ESC European Society of Cardiology

Europace (2023) **25**, 156–163
https://doi.org/10.1093/europace/euac104

CLINICAL RESEARCH
Electrocardiography and risk stratification

An evaluation of 24 h Holter monitoring in patients with myotonic dystrophy type 1

Isis B. T. Joosten [1]*, Cheyenne E.W. Janssen[1], Corinne G.C. Horlings[1,2], Dennis den Uijl [3], Reinder Evertz[4], Baziel G.M. van Engelen[5], Catharina G. Faber[1], and Kevin Vernooy [3,4]

[1]Department of Neurology, School for Mental Health and Neuroscience (MHeNS), Maastricht University Medical Centre+, Maastricht, The Netherlands; [2]Department of Neurology, Medical University Innsbruck, Innsbruck, Austria; [3]Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre+, Maastricht, The Netherlands; [4]Department of Cardiology, Radboud University Medical Centre, Nijmegen, The Netherlands; and [5]Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, The Netherlands

Received 22 February 2022; editorial decision 27 May 2022; online publish-ahead-of-print 19 July 2022

Aims To evaluate the clinical effectiveness of routine 24 h Holter monitoring to screen for conduction disturbances and arrhythmias in patients with myotonic dystrophy type 1 (DM1).

Methods and results A retrospective two-centre study was conducted including DM1-affected individuals undergoing routine cardiac screening with at least one 24 h Holter monitoring between January 2010 and December 2020. For each individual, the following data were collected: Holter results, results of electrocardiograms (ECGs) performed at the same year as Holter monitoring, presence of cardiac complaints, and neuromuscular status. Holter findings were compared with the results of cardiac screening (ECG + history taking) performed at the same year. Cardiac conduction abnormalities and/or arrhythmias that would have remained undiagnosed based on history taking and ECG alone were considered *de novo* findings. A total 235 genetically confirmed DM1 patients were included. Abnormal Holter results were discovered in 126 (54%) patients after a mean follow-up of 64 ± 28 months in which an average of 3 ± 1 Holter recordings per patient was performed. Abnormalities upon Holter mainly consisted of conduction disorders (70%) such as atrioventricular (AV) block. Out of 126 patients with abnormal Holter findings, 74 (59%) patients had *de novo* Holter findings including second-degree AV block, atrial fibrillation/flutter and non-sustained ventricular tachycardia. Patient characteristics were unable to predict the occurrence of *de novo* Holter findings. In 39 out of 133 (29%) patients with normal ECGs upon yearly cardiac screening, abnormalities were found on Holter monitoring during follow-up.

Conclusion Twenty-four hour Holter monitoring is of added value to routine cardiac screening for all DM1 patients.

Keywords Myotonic dystrophy • Neuromuscular disease • Electrocardiogram • Holter monitoring • Ambulatory monitoring

Introduction

Myotonic dystrophy type 1 (DM1, also known as Steinert disease) is a highly variable neuromuscular disease with frequent cardiac involvement.[1] DM1 is caused by a cytosine-thymine-guanine (CTG)-repeat expansion on chromosome 19 and symptom severity has been demonstrated to correlate with increasing repeat lengths.[2,3] At present, curative or disease modifying treatment options are still unavailable, and disease management focusses on early detection of organ complications and improving quality of life.

Since as many as 50% of DM1 patients may experience cardiac involvement, and arrythmias are among the most frequent causes of death in the DM1 population, cardiac screening is a significant part of disease management.[1,4] Even though strict guidelines on the cardiac management of DM1 are still lacking, consensus-based care recommendations describe the necessity of annual screening through history taking and electrocardiogram (ECG).[5,6] Apart from ECG, routine cardiac imaging and 24 h Holter monitoring are commonly carried out, even though the exact role of Holter monitoring has not yet been validated.[6]

* Corresponding author. Tel: +31 43 3877059; fax: +31 43 3877055. *E-mail address*: isis.joosten@mumc.nl

What's new?

- Heart rhythm or conduction abnormalities were present on 24 h Holter monitoring in 54% of the screened myotonic dystrophy type 1 (DM1) population, after a mean follow-up of approximately 5 years.
- In 59% of cases, discovered abnormalities upon Holter monitoring were classified as *de novo* findings, meaning they would have remained undiagnosed through ECG and history taking alone. *De novo* Holter findings included second-degree AV block, AV block combined with bundle branch block, atrial fibrillation/flutter, and non-sustained ventricular tachycardia.
- Abnormalities upon Holter monitoring were not only present in patients with previously ascertained ECG abnormalities, but also in 29% of patients without ECG abnormalities upon yearly cardiac screening.
- Patient characteristics were unable to predict the occurrence of *de novo* Holter findings upon screening.
- Based on the current study, 24 h Holter monitoring is an important tool for routine cardiac screening in all DM1 patients.

