PRELIMINARY COMMUNICATION

Electrophysiological Study With Prophylactic Pacing and Survival in Adults With Myotonic Dystrophy and Conduction System Disease

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Context Up to one-third of patients with myotonic dystrophy type 1 die suddenly. Thus far, no intervention has effectively prevented sudden death.

Objective To determine whether an invasive strategy based on systematic electrophysiological studies and prophylactic permanent pacing is associated with longer survival in patients presenting with myotonic dystrophy type 1 and major infranodal conduction delays than a noninvasive strategy.

Design, Setting, and Patients A retrospective study, the DM1 Heart Registry included 914 consecutive patients older than 18 years with genetically confirmed myotonic dystrophy type 1 who were admitted to the Neurological Unit of the Myology Institute of Pitié-Salpêtrière Hospital, a teaching medical center in Paris, France, between January 2000 and December 2009.

Interventions Among 486 patients whose electrocardiogram showed a PR interval greater than 200 milliseconds, a QRS duration greater than 100 milliseconds, or both, the outcome of 341 (70.2%) who underwent an invasive strategy was compared with 145 (29.8%) who underwent a noninvasive strategy. A propensity score risk adjustment and propensity-based matching analysis was used to account for selection biases.

Main Outcome Measures Rates of overall survival (main outcome measure) and sudden death, respiratory death, and other deaths (secondary outcome measures).

Results Over a median follow-up of 7.4 years (range, 0-9.9 years), 50 patients died in the invasive strategy group and 30 died in the noninvasive strategy group (hazard ratio [HR], 0.74 [95 CI, 0.47-1.16]; $P=.19$), corresponding to an overall 9-year survival of 74.4% (95% CI, 69.2%-79.9%). Regardless of the technique used to adjust for between-group differences in baseline characteristics, the invasive strategy was associated with a longer survival, with adjusted HRs ranging from 0.47 (95% CI, 0.26-0.84; $P=.01$) for a covariate-adjusted analysis of propensity-matched data to 0.61 (95% CI, 0.38-0.99; $P=.047$) for an analysis adjusted for propensity score quintiles. The survival difference was largely attributable to a lower incidence of sudden death, which occurred in 10 patients in the invasive strategy group and in 16 patients in the noninvasive strategy group, with HRs ranging from 0.24 (95% CI, 0.10-0.56; $P=.001$) for an analysis adjusted for propensity score quintiles and covariates to 0.28 (95% CI, 0.13-0.61; $P=.001$) for an unadjusted analysis of propensity-matched data.

Conclusion Among patients with myotonic dystrophy type 1, an invasive strategy was associated with a higher rate of 9-year survival than a noninvasive strategy.

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STEINERT DISEASE, ALSO KNOWN AS myotonic dystrophy type 1 (DM1), is the most common inherited neuromuscular disease in adults, with an incidence of 1:8000.[1] It is an autosomal, dominant disorder caused by the expansion of a (CTG)n triplet repeat in the untranslated 3′ region of the gene encoding dystrophia myotonica protein kinase (DMPK).[2] The manifestations of the disease include muscle weakness, myotonia, multiple endocrine disorders, respiratory insufficiency, and cardiac abnormalities.[3,4]

The prevention of sudden death (the mode of death in up to one-third of patients) is central to patient management.[5-7] Progression of conduction system disease to complete atrioventricular block is the presumed cause of sudden death in a high proportion of patients. Therefore, permanent pacing has been recommended by the American College of Cardiology and the American Heart Association[8] when complete atrioventricular block or advanced high-degree atrioventricular block are detected (class I indication), or prophylactically for patients presenting with first-degree atrioventricular or fascicular block on the electrocardiogram (class

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IIb indication). However, the benefit associated with prophylactic pacing for the prevention of sudden death has never been confirmed by the results of a clinical study.[9,10]

In addition, prophylactic pacing is rarely implemented solely for the first observation of a conduction defect on the electrocardiogram[10] because the estimated ability of the latter to predict sudden death is only approximately 12%.[7] Therefore, a strategy based on an electrophysiological study was proposed to improve the selection of candidates for prophylactic pacing. The rationale for this strategy derives from an observational study in which patients presenting with DM1 with conduction abnormalities on the surface electrocardiogram and an HV interval greater than 70 milliseconds (even as an isolated finding) had a high rate of high-degree atrioventricular block.[9]

The objective of our study was to determine the overall survival rates of patients presenting with conduction abnormalities on the electrocardiogram and managed with a noninvasive strategy and regular surveillance compared with patients managed with an invasive strategy with electrophysiological study and prophylactic pacing when the HV interval exceeded 70 milliseconds.[9,10]

METHODS

The DM1 Heart Registry

The DM1 Heart Registry was designed and organized by the Neurological Unit of the Myology Institute of Pitié-Salpêtrière Hospital. We retrospectively identified and included 914 consecutive patients older than 18 years, who were admitted between January 2000 and December 2009 for the management of DM1 (diagnosed by the presence of ≥50 CTG triplets in the 3′ untranslated region of the *DMPK* gene on blood leukocytes).

We retrospectively reviewed the patients' medical records and entered the results of genetic testing and all neurological and cardiac investigations into a dedicated database. The patient follow-up routinely included yearly ambulatory examinations by a neurologist who specialized in the management of muscular diseases. At each visit, the severity of the muscular disease was graded using the Muscular Disability Rating Score[11] (scale from 1-5, a score of 1 indicated absence of muscular involvement and a score of 5 indicated presence of severe proximal weakness) and the Walton Muscle Weakness Score[12] (scale from 0-10, a score of 0 indicated absence of symptoms and a score of 10 was given for patients confined to bed and requiring assistance for all activities). When patients missed a scheduled visit, they or their primary physician were contacted to ascertain their vital status and, when applicable, the circumstances and cause of death. Yearly follow-up visits also were scheduled with a cardiologist affiliated with our medical center or with a cardiologist at another French tertiary center who specialized in the management of muscular diseases.

