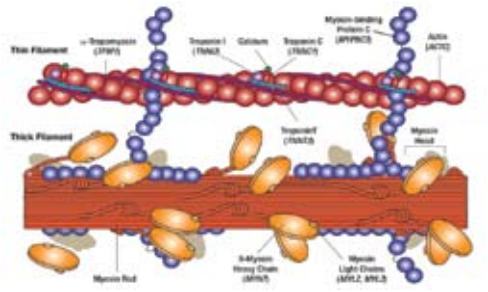
SCD and Associated Syndromes in the Young

Sudden cardiac death (SCD) is a leading cause of death in the United States (amounting to 1 death every 80 seconds, or 450,000 deaths annually), with >50% of these events having a genetic etiology [Behr ER et al. *Eur Heart J* 2008]. There are several syndromes that are associated with SCD in the young, including congenital long QT syndrome (LQTS), hypertrophic cardiomyopathy (HCM), arrhythmic right ventricular dysplasia (ARVD), Brugada syndrome (BrS), and cathecholamine polymorphic ventricular tachycardia (CPVT). Kent Stephenson, MD, Huntington Hospital, Huntington, New York, USA, discussed ways to identify these high-risk syndromes and current clinical approaches to SCD prevention in the young.

HCM is the major cause of SCD among athletes and people aged ≤30 years in the United States. It is the most common inherited cardiac disorder, with mutations occurring primarily within the cardiac sarcomere, particularly involving the β-myosin heavy chain (Figure 1) [Keren A et al. *Nature* 2008; Spirito P et al. *N Engl J Med* 1997]. HCM is characterized by unexplained thickening of the heart, and presentation varies from asymptomatic to severe limitation. Overall, mutation carriers tend to be younger, have greater left ventricular hypertrophy, and have a reverse curvature septal morphology (p<0.001) [Binder J et al. *Mayo Clinic Proc* 2006]. Calcium channel blockers, β-blockers, pacemakers, and implantable defibrillators are viable treatment options for HCM. However, in patients with obstructive symptoms, septal myomectomy is preferred over alcohol septal ablation (ASA), as ASA is associated with less favorable long-term outcomes [ten Cate FJ et al. *Circ Heart Fail* 2010].

Figure 1. Cardiac Sarcomere.



The cardiac sarcomere is the basic structural and functional contractile unit of the heart muscle.

Mutations in the gene coding for these proteins are the cause of most HCM.

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BrS is a syndrome that is associated with SCD that often stems from genetic mutations of the SCN5A gene (which regulates the sodium channel), among others. The BrS phenotype is most commonly found in males aged 30 to 40 years with malignant arrhythmias and a history of syncope. BrS can be identified by the presence of coved- or saddleback-shaped ST-segment elevation in ECG leads V1 through V3, complete or incomplete right bundle branch block (RBBB), or T-wave inversion, but there are BrS mimics that may contribute to ST-segment elevation in the right precordial leads that should be considered [Wilde et al. *Circulation* 2002]. Potential treatments for BrS include quinidine to prevent recurrent syncope, isuprel to treat ventricular electrical storm, and implantable defibrillators for treatment of ventricular tachycardia/fibrillation and prophylaxis of sudden cardiac death.

Highlights from the

25th Annual Caribbean Cardiology Conference

LQTS is characterized by delayed repolarization of individual action potentials and ECG, potentially resulting in QT interval prolongation and subsequent tachyarrhythmias [Roden DM et al. *J Cardiovasc Electrophysiol* 1999]. The most common LQTS genotype that is associated with sudden cardiac arrest at age <40 years is LQT1, though LQTS patients maintain a high risk for life-threatening cardiac events even after age 40. β-blockers are effective for treatment of LQTS, particularly among patients with LQT1 and LQT2 genotypes ($p<0.001$) [Moss AJ et al. *Circulation* 2000].