While ECG abnormalities such as prolonged PR interval, widened QRS complex and prolonged QTc interval are known to be common in DM1 patients, ambient conduction abnormalities and arrhythmias such as advanced (nocturnal) atrioventricular (AV) block and non-sustained ventricular arrhythmias could remain unnoticed on ECG.[1,7,8] Therefore, 24 h Holter monitoring may be of added value, even more so since conduction disorders tend to remain asymptomatic in most patients.[8] In case of (progressive) conduction disorders or arrhythmias on Holter monitoring or ECG, a diagnostic electrophysiological study (EPS) and subsequent cardiac device implantation can be considered.[9,10]

The current study aims to evaluate the clinical effectiveness of routine 24 h Holter monitoring to screen for conduction disturbances and arrhythmias in DM1 patients.

Methods

Study population

A retrospective two-centre study was conducted at the Maastricht University Medical Centre+ (MUMC+) and Radboud University Medical Centre (Radboudumc). The MUMC+ and Radboudumc form the Myotonic Dystrophy Expertise Centre in The Netherlands. The Dutch DM1 patient registry (MYODRAFT study) was used to identify adult DM1-affected individuals who underwent routine cardiac screening including at least one 24 h Holter monitoring at one of both centres between January 2010 and December 2020. For each individual, the following data were collected: 24 h Holter monitoring results, results of 12-lead ECGs performed at the same year as the Holter monitoring, the presence of cardiac complaints, the occurrence of cardiac treatment consequences during follow-up, baseline left ventricular ejection fraction (LVEF), neurological assessment consisting of muscular impairment rating scale (MIRS) score, DM1 DNA analysis results consisting of the CTG-repeat size, and the presence of an indication for nightly non-invasive ventilation (NIV). Follow-up time was based on the number of months between the first 24 h Holter monitoring and December 2020.

Data were collected as part of the Dutch DM1 patient registry (MYODRAFT study) for which written informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki, and the research protocol was approved by the institutional Medical Ethics Committee (METC 16-4-001, approved on 18 March 2016). All clinical measurements were carried out as part of routine clinical care. The data underlying this article will be shared on reasonable request to the corresponding author.

Cardiac assessment

At each yearly visit of DM1 patients, history taking, physical examination, and resting 12-lead ECG were performed. The presence of cardiac related symptoms was assessed. Twenty-four hour Holter monitoring was performed every other year. Echocardiography was conducted with a 3-year interval.

In case of (progressive) conduction disorders on resting ECG, conduction disorders or arrythmias on Holter monitoring, or clinical symptomatology (palpitations, dizziness, or (pre)syncope), an EPS was considered. The decision whether to perform an EPS was always left to the discretion of a cardiac electrophysiologist with DM1 expertise, and was performed independent of inclusion in the DM1 observational registry.

Twenty-four hour Holter monitoring

Holter monitoring data were evaluated by a qualified cardiac electrophysiologist and the first Holter evaluation was considered the baseline measurement. The following parameters were considered clinically relevant in DM1 follow-up: first-, second-, or third-degree AV block, bundle branch block, atrial fibrillation/flutter (episodes lasting >30 s), supraventricular tachycardia other than atrial fibrillation/flutter (episodes lasting >30 s), non-sustained ventricular tachycardia (NSVT; ≥ 3 consecutive ventricular beats at ≥ 120 b.p.m. lasting <30 s) and sustained ventricular tachycardia, symptomatic sinus bradycardia <40 b.p.m., frequent ventricular extrasystoles ($>5\%$ of total number of heartbeats), and sinus arrest >3 s.

Holter findings were compared with the results of DM1 screening (history taking, physical examination, and resting 12-lead ECG) performed at the same year. Cardiac conduction abnormalities and/or arrhythmias upon Holter monitoring that would have remained undiagnosed based on history taking and ECG alone were considered as *de novo* findings.

Electrocardiogram

Standard 12-lead ECG results, performed at the same year as each 24 h Holter monitoring evaluation, were collected. All ECGs were evaluated by a qualified cardiac electrophysiologist for the following parameters: cardiac rhythm, heart rate in beats per minute, heart axis, PR interval, categorical assessment of AV conduction [normal PR interval (PR$\leq$200 ms) or prolonged PR interval (PR $>$ 200 ms), and further categorized into first-, second-degree Wenckebach, second-degree Mobitz, third-degree AV block], QRS duration, categorical assessment of QRS complex (narrow in case of QRS $\leq$120 ms or widened in case of QRS $>$ 120 ms), QTc time, and categorical assessment of QTc time (normal, or abnormal in case of QTc $\geq$450 ms in men or $\geq$460 ms in women).

Neurological assessment

As standard of care, DM1-affected individuals visit the neurology outpatient clinic annually to determine disease progression and muscle status. In order to define neuromuscular progression at the time of 24 h Holter monitoring, MIRS scores determined at the same year were collected. The MIRS score is a disease-specific ordinal 5-point rating scale, based on manual muscle testing of 11 muscle groups.[11]

The DM1-affected individuals with a MIRS score of 1–3, indicating distal muscle weakness, were categorized as having a low MIRS score. The DM1-affected individuals with a MIRS score of 4 or 5, indicating proximal muscle weakness, were categorized as having a high MIRS score.