After the end of the observation period in December 2009, the vital status of patients who were not seen in our neurological unit or whose circumstances and cause of death were not known was ascertained by consulting the National Death Registry or by contacting their primary physician. Two investigators (C.M. and D.D.), who were not involved in the data collection and who were unaware of the patients' clinical status and medical management, reviewed the circumstances and causes of death and classified all deaths.

This study, which was in compliance with the ethical principles formulated in the Declaration of Helsinki, was approved by our local ethics committee, and all patients, except those who had died before initiation of the study, granted their written, informed consent to participate in the registry.

Patient Selection

Among the 914 patients included in the DM1 Heart Registry, we selected patients whose electrocardiogram showed the presence of impulse propagation abnormalities (defined as a PR interval >200 milliseconds, a QRS duration >100 milliseconds, or both) at registry entry or during follow-up. These criteria are the same as those chosen in a prior study, which suggested a benefit conferred by electrophysiological study–based management.[13]

We excluded (1) recipients of a pacing device implanted before their inclusion in the registry, (2) patients presenting with high-degree atrioventricular block or sinus node dysfunction, who had a class I indication for permanent pacing according to the American College of Cardiology and the American Heart Association recommendations,[10] and (3) patients who, following baseline evaluation or during follow-up, underwent prophylactic implantation of a pacing device for first-degree atrioventricular or fascicular block on surface electrocardiogram without having undergone electrophysiological study.

We divided the patients into 2 groups based on the strategy chosen to treat their conduction system disease. The invasive strategy group included all patients who underwent a systematic electrophysiological study and prophylactic permanent pacing if the HV interval was greater than 70 milliseconds.[14] The noninvasive strategy group included patients who underwent neither electrophysiological study nor implantation of a pacing device, unless they presented with high-degree atrioventricular block on surface electrocardiogram. The decision of whether to perform an electrophysiological study for the diagnosis of conduction system disease was left to the discretion of the cardiologist caring for the patient, and was not influenced by inclusion in our registry, which was performed after the end of the observation period.

The electrophysiological study was performed using standard techniques with 1 bipolar catheter and 1 quadripolar electrode catheter introduced into the femoral vein and advanced to the right atrium and right ventricle, respectively. The HV interval was measured with the quadripolar electrode catheter before its introduction into the right ventricle for programmed ventricular stimulation. The latter was performed with 3 extra stimuli that were delivered at a strength equal to twice the end-diastolic threshold during spontaneous rhythm and after trains of regular pacing stimuli at rates of 100 and 150

beats/min in the high right atrium and at 2 right ventricular sites (usually the apex and the pulmonary outflow tract). A ventricular tachyarrhythmia was classified as sustained if it lasted longer than 30 seconds or was hemodynamically unstable and required immediate termination by direct current shock. When the placement of an implantable cardioverter-defibrillator (ICD) was not followed by the delivery of 1 or more appropriate shocks, it was classified as a prophylactic pacing implant device and its recipient was assigned to the invasive strategy group.

Study End Points

The primary end point of the study was overall survival. The secondary end points were incidence of sudden death, respiratory death, and death from other causes. Sudden death was defined as the unexpected death of a patient who was previously clinically stable according to the World Health Organization definition. Witnessed deaths were classified as sudden if the patient died within 1 hour after the onset of new symptoms. Nonwitnessed deaths were classified as sudden if the patient was known to be alive and clinically stable 24 hours before dying. Respiratory deaths included those due to terminal respiratory insufficiency and pulmonary infections. Death from other causes included all nonsudden and nonrespiratory deaths.

Statistical Analyses

Except when stated otherwise, the data are presented as means and standard deviations or numbers and percentages. The results of the outcome comparisons between the 2 study groups are presented as estimates and 95% confidence intervals.

In the noninvasive strategy group, overall survival was measured between the date of first identification of a minor conduction defect on the electrocardiogram and the date of death or last follow-up. In the invasive strategy group, overall survival was measured between the date of electrophysiological study and the date of death or last follow-up. We chose the date of electrophysiological study instead of the date of first identification of a conduction defect to eliminate the overestimation of benefit associated with the invasive strategy due to an immortal time bias. Overall survival curves were constructed using the Kaplan-Meier product limit estimator. Cox proportional hazards models were used to compare mortality hazards between the noninvasive strategy group and the invasive strategy group and to adjust for potential confounders.

Instead of using a purposeful variable selection procedure, we adjusted the models for known prognostic factors, including age, sex, history of supraventricular tachyarrhythmia, left ventricular ejection fraction, PR interval, QRS duration, ventricular tachyarrhythmias, and heart rate. The proportional hazards assumption was verified by examination of Schoenfeld residuals and by using the lack-of-fit test created by Grambsch and Therneau.[15] Causes of death were analyzed in a competing risks framework, with death from other causes as a competing event. Cumulative incidence functions were estimated using standard methods.[16] Cox proportional cause-specific hazards models were used for competing risk end points,[17] in which case, the same analytical method was used as for overall survival.

Because this was an observational study, a propensity score–based approach was used to limit the biases of between-group comparisons.[18] The propensity score is the probability that a patient with specific baseline characteristics would receive an experimental intervention (in this case, the invasive strategy). Two patients with identical propensity scores included in the invasive strategy group and in the noninvasive strategy group could be considered randomly assigned to each group, and conditioning on the propensity score theoretically leads to unbiased estimates of between-group differences.[19,20] We computed the propensity score using logistic regression, in which the comparison between the invasive strategy group and the noninvasive strategy group was the dependent variable and the baseline characteristics were the independent variables (eTable 1 at http://www.jama.com).

