

Conference Report

Report from the Scientific Poster Session at the 16th Annual Cardiometabolic Health Congress in National Harbor, USA, 14–17 October 2021

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Tarsus Cardio dba Cardiometabolic Health Congress (CMHC), Boca Raton, FL 33431, USA

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1. Preface

The ever-increasing presence of cardiometabolic risk continues to be a major challenge for health care providers in the United States (US). Current estimates suggest approximately 23–38% of all adults in the US have metabolic syndrome, a constellation of cardiometabolic risk factors, including excessive abdominal fat, insulin resistance, inflammation, dyslipidemia, and hypertension. Patients with multiple cardiometabolic risk factors have twice the likelihood of developing and dying from cardiovascular disease (CVD) and more than seven times the risk of developing diabetes compared to those with no cardiometabolic risk factors. The global epidemic of metabolic syndrome, a constellation of cardiometabolic risk factors, and that of obesity, type 2 diabetes, atherosclerosis, chronic kidney disease, cardiovascular disease, and NAFLD/NASH, have become the modern-day health hazard across the world. Lifestyle factors, including a lack of physical activity and proper nutrition, as well as smoking, can further exacerbate the impacts of cardiometabolic risk or disease, which is showing no signs of slowing down. As such, there is an ongoing need for medical education focused on all aspects of cardiometabolic risk.

In its 16th year, the Cardiometabolic Health Congress (CMHC) is the largest, US-based, multidisciplinary conference focused solely on the management of cardiometabolic risk and the prevention of cardiovascular and metabolic disease, and is chaired by top experts: Christie M. Ballantyne, MD; Robert H. Eckel, MD; George L. Bakris, MD; and Anne Peters, MD. The event was delivered in a true hybrid fashion, both in-person and livestreamed, and was attended by over 500 cardiologists, endocrinologists, lipidologists, primary care physicians, nephrologists, and allied healthcare professionals from across the world and presented a unique opportunity to learn practical solutions to consolidate into clinical practice.

In addition to offering cutting-edge and comprehensive education, the 2021 CMHC hosted its fifth annual Scientific Poster Session, where investigators from around the world brought the latest data from current research and clinical findings to share with attendees.

2. Keynote Poster Abstracts

2.1. Association of Hyperuricemia with Length of Stay, Hospital Readmissions and in-Hospital Mortality in Patients Admitted with an Acute Heart Failure Exacerbation

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Purpose: In acute congestive heart failure (CHF) management, uric acid levels increase with IV diuresis, but an acute therapeutic uric acid lowering was not found to decrease BNP levels or improve LV ejection fraction. Hyperuricemia (HU) has been noted to be

associated with increased mortality in patients with chronic CHF. However, an association between HU and outcomes of acute CHF has not been well investigated.

Methods: To study the association between HU and length of stay (LOS), hospital readmission (s) and in-hospital mortality in acute heart failure, we conducted a single tertiary academic medical center retrospective cohort study of 586 consecutive patients with known uric acid levels. Acute heart failure diagnosis was ascertained according to the GWG-HF definitions. Uric acid values were divided into quartiles of less than 3.39 (UAQ1), 4–6.79 (UAQ2), 6.8–10.19 (UAQ3) and 10.2 mg/dL or above (UAQ4). The normal reference range for our laboratory is 3.6–8.0 mg/dL in males and 2.6–6.8 mg/dL in females.

Results: Of the study patients, 39% (226) were females, 68+/-15 years old, 40% (236) with a history of diabetes, 70% (410) with treated hypertension, 47% (275) with a history of CAD, and 37% (218) with history of chronic kidney disease (CKD), including those on hemodialysis. HU was not associated with an increased prevalence of diabetes, hyperlipidemia, hypertension, or prior known CAD or CKD. Uric acid levels were significantly increased in patients who expired (12.3+/-3.3 vs. 7.6+/-2.9 in survivors, $p = 0.004$). Furthermore, there were strong trends towards longer LOS (UAQ1 7.8+/-7.9 vs. UAQ2 8.6+/-10.9 vs. UAQ3 9.5+/-10.5 vs. UAQ4 8.5+/-6.3 days, $p = 0.7$) and more frequent readmissions associated with increasing levels of uric acid (UAQ1 32%, UAQ2 31%, UAQ3 38%, UAQ4 47%, $p = 0.06$).

