

10 Pre-clinical studies of sotagliflozin in hypertrophic cardiomyopathy

Rebecca Taichman, Benjamin Lee, Kenneth Margulies and Sharlene Day

Perelman School of Medicine at the University of Pennsylvania

OBJECTIVES/GOALS: Study the regulatory role of sodium glucose co-transporter 1 (SGLT1) in cardiomyocytes and the therapeutic potential of sotagliflozin in hypertrophic cardiomyopathy (HCM) by (a) quantifying SGLT1 expression in HCM and (b) examining the impact of sotagliflozin on cardiac mechanics. **METHODS/STUDY POPULATION:** * Use Western Blot in cardiac tissue from HCM and non-HCM patients and pre-existing RNA seq and proteomics datasets to quantify SGLT1 levels in HCM. Hypothesis: SGLT1 is upregulated in HCM * Determine how SGLT1/2 inhibition by sotagliflozin will affect cardiac mechanics using living myocardial slice (LMS) preparations. A vibratome creates 200um-thick slices from (a) failing HCM heart explants, (b) septal myectomy samples from HCM patients, and (c) nonfailing rejected donor hearts. LMS are mounted on a force transducer and work-loops are stimulated under varying pre- and after-loads. Collecting baseline and post-drug work loops allows each slice to function as its own control. Hypothesis: sotagliflozin will improve diastolic mechanics by reducing stiffness in the end-diastolic pressure-volume relationship **RESULTS/ANTICIPATED RESULTS:** * Preliminary results from RNA seq data indicate that SLC5A1 mRNA (encoding gene for SGLT1) is significantly decreased in HCM. No proteomics study examined thus far has detected SLC5A1, indicating that overall SGLT1 levels in cardiac tissue are quite low. We will examine SGLT1 levels in our own HCM and non-HCM tissue samples with both mass-spectrometry and Western Blot. * We analyze six slices from each heart and expect 15 donor hearts and 15 HCM hearts/myectomy samples. We visualize the work loop by plotting stress/strain. Stress/strain at mitral valve closure represents exponential end diastolic pressure-volume relationship; Stress/strain at aortic valve closure represents linear end systolic pressure volume relationship. A two-sample paired t-test will compare change in stiffness and elastance. **DISCUSSION/SIGNIFICANCE:** This project contributes to a growing body of research surrounding the currently unknown cardioprotective mechanism of SGLT 1/2 inhibitors, furthers the technique of using living myocardial slices to study cardiac mechanics, and supports a trial examining sotagliflozin in HCM, for which disease modifying therapy remains a prevailing unmet need.

11

Novel Systematic Method for Identifying Congenital Anomaly Cases in Electronic Health Record Databases

Elly Brokamp¹, Lisa Bastarache², Nancy Cox¹, Rizwan Hamid³, Nikhil K. Khanakari¹, Gillian Hooker¹ and Megan Shuey⁴

¹Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA, 37203; ²Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN 37203, USA;

³Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN 37232, USA and ⁴Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA, 37203

OBJECTIVES/GOALS: Congenital anomalies (CAs) affect 3% of live births, yet the cause of 80% of CAs is unknown and for the 20% with

an identified cause, variability in penetrance suggests additional risk drivers exist. Our method for identifying and categorizing CAs in electronic health record (EHR) linked biobank databases can expand and improve CA etiologic research. **METHODS/STUDY POPULATION:** We identified individuals with CAs in three groups: 1. Those with at least one CA 2. Those with multiple CAs (MCA), those with two or more 'major' CAs, and 3. Those with CAs in a specific organ system. We also created a novel quantitative approach, using phenome-wide association studies (pheWAS), for determining CA-associated genetic disease billing codes in order to separate individuals that have a known genetic cause for their CAs from those with idiopathic CAs. We updated CA phecodes, aggregates of clinical billing codes, which we used to identify CA cases in Vanderbilt's EHR-linked biobank database, BioVU. We create a new phecode, 'All CAs', for researchers to quickly identify all individuals with at least one CA. We evaluate the definition of MCA using pheWAS analyses to compare 'minor' vs 'major' CA. **RESULTS/ANTICIPATED RESULTS:** The new CA phecode nomenclature includes 5.8 times more codes for CAs compared with the previous version (365 vs 56), improving granularity. 85 (19.7%) CA-associated genetic disease billing codes were identified through literature review. PheWAS analyses revealed an additional 16 (3.7%) genetic disease billing codes with one or more significant ($p < 2.75 \times 10^{-5}$) association with CA-related phecodes. Identifying CA-associated genetic disease billing codes allows researchers to differentiate between idiopathic CAs and those that have a known genetic cause. PheWAS analyses of individuals with previously considered "minor" CAs showed many associated severe health problems, revealing that the differentiation between "minor" vs "major" CAs when identifying individuals with MCA in the EHR is arbitrary. **DISCUSSION/SIGNIFICANCE:** Our CA identification method is scalable for the growing number of EHR-linked biobanks. Differentiating between idiopathic CAs from those with known causes will increase power in studies discovering additional genetic drivers of CAs. Our novel method allows for expansion and acceleration of CA epidemiological research in EHR-linked biobank data.

12

Time to Sustained Recovery between Oral Tablet and Inhaler Placebos in the ACTIV-6 Platform Clinical Trial

Yue Gao¹, Ahmad Mourad², Chris Lindsell³ and Thomas Stewart⁴

¹Vanderbilt University Medical Center; ²Department of Medicine, Division of Infectious Diseases, Duke University Medical Center;

³Department of Biostatistics and Bioinformatics, Duke Clinical Research Institute and ⁴School of Data Science, University of Virginia

OBJECTIVES/GOALS: Platform trials gain efficiency by sharing placebo controls among different study arms. However, the varying routes of administration make it unclear whether participants exposed to different placebos have similar outcomes. As such, we seek to compare outcomes between participants receiving tablet and inhaler placebos in the ACTIV-6 trial. **METHODS/STUDY POPULATION:** ACTIV-6 is a large, decentralized platform trial exploring repurposed drugs for the treatment of adults with mild to moderate COVID-19. Enrolled participants were randomly assigned to a study arm vs. placebo and then mailed the study drug. They were monitored until symptom resolution or Day 28. Here, we compare outcomes for control participants contributing to the fluticasone furoate study arm, in which 251 were assigned to a tablet