In a primary analysis, Cox proportional hazards models were first adjusted for propensity score quintiles, and were adjusted later for propensity score quintiles plus the other baseline prognostic factors. In a secondary analysis, the models were first adjusted for the propensity score (on the linear predictor scale), and were adjusted later for the propensity score plus the other baseline prognostic factors. A third analysis relied on propensity score matching, which has been found to be one of the most appropriate means of limiting biases with propensity scores.[21] Because the number of patients who underwent the invasive strategy was 2-fold greater than the number who underwent the noninvasive strategy, we applied a 2:1 matching algorithm without replacement, with each patient in the noninvasive strategy group matched to the 2 closest patients in the invasive strategy group within a range of 0.20 SDs of the logit of the estimated propensity score.[22]

The success of the propensity score was estimated by assessing the balance of baseline characteristics after propensity score matching. The balance of each variable between the 2 groups was evaluated by the standardized difference (ie, the absolute difference in sample means divided by an estimate of the pooled standard deviation of the variable expressed as a percentage).[23] Balancing was considered successful when all standardized differences were less than 10%. Analysis of the propensity score–matched data relied on marginal Cox models accounting for potential correlations within matched sets.[24] Analyses using the same model but adjusted for other variables also were performed.

The missing data on vital capacity for 60 patients, size of CTG amplification for 38 patients, left ventricular ejection fraction for 11 patients, PR interval for 10 patients, and QRS duration for 5 patients were handled through multiple imputations using the chained equations method,[25] taking into account the baseline mortality hazard.[26] The 30 independent, imputed data sets that were generated were analyzed sepa-

rately. Estimates of the model variables were then pooled over the 30 imputations (according to the rule by Rubin and Schenker[25]) to present single estimates and standard errors for each variable. All analyses were repeated in the complete cases data set (ie, the data set with no missing data) to examine whether imputations might have qualitatively modified the results. For overall survival, adjusted survival curves accounting for the covariate effects were constructed using the exact estimate method by Ederer et al.[27]

All tests were 2-sided and a *P* value of less than or equal to .05 was considered to indicate a significant association. Given the sample size, and assuming an overall death rate of 20%, the power to detect a hazard ratio (HR) of 0.50 was 88%. Analyses were performed using R statistical software version 2.10.1.[28] Propensity scores were matched using the Matching Package for R,[29] and multiple imputations were performed using the MICE package.[30]

RESULTS

Patient Sample

Among the 914 patients who were evaluated for conduction defects and entered in the DM1 Heart Registry between January 2000 and December 2009, 373 did not have a conduction defect; 55 patients were excluded from the study. Of those excluded, 46 had prior implantation of a pacing device, 5 had a high-degree atrioventricular block at study entry requiring emergent permanent pacing, and 4 had prophylactic permanent pacing without an electrophysiological study. Our analysis includes the remaining 486 patients who presented with minor conduction defects.

Among these 486 patients, 341 were assigned to the invasive strategy group and 145 were assigned to the noninvasive strategy group. In the noninvasive strategy group, electrophysiological study was performed in 287 patients when minor conduction defects were identified on the electrocardiogram and in 54 patients after a mean delay of 3.6 years (range, 0.5-9 years). The baseline characteristics of the overall sample and of each study group are shown in TABLE 1. The prevalence of history of syncope, supraventricular tachyarrhythmia, and heart failure was higher in the invasive strategy group than in the noninvasive strategy group. A trend was observed toward a lower left ventricular ejection fraction and longer PR and QRS intervals on the electrocardiogram in the invasive strategy group compared with the noninvasive strategy group.

Electrophysiological study revealed the presence of an HV interval greater than 70 milliseconds in 164 patients, and sustained ventricular tachyarrhythmias were induced by programmed ventricular stimulation in 70 patients. After electrophysiological study, pacemakers were implanted in 150 patients (44.0%) and ICDs were implanted in 14 patients (4.1%); of whom, none received a shock or were paced for the treatment of a ventricular tachyarrhythmia. The indications for ICD implantation were ventricular tachyarrhythmias induced by programmed ventricular stimulation (n=12) and a left ventricular ejection fraction of less than 30% (n=2, of whom, 1 had a history of sustained ventricular tachyarrhythmia). In addition, 49 patients (14.3%) received various antiarrhythmic drugs for ventricular tachyarrhythmias induced by programmed ventricular stimulation, including amiodarone (n=11) and β-adrenergic blockers (n=25).

Among the 486 patients, 140 had severe conduction defects on the electrocardiogram (described by Groh et al[7]), including a PR interval of 240 milliseconds or greater, a QRS duration of 120 milliseconds or greater, or both. Among these 140 patients, 112 were included in the invasive strategy group and underwent electrophysiological study. Of these 112 patients, 70 underwent pacemaker implantation, 7 received an ICD, and 35 remained device-free. The 10 patients with missing PR intervals and the 5 patients with missing QRS durations were in atrial fibrillation or flutter at the time of recording of the first electrocardiogram, precluding reliable measurements of the conduction time intervals. These 15 patients underwent cardioversion or catheter ablation of their arrhythmia. Within the first week following cardioversion to sinus rhythm, their electrocardiogram showed minor conduction defects.

During follow-up, the yearly lengthening of the PR interval was greater in the invasive strategy group (median, 1.9 milliseconds [interquartile range {IQR}, 0-3.4 milliseconds]) than in the noninvasive strategy group (median, 1.2 milliseconds [IQR, 0-3.1 milliseconds]), whereas the QRS lengthening was 0.9 milliseconds/year (IQR, 0-1.8 milliseconds/year) in the invasive strategy group and 0.8 milliseconds/year (IQR, 0-2.0 milliseconds/year) in the noninvasive strategy group.

