENTATION. A higher LVEF at diagnosis did confer a survival advantage. In Figure 4, the survival probability based on the LVEF at diagnosis is displayed with patients segregated into the tertiles of >35% (nominally mild dysfunction), <20% (severe dysfunction), or in between these 2 tertiles (moderate dysfunction). Patients with an EF at diagnosis of <20%
had a far less favorable survival probability of 37% at 5 years post-diagnosis (p < 0.01) than the remainder of patients. **Risk factors in a multivariable model.** Our multivariable analysis considered several putative risk factors for death or cardiac transplantation (Table 2). Age at presentation did not confer significant risk, although there was a trend toward increased risk with increasing age. A lower EF at presentation, however, substantially increased the risk of this composite outcome measure. The incremental risk was calculated to increase by 35% for every 10% decrease in LVEF at presentation. Regarding diagnosis, those with myocarditis did significantly better in the multivariable model than those with idiopathic DC (hazard ratio: 0.41), and patients with a neuromuscular disease diagnosis tended to do more poorly than the idiopathic group. With regard to treatment strategy, those patients who were not started on any of the 3 oral maintenance medications (digoxin, ACEI, or BB) were at substantially greater risk. An analysis of these 13 patients indicated that most of those in this group either died or underwent transplantation soon after their diagnosis and were too unstable to be weaned off inotropic agents and commence oral therapy. In the entire cohort, we once again found that the addition of an ACEI or combination therapy with an ACEI and BB did not decrease the risk of death or transplantation by multivariable analysis.

**Discussion**

Pediatric DC continues to pose a major clinical challenge, with mortality greatly exceeding most other forms of heart disease in children (14). Although our understanding of the etiology and pathophysiology of DC has undoubtedly improved, the response to therapeutic algorithms successfully applied to treat DC in adults remains uncertain. Similar to the management of advanced heart failure in adult patients, transplantation is of proven benefit (11), and, accordingly, mechanical circulatory support is increasingly promoted in children as a bridge to transplantation (15) or even to recovery (16). Similarly, the entire portfolio of medical therapies proven effective in adults is available to treat children, but the response to these medications is much less well understood. In the current study, we documented the outcomes of pediatric DC and identified risk factors for death or transplantation. Our data, however, raise questions as to whether evolving pharmacologic treatments for heart failure in these patients are independently improving survival.

Several retrospective studies have reported outcomes for children with DC in cohorts between the 1970s and the 1990s (4–7,11). These have all been relatively small and carefully selected cohorts with specific phenotypic features and have quoted widely divergent survival rates. Our data represent the largest retrospective study comparing the impact of medical therapies as a risk factor for outcome in pediatric DC. Overall, our patients had a 10-year freedom from death rate of 70%, which is consistent with multi-institutional registry data. The National Australian Childhood Cardiomyopathy Study, representing outcomes of children younger than age 11 years between 1987 and 1996, found a 5-year transplantation-free survival rate of 63% (17). In that study, patients presenting as a sudden unexpected death were included, and patients with inborn errors of metabolism or progressive neuromuscular disease were specifically excluded. The North American Pediatric Cardiomyopathy Registry, which excludes patients with anthracycline- and neuromuscular disease-related DCs, cited a similar 5-year absolute survival rate of 70% and transplantation-free survival rate of 55% in their most recent report (18). Furthermore, as in the current study, early age at presentation, a low z-score of fractional shortening, and

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**Table 2** Multivariable Probability/Hazard Analysis for Death or Transplantation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chi-Square Test</th>
<th>p Value</th>
<th>Hazard Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting features</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>3.09</td>
<td>0.08</td>
<td>1.04 (0.99–1.09)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>15.16</td>
<td>&lt;0.01</td>
<td>0.66 (0.53–0.81)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline toxicity</td>
<td>2.60</td>
<td>0.10</td>
<td>0.37 (0.12–1.23)</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>4.87</td>
<td>0.02</td>
<td>0.41 (0.19–0.91)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>0.19</td>
<td>0.66</td>
<td>0.63 (0.08–4.89)</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>0.67</td>
<td>0.41</td>
<td>1.42 (0.61–3.28)</td>
</tr>
<tr>
<td>Neuromuscular disease</td>
<td>3.30</td>
<td>0.07</td>
<td>2.27 (0.94–5.50)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No oral maintenance therapy</td>
<td>15.26</td>
<td>&lt;0.01</td>
<td>6.17 (2.48–15.38)</td>
</tr>
<tr>
<td>Digoxin only</td>
<td>1.59</td>
<td>0.20</td>
<td>1.59 (0.77–3.28)</td>
</tr>
<tr>
<td>ACEI ± digoxin</td>
<td>0.60</td>
<td>0.44</td>
<td>1.27 (0.69–2.33)</td>
</tr>
</tbody>
</table>

The risk of death or transplantation was found to decrease by 35% for every 10% increase in ejection fraction at presentation in this model. Diagnosis group hazard ratio is expressed with reference to idiopathic dilated cardiomyopathy. Treatment group hazard ratio is expressed with reference to combined therapy with ACEI and beta-blocker, with or without digoxin. ACEI = angiotensin-converting enzyme inhibitor; CI = confidence interval.
etologies other than acute myocarditis were identified as risk factors in the North American Pediatric Cardiomyopathy Registry cohort. In this respect, it is noteworthy that patients with a metabolic disease or with a neuromuscular disease in our study could not be determined retrospectively to have died of their cardiomyopathy solely, and it may be assumed that their neurologic or metabolic status contributed to some degree.