Conclusions: In patients admitted with acute heart failure, elevated uric acid levels portend a poor prognosis and are associated with increased mortality. Increased uric acid levels may also aid in identifying acute CHF patients who require increased hospital resource utilization by prolonging LOS and increasing readmission rates.

2.2. Clinical and Echocardiographic Findings in Black Heart Failure Patients with Rheumatoid Arthritis

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Purpose: Studies have reported a higher incidence of heart failure among rheumatoid arthritis (RA) patients with heart failure with preserved ejection fraction being most prevalent in White RA cohorts. Previous work by our group demonstrated a prevalence of heart failure of 14.8% in the Black RA population. Utilizing clinical and echocardiographic data, we aimed to further characterize left ventricular function and associated risk factors. Our hypothesis was that HF with preserved EF (diastolic heart failure) would be the predominant type of HF among Black RA patients, as similarly described for Caucasian RA patients with HF.

Methods: Cross-sectional analysis of electronic medical record data of RA patients with HF was compared to age, sex, and a race-matched cohort of RA patients without HF. 2D-echocardiograms of RA-HF were reviewed for left ventricular ejection fraction, wall motion abnormalities and Global longitudinal strain/Relative wall thickness calculations. Descriptive statistics using SPSS version 29 were applied; a logistic regression model was used to assess the strength of association between HF and cardiovascular risk factors.

Results: Sixty-four patients with RA-HF were studied, the mean age of 69.6 ± 1.38 ($\bar{A} \pm \text{SEM}$); 87.3% were Black, 84.4% were women, and mean BMI was $29.6 \pm 1.07 \text{ Kg/m}^2$. Compared to the RA without HF cohort, RA-HF patients had significantly higher rates of HTN, CKD and atrial fibrillation, 66.7% had $\hat{a}\% \pm 3$ CV risks. 2D-echos demonstrated LVEF < 50% in 37.7%, and LVEF 50% in 62.3%. Diastolic dysfunction (DD) was found in 37% with grade 1 DD being most prevalent (75%). Wall motion abnormalities were found in 43.1% of the patients. Global Longitudinal Strain was -8.41 ± 1.85 , left ventricular mass was

187.03 ± 8.66 and Relative Wall Thickness was 0.399 ± 0.001 . RA patients with HTN had an OR of 4.7 (1.5–14.53 CI) for HF, (95% CI), $p < 0.01$ and those who had a smoking history had 3.5 times the risk of developing HF (OR of 3.5) (1.091–11.7 CI) (95% CI), $p < 0.01$.

Conclusions: Heart failure with preserved ejection fraction was the most prevalent among the Black RA patients with HF, which is similar to the HF findings observed in Caucasian RA patients. Black RA patients with HF had higher rates of HTN than RA patients without HF. HTN and smoking conferred the highest odds of HF in this patient population. The low Global Longitudinal Strain found in the study patients predicts higher morbidity and mortality; further studies are needed to confirm our findings in Black RA patients with HF.

2.3. Blood Pressure Improvement in People Using a Digital Health Solution for Comprehensive Diabetes Self-Management

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Purpose: There is a growing recognition of the need to develop digital health solutions that address the total health of a user, including the management of significant comorbidities. Hypertension affects roughly 70% of people with diabetes (PWD) and is twice as common in PWD compared to those without. Moreover, hypertension in PWD amplifies the risk of chronic kidney disease, cardiovascular complications, ischemic cerebrovascular disease, retinopathy, and sexual dysfunction. We have previously shown in multiple studies that a mobile application that supports diabetes self-management and delivers clinical decision support to healthcare providers can lower A1C by approximately 2.0%. Though this digital diabetes solution focuses on glucose control, medication management, and nutrition, the purpose of the current study is to examine user engagement with the app with regard to the important comorbidity of hypertension. In addition, since the current version of the app also provides some clinical coaching on hypertension and delivers decision support to clinicians around hypertension, we wanted to explore blood pressure outcomes.