Overall Survival

Of the 486 patients included in this analysis, 7 patients (1.4%) were lost to follow-up; these patients could not be reached in person or through their families to ascertain their precise medical status. However, by consulting our National Death Registry, we determined that the 7 patients were alive at the end of the observation period. The median patient follow-up was 7.4 years (range, 0-9.9 years). The mean duration of follow-up was 5.9 years (range, 0-9.9 years) in the invasive strategy group and 6.5 years (range, 0-9.9 years) in the noninvasive strategy group. The mean times to last ambulatory visits were 4.7 years (range, 0-9.8 years) in the invasive strategy group and 5.0 years (range, 0-9.7 years) in the noninvasive strategy group. The numbers of ambulatory visits were similar in both groups. There were a median of 5 visits to the neurology department (IQR, 2-7 visits) in the invasive strategy group and 4 visits (IQR, 2-7 visits) in the noninvasive strategy group. Similarly, there were a median of 7 visits to the cardiology department (IQR, 3-10 visits) in the invasive strategy group and 6 visits (IQR, 3-9 visits) in the noninvasive strategy group.

Among the 486 patients presenting with conduction abnormalities, 80 died during follow-up, corresponding to a 9-year survival of 74.4% (95% CI, 69.2%-79.9%). Of these, 50 patients died while in the invasive strategy group and 30 died while in the noninvasive strategy group.

Survival in the invasive strategy group was consistently higher than in the noninvasive strategy group (FIGURE 1), and their respective 9-year survival rates were 76.7% (95% CI, 70.7%-83.2%) and 69.2% (95% CI, 59.7%-80.3%). In the absence of data adjustment, this difference was not statistically significant (HR, 0.74 [95% CI, 0.47-1.16]; *P*=.19; FIGURE 2). After adjustment for age, sex, history of supraventricular tachyarrhythmia, left ventricular ejection fraction, PR interval, QRS duration, and heart rate, the hazard of dying was nearly 40% lower in the invasive strategy group than in the noninvasive strategy group (HR, 0.61 [95% CI, 0.38-0.98]; *P*=.04; Figure 2).

An analysis of the complete cases (ie, patients without missing data) yielded similar results (HR, 0.57 [95% CI, 0.35-0.95]; *P*=.03). We obtained similar results when the analysis was adjusted for propensity score quintiles (HR, 0.61 [95% CI, 0.38-0.99]; *P*=.047) and for propensity score quintiles plus baseline prognostic factors (HR, 0.55 [95% CI,

Table 1. Baseline Characteristics of Patients at Entry Into the DM1 Heart Registry