Respiratory follow-up

Respiratory involvement was assessed through history taking by the coordinating neuromuscular neurologist upon yearly visits. In case of (suspected) respiratory involvement, patients were referred to a pulmonologist for detailed screening consisting of pulmonary function testing, polysomnography (PSG), and blood gas analysis. Data on NIV indications were collected as part of the MYODRAFT registry. The indication for NIV was based on the 207th European Neuromuscular Centre Workshop (21 July 2014).

DNA analysis

The DNA analysis took place at DM1 diagnosis. All CTG-repeat lengths were determined by analysing DNA extracted from peripheral blood samples through polymerase chain reaction, followed by fragment length analysis and Southern blot analysis.

Data analysis

Statistical analysis was performed using IBM SPSS statistics software version 25 (SPSS Inc, Chicago, IL, USA). The distribution of continuous variables was assessed for normality using Shapiro–Wilk test or Kolmogorov–Smirnov when appropriate, and was visually evaluated by inspection of histograms and standardized normal probability plots. Continuous variables are expressed as mean ± standard deviation or as median with interquartile range in case of skewness. Categorical variables are expressed as counts (percentages). Differences between groups were compared using the χ^2 test or Fisher's exact test (categorical data), and the unpaired Student's *t*-test or the Mann–Whitney *U* test (continuous variables).

Univariable binary logistic regression using pre-defined variables was performed to identify predictors for the presence of *de novo* findings upon 24 h Holter monitoring. Selection of variables was based on literature and clinical experience of a qualified electrophysiologist with DM1 expertise.[1,12] Variables with $P < 0.20$ on univariable analysis were considered important and were included in the multivariable logistic regression analysis for identification of independent predictors, presented as odds ratios (ORs) with confidence intervals (CI). *P*-values of <0.05 were considered statistically significant.

Results

Study population

The MYODRAFT registry consisted of 293 patients undergoing routine cardiac evaluation in the Myotonic Dystrophy Expertise Centre (Figure 1). Fifty-eight patients were excluded due to reasons listed in *Figure 1*. Mean age of the study population was 46 ± 14 years old. Patients were followed up for a mean timeframe of 64 ± 28 months, in which an average of 3 ± 1 Holters was performed per patient. The total number of Holters per patients can be found in *Supplementary material online, Table S1*. Other baseline characteristics are presented in *Table 1*.

Rhythm or conduction abnormalities had been discovered in 126 out of 235 (54%) included patients by the end of follow-up. Patients in whom rhythm or conduction abnormalities were found on 24 h Holter monitoring, were significantly older than patients without abnormalities on Holter monitoring (50 vs. 41 years old, $P < 0.001$, *Table 1*).

ECG abnormalities (described in *Table 1*) were more frequently present in the group of patients with abnormalities upon 24 h Holter monitoring compared with patients without abnormalities upon Holter monitoring (69 vs. 14%, $P < 0.001$, *Table 1*). Moreover, high MIRS score upon neurological evaluation (27 vs. 12%, $P = 0.006$, *Table 1*) and NIV indications (48 vs. 28%, $P = 0.002$, *Table 1*) were more common in DM1 patients with abnormalities upon Holter monitoring. There was no significant difference in sex (53 vs. 49% male, $P = 0.572$, *Table 1*), median CTG-repeat size (150 vs. 150, $P = 0.570$, *Table 1*) or LVEF (59 vs. 60%, $P = 0.277$, *Table 1*). Mean follow-up time was longer in the group of patients with rhythm or conduction abnormalities upon Holter monitoring (68 vs. 59 months, $P = 0.024$, *Table 1*), with a higher mean number of Holters per patient (3 vs. 2, $P = 0.001$, *Table 1*).

Holter monitoring abnormalities

The incidence of abnormalities upon Holter monitoring increased over time (*Figure 2A*). Holter abnormalities mainly consisted of conduction disorders (70%) such as intermittent first-degree AV block and bundle branch block (*Table 2*). A combination of intermittent first-degree AV block + bundle branch block had been discovered in 10 patients by the end of follow-up. Moreover, a second-degree AV block was observed in 14 patients.

Arrhythmias such as atrial fibrillation/flutter were present in eight patients and NSVT had been observed in 5 patients by the end of follow-up (*Table 2*). Holter monitoring revealed other abnormalities such as frequent ventricular extrasystoles, symptomatic bradycardia <40 b.p.m. and sinus arrest (>3 s) in 12 patients (9%, *Table 2*).

Out of 126 patients with discovered abnormalities upon 24 h Holter monitoring during follow-up, 74 (59%) patients were classified as having *de novo* findings that would have remained undiagnosed by ECG and history taking alone (*Figure 1*). The remaining 41% of patients had abnormal findings on Holter monitoring that had already been ascertained through ECG and/or history taking. Cardiac complaints were present in 9 out of 126 (7%) patients with *de novo* findings upon Holter screening.