Methods: Data from 84 users of the digital solution were analyzed. Our primary outcome variable was a meaningful improvement in blood pressure (BP) from baseline to month 3 of using the digital health solution. Meaningful improvement in BP was defined as at least a 5 mmHg drop in systolic BP from baseline to month 3. To identify important self-management behaviors that correlate to our meaningful BP drop outcome variable, we included the first 3 months of engagement data and user demographics as predictor variables in a logistic regression model.

We also statistically validated BP improvement among the 84 users split into three groups; Group 1 included users with average baseline systolic BP greater than 140 mmHg ($n = 12$), and Group 2 included users with average baseline systolic BP greater than 130 mmHg ($n = 34$), and Group 3 included users with average baseline systolic BP less than or equal to 130 mmHg (Group 3, $n = 50$). We performed a paired, one-tailed t-test to test our null hypothesis of no significant change in average BP from baseline to month 3 for each group.

Results: Results of a logistic regression indicated that logging exercise, sleep, along with BP annotations were significant predictors ($p < 0.05$) of a meaningful improvement in systolic BP. Group 1, on average, had a 12 mmHg drop in BP from baseline to month 3 ($p = 0.0046$). Group 2 on average, had a 7.2 mmHg drop in BP from baseline to month 3 ($p = 0.0004$), and Group 3 had no significant change in BP from baseline to month 3.

Conclusions: Although entering BP was not required in the digital solution, we found that users of a diabetes coaching app had significant engagement with logging BP in the product. Meaningful improvements in BP were more likely to occur in users who also tracked other activities such as exercise and sleep. Significant reductions in BP were identified in those users whose baseline systolic BP was elevated. In summary, based on this sample of users, digital health solutions for people with diabetes that support blood pressure self-management have the potential to help diabetes patients with the common

and serious comorbidity of hypertension. Further studies with a larger number of users may help us to uncover the mechanisms for improving BP such as medication adherence, improved activity or sleep, or dietary modifications.

2.4. Prevalence of Nonalcoholic Fatty Liver Disease in Patients with Severe Hypertriglyceridemia-Initial Baseline Data from an Ongoing Phase 2 Study

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Purpose: Hypertriglyceridemia is common in patients with insulin resistance, type 2 diabetes (T2D), obesity, and metabolic syndrome. Nonalcoholic fatty liver disease (NAFLD) is also associated with this same constellation of disorders, yet the prevalence of NAFLD in patients with severe hypertriglyceridemia (SHTG), defined as TG 500 mg/dL, is not well characterized. Fibroblast growth factor 21 (FGF21) is an endogenous metabolic hormone that regulates energy expenditure, lipid, and carbohydrate metabolism. BIO89-100, a glycoPEGylated FGF21 analog, has previously been shown to markedly decrease liver fat, reduce ALT, and improve TG and other lipids in nonalcoholic steatohepatitis (NASH) patients. BIO89-100 is currently being evaluated in ENTRIGUE, a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Explore the Efficacy and Safety in Subjects with Severe Hypertriglyceridemia; this sub-study aims to elucidate the baseline prevalence of hepatic steatosis in SHTG patients participating in ENTRIGUE. Key metabolic parameters associated with SHTG and NAFLD such as BMI, HbA1c, HOMA-IR, Adipo-IR are also described.

Methods: Descriptive statistics summarize baseline characteristics of screened/enrolled SHTG participants opting to obtain MRI-PDFF.

Results: Demographic characteristics were as follows: age range 40–70 years, male 54.5%, white 100%, Hispanic/Latino 36.4%, BMI range 27.4–40.1, T2D 27.3%, and on background lipid therapy 36.4%. Metabolic baseline measurements included TG median 615 mg/dL (range 499–1054), glucose median 119 mg/dL (range 82–254), HbA1c median 5.6% (range 5.2–9.8), HOMA-IR median 7.98 mg/dL × mL/U (range 3.08–26.45) and Adipo-IR median 16.10 mmol/L × U/mL (range 6.87–33.65). Baseline MRI-PDFF demonstrated clinically meaningful liver fat content (MRI-PDFF 5%) in 100% of these first 11 participants (range 6.2–29.0%). The percentage of hepatic steatosis did not appear to correlate with baseline TG values, BMI, or T2D status. Presented results will be updated for any new participants with baseline MRI-PDFF data.