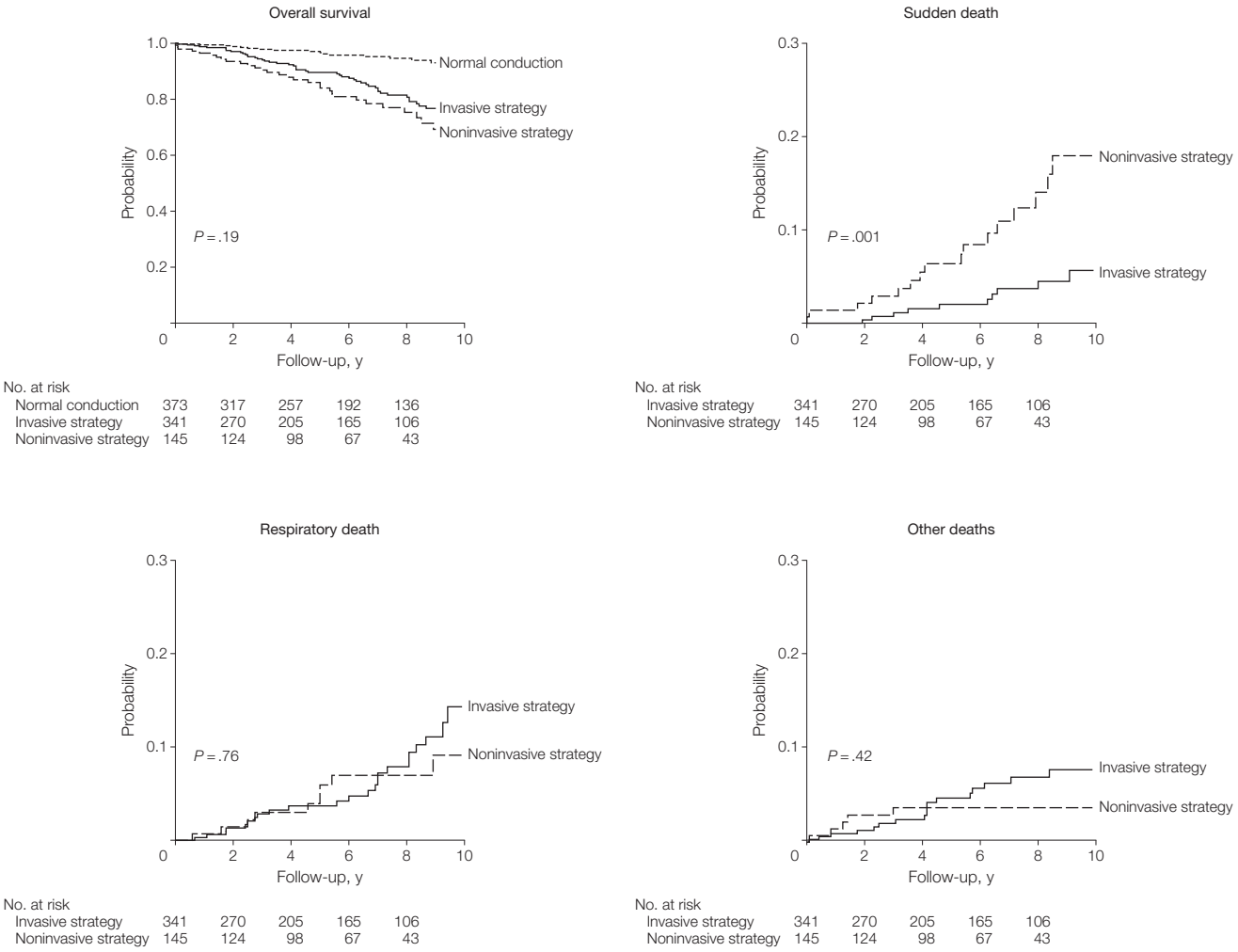
	All Patients (N = 859)	Normal Conduction (n = 373)	Noninvasive Strategy (n = 145)	Invasive Strategy (n = 341)	Standardized Difference, %[a]
Men, No. (%)	404 (47.0)	140 (37.5)	78 (53.8)	186 (54.5)	1.5
Family history of sudden death, No. (%)	70 (8.1)	23 (6.2)	14 (9.7)	33 (9.7)	<1.0
Mean (SD)					
Age, y	38.4 (13.6)	33.4 (12.7)	41.9 (13.3)	42.3 (13.0)	3.2
Log number of CTG repeats	2.66 (0.35)	2.60 (0.35)	2.69 (0.37)	2.71 (0.33)	7.4
Age at disease onset, y	25.1 (14.8)	23.1 (13.7)	27.0 (14.8)	26.4 (15.8)	3.7
Muscular Disability Rating Score[11], [b]	2.7 (1.0)	2.3 (0.9)	2.9 (1.1)	3.0 (0.9)	13.4
Walton Muscle Weakness Score[12], [c]	1.7 (1.7)	1.1 (1.4)	2.0 (1.9)	2.2 (1.7)	8.5
Personal medical history, No. (%)					
Diabetes	63 (7.3)	11 (2.9)	15 (10.3)	37 (10.9)	1.6
Dyslipidemia	134 (15.6)	30 (8.0)	30 (20.7)	74 (21.7)	2.5
Smoking	147 (17.1)	53 (14.2)	25 (17.2)	69 (20.2)	7.7
Coronary artery disease	34 (4.0)	4 (1.1)	4 (2.8)	26 (7.6)	22.0
Syncope	44 (5.1)	20 (5.4)	4 (2.8)	20 (5.9)	15.3
Supraventricular tachyarrhythmia	65 (7.6)	8 (2.1)	11 (7.6)	46 (13.5)	19.3
Ventricular tachyarrhythmia	9 (1.0)	5 (1.3)	1 (0.7)	3 (0.9)	2.1
Heart failure	18 (2.1)	4 (1.1)	1 (0.7)	13 (3.8)	21.1
Disease-related symptoms and signs					
No. (%)					
None	507 (59.0)	264 (70.8)	84 (57.9)	159 (46.6)	22.7
Dyspnea	214 (24.9)	57 (15.3)	46 (31.7)	111 (32.6)	1.8
Light-headedness	102 (11.9)	31 (8.3)	20 (13.8)	51 (15.0)	3.3
Palpitation	95 (11.1)	29 (7.8)	15 (10.3)	51 (15.0)	13.9
First-degree atrioventricular block	293 (34.1)	0	80 (55.2)	213 (62.5)	14.8
Left bundle-branch block	101 (11.7)	0	22 (15.2)	79 (23.2)	20.4
Right bundle-branch block	58 (6.7)	0	13 (9.0)	45 (13.2)	13.5
Mean (SD)					
Systolic blood pressure, mm Hg	116.6 (13.8)	115.1 (13.2)	119.7 (13.2)	117.0 (14.5)	20.1
Diastolic blood pressure, mm Hg	69.3 (9.4)	68.1 (8.9)	71.6 (9.2)	69.6 (9.8)	20.5
Heart rate, beats/min	69.0 (12.9)	69.6 (12.3)	70.4 (14.2)	67.8 (13.0)	19.4
PR interval, ms	189 (32)	168 (17)	200 (29)	207 (32)	22.9
QRS interval, ms	99 (18)	89 (8)	104 (17)	109 (21)	26.7
Left ventricular ejection fraction, %	63.7 (6.7)	65.4 (5.5)	64.0 (6.5)	61.8 (7.4)	31.7
Vital capacity, % predicted value	80.6 (20.1)	84.6 (18.1)	77.3 (21.2)	78.1 (20.8)	3.7
Drug therapy, No. (%)					
Mexiletine	7 (0.8)	5 (1.3)	2 (1.4)	0	16.7
Amiodarone	15 (1.7)	2 (0.5)	4 (2.8)	9 (2.6)	<1.0
Oral anticoagulant	28 (3.3)	2 (0.5)	3 (2.1)	23 (6.7)	22.9
Aspirin	30 (3.5)	4 (1.1)	6 (4.1)	20 (5.9)	7.9
Class I antiarrhythmic drug	7 (0.8)	1 (0.3)	0	6 (1.8)	18.9
β-Adrenergic blocker	31 (3.6)	5 (1.3)	3 (2.1)	23 (6.7)	22.9
ACE inhibitor or ARB	35 (4.1)	4 (1.1)	3 (2.1)	28 (8.2)	28.0

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
[a] Calculated as the absolute value of the mean difference between the noninvasive and invasive groups divided by the pooled standard deviation.
[b] Scale range from 1 to 5; a score of 1 indicated absence of muscular involvement and a score of 5 indicated presence of severe proximal weakness.
[c] Scale range from 0 to 10; a score of 0 indicated absence of symptoms and a score of 10 was given for patients confined to bed and requiring assistance for all activities.

0.33-0.92]; *P*=.02; Figure 2). These results were confirmed by an analysis of the complete cases only, as well as by an analysis adjusted for the propensity score on the linear predictor scale (eResults at http://www.jama.com).

