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► **To cite this version:**

Maximilien Sochala, Raphaël Porcher, Tanya Stojkovic, Henri Marc Bécane, Anthony Behin, et al..  
High Risk of Fatal and Nonfatal Venous Thromboembolism in Myotonic Dystrophy. *Circulation*, 2018,  
138 (11), pp.1169-1171. 10.1161/CIRCULATIONAHA.118.035035 . hal-02357318

**HAL Id: hal-02357318**

**<https://hal.science/hal-02357318>**

Submitted on 9 Nov 2019

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## High Risk of Fatal and Nonfatal Venous Thromboembolism in Myotonic Dystrophy

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Publication: 10 Sep 2018 ; Circulation. 2018;138:1169–1171

Myotonic dystrophy (MD), the most common inherited myopathy, is associated with high cardiovascular mortality<sup>1</sup>. A preliminary analysis of the DM1 Heart Registry (URL: ClinicalTrials.gov. Unique identifier: NCT01136330), a comprehensive database that captures information relative to the cardiac management of adults presenting to our center with MD<sup>2</sup>, revealed a high prevalence of venous thromboembolism (VTE). We designed this study to estimate the risk of VTE in MD and its survival consequences.

We retrospectively analyzed the data relative to patients referred to our center between January 2000 and January 2015, including 1148 with MD and 1662 with other inherited myopathies (facioscapulohumeral, dystrophinopathy, mitochondrial, glycogen- and lipid-storage diseases, limb-girdle muscular dystrophies, nucleopathies, collagen VI-related disorders, myofibrillar, and congenital). This study was approved by our local Ethics Committee, and all patients granted their written informed consent to participate. We compared patient baseline characteristics using Wilcoxon rank-sum or Fisher exact tests as appropriate. VTE, defined as  $\geq 1$  episode of deep vein thrombosis or pulmonary embolism, was analyzed in a competing-risks framework, with death as a competing event. Cumulative incidences (probability of occurrence over follow-up), hazard ratios (HRs), and cumulative hazards of VTE were estimated. We searched for predictors of the hazard of VTE using Cox proportional hazards models for the cause-specific hazards on the time of study scale, with follow-up beginning on the date of inclusion in the study until the occurrence of VTE, death, or last follow-up, whichever occurred first. All patient characteristics described in the results were included in this analysis, including all variables from our database that represent known VTE risk factors.

At first presentation, patients with MD, compared with others, were older (40 [29–51] years versus 39 [25–52] years;  $P=0.029$ ); had a lower proportion of men (556 [48.4%] versus 990 [59.6%];  $P<0.0001$ ); had a more frequent personal history of VTE (40 [3.5%] versus 9 [0.5%];  $P<0.0001$ ), heart failure (12 [1.0%] versus 128 [7.7%];  $P<0.0001$ ), and conduction disease (461 [40.2%] versus 195 [11.7%];  $P<0.0001$ ); were treated with vitamin K antagonists (32 [3.0%] versus 25 [1.5%],  $P=0.009$ ) and estrogen contraceptives (137 [11.9%] versus 140 [8.4%],  $P=0.002$ ); and had a lower Walton score<sup>3</sup> (1 [0–3] versus 3 [1–6];  $P<0.0001$ ) and less frequent ambulation loss (80 [6.9%] versus 405 [24.4%],  $P<0.0001$ ). A similar prevalence was observed for obesity (123 [10.9%] versus 183 [11.2%];  $P=0.85$ ), respiratory failure (133 [13.2%] versus 257 [15.8%];  $P=0.071$ ), and cancer (31 [2.8%] versus 33 [1.9%];  $P=0.25$ ). VTE

occurred in 82 patients with MD over a 10.9-year follow-up (95% CI, 2.4–14.7), representing an 8.3 per 1000 patient-year incidence (95% CI, 6.6–10.3) and a 10.3% cumulative incidence (95% CI, 7.8–12.7), and in 20 patients with other myopathies over a median 8.5-year follow-up, representing a 1.6 per 1000 patient-year incidence (95% CI, 1.0–2.5) and a 2.2% cumulative incidence (95% CI, 1.1–3.3; Figure A). VTE developed in the absence of predisposing factors in 48 patients with MD (58.5%) and in 6 with other myopathies (30.0%). Among the 1148 patients with MD, 253 (22.0%) died during follow-up, 39 suddenly. Among the 83 cardiovascular deaths, pulmonary embolism was the cause of death in 26 patients (10.3% of all deaths) and the second most frequent cause of cardiovascular death (31.3%) after sudden cardiac death (Figure B).