Conclusions: The prevalence of hepatic steatosis was greater than expected in this study population, especially given that not all the patients were obese, and the majority did not have T2D. Patients with SHTG have an increased risk for multiple serious conditions such as cardiovascular disease and acute pancreatitis. However, these data suggest they also have a substantial risk of developing NAFLD. Given the potential broad metabolic benefits of BIO89-100, including improvements in liver fat, circulating TGs, and glycemic control, it is important to understand the prevalence of NAFLD in patients with SHTG. The preliminary baseline findings from ENTRIGUE suggest that routine assessment of hepatic steatosis may be warranted in SHTG patients.

2.5. BIO89-100 Demonstrated Robust Reductions in Liver Fat, Improved Metabolic Parameters, Favorable Tolerability and Potential for Weekly (QW) or Every 2 Weeks (Q2W) Dosing in a Phase 1b/2a Placebo-Controlled, Double-Blind, Multiple Ascending Dose Study in NASH

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Purpose: It is well established that nonalcoholic steatohepatitis (NASH), in addition to the hallmarks of hepatic steatosis, inflammation and ballooning with and without fibrosis, is often associated with systemic alterations such as aberrant lipid profile, insulin resistance and comorbidities including obesity, metabolic syndrome and type 2 diabetes (T2D). Indeed, cardiovascular disease is the leading cause of morbidity and mortality in this population. Therefore, an ideal treatment for NASH should simultaneously address the liver manifestations of the disease while targeting the underlying metabolic overload driving the hepatic pathology. Fibroblast growth factor 21 (FGF21) is an endogenous metabolic hormone that regulates carbohydrate, lipid and energy metabolism. FGF21 analogs have demonstrated the capability to improve both hepatic and metabolic abnormalities in NASH. BIO89-100 is a long-acting glycoPEGylated FGF21 analog, with promising tolerability and pharmacodynamic effects and is the only FGF21 analog with the potential for once every 2 weeks (Q2W) dosing.

Methods: This Phase 1b/2a trial enrolled 81 subjects with liver fat 10% by MRI-PDFF and either biopsy-confirmed NASH (BC-NASH) or phenotypic NASH (PNASH: central obesity with either T2D or with evidence of liver injury by ALT or FibroScan vibration controlled transient elastography score above defined thresholds). Subjects were randomized to 12 weeks of treatment at one of 6 doses (3, 9, 18 or 27 mg weekly [QW]; 18 or 36 mg Q2W) or placebo. Key endpoints were safety, tolerability, pharmacokinetics, change in liver fat content as measured by MRI-PDFF and liver and metabolic markers.

Results: Baseline characteristics were similar between pooled BIO89-100 vs. pooled placebo groups, and between BC-NASH vs. PNASH subjects. At week 13, all BIO89-100 dose groups showed significant relative reductions up to 70% in MRI-PDFF (placebo adjusted $p < 0.001$). Up to 88% of BIO89-100 subjects achieved 30% MRI-PDFF reduction vs. baseline ($p < 0.001$), while up to 71% of subjects achieved the higher threshold of 50% relative fat reduction in the absence of weight loss ($p < 0.0004$). Decreased liver fat was accompanied by a corresponding decrease in liver fat volume (LFV) of up to 305 mL or 65% from baseline ($p < 0.001$). Significant decreases in ALT vs. placebo were observed with BIO89-100, maximal with 27 mg QW (30 U/L decrease from baseline, $p < 0.001$) with the most prominent reduction in the subgroup ($n = 17$) with baseline ALT > 45 U/L (35 U/L decrease from baseline, $p < 0.05$). Additionally, reductions of up to 28% were observed in levels of PRO-C3, an emerging non-invasive biomarker of fibrosis. Metabolic benefits of BIO89-100 included a favorable effect on lipids with significant improvements in triglycerides (TG; up to 28% reduction in the overall population and up to 49% in the subgroup [$n = 15$] with baseline TG 200 mg/mL); non-HDL cholesterol and LDL-C (reductions up to 15% and 16% respectively). Increases of up to 20% in HDL cholesterol were observed, as well as increases in adiponectin of up to 61%. There were no deaths or related serious adverse events; one BIO89-100 treated subject was discontinued due to a treatment-related adverse event (localized skin rash). The mildly increased appetite (15.9% in pooled BIO89-100) was the most common treatment-related AE. The frequency of gastrointestinal (GI) AEs compared favorably to placebo; diarrhea (BIO89-100 12.7%, placebo 22.2%) and nausea (BIO89-100 7.9%, placebo 16.7%) were the only GI AEs in 5% BIO89-100-treated subjects. There were no hypersensitivity reactions or adverse effects on blood pressure or heart rate.