In addition, we successfully matched 212 patients in the invasive strategy group with 106 patients in the noninvasive strat-

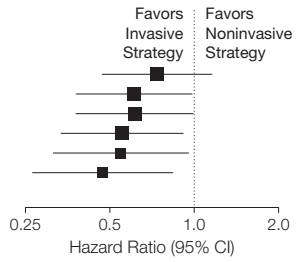
Figure 1. Overall Survival and Cumulative Incidence of the Various Causes of Death



The overall survival of patients without conduction defects was added for comparative purposes. Likelihood ratio tests in Cox proportional hazards models were used to compare the data and generate the *P* values.

Figure 2. Death Risk by Invasive Strategy Group Compared With Noninvasive Strategy Group

Analysis Method	No. of Patients: Noninvasive Strategy	No. of Patients: Invasive Strategy	No. of Events: Noninvasive Strategy	No. of Events: Invasive Strategy	Hazard Ratio (95% CI)
Unadjusted	145	341	30	50	0.74 (0.47-1.16)
Adjusted	145	341	30	50	0.61 (0.38-0.98)
Propensity quintile	145	341	30	50	0.61 (0.38-0.99)
Propensity quintile plus covariates	145	341	30	50	0.55 (0.33-0.92)
Propensity matched	113	226	27	27	0.55 (0.31-0.96)
Propensity matched plus covariates	113	226	27	27	0.47 (0.26-0.84)



For propensity score–matched samples, the average numbers over the imputed data sets are shown. The size of the data markers is proportional to the number of events.

egy group. Their main baseline characteristics are shown in TABLE 2. The propensity score successfully balanced the baseline characteristics of the 2 groups, and all of the standardized differences were below 10%. In the invasive strategy group, 95 patients (40.6%) underwent implantation of pacing devices, including 81 pacemakers and 5 ICDs. The follow-up characteristics were similar in both study groups, including follow-up duration (mean of 5.5 years [range, 0-9.9 years] in the invasive strategy group and 6.6 years [range, 0-9.9 years] in the noninvasive strategy group), time to last ambulatory visit (mean of 4.5 years [range, 0-9.8 years] vs 5.1 [range, 0-9.7 years], respectively), number of ambulatory visits to the neurology department (median of 5 visits [IQR, 2-7 visits] vs 5 visits [IQR, 2-7 visits]), and number of visits to the cardiology department (median of 7 visits [IQR, 3-10 visits] vs 7 visits [IQR, 3-10 visits]).

Table 2. Baseline Characteristics of Patients Matched 2:1 by Propensity Score

	Noninvasive Strategy (n = 106)	Invasive Strategy (n = 212)	Standardized Difference, %[a]
Men, No. (%)	57 (53.8)	117 (55.2)	2.8
Family history of sudden death, No. (%)	10 (9.4)	23 (10.8)	4.7
Mean (SD)			
Age, y	40.8 (13.5)	40.4 (12.6)	2.7
Log number of CTG repeats	2.69 (0.38)	2.71 (0.32)	6.4
Age at disease onset, y	26.7 (14.5)	25.8 (15.1)	6.1
Muscular Disability Rating Score[11], [b]	2.9 (1.1)	3.0 (0.9)	3.9
Walton Muscle Weakness Score[12], [c]	1.9 (1.9)	2.0 (1.4)	2.0
Personal medical history, No. (%)			
Diabetes	12 (11.3)	21 (9.9)	4.6
Dyslipidemia	22 (20.8)	50 (23.6)	6.8
Smoking	22 (20.8)	42 (19.8)	2.3
Coronary artery disease	4 (3.8)	11 (5.2)	6.8
Syncope	4 (3.8)	5 (2.4)	8.2
Supraventricular tachyarrhythmia	7 (6.6)	18 (8.5)	7.1
Ventricular tachyarrhythmia	0	1 (0.5)	9.7
Heart failure	1 (0.9)	3 (1.4)	4.4
Disease-related symptoms and signs No. (%)			
None	57 (53.8)	111 (52.4)	2.8
Dyspnea	36 (34.0)	68 (32.1)	4.0
Light-headedness	17 (16.0)	30 (14.2)	5.3
Palpitation	14 (13.2)	22 (10.4)	8.8
First-degree atrioventricular block	63 (59.4)	122 (57.5)	3.8
Left bundle-branch block	18 (17.0)	39 (18.4)	3.7
Right bundle-branch block	11 (10.4)	21 (9.9)	1.6
Mean (SD)			
Systolic blood pressure, mm Hg	118.3 (13.2)	118.3 (14.2)	<1.0
Diastolic blood pressure, mm Hg	70.5 (9.2)	71.0 (9.3)	5.5
Heart rate, beats/min	68.6 (13.3)	68.8 (13.0)	1.4
PR interval, ms	204 (27)	204 (28)	1.6
QRS interval, ms	105 (18)	106 (18)	5.8
Left ventricular ejection fraction	63.5 (5.8)	63.7 (5.2)	5.3
Vital capacity, % predicted value	77.3 (21.7)	78.7 (19.2)	6.7
Drug therapy, No. (%)			
Mexiletine	0	0	<1.0
Amiodarone	2 (1.9)	5 (2.4)	3.3
Oral anticoagulant	3 (2.8)	6 (2.8)	<1.0
Aspirin	5 (4.7)	12 (5.7)	4.2
Class I antiarrhythmic drug	0	0	<1.0
β-Adrenergic blocker	3 (2.8)	7 (3.3)	2.7
ACE inhibitor or ARB	2 (1.9)	5 (2.4)	3.3

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
[a] Calculated as the absolute value of the mean difference between the noninvasive and invasive groups divided by the pooled standard deviation.
[b] Scale range from 1 to 5; a score of 1 indicated absence of muscular involvement and a score of 5 indicated presence of severe proximal weakness.
[c] Scale range from 0 to 10; a score of 0 indicated absence of symptoms and a score of 10 was given for patients confined to bed and requiring assistance for all activities.

