Tayal, Upasana; Newsome, Simon; Buchan, Rachel; Whiffin, Nicola; Walsh, Roddy; Barton, Paul J; Ware, James S; Cook, Stuart A; Prasad, Sanjay K; (2017) Truncating Variants in Titin Independently Predict Early Arrhythmias in Patients With Dilated Cardiomyopathy. Journal of the American College of Cardiology, 69 (19). pp. 2466-2468. ISSN 0735-1097 DOI: https://doi.org/10.1016/j.jacc.2017.03.530

Downloaded from: http://researchonline.lshtm.ac.uk/id/eprint/4086840/

DOI: https://doi.org/10.1016/j.jacc.2017.03.530

Usage Guidelines:

Please refer to usage guidelines at https://researchonline.lshtm.ac.uk/policies.html or alternatively contact researchonline@lshtm.ac.uk.

Available under license: http://creativecommons.org/licenses/by/2.5/
to the general population. Acquired cardiovascular diseases such as myocardial infarction and CVA had a limited role when compared to heart failure.

Jouke P. Bokma, MD
Michiel M. Winter, MD, PhD
Joey M. Kuipers, MD
Monique R. Jongbloed, MD, PhD
Anthonie L. Duijnhouwer, MD, PhD
Gert-Jan T. Sieswerda, MD, PhD
Martijn C. Post, MD, PhD
Barbara J.M. Mulder, MD, PhD
*Berto J. Bouma, MD, PhD
*Academic Medical Center Amsterdam
Department of Cardiology, Room B2-256
Meibergdreef 9
1105 AZ Amsterdam
the Netherlands
E-mail: b.j.bouma@amc.uva.nl

http://dx.doi.org/10.1016/j.jacc.2017.03.529

Please note: This work was supported by the Netherlands Heart Institute (NL-HI) and Nuts Ohra Foundation. The work described in this study was carried out in the context of the Parelloer Institute. Parelloer Institute is part of and funded by the Dutch Federation of University Medical Centers. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES


Truncating Variants in Titin Independently Predict Early Arrhythmias in Patients With Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) has a population prevalence of ~1 in 500 and is associated with prognostically adverse arrhythmias at initial disease presentation in up to one-third of patients (1). While
increasing age, male sex, and impaired ventricular function are established arrhythmic risk factors, arrhythmias also occur in patients without known risk factors.

Recently, the advent of high-throughput sequencing technologies has enabled new insights into the genetic predisposition of DCM. In particular, titin-truncating variants (TTNtv) are now known to occur in ~15% of cases of DCM and represent the commonest genetic cause of DCM (2,3). We evaluated whether genetic information can be used as an additional tool to identify patients at risk for arrhythmias by exploring whether there is an association between TTNtv and the occurrence of arrhythmias at the time of first diagnosis in a large cohort of patients with DCM.

In total, 572 prospectively recruited patients fulfilling diagnostic criteria for DCM by cardiovascular magnetic resonance were recruited between 2009 and 2015 (68% men, mean age 53.5 ± 14.4 years). All patients had detailed clinical assessment and sequencing for novel or rare (Exome Aggregation Consortium frequency <0.001) truncating variants in constitutively expressed TTN exons. Focusing on early arrhythmic risk, data on arrhythmia history (atrial fibrillation [AF], nonsustained ventricular tachycardia [VT], and sustained VT) on recruitment to the study were collated from hospital and primary care notes. Multivariable logistic regression was used to evaluate variables associated with arrhythmias at presentation.

In the cohort, mean left ventricular ejection fraction was 39.0 ± 12.6% (median = 40%; interquartile range: 29% to 49%). Midwall late gadolinium enhancement (LGE) myocardial fibrosis was detected in 198 patients (35%). A family history of DCM was found in 82 patients (14%) and a family history of sudden cardiac death in 76 patients (13%).