Although registry data include much larger numbers of patients than can be expected in single-center studies, the data collection has been relatively brief and neither the National Australian Childhood Cardiomyopathy Study data nor the North American Pediatric Cardiomyopathy Registry data analyzed the effect of drug therapies on outcomes. Our data span a greater time period and report outcomes across a wider etiologic range than either of these reports. In our cohort, there has been no clear improvement in survival probability when the 30-year period of analysis is divided into earlier and later 15-year eras. Furthermore, there was no survival advantage associated with the use of ACEIs or BBs. Although EF tended to improve with time, both for the group as a whole and for many of the phenotypic categories, this trend may reflect the attrition of cases with very poor function to death or transplantation as time progresses. Some degree of spontaneous improvement seems to be possible in pediatric DC; however, a trend toward improving EF was also noted by Canter et al. (19) in their recently reported placebo-controlled trial of carvedilol in selected children with moderate heart failure. In the Canter et al. (19) study, children with structural congenital heart disease or cardiomyopathy randomized to therapy with carvedilol (in addition to the usual treatment) did show a modest improvement in EF, but no improvement in a composite score of clinical status over a 6-month period of treatment. With the exception of these data, the efficacy of medical treatments for heart failure in pediatric populations has not been rigorously assessed prospectively. Of relevance to our study, Lewis and Chabot (20) reviewed the institutional experience with 81 patients in the era before carvedilol and found a marginal improvement in survival over univariate analysis for patients treated with an ACEI extending as long as 2 years post-diagnosis. However, Burch et al. (5) found no reduction in the risk of death or cardiac transplantation in their retrospective series of 61 patients treated with captopril.

It is important to note that the failure of BB and ACEI to affect long-term survival in pediatric DC in our experience does not imply a lack of efficacy of these medications. Statistically significant efficacy in a controlled setting with large numbers of carefully selected patients has already been demonstrated in numerous trials in adults with heart failure. Rather, we believe that our data highlight a lack of overall clinical effectiveness of these treatments in a real-world situation when faced with the range of aggressive disease phenotypes seen in pediatric patients with symptomatic DC. This is reinforced by the observations made in our study that there is an important early hazard phase for death after initial presentation and that the presenting severity of LV dysfunction strongly predicts outcome, implying that an irreversible loss of myocardial function has already been sustained by the time many patients come to clinical attention.

Study limitations. Although this study attempts to determine differences resulting from a change in treatment approach, the era has also changed and along with it the availability of surgical mechanical support and transplantation therapies. The propensity to select transplantation during the latter period (1990 to 2005) may also have changed. Other confounding factors affecting disease detection and outcome may also obscure either a beneficial or even a deleterious effect of current medical treatment choices.

Our institution has been a quaternary referral center for the Province of Ontario throughout the 30-year period and, therefore, our case severity and representation are subject to referral bias. Indeed, the relatively smaller cohort size from 1976 to 1989 may reflect changing diagnostic accuracy and referral patterns during that time period.

Our dataset is limited in size compared with those of large prospective, randomized trials of carvedilol and other medical therapies. We were able to calculate, based on the method of Machin et al. (21), that the transient trend toward a survival benefit that we observed with the combined BB and ACEI therapy versus treatment with an ACEI alone between 11 and 24 months after diagnosis would have required a 25.9% difference in survival at 2 years after diagnosis to reach significance in this cohort. Although not statistically significant in this cohort, the actual observed survival advantage would have proved significant with a power of 0.8 if the groups in question had contained 776 subjects equally apportioned.

However, it is unlikely that a large randomized trial of any one therapy could now be conducted prospectively, given the relative rarity of pediatric DC and the established practice patterns that have developed with time.

Our dataset must be interpreted with the same caution as those of all retrospective or registry-based studies. With regard to treatments given, we carefully documented the continued use of medical treatments, but not the variations in their dosage that occurred with physical growth and change in symptom status. This information was considered to be difficult to interpret because there were (and are) few clear guidelines for optimal dosing of ACEIs and BBs in children. Furthermore, patient weight and adverse symptoms were not consistently recorded in the medical records of all patients.

The analysis is intrinsically complicated by variations in medical treatment combinations given to patients because, theoretically, a patient may have been classified to destination therapy in a group, which did not reflect their predominant medication regimen throughout their experience. We believe that these limitations are largely offset by the ability
Conclusions

Children with DC vary considerably in underlying cause, severity, and age at presentation. These factors have a major role in determining survival, which remains relatively poor and has changed little in the past 30 years. We identified lower EF at presentation and the absence of acute mycarditis as primary risk factors for poor outcome. Additionally, we excluded a statistically significant survival benefit from more recently adopted medical therapies (within the constraints of the cohort size already noted). According to our experience, the outcome of pediatric DC is more likely to be determined by the etiology of the disease than the choice of medical therapy applied within the current framework of heart failure management options. It is important to note, however, that the undefined nature of idiopathic and unclassified DC presents the possibility that, in the future, specific molecular diagnosis may reveal subgroups of patients who will in fact respond well to specific medical therapies.

Further prospective study, including completion of randomized clinical trials in well-defined, etiology-specific subgroups, will be required to determine the true efficacy of any particular drug with regard to morbidity and mortality. At present, cardiac transplantation remains the most viable long-term option for patients with severe symptomatic disease at presentation.

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Key Words: carvedilol • children • dilated cardiomyopathy • survival.