In the 30 imputed data sets, a similar method allowed matching on an average of 226 patients in the invasive strategy group with 113 in the noninvasive strategy group. In a Cox model accounting for the correlation within matched sets, the HR for mortality was 0.55 (95% CI, 0.31-0.96; $P=.03$) for the invasive strategy group and 0.47 (95% CI, 0.26-0.84; $P=.01$) for the noninvasive strategy group when the analysis was adjusted for known baseline prognostic factors (Figure 2). These results were confirmed by similar analyses of the complete cases (eResults). All adjustment methods lead to HRs for overall survival ranging from 0.47 to 0.61, corresponding to an 11.3% to 16.9% higher probability of survival at 9 years associated with the invasive strategy.

Causes of Death

Among the 80 patients who died, the cause of death was determined at the time of death in 69 patients and retrospectively in 11 patients. In the invasive strategy group, 10 patients died suddenly, including 8 pacemaker recipients, 1 ICD recipient, and 1 patient without a pacing device, whose HV interval was less than 70 milliseconds. Their individual characteristics are summarized in eTable2. In brief, the memories of the devices could be analyzed in 7 of these patients, which revealed ventricular fibrillation in 3 patients, asystole with pacing stimuli in 3 patients, and asystole without pacing stimuli in 1 patient. In the noninvasive strategy group, 16 patients died suddenly.

Among the entire sample, sustained ventricular tachyarrhythmias were diagnosed in 5 patients, including 4 patients in the invasive strategy group (of whom, 3 had pacemakers) and 1 in the noninvasive strategy group. The 9-year

cumulative incidence of sudden death was 4.5% (95% CI, 2.1%-7.8%) in the invasive strategy group and 18.0% (95% CI, 10.2%-27.4%) in the noninvasive strategy group ($P=.001$). The hazard of dying suddenly was 75% lower in the invasive strategy group than in the noninvasive strategy group, regardless of the analytical method applied (FIGURE 3); the HRs ranged between 0.24 (95% CI, 0.10-0.56; $P=.001$) and 0.28 (95% CI, 0.13-0.61; $P=.001$), depending on the method used. The analyses of the complete cases yielded similar results (eResults).

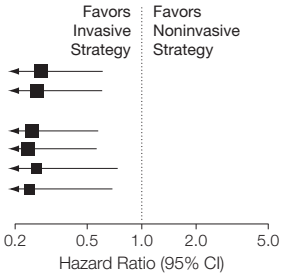
Respiratory failure was the cause of death in 23 patients in the invasive strategy group and in 9 patients in the noninvasive strategy group. At 9 years, the cumulative incidence of death from respiratory failure was 11.1% (95% CI, 6.9%-16.4%) in the invasive strategy group and 9.1% (95% CI, 4.1%-16.6%) in the noninvasive strategy group ($P=.76$). No significant difference in the rate of respiratory death was observed between the 2 groups, regardless of the analysis method applied (Figure 3).

Death from other causes occurred in 17 patients in the invasive strategy group and in 5 patients in the noninvasive strategy group, including 3 deaths from heart failure, 10 deaths from cancer, and 9 deaths from other causes. Although the cumulative incidence of death from other causes was higher in the invasive strategy group (7.7%; 95% CI, 4.6%-11.9%) than in the noninvasive strategy group (3.7%; 95% CI, 1.4%-7.9%) ($P=.42$), no analysis revealed a significant increase in mortality from other causes (Figure 3). The highest HR was observed for the unadjusted analysis, whereas the different adjustment methods yielded smaller HRs. It is, however, noteworthy that the

Figure 3. Various Causes of Death by Invasive Strategy Group Compared With Noninvasive Strategy Group

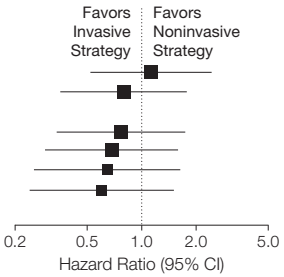
Sudden death

Analysis Method	No. of Patients: Noninvasive Strategy	No. of Patients: Invasive Strategy	No. of Events: Noninvasive Strategy	No. of Events: Invasive Strategy	Hazard Ratio (95% CI)
Unadjusted	145	341	16	10	0.28 (0.13-0.61)
Adjusted	145	341	16	10	0.26 (0.11-0.61)
Propensity score					
Quintile	145	341	16	10	0.25 (0.11-0.58)
Quintile plus covariates	145	341	16	10	0.24 (0.10-0.56)
Matched	113	226	14	7	0.26 (0.09-0.73)
Matched plus covariates	113	226	14	7	0.24 (0.08-0.69)



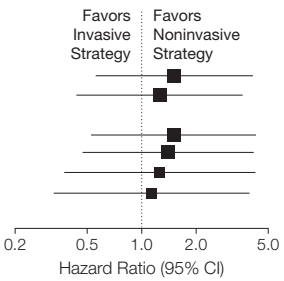
Respiratory death

Analysis Method	No. of Patients: Noninvasive Strategy	No. of Patients: Invasive Strategy	No. of Events: Noninvasive Strategy	No. of Events: Invasive Strategy	Hazard Ratio (95% CI)
Unadjusted	145	341	9	23	1.13 (0.52-2.43)
Adjusted	145	341	9	23	0.79 (0.36-1.77)
Propensity score					
Quintile	145	341	9	23	0.77 (0.34-1.74)
Quintile plus covariates	145	341	9	23	0.68 (0.29-1.59)
Matched	113	226	9	11	0.64 (0.25-1.63)
Matched plus covariates	113	226	9	11	0.60 (0.24-1.51)



