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Pre-clinical studies of sotagliflozin in hypertrophic cardiomyopathy

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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.

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

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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 ($p< 2.75$ x10-5) 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.

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

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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

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placebo and 370 an inhaler placebo. Time to sustained recovery and time to resolution of individual symptoms are compared between groups using Kaplan-Meier curves and unadjusted log-rank tests. A step-down procedure is applied to control the false discovery rate. RESULTS/ANTICIPATED RESULTS: Control participants assigned to tablet placebos had shorter time to sustained recovery (adjusted hazard ratio (HR) 1.34 (95% CI 1.11, 1.62)). When examining each of the eleven individually reported symptoms on study Day 14, nasal symptoms (adjusted odds ratio (OR) 0.44 (0.27, 0.72), p<0.01), dyspnea (OR 0.44 (0.22, 0.87), p = 0.02), and cough (OR 0.54 (0.35, 0.83), p<0.01) were identified as symptoms in which the tablet-placebo group performed notably better than those who received inhaler-placebos. In the follow-up, longitudinal analysis, we anticipate similar results. DISCUSSION/SIGNIFICANCE: Among ACTIV-6 control participants, those receiving a tablet placebo had a significantly shorter time to sustained recovery than those receiving an inhaler placebo. Platform trials using shared controls should consider efficiency in the context of the additional variability when sharing controls with a different route of administration.

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Prognostication in super refractory status epilepticus: Preliminary results from an international survey study

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OBJECTIVES/GOALS: Super refractory status epilepticus (SRSE) is associated with high mortality, often due to withdrawal of life sustaining therapy (WLST) based on perceived poor neurological prognosis. Factors influencing decision making are underreported and poorly understood. We surveyed clinicians who treat SRSE to identify factors that influence WLST. METHODS/STUDY POPULATION: Health care providers (HCP), including physicians, pharmacists, and advanced practice providers, who treat SRSE answered a 51-question survey on respondent demographics, institutional characteristics and SRSE management that was distributed though professional societies. Respondents described approaches to prognostication and rated the importance of clinical factors in the management of two hypothetical clinical cases followed by their prediction of recovery potential for the same two cases. Neurointensivists and other HCP responses were compared using descriptive statistics to differentiate group characteristics; a p-value <0.05 was considered significant. Logistical regression models were employed to identify associations between clinician specific factors and prognostication. RESULTS/ANTICIPATED RESULTS: One-hundred and sixty-four respondents were included in the analysis. Compared to other HCPs (neurologists, epileptologists, neurosurgeons, other intensivists; n=122, 74%), neurointensivists (n=42, 26%) [Odds ratio (OR) 0.3, 95% confidence interval (CI) 0.14-0.68), p=.004)] were less likely to use prognostic severity scores and were less likely to prognosticate likelihood of good functional recovery (OR: 0.28 (95% CI: 0.13-0.62), p=.002) compared to non-neurointensivist HCPs, controlling for potential confounders including professional degree, years of experience, country of practice, and annual volume of SRSE cases. There was, however, significant overlap in factors deemed necessary for determining futility in care escalation. DISCUSSION/SIGNIFICANCE: Neurointensivists value similar clinical factors to other HCPs when evaluating medical futility in SRSE but are less likely to predict definitive outcomes. Pending final survey results, future studies aimed at understanding why neurointensivists may be less likely to decisively prognosticate (i.e. avoiding nihilism) in SRSE may be warranted.

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Characterization of Xylazine-Related Overdose Deaths in Maryland (2020-2022)*

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OBJECTIVES/GOALS: Xylazine is a strong sedative and fentanyl contaminant which has been increasingly detected in drug overdose deaths in Maryland. The goal of this project is to analyze the demographic characteristics and time trends of xylazine-related overdose deaths (XROD) in Maryland from 2020-2022. METHODS/STUDY POPULATION: This cross-sectional study utilizes the Maryland medical examiner's autopsy reports from 2020-2022. These reports include every death in the state that was investigated by the medical examiner, with demographic and toxicological data showing the presence of various substances at the time of death. An XROD was defined as someone who died from drug overdose and had a positive serum xylazine test at time of death. Demographic characteristics and time trends for XROD were analyzed. Multivariable logistic regression modeled associations between demographic variables and the presence of other substances with XROD. RESULTS/ANTICIPATED RESULTS: A total of 1,509 people died from XROD, of which the mean age was 44.4 years and 73.3% were male. The majority were White (57.6%), 39.2% were Black, and 3.2% identified as another race. Over 99.9% of individuals who died from XROD tested positive for fentanyl. XROD peaked in January 2021 and has been trending downwards since then. Adjusted multivariable logistic regression revealed that White individuals had greater odds of XROD relative to Black individuals (OR=1.22, 95% CI=1.07-1.37), and adults aged 30-45 years had higher odds of XROD relative to adults over age 60 (OR=1.26, 95%CI=1.04-1.54). Individuals who used fentanyl had higher odds of XROD relative to those who did not use fentanyl (OR=327.4, 95%CI=46.0-2331.3). DISCUSSION/SIGNIFICANCE: This study demonstrates that middle age, White race, and fentanyl use are associated with xylazine-related overdose deaths in Maryland. Efforts to reduce xylazine-related mortality in the state should address the unique social and geographic factors that influence substance use in this population.

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Discrepancies in Medication Usage and Lifestyle Modification Referrals in Metabolic Syndrome is Dependent on how the Syndrome is Coded: A TriNetX Study

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OBJECTIVES/GOALS: ICD-10 coding inconsistencies hinder timely recognition and treatment of metabolic syndrome (MetS), posing a significant risk for cardiometabolic disease progression. This study employed a digital phenotype for MetS and compared odds for medication and lifestyle intervention compared to those coded for MetS. METHODS/STUDY POPULATION: MetS is a cluster of cardiometabolic risk factors that increase risk for numerous adverse clinical outcomes. Patients with MetS were identified through electronic

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