Conclusions: In this study, treatment with BIO89 100 for 12 weeks resulted in robust, clinically meaningful improvements in liver fat and volume and markers of liver stress and fibrosis. Additionally, metabolic improvements as exhibited by reductions in triglycerides and LDL cholesterol and increases in HDL cholesterol and adiponectin were observed; these beneficial hepatic and systemic effects were shown in subjects who were treated by BIO89-100 QW or Q2W. Moreover, treatment was associated with a favorable safety and tolerability profile. There are currently no approved therapies available for NASH. While there are

many therapeutic targets under investigation to date the results have been modest at best and many agents, while showing benefit on liver-related parameters, may in fact worsen lipids or result in weight gain that could potentially exacerbate cardiovascular risk. The data presented here indicate that BIO89-100 has significant potential as a new therapeutic for the treatment of NASH to improve liver-related parameters while simultaneously shifting whole-body metabolism towards a more normal state in these patients. Collectively, these data support the further investigation of BIO89-100 in NASH and other metabolic diseases. A Phase 2b study in NASH is currently underway, as well as ongoing proof of concept study in patients with severe hypertriglyceridemia.

2.6. Cardiovascular Risk Factors in Patients with Coronary Artery Disease Who Are Re-Hospitalized in the Service of Cardiology

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Purpose: Coronary artery disease is one of the main causes of cardiovascular disease. Secondary prevention based on pharmacological treatment and lifestyle changes maintained over time is fundamental to diminish the risk factors and guarantee the success of the treatment. Our objective was to analyze cardiovascular risk factors in patients with coronary artery disease who were re-admitted to the hospital.

Methods: Descriptive prevalence study was carried out from September 2018 to August 2019. The number of patients: 537 patients hospitalized at the Service of Cardiology. Sample: 77 patients with antecedents of ischemic heart disease who were re-admitted. Variables: age, sex, risk factors: diabetes, hypertension, dyslipidemia, smoking, overweight, or obesity (Body Mass index (BMI) (weight/height²) (25 Kg/m²), a sedentary lifestyle was not evaluated. Laboratory values: HDL Cholesterol (60: low), LDL Cholesterol (130: high), triglycerides (150: high), fasting blood glucose (110: impaired); reason for hospitalization (discharge diagnoses classified according to ICD-10 coding). BMI was obtained from 39 patients. Lipid values were taken from 47 patients and fasting blood glucose values from 75 patients. We calculated relative frequencies and percentages. We used Microsoft Excel 2013 and R Studio 4.0.3 for data processing.

Results: The readmission percentage was 14.3%, of which, 66% (51/77) were males and 96% (74/77) were over 50 years old. As for risk factors in regard to the risk of cardiovascular disease: 35% of the patients presented diabetes mellitus, 84% presented hypertension, 29% dyslipidemia, 27% were smokers at the moment of readmission and 33% had stopped smoking. An 82% presented overweight, or obesity. As for the distribution of laboratory results: it was found that 98% presented a low-value HDL Cholesterol; 30% had a high level of triglycerides; and high LDL Cholesterol in 6% of the patients. A 48% presented impaired fasting blood glucose. In regard to the discharge diagnoses: 40% were for heart failure, 21% for acute myocardial infarction, 14% for angina pectoris and 11% for chronic ischemic heart disease.