Other deaths

Analysis Method	No. of Patients: Noninvasive Strategy	No. of Patients: Invasive Strategy	No. of Events: Noninvasive Strategy	No. of Events: Invasive Strategy	Hazard Ratio (95% CI)
Unadjusted	145	341	5	17	1.51 (0.56-4.09)
Adjusted	145	341	5	17	1.25 (0.44-3.59)
Propensity score					
Quintile	145	341	5	17	1.50 (0.53-4.26)
Quintile plus covariates	145	341	5	17	1.40 (0.47-4.14)
Matched	113	226	4	10	1.26 (0.37-4.23)
Matched plus covariates	113	226	4	10	1.13 (0.33-3.92)



For propensity score–matched samples, the average numbers over the imputed data sets are shown. The size of the data markers is proportional to the number of events.

proportional hazards assumption was slightly violated when comparing the hazards of other deaths between both groups, which might complicate the interpretation of these results. The hazard was lower in the invasive strategy group for up to approximately 5 years. No other death was observed thereafter in the noninvasive strategy group, such that the hazard became greater in the invasive strategy group.

COMMENT

The main observation made in our study was a higher survival rate and lower incidence of sudden death associated with the invasive strategy compared with the noninvasive strategy in patients presenting with DM1 and surface electrocardiogram manifestations of cardiac conduction system disease after careful adjustment for differences between the 2 groups.

A potential benefit conferred by the invasive strategy had already been suggested by the results of our pilot study limited to 49 patients having DM1, who had no history of high-degree atrioventricular block, and who underwent prophylactic pacing for conduction defects on surface electrocardiogram and had an HV interval greater than 70 milliseconds measured during electrophysiological study.[13] Over a mean (SD) follow-up of 53.5 (27.2) months, 1 or more episodes of complete atrioventricular block was recorded in the memories of the devices of 42.8% of the patients. These observations have not been confirmed in the interim, and no study has examined the potential merit of implementing an electrophysiological study–based strategy upon the detection of minor electrocardiogram conduction defects, followed by permanent pacing if the HV interval is greater than 70 milliseconds. Therefore, prophylactic pacing has, thus far, been assigned a class IIb indication by the American College of Cardiology and the American Heart Association.

In a long-term, observational study, Groh et al[7] found that "severe" abnormalities on the surface electrocardiogram and a clinical diagnosis of atrial tachyarrhythmia were independent risk factors for sudden death in 406 patients with genetically confirmed DM1. By multiple variable analysis, these authors found no correlation between implantation of a pacemaker (either prophylactic or for high-degree atrioventricular block) and total mortality or sudden death. However, that study was designed to identify predictors of sudden death, and not specifically to ascertain the impact of permanent pacing on mortality. Compared with that study, the main advantages of our analysis are a definition of an invasive strategy not limited to the implantation of a pacemaker, the implementation of a propensity risk score to adjust the baseline patient characteristics and eliminate potential biases, the larger study sample size, and the higher proportion of patients who underwent the invasive strategy.

Analyses of the causes of death in our population showed that the higher overall survival rate in the invasive strategy group was largely attributable to a considerably lower incidence of sudden death, without significant effects on respiratory death and deaths from other causes. This global benefit was observed independently of the underlying mechanisms of sudden death which are, in most cases, difficult to determine and include ventricular arrhythmias, pulmonary embolism, respiratory failure, and major conduction defects leading to asystole.[13] The markedly lower incidence of sudden death in the invasive strategy group suggests that (1) conduction system disease is a major cause of sudden death that appears to be preventable by implementation of an invasive strategy, (2) electrophysiological study might have contributed to the identification of malignant ventricular arrhythmias, and might account for some of the observed differences between the invasive strategy group and the noninvasive strategy group, and (3) additional studies are needed, perhaps to test the efficacy of antiarrhythmic drugs or ICD.

The main strengths of our study are (1) the size of our sample of consecutive patients, (2) the use of all-cause mortality as the primary end point, which is clinically relevant, objective, and wholly unbiased,[31] (3) the use of a blinded review of all causes of death, (4) the use of a propensity analysis including all known prognostic factors of DM1 to adjust for potential selection biases, and (5) the importance of the benefit observed, regardless of the statistical method used to compare the 2 strategies.

The main limitation of this study was that the comparison of an invasive strategy vs a noninvasive strategy was not based on random assignments. Observational studies can only partially control for factors actually measured and can adjust for these factors only to the extent of the power of the measuring instrument. However, we used a propensity analysis, which is the most effective method of adjustment for selection biases and confounding factors.[18] Several points limit the probability of differences exclusively due to bias: (1) the major effect on sudden death without significant effects on other deaths, (2) the magnitude of the effect observed, with a risk of sudden death that was 75% lower in the invasive strategy group than in the noninvasive strategy group, regardless of the analytical method applied, and (3) the significantly lower risk for sudden death in the invasive strategy group using unadjusted values, despite a higher baseline risk profile.

The inevitable variability in the management of these patients, particularly with respect to the timing of electrophysiological study during their follow-up, is another potential concern. Of the 314 patients in the invasive strategy group, 54 underwent electrophysiological study long after the first identification of conduction defects. Because this follow-up period preceded the electrophysiological study, it might have introduced an immortal bias in our analyses. Therefore, when comparing the noninvasive strategy group with the invasive strategy group, we replaced the time when conduction defects were initially diagnosed with the time when the electrophysiological study was performed.

Finally, a low adverse event rate is another potential limitation of our study, which limited the accuracy of our estimates of the survival benefit.

CONCLUSION

In summary, among patients with DM1 with major infranodal conduction delays, management with an invasive strategy based on systematic electrophysiological studies and prophylactic permanent pacing is associated with longer survival. While other studies are needed to confirm these findings, consideration of this strategy may be prudent in this population at higher than average risk for sudden death.

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