A total of 133 out of the 235 included patients had normal ECGs upon yearly screening during follow-up. In 39 out of 133 (29%) patients, abnormal Holter findings had been discovered by the end of follow-up, while ECG remained normal. The incidence of *de novo* Holter findings in patients without ECG abnormalities, increased over time (*Figure 2B*). *De novo* findings included 4 patients with a (intermittent) second-degree AV block, 2 patients with NSVT, 1 patient with atrial fibrillation, and 1 patient with a combination of first-degree AV block + bundle branch block.

Predictors of Holter findings

Logistic regression analysis was performed to assess the impact of pre-defined predictors on having *de novo* findings upon 24 h Holter monitoring (*Table 3*). The multiple logistic regression model contained two independent variables (age and high MIRS score). As displayed in *Table 3*, neither independent variable made a statistically

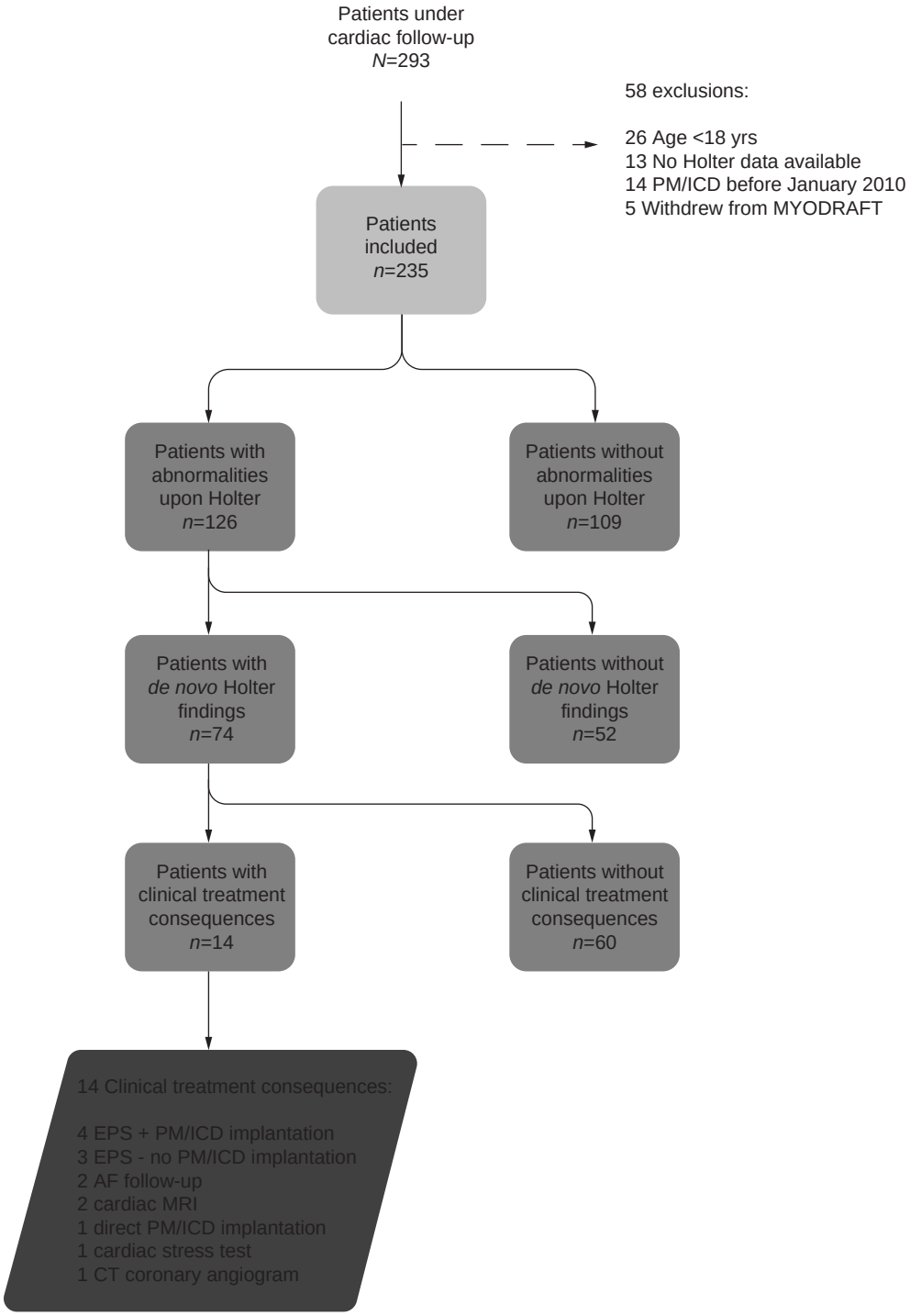

Figure 1 Flow chart of included myotonic dystrophy type 1 patients. AF, atrial fibrillation; CT, computed tomography; EPS, electrophysiologic study; ICD, implantable cardioverter defibrillator; MRI, magnetic resonance imaging; PM, pacemaker.

significant contribution to the model [age (OR 1.017, CI 0.997–1.038) and high MIRS score (OR 1.447, CI 0.738–2.835)]. Binary logistic regression analysis was repeated to assess the impact of predefined predictors on having abnormal findings upon 24 h Holter monitoring in general (see *Supplementary material online, Table S2*). Age (OR 1.037, CI 1.012–1.062) and the presence of ECG abnormalities (OR 11.225, CI 5.600-22.502) made a statistically significant contribution to the multiple regression model.