Conclusions: Those patients who were re-admitted having coronary artery disease presented: hypertension, overweight and obesity as the main risk factors. Lipid values of LDL Cholesterol and triglycerides were optimal in most cases in respect of the mandatory use of statins; however, they presented low values of HDL Cholesterol. Almost half of them presented fasting hyperglycemia. The main discharge diagnosis was heart failure, favored by the predominant risk factors, though the prevalence of ischemic manifestations in different presentations shows the progression of the atherosclerotic pathology before the insufficient global checkup of cardiovascular risk factors. It is necessary to set up integral monitoring and educational programs, as well as constant follow-ups of patients with

coronary artery disease, which may lead towards active participation and access to cardiac rehabilitation in order to achieve treatment success and adherence.

2.7. Assessment of Heart Failure risk and Characteristics in the Black population with Gout.

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Purpose: Prior studies have documented a higher prevalence of heart failure (HF) in the non-black gout population. Literature has shown a systolic dysfunction of about 12.7% among the Framingham Offspring cohort. Using clinical and echocardiographic data, we aimed to compare the characteristics of left ventricular dysfunction and associated risk factors of HF in Black patients with and without gout.

Methods: Cross-sectional analysis of electronic medical record data of gout patients was compared to age, sex, and race matched cohort of the non-gout patients. Clinical parameters and 2D echocardiograms were reviewed for the patients with gout and heart failure. Left ventricular ejection fraction (LVEF), left ventricular wall motion and size abnormalities, and diastolic dysfunction was evaluated. HF patients with gout were further categorized based on LVEF % into three groups: <40%, 41–55% and >55%. Descriptive statistics using SPSS version 29 was applied; a logistic regression model was used to assess the strength of association between HF and cardiovascular risk factors.

Results: The gout population of 471 patients with a mean age of 63.7 ± 0.53 years, 89% being Black, and 63% men were compared to an age, sex, race matched non-gout cohort. Body mass index (BMI) for those with gout was 31.3 ± 0.35 kg/m² compared to 28.2 ± 0.2 kg/m² in those without gout ($p < 0.01$). The gout patients had higher rates of Hypertension (HTN), Hyperlipidemia (HLD), Diabetes mellitus (DM), and chronic kidney disease compared to the non-gout cohort. Gout patients had a higher prevalence of heart failure with 45.2% ($n = 213$) compared to controls with 9.4% ($n = 44$). HF patients with gout were categorized utilizing the LVEF into 3 groups. Systolic dysfunction was encountered at a higher proportion with 46.3% in EF < 40%, 22.7% in EF 41–55% and 31% in EF > 55%. Diastolic dysfunction (DD) was found in 45.9% of which Grade 1 DD was observed in 70%. Left ventricular hypertrophy was found in 22.6% of gout patients compared to 24.2% in the non-gout group ($p = \text{NS}$). The mean highest serum uric acid levels among the 3 gout subgroups were 10 ± 0.60 mg/dL without an intergroup significance ($p = \text{NS}$). In the logistic regression model, the unadjusted Odds ratio (OR) of HF in patients with gout was 7.97 (5.5–11.4, 95% CI), $p < 0.01$. After adjusting for traditional risk factors including age, BMI, HTN, DM, and HLD, the OR of HF in patients with gout was 7.1 (4.7–10.6, 95% CI), $p < 0.01$. There were at least one or more all-cause readmissions in 54.1% of gout patients as opposed to only 19% in the non-gout group ($p < 0.01$).

Conclusions: Black population with gout had a very high prevalence of cardiovascular risk factors and congestive heart failure as well as hospital readmission compared to the non-gout cohort. Systolic dysfunction (46.3%) was found to be more prevalent than previously studied in the Caucasian population (12.7%). Larger studies are needed to confirm our findings and develop management strategies in black gout patients with HF.

2.8. Burden of influenza and use of antiviral treatments in Cardiovascular Disease Patients

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Purpose: People with Cardiovascular Disease (CVD) are at higher risk for developing serious complications from flu. Among adults hospitalized with flu during recent flu seasons, heart disease was one of the most commonly-occurring chronic conditions about half of the adults hospitalized with flu that season had heart disease. Studies have shown that flu illness is associated with an increase in heart attacks and stroke; these patients are also more susceptible to respiratory-related influenza complications; this study explored the effect of antiviral medication on influenza-related complications and healthcare resource utilization in CVD patients who contracted the flu.

