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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.

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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

approach in view of the current evidence and the patient should be informed that the evidence is not conclusive. We agree with the authors on the importance of demonstrating the long-term safety of PCSK9 inhibitors because of the potential for lifelong therapy, which will be provided by the ongoing outcome studies.

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The Enigma of Left Ventricular Hypertrabeculation

Knowledge About Pregnancies, Sports, and Neuromuscular Disorders Is Needed

With interest we read the study by Weir-McCall et al. (1) who assessed the prevalence of left ventricular hypertrabeculation/noncompaction (LVHT) in a healthy population using cardiac magnetic resonance imaging. We have several questions. Why did the authors use different ratio values as reference limits in the short- and long-axis views? How did they exclude misinterpretation of papillary muscles and LVHT? Which was the fourth diagnostic criterion? Which was the golden standard for LVHT with which cardiac magnetic resonance imaging was compared? Which was the sensitivity and specificity for diagnosing LVHT?

Nineteen patients met all diagnostic criteria, and were therefore considered to exhibit the LVHT phenotype. How many of these 19 patients were investigated echocardiographically and was LVHT also confirmed by echocardiography? Did these 19 patients show any electrocardiographic abnormalities? Were they investigated by a neurologist, because LVHT is known to be associated with neuromuscular disorders when patients are screened systematically (2)? Did they have a family history of cardiac or neuromuscular disorders? How many had symptoms of muscle disease or elevated creatine kinase values?

How to explain that the amount of trabeculations as detected by magnetic resonance imaging was larger in females than in males? This finding was also reported in a previous magnetic resonance imaging study in patients with asymptomatic LVHT (3). There was also a female preponderance in the 19 patients in the present study who met all diagnostic criteria for LVHT (13 females). This is in contrast to the male preponderance in most of the LVHT cohort studies (2). Gati et al. (4) showed echocardiographically that during pregnancy de novo trabeculations may develop in the left ventricle. Thus, it would be interesting to know if the amount of trabeculations in the females differed among nulliparous, primiparous, and polyparous subjects and if there was any association between the time since the last delivery and the amount of trabeculations.

Intensive physical activity may also induce growth of ventricular trabeculations (5). Thus, it would be of interest if there was any association between physical activity and the amount of trabeculations. How many of the investigated subjects were highly trained athletes in former years?

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