Table 1 Baseline characteristics

	Total ($n = 235$)	Patients with abnormalities upon Holter screening ($n = 126$)	Patients without abnormalities upon Holter screening ($n = 109$)	*P*-value
Age (years), mean ± SD	46 ± 14	50 ± 14	41 ± 13	<0.001
Male, *n* (%)	120 (51%)	67 (53%)	53 (49%)	0.572
ECG abnormalities, *n* (%)	102 (43%)	87 (69%)	15 (14%)	<0.001
First-degree AV block	53	44	9	
Second-degree AV block	1	1	0	
Bundle branch block	10	6	4	
Bundle branch block + first-degree AV block	34	32	2	
Atriumfibrillation/flutter	4	4	0	
CTG-repeat size, median (IQR)	150 (120–200)	150 (120–200)	150 (100–200)	0.570
High MIRS score (4–5), *n* (%)	47 (20%)	34 (27%)	13 (12%)	0.006
NIV indication	90 (38%)	60 (48%)	30 (28%)	0.002
Follow-up time in months, mean ± SD	64 ± 28	68 ± 26	59 ± 30	0.024
Mean no. of Holters, mean ± SD	3 ± 1	3 ± 1	2 ± 1	0.001
LVEF, mean % ± SD	59% ± 6	59% ± 7	60% ± 5	0.277

AV, atrioventricular; CTG, cathepsin G; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MIRS, muscular impairment rating scale with high MIRS scores (4–5) indicating proximal muscle weakness; NIV, non-invasive ventilation; SD, standard deviation.

Clinical treatment consequences

In our study population, *de novo* findings upon Holter monitoring had clinical treatment consequences in 14 out of 74 (19%) patients (*Figure 1*). Treatment consequences were not solely based on the presence of cardiac conduction abnormalities and/or observed arrythmias specific for DM1, but could also be based on other abnormalities such as frequent ventricular extrasystoles, described in *Table 2*. The decision whether to take clinical treatment consequences was always left to the discretion of a cardiac electrophysiologist with DM1 expertise.

Discussion

In a population of 235 patients with genetically confirmed DM1, abnormalities upon 24 h Holter monitoring had been discovered in 54% of patients after a mean follow-up of approximately 5 years. In 59% of cases, abnormal findings were classified as *de novo* findings, meaning they would have remained undiagnosed through ECG and history taking alone. Abnormalities upon 24 h Holter screening were not only present in patients with previously ascertained ECG abnormalities, but also in 29% of patients without ECG abnormalities upon yearly cardiac screening during follow-up. Even though the exact role of 24 h Holter monitoring has remained unclear in DM1 cardiac care recommendations due to lack of evidence, the current results demonstrate the added value of routine 24 h Holter monitoring.

Prevalence of cardiac abnormalities and the role of 24 h Holter monitoring in DM1

Conduction abnormalities such as AV blocks and bundle branch blocks are observed in 17–45% of patients, while atrial fibrillation/flutter and ventricular arrhythmias are described to be present in, respectively, 5–13 and 1–4% of the DM1 population.[1,13,14] In the current study, ECG abnormalities were present in 43% of patients, with conduction disorders being the most prevalent. In the group of patients with abnormalities upon Holter monitoring, ECG abnormalities were even more common, which is a logical consequence of most ECG abnormalities also being present upon ambulatory monitoring.

Outcomes of Holter screening in DM1 have been evaluated in a small number of studies so far. A retrospective study of 47 DM1 patients reported that ambulatory monitoring was unable to predict sudden cardiac death or other cardiovascular events, and therefore did not consider Holter monitoring to be useful.[15] However, data of a second Holter were only available for 32 patients after a 5-year follow-up period. In several other small studies, Holter screening did appear to have an additional value by establishing *de novo* conduction delay or arrhythmias in approximately 30% of patients with normal baseline ECGs.[7,16,17] *De novo* abnormalities included findings such as second-degree AV block, AF and NSVT warranting treatment consequences such as cardiac device implantation.[7,16,17] Even though the results of these studies are in line with the current data, we are the first to describe 24 h Holter monitoring data in a large DM1 cohort with multiple measurements during follow-up in a multicentre setting.