In multivariable analysis, among the 2810 patients with inherited myopathies, predictors of VTE were MD (HR, 5.35; 95% CI, 2.85–10.0;  $P<0.0001$ ), increasing age (HR, 1.02; 95% CI, 1.00–1.03;  $P=0.031$ ), personal history of VTE (HR, 4.56; 95% CI, 2.28–9.10;  $P=0.0001$ ), obesity (HR, 2.66; 95% CI, 1.64–4.32;  $P<0.0001$ ), high Walton score (HR, 1.20; 95% CI, 1.09–1.32;  $P=0.0003$ ), cancer (HR, 4.32; 95% CI, 2.05–9.08;  $P<0.0001$ ), conduction disease (HR, 1.63; 95% CI, 1.06–2.51;  $P=0.025$ ), and ambulation loss in patients with MD (HR, 7.18; 95% CI, 1.88–27.4;  $P=0.004$ ). The standardized rate ratio for VTE between our sample and an age- and sex-matched community-based French population<sup>4</sup> was higher in MD (7.53; 95% CI, 6.02–9.28) than in other myopathies (1.23; 95% CI, 0.77–1.85;  $P<0.0001$ ).

The association between MD and VTE has not been previously reported and is supported in this study by the magnitude of the risk of VTE observed in patients with MD, its independence from the muscular functional status, and a majority of idiopathic events. The burden represented by VTE on survival was remarkably heavy, with pulmonary embolism representing one of the most common causes of death. Although the optimal VTE risk mitigation strategy for these patients remains to be defined, our study supports a more systematic VTE prophylaxis that should be extended to any medical or surgical setting. The association between MD and VTE may rely on the complex pathogenic mechanisms of MD, which involve the toxic effect of RNA, resulting in alterations of several cellular functions such as alternative splicing<sup>5</sup>. One might hypothesize that missplicing of factors involved in the coagulation process contributes to the development of VTE.

Sources of Funding: funding was provided by AFM-Téléthon (Association Française contre les Myopathies [French Alliance Against Myopathies]).

Disclosures: none.

Data sharing: the data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

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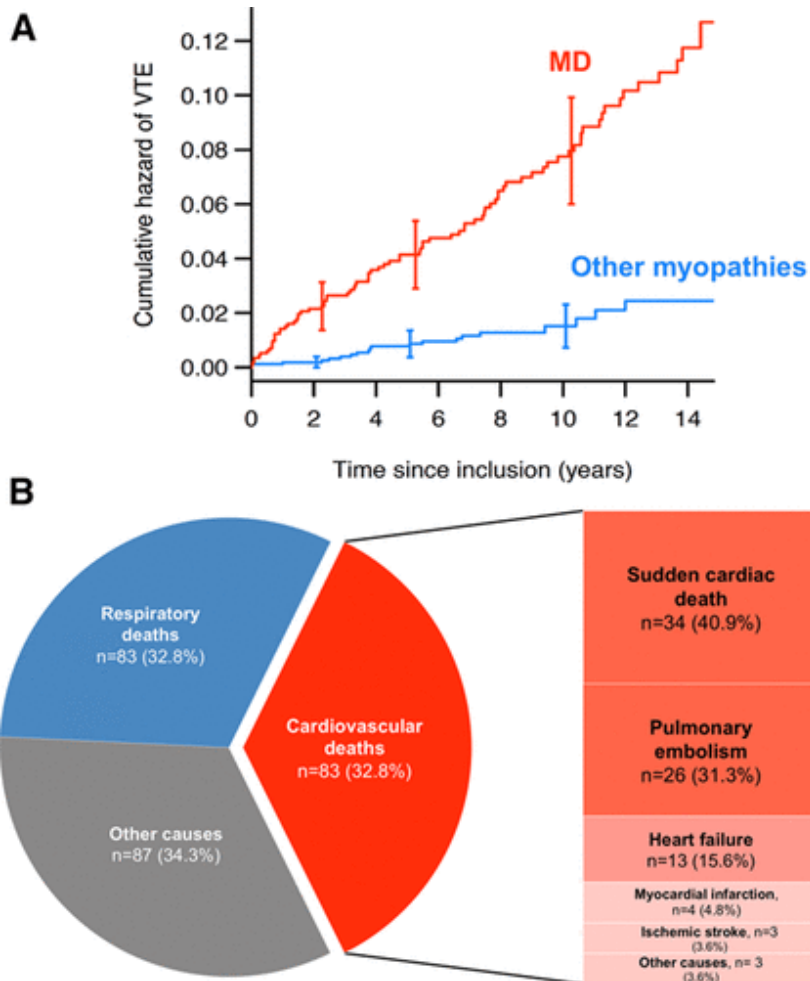


Figure. A, Cumulative hazard of venous thromboembolism (VTE) during follow-up according to the disease on the time of study scale (The Nelson-Aalen estimator was used to generate the curves. Error bars indicate pointwise 95% CIs) and B, distribution of the causes of 253 deaths in patients with myotonic dystrophy. MD indicates myotonic dystrophy.