Arrhythmias prior to recruitment were documented in 196 (34%) patients. Specifically, 139 (24%) patients had confirmed AF, 69 (12%) patients had confirmed nonsustained VT and 11 (2%) patients had confirmed sustained VT. Of these, 22 patients had more than 1 type of arrhythmia: 15 had both AF and nonsustained VT; 1 had both AF and sustained VT; 5 had both sustained VT and nonsustained VT; and 1 had AF, nonsustained VT, and sustained VT.

Patients with arrhythmia were more likely to be older, be men, and have worse biventricular function (age 58.7 ± 12.2 years vs. 50.8 ± 14.7 years; 161 [82.1%] men vs. 227 [60.4%] men; left ventricular ejection fraction 36.1 ± 12.1% vs. 40.4 ± 12.7%; right ventricular ejection fraction 33.9 ± 13.7% vs. 40.7 ± 13.8%; p < 0.0001 for all). Although LGE is associated with arrhythmia later in established disease, there was no significant difference in the proportion of patients with LGE between the arrhythmia positive and negative groups at presentation (122 [32.4%] vs. 76 [38.8%]; p = 0.16).

TTNtv were observed in 13.3% (n = 26) of patients with a history of arrhythmia compared to 8% (n = 30) of patients without a history of arrhythmia (p = 0.05). Conversely, an arrhythmia was documented in 26 patients (46%) with TTNtv compared to 170 patients (33%) without TTNtv (p = 0.05). In exploratory univariable analysis, the presence of a TTNtv was predictive of baseline arrhythmia in DCM patients (unadjusted odds ratio: 1.76; 95% confidence interval: 1.01 to 3.08; p = 0.05) (Table 1).

This association was stronger in multivariable regression analyses, adjusting for variables associated with baseline arrhythmia in this cohort (age, gender, indexed left atrial volume, and ventricular function). TTNtv independently predicted early arrhythmias in DCM (adjusted odds ratio: 2.90; 95% confidence interval: 1.48 to 5.78; p = 0.002) (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>p Value</th>
<th>95% Confidence Interval</th>
<th>OR</th>
<th>p Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 yrs)</td>
<td>1.53</td>
<td>&lt;0.0001</td>
<td>1.33-1.76</td>
<td>1.60</td>
<td>&lt;0.0001</td>
<td>1.36-1.89</td>
</tr>
<tr>
<td>Male</td>
<td>3.02</td>
<td>&lt;0.0001</td>
<td>2.00-4.65</td>
<td>2.33</td>
<td>&lt;0.0001</td>
<td>1.44-3.83</td>
</tr>
<tr>
<td>LVEF (per 10%)</td>
<td>0.76</td>
<td>&lt;0.001</td>
<td>0.66-0.87</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>RVEF (per 10%)</td>
<td>0.71</td>
<td>&lt;0.0001</td>
<td>0.62-0.80</td>
<td>0.79</td>
<td>&lt;0.0001</td>
<td>0.67-0.92</td>
</tr>
<tr>
<td>TTNtv positive</td>
<td>1.76</td>
<td>0.05</td>
<td>1.01-3.08</td>
<td>2.90</td>
<td>0.002</td>
<td>1.48-5.78</td>
</tr>
<tr>
<td>LAVi (per 1 ml/m²)</td>
<td>1.03</td>
<td>&lt;0.0001</td>
<td>1.02-1.04</td>
<td>1.03</td>
<td>&lt;0.0001</td>
<td>1.02-1.04</td>
</tr>
<tr>
<td>LGE present</td>
<td>1.32</td>
<td>0.13</td>
<td>0.92-1.89</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FHx DCM</td>
<td>0.59</td>
<td>0.06</td>
<td>0.34-1.00</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FHx SCD</td>
<td>0.62</td>
<td>0.09</td>
<td>0.35-1.06</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Results of logistic regression model of predictors of early arrhythmias in dilated cardiomyopathy (DCM). Variables with p < 0.10 from the univariable analysis were considered for inclusion in an optimized multivariable model, created using backward stepwise selection until only significant variables remained. Truncating variant in titin (TTNtv) was added to this optimized model.