Patient characteristics as predictors of cardiac abnormalities

Even though there seems to be a correlation between CTG-repeat size and the degree of clinical symptomatology in DM1 in general, the relationship between cardiac involvement and repeat expansion size

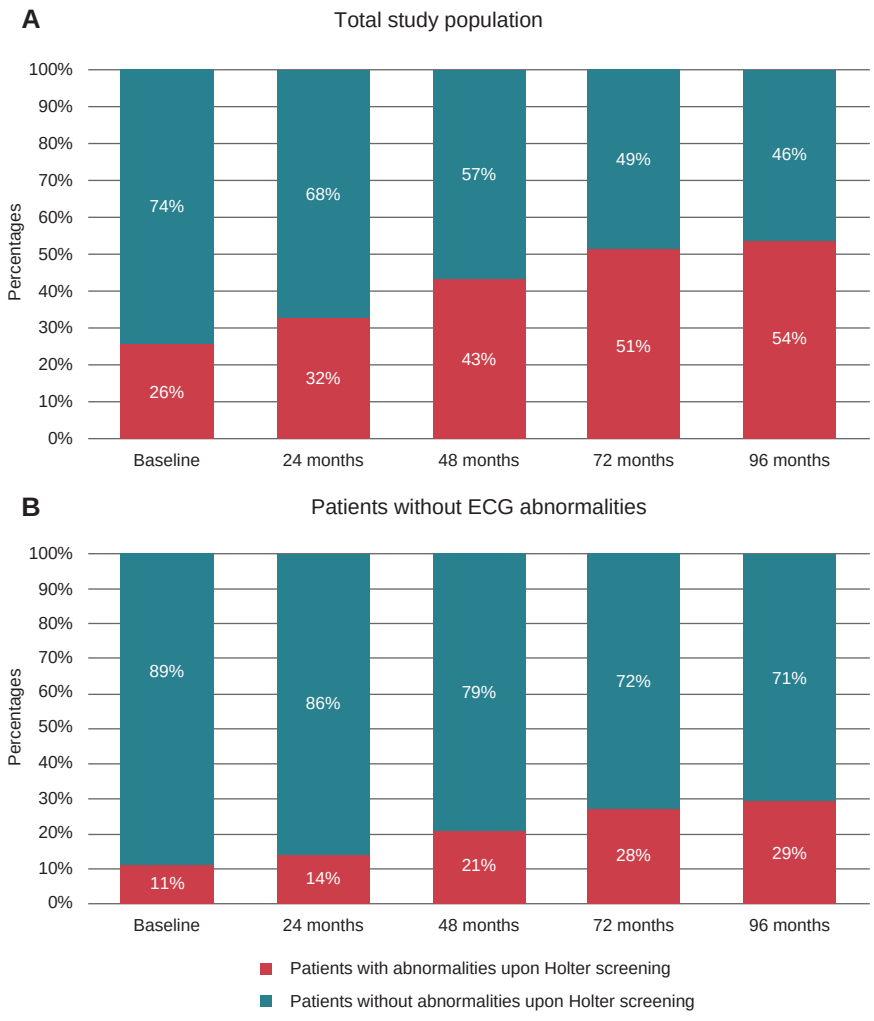

Figure 2 Percentages of DM1 patients with Holter abnormalities during follow-up. (*A*) Total study population, (*B*) Patients without electrocardiogram abnormalities. DM1, myotonic dystrophy Type 1; ECG, electrocardiogram.

has remained ambiguous.[1,8] Increasing age and male sex, however, do seem to influence the risk of developing cardiac abnormalities over time.[18] In our study population, median age was higher in the group of patients with abnormalities on Holter screening and an increased risk based on age could be verified for having Holter abnormalities in general (*Supplementary material online, Table S2*). Age did not increase the risk of having *de novo* abnormalities (*Table 3*). While more severely affected DM1 patients with proximal muscle weakness and NIV indications presented with abnormalities upon Holter more often (*Table 1*), the presence of a NIV indication and high MIRS score did not make a significant contribution to the regression analysis either.

Treatment consequences

De novo findings upon Holter screening had clinical treatment consequences in 14 out of 74 patients (19%, *Figure 1*) during follow-up. Nevertheless, it is of importance to point out that the current study was merely of a retrospective observational nature. As a result, our data give an overview of treatment consequences taken in clinical practice before 2020 based on expert opinion, since guidelines and/or clinical care recommendations were unavailable at that time. Based on current knowledge, however, the actual percentage of patients having an indication for treatment consequences may be higher than described in the current study. The most recently published ESC guidelines on cardiac pacing recommend direct pacemaker implantation in DM1 patients with any second- or third-degree AV block or abnormal EPS result.[9] As second-degree AV block was a *de novo* finding in 14 patients on Holter screening (*Table 2*), pacemaker implantation would have been warranted. Also for patients with a *de novo* finding of a combined AV block and bundle branch block, EPS and possible device implantation could have been advisable.[8]

Clinical implications

While specific guidelines for the cardiac follow-up of DM1 are still lacking, an overview of clinical care recommendations for cardiologists treating adults with myotonic dystrophy were published in 2020.[6] Even though the publication of these expert consensus-based recommendations are a step forward in DM1 care, the role of Holter

Table 2 Abnormalities on 24 h Holter monitoring

	Total number of patients ($n = 126$)	Patients with *de novo* Holter findings ($n = 74$)	Patients without *de novo* Holter findings ($n = 52$)
Conduction disorders, *n* (%)	88 (70%)	42 (57%)	46 (88%)
First-degree AV block	43	18	25
Second-degree Wenckebach block	13	13	0
Second-degree Mobitz block	1	1	0
Bundle branch block	21	8	13
First-degree AV block + bundle branch block	10	2	8
Arrhythmias, *n* (%)	26 (21%)	21 (28%)	5 (10%)
Supraventricular tachycardia	13	13	0
Atrial fibrillation/flutter	8	3	5
Non-sustained ventricular tachycardia	5	5	0
Other, *n* (%)	12 (9%)	11 (15%)	1 (2%)
Symptomatic bradycardia <40 b.p.m.	2	1	1
Frequent ventricular extrasystoles	9	9	0
Sinus arrest/RR > 3 s	1	1	0

AV, atrioventricular; b.p.m., beats per minute.