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a genetically transmitted cardiac ion channel disorder with an extremely high risk of SCD. If untreated, approximately 50% of individuals will present with a cardiac event that is possibly lethal by the age of 30 years. First recognized in 1975, this disorder involves mutations that lead to loss of calcium homeostasis in the heart, resulting in malignant arrhythmias.

The most common symptom is syncope, usually during periods of emotional or exertional stress. Syncope most often appears during the first or second decade of life. It is important to distinguish this from LQTS, since β-blocker therapy in individuals with this syndrome is less effective. In addition, the cardinal finding of prolongation of the QT interval that is seen in LQTS is absent in this disorder [Liu N et al. *Progress in Cardiovascular Diseases* 2008].

ARVD is a genetically determined disease of the heart muscle that is associated with arrhythmia, heart failure, and SCD. It is thought to be most common cause of SCD in the young in European countries. Unfortunately, SCD is often the first clinical manifestation of ARVD, especially among young people who are engaged in strenuous activity. While ARVD is often characterized by intramyocardial RV fatty infiltration, as seen on MRI, Dr. Stephenson cautions that reliance on this diagnostic indicator alone is not sufficient. Therefore, it is important to determine the diagnosis of ARVD, based on the composite of a number of possible findings, including ECG abnormalities (T-wave inversion in V1 to V3, RBBB, and/or epsilon wave), right ventricular structural abnormalities that are seen on imaging, abnormal myocardial biopsy, positive family history, and genetic testing. No one criterion is robust enough to adequately diagnose ARVD with confidence.

Detecting an increased risk of SCD in young patients is a clinical challenge, and often this risk is not detected until an event occurs, at which point it may be too late. However, there are various syndromes that may serve as early indicators of SCD risk. Thus, identifying these predictive markers is crucial to early detection and risk reduction. Recognizing the ECG footprints of these disorders is paramount to making a diagnosis in the asymptomatic individual. Genetic testing may also provide valuable prognostic and diagnostic data, as genetic mutations play a large role in SCD in the young.

CLARIFY and Its Relevance to the Caribbean Population

The Prospective Observational Longitudinal Registry of Patients with Stable Coronary Artery Disease (CLARIFY) study is a large (n=31,040) international trial that is aimed at evaluating outcomes and long-term prognostic determinants in outpatients with stable coronary artery disease (CAD), including heart rate (HR), that adequately represent this contemporary population worldwide. Ronald Henry, MD, Regional Coordinator of the CLARIFY study, Trinidad and Tobago, discussed the significance of the CLARIFY trial as it applies to the Caribbean.

While there is evidence that HR may be a prognostic indicator for cardiovascular (CV) outcomes, it has not yet been incorporated into CV risk assessment or therapeutic guidelines [Fox K et al. *Lancet* 2008]. Therefore, the CLARIFY registry offers a unique perspective regarding the role of HR in the setting of stable CAD, and this study may provide robust data about the disease presentation, risk management, and therapeutic strategies that are associated with HR. The prevalence of CAD has declined in developed countries, but this decline is offset by its increase in developing countries [Allender S et al. *British Heart Foundation* 2007]. Thus, CLARIFY may offer solutions to help alleviate the disease burden in regions where CAD is increasing despite contemporary drug therapies, such as the Caribbean. Additionally, Caribbean involvement in this study allows for soft entry of the region into international CV studies while adding to the learning curve for regional networking. This involvement also fosters the alignment of clinical practices with regional or international guidelines.

Data will be collected at baseline and every 6 months over the course of 5 years. CLARIFY analyses will include demographic data; risk factors and lifestyle; medical history; physical examination and vital signs, including resting HR, measured by pulse palpation and standard 12-lead ECG; current symptoms; medications; and most recent laboratory (eg, fasting blood glucose, lipid panel) and CAD assessment measurements (eg, stress testing results, echocardiography, myocardial imaging), when available. This comprehensive analysis will provide important information on the demographic and clinical