FHx = family history; LAVi = indexed left atrial volume; LGE = midwall fibrosis late gadolinium enhancement; LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death.
Our data demonstrate that TTNtv are associated with early arrhythmic risk in patients with DCM, independent of conventional arrhythmic risk factors. Although all patients were identified prospectively, baseline arrhythmia data were collected retrospectively and we have consolidated ventricular and atrial arrhythmias into 1 arrhythmia category, with a modest absolute increase in arrhythmic risk (13%). However, these findings have relevance for all DCM cases with TTNtv, representing ~15% of all DCM. This study provides insights into the arrhythmic burden associated with TTNtv and highlights additional genetic tools for the stratification of high-risk DCM patients.

Upasana Tayal, BMBCh
Simon Newsome, MSc
Rachel Buchan, MSc
Nicola Whiffin, PhD
Roddy Walsh, MSc
Paul J. Barton, PhD
James S. Ware, PhD
Stuart A. Cook, PhD

*Sanjay K. Prasad, MD
*Cardiovascular BRU
Royal Brompton Hospital
National Heart and Lung Institute
Sydney Street
London SW3 6NP
United Kingdom
E-mail: s.prasad@rbht.nhs.uk
http://dx.doi.org/10.1016/j.jacc.2017.03.530
©2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Please note: This project was funded by the Medical Research Council UK; the Rosetrees Foundation; the Jansons Foundation; the National Institute for Health Research Cardiovascular Biomedical Research Unit of Royal Brompton and Harefield National Health Service Foundation Trust and Imperial College London; a Health Innovation Challenge Fund (HICF-RB-673); and the Wellcome Trust and Department of Health, UK; and the British Heart Foundation. This publication includes independent research commissioned by the Health Innovation Challenge Fund (HICF-RB-673), a parallel funding partnership between the Department of Health and the Wellcome Trust. The views expressed in this work are those of the authors and not necessarily those of the Department of Health or the Wellcome Trust. The views expressed in this work are those of the authors and not necessarily those of the Department of Health or the Wellcome Trust. Dr. Cook has served as a consultant for Illumina. The other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Cook and Prasad contributed equally to this work and are joint senior authors.

REFERENCES

Neurocognitive Risk With PCSK9 Inhibitors

Need for More Robust Evidence

In a pooled analysis of 14 trials of alirocumab, Robinson et al. (1) reported the safety of alirocumab even with very low levels of low-density lipoprotein cholesterol (LDL). They found that 25% of the patients who received alirocumab had an LDL level <25 mg/dl with the median duration of low LDL level being ~43 weeks. In these patients with very low LDL levels, they found no increase in treatment-emergent serious adverse events or neurocognitive adverse effects (NCE). We recognize the overall safety of alirocumab as demonstrated in their analysis, but there are some limitations that need to be highlighted. Out of the 14 trials pooled, 4 were phase 2 studies with a total duration between 8 and 12 weeks and 3 were phase 3 studies with a duration of 24 weeks. This is a very short duration to assess the safety of an agent that will be required for life-long therapy. Seven trials had a longer follow-up, between 52 and 104 weeks, but almost all were limited by their sample size. Almost all of these trials were small-size, early phase studies designed to demonstrate LDL lowering efficacy.

The only trial (ODYSSEY LONG TERM [Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy]) designed to assess clinical outcomes suggested an increased risk of NCEs (2). Similarly, the only large open-label trial (OSLER [Open Label Study of Long Term Evaluation Against LDL-C Trial]) to assess the safety and clinical efficacy of evolocumab, the other proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, suggested an increased risk of NCE (3). Pooling only these 2 trials, which had a larger sample size and a longer follow-up, suggested an increased risk of NCE as reported in 2 recent meta-analyses (4,5). However, these analyses were also limited by lack of data on baseline cognition of the patients included in the studies and lack of an objective assessment of cognitive ability.

As mentioned, the current evidence is limited. Also, the overall low incidence of NCEs in control and PCSK9-treated groups does not preclude the use of PCSK9 inhibitors in appropriate patient populations. But there should be a discussion with the patient regarding the risks and benefits of the therapeutic