Table 3 Binary logistic regression analysis for the presence of *de novo* Holter findings

	Univariate			Multivariate		
	OR	CI	*P*-value	OR	CI	*P*-value
Age	1.017	0.998–1.037	0.087	1.017	0.997–1.038	0.095
Sex	1.101	0.634–1.910	0.733			
CTG-repeat length	1.000	0.999–1.002	0.520			
ECG abnormalities	1.364	0.784–2.372	0.272			
Cardiac complaints	1.441	0.344–6.045	0.617			
High MIRS score (4–5)	1.571	0.808–3.052	0.183	1.447	0.738–2.835	1.447
NIV indication	1.148	0.653–2.016	0.632			

CI, confidence interval; CTG, cathepsin G; ECG, electrocardiographic; MIRS, muscular impairment rating scale; NIV, non-invasive ventilation; OR, odds ratio.

monitoring has remained uncertain. Ambulatory monitoring is described to possibly be helpful in detecting ambient or asymptomatic arrhythmias, while it is advised only to perform this type of monitoring in case of ECG abnormalities or in patients with symptoms suggestive of arrhythmias.[6] Based on the data presented in the current study, in which abnormalities on Holter were ascertained in 54% of the screened DM1 population and even in 29% of patients with normal baseline ECGs, we believe that Holter monitoring should be considered an important factor in DM1 cardiac care. In addition, *de novo* Holter findings were of such nature that they are considered clinically relevant and influence treatment. Another retrospective study has suggested that cardiac conduction abnormalities and arrhythmias detected through Holter monitoring seem to be predictive of future cardiac events and death in DM1 patients as well.[19] Since only 7% of patients with *de novo* Holter findings experienced cardiac symptoms and specific patient characteristics such as muscle weakness, NIV indication or age did not seem to influence the risk of having *de novo* findings either, ambulatory monitoring should be part of DM1 screening in all patients. Due to the slowly progressive nature of disease and lack of prospective studies on the value of Holter screening, however, it remains difficult to determine an optimal interval for this screening modality at the current time. Also, future studies should provide more data on the prognostic value of Holter monitoring abnormalities.

Limitations

The main limitations of this study consist of its retrospective nature and the relatively short period of follow-up for a slowly progressive disorder. Moreover, patients with abnormalities upon Holter screening had a longer mean follow-up time with more frequent Holter examinations (*Table 1*). As a result, chances of abnormalities being present in this group were higher to begin with. Holter monitoring data were not compared with PSG data, while previous reports have described that arrhythmias may sometimes be precipitated by functional triggers.[20] Due to the fact that this study only used data of patients under cardiac follow-up in the Dutch DM1 expertise centre, a possible bias could have resulted from the fact that more severely affected patients are more likely to be under follow-up in a DM1-specific care centre.

Conclusion

This retrospective study evaluated the clinical effectiveness of routine 24 h Holter monitoring in a large cohort of 235 DM1 patients. Abnormalities upon Holter screening were present in 54% of patients after a mean follow-up of approximately 5 years. In 59% of patients with discovered abnormalities on Holter, the ascertained conduction abnormalities and/or arrhythmias would have remained undiagnosed through cardiac screening with ECG and history taking alone. *De novo* findings were common not only in patients with ECG abnormalities but also in patients with normal ECGs upon yearly cardiac screening. Moreover, specific patient characteristics were unable to predict the occurrence of *de novo* Holter findings. Consequently, we believe that 24 h Holter monitoring is of additional value to routine cardiac screening in all DM1 patients, even though an optimal screening interval is to be investigated in a prospective trial. Yet again, we would like to stress the need for clear DM1-specific cardiac guidelines, to improve cardiac care for this vulnerable patient population.

Supplementary material

Supplementary material is available at *Europace* online.

Acknowledgements

The authors thank Danielle Jeurissen and Fran Smulders for their support in MYODRAFT data collection.

Funding

This work was supported by the Prinses Beatrix Spierfonds (grant numbers W.OR15-25 and W.TR19-01).