Methods: A retrospective claims analysis, using IBM Watson MarketScan Commercial claims data, in patients with cardiovascular disease by flu season (October to April of the following year). The study period encompasses three flu seasons: 2016–2017, 2017–2018, and 2018–2019. Patients were included if they had: 1+ inpatient diagnosis or 2+ outpatient diagnoses of the same CVD condition at least 30 days apart; the Flu index date was the first flu diagnosis date within each season and included only patients with flu diagnosis as the primary diagnosis. Patients were 18 or older with continuous enrollment: 12 months pre-flu index (baseline) and 1-month post-flu index. Patients were excluded who received prophylaxis antiviral treatment, defined as any flu treatment in the month prior to flu index date. Cases (treated): Patients who received antiviral flu treatment within 2 days of index flu diagnosis. Excluded patients who received prophylactic antiviral flu treatment with 10-day supply as their index treatment. Controls (untreated): Patients who did not receive any antiviral flu treatment in the 30 days post index of flu diagnosis; Exclude all patients who were hospitalized between index flu and two days post-index. Treated and untreated CVD-flu patients were propensity score matched 1:1 (case:control) with nearest neighbor matching (without replacement).

Results: There were $n = 4323$ treated and $n = 4323$ matched, untreated patients. Baseline characteristics were similar between the two groups; mean age and proportion of males were well balanced between the cohorts. Mean age at flu index date for treated and untreated, respectively, was 63 vs. 64 years; the proportion of males was 51.4% vs. 51.0%. Across treated and untreated cohorts, the majority of patients were located in the southern United States, covered under PPO/EPO insurance, 2018 had the highest ratio of flu index. Additionally, among all patients, many had a previous diagnosis of myocardial infarction, heart failure, atrial fibrillation and stroke. The mean Charlson Comorbidity Index (CCI) score was 1.41 for Treated and 1.45 for Untreated patients.

After matching, in both Treated and Untreated cohorts: ($n = 4321$) after 30 days; ($n = 4109$) within 60 days; ($n = 3964$) after 90 days and ($n = 3664$) after 180 days.

All cause hospitalizations: (At least 1 ER visit (30 days: 11.9% vs. 15.8%, $p < 0.01$), (60 days: 17.2% vs. 22.0%, $p < 0.01$), (90 days: 21.4% vs. 25.9%, $p < 0.01$), (180 days: 32.1% vs. 34.6%, $p = 0.021$);

At least 1 pharmacy fill (30 days: 87.6% vs. 78.9% $p < 0.01$), (60 days: 95.0% vs. 87.7% $p < 0.01$), (90 days: 97.4% vs. 90.6% $p < 0.01$), (180 days: 98.8% vs. 92.7% $p < 0.01$);

Any Respiratory-related HRU (30 days: 25.6% vs. 33.1%, $p < 0.01$), (60 days: 30.6% vs. 37.8%, $p < 0.01$), (90 days: 34.5% vs. 41.4%, $p < 0.01$), (180 days: 42.5% vs. 47.9%, $p < 0.01$);

At least 1 outpatient visit (30 days: 25.3% vs. 32.9%, $p < 0.01$), (60 days: 30.4% vs. 37.6%, $p < 0.01$), (90 days: 34.3% vs. 41.3%, $p < 0.01$), (180 days: 42.4% vs. 47.8%, $p < 0.01$);

At least 1 ER visit (30 days: 4.2% vs. 5.7%, $p < 0.01$), (60 days: 5.0% vs. 6.9%, $p < 0.01$), (90 days: 5.4% vs. 7.5%, $p < 0.01$), (180 days: 6.6% vs. 9.1%, $p < 0.01$);

Specific to Cardiovascular-related outcomes (30 days: 8.5% vs. 12.4%, $p < 0.01$), (60 days: 13.7% vs. 17.4%, $p < 0.01$), (90 days: 17.6% vs. 21.4%, $p < 0.01$), (180 days: 25.9% vs. 29.0%, $p < 0.01$);

Heart failure (30 days: 3.7% vs. 6.7%, $p < 0.01$), (60 days: 5.6% vs. 8.5%, $p < 0.01$), (90 days: 7.3% vs. 10.1%, $p < 0.01$), (180 days: 10.5% vs. 12.6%, $p < 0.01$);

Acute kidney failure (30 days: 0.7% vs. 1.7%, $p < 0.01$), (60 days: 0.9% vs. 2.0%, $p < 0.01$), (90 days: 1.0% vs. 2.2%, $p < 0.01$), (180 days: 1.7% vs. 2.8%, $p < 0.01$) were the most statistically significantly different.

Conclusions: Among adults with CVD hospitalized with flu during three recent flu seasons, heart disease was one of the most commonly occurring chronic conditions. Cardiovascular patients who contracted the flu and took antiviral medication suffered fewer all-cause hospitalizations, respiratory-related influenza complications, underlying disease complications and overall healthcare resource utilization compared to CVD patients who were not prescribed antiviral treatments; these conditions worsened over time.

2.9. Real-World Treatment Patterns among Patients with Atherosclerotic Cardiovascular Disease (ASCVD) Using Lipid-Lowering Therapy in the HealthCore Integrated Research Database (HIRD)

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Purpose: Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in the US and includes coronary heart diseases such as myocardial infarction, ischemic stroke, and peripheral artery disease. High levels of low-density lipoprotein cholesterol (LDL-C) is one of the primary causes of ASCVD. The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines recommend lipid-lowering therapies (LLTs) to reduce LDL-C by 50% and recommend that patients should be treated to an LDL-C < 70 mg/dL. Statins are the preferred first-line LLT, however, around 80% of patients on statins do not achieve recommended LDL-C goals. Other treatments, including ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitor monoclonal antibodies (PCSK9is), are recommended as next line of treatment. With these newer treatments, the knowledge regarding adherence, persistence, and discontinuation among LLTs remains limited; this study examined real-world treatment patterns of LLTs including statins, ezetimibe, and PCSK9is as well as LDL-C goal attainment among patients with ASCVD using a large claims-based database. Treatment patterns included: adherence, persistence, and discontinuation for LLTs, measured over 12 and 24 months from the first LLT claim after the first outpatient ASCVD visit during the predefined study period.

Methods: The research questions were addressed using a retrospective, observational study using claims, eligibility, and outpatient lab data from the HealthCore Integrated Research Database (HIRD[®]) between 1 October 2014–31 December 2020 (study period). Patients 18 years with an ASCVD diagnosis between 1 October 2015 and 31 December 2019 were included. The index date was the earliest claim date for an LLT (statins, ezetimibe, PCSK9is) between the first ASCVD diagnosis date and first ASCVD diagnosis date + 365 days/730 days for patients with 12/24-months of follow-up during the study period. LLTs provided within 30 days of index date were considered as combination treatments for cohort assignments. Patients with 12 or 24 months continuous health plan enrollment after the index date (i.e., follow-up) were included. A subset of patients with 2 outpatient lab results during baseline (index date \pm 90 days) and follow-up periods (index date + 183/365 to index + 365/730) days was used to report LDL-C change.

The outcomes of interest included adherence, persistence, discontinuation of LLTs, and LDL-C change. Adherence was defined as having the proportion of days covered (PDC) as 80%. PDC was calculated as days covered by a drug (or overlap days for combinations) during the follow-up period. Persistence was defined as the number of days from index until LLT discontinuation (<60 days allowed gap) or end of follow-up. Discontinuation was defined as having a gap in LLT days supplied \geq 60 days without additional claims for the same LLT over the remainder of the follow-up period.

Results: Among ASCVD patients with 12 and 24 months of follow-up (n = 642,005, n = 461,050; respectively), only 65.1% and 68.1% patients used an LLT, respectively. Treated patient characteristics were similar across cohorts: the mean (SD) age was 66.5 (11.9) years, 63.8% male, and 19.1% had Medicare Advantage coverage.

Conclusions: It was observed that