Conflict of interest: B.G.M.V.E. reports grants from Spieren voor Spieren, grants from Prinses Beatrix Spierfonds, grants from Dutch FSHD foundation, grants from Marigold foundation, grants from Netherlands Organisation for Scientific Research (NWO), grants from The Netherlands Organisation for Health Research and Development (ZonMw), grants from Association Francaise contre les Myopathies, grants and personal fees from Fulcrum, personal fees from Facio, personal fees from Arrowhead, all payed to the institution and outside the submitted work. C.G.F. reports grants from European Union's Horizon 2020 research and innovation programme Marie Sklodowska-Curie grant for PAIN-Net, molecule-to-man pain network (grant no. 721841), grants from Grifols and Lamepro for a trial on IVIg in small fibre neuropathy, grants from Prinses Beatrix Spierfonds, Steering committees/advisory board for studies in small fibre neuropathy of Biogen/Convergence, Vertex, Lilly and OliPass, outside the submitted work. K.V. reports grants from Medtronic, Abbott and Biotronik, and a consultancy agreement with Medtronic, outside the submitted work. All remaining authors have declared no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Petri H, Vissing J, Witting N, Bundgaard H, Kober L. Cardiac manifestations of myotonic dystrophy type 1. *Int J Cardiol* 2012;**160**:82–8.
2. Brook JD, McCurrach ME, Harley HG, Buckler AJ, Church D, Aburatani H *et al.* Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. *Cell* 1992;**69**:385.
3. De Antonio M, Dogan C, Hamroun D, Mati M, Zerrouki S, Eymard B *et al.* Unravelling the myotonic dystrophy type 1 clinical spectrum: a systematic registry-based study with implications for disease classification. *Revue Neurologique* 2016;**172**:572–80.
4. de Die-Smulders C, Howeler CJ, Thijs C, Mirandolle JF, Anten HB, Smeets HJ *et al.* Age and causes of death in adult-onset myotonic dystrophy. *Brain* 1998;**121**:1557–63.
5. Ashizawa T, Gagnon C, Groh WJ, Gutmann L, Johnson NE, Meola G *et al.* Consensus-based care recommendations for adults with myotonic dystrophy type 1. *Neurol Clin Pract* 2018;**8**:507–20.
6. McNally EM, Mann DL, Pinto Y, Bhakta D, Tomaselli G, Nazarian S *et al.* Clinical care recommendations for cardiologists treating adults with myotonic dystrophy. *J Am Heart Assoc* 2020;**9**:e014006.
7. Merlevede K, Vermander D, Theys P, Legius E, Ector H, Robberecht W. Cardiac involvement and CTG expansion in myotonic dystrophy. *J Neurol* 2002;**249**:693–8.
8. Joosten IBT, van Lohuizen R, den Uijl DW, Evertz R, de Greef BTA, van Engelen BGM *et al.* Electrocardiographic predictors of infrahissian conduction disturbances in myotonic dystrophy type 1. *Europace* 2021;**23**:298–304.
9. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM *et al.* 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Europace* 2022;**24**:71–164.
10. Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR *et al.* 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;**74**:932–87.
11. Mathieu J, Boivin H, Meunier D, Gaudreault M, Begin P. Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. *Neurology* 2001;**56**:336–40.
12. Wahbi K, Porcher R, Laforêt P, Fayssoil A, Bécane HM, Lazarus A *et al.* Development and validation of a new scoring system to predict survival in patients with myotonic dystrophy type 1. *JAMA Neurol* 2018;**75**:573–81.
13. Wahbi K, Furling D. Cardiovascular manifestations of myotonic dystrophy. *Trends Cardiovasc Med* 2020;**30**:232–8.
14. Groh WJ, Groh MR, Saha C, Kincaid JC, Simmons Z, Ciafaloni E *et al.* Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. *N Engl J Med* 2008;**358**:2688–97.
15. Gamet A, Degand B, Le Gal F, Bidegain N, Delaubier A, Gilbert-Dussardier B *et al.* Twenty-four-hour ambulatory ECG monitoring relevancy in myotonic dystrophy type 1 follow-up: prognostic value and heart rate variability evolution. *Ann Noninvasive Electrocardiol* 2019;**24**:e12587.
16. Brembilla-Perrot B, Luporsi JD, Louis S, Kaminsky P. Long-term follow-up of patients with myotonic dystrophy: an electrocardiogram every year is not necessary. *Europace* 2011;**13**:251–7.
17. Sá MI, Cabral S, Costa PD, Coelho T, Freitas M, Gomes JL. Ambulatory electrocardiographic monitoring in type 1 myotonic dystrophy. *Rev Port Cardiol* 2007;**26**:745–53.
18. Dogan C, De Antonio M, Hamroun D, Varet H, Fabbro M, Rougier F *et al.* Gender as a modifying factor influencing myotonic dystrophy type 1 phenotype severity and mortality: a nationwide multiple databases cross-sectional observational study. *PLoS One* 2016;**11**:e0148264.
19. Kaminsky P, Brembilla-Perrot B, Pruna L, Poussel M, Chenuel B. Age, conduction defects and restrictive lung disease independently predict cardiac events and death in myotonic dystrophy. *Int J Cardiol* 2013;**162**:172–8.
20. Lazarus A, Varin J, Jauvert G, Alonso C, Duboc D. Relationship between cardiac arrhythmias and sleep apnoea in permanently paced patients with type I myotonic dystrophy. *Neuromuscul Disord* 2007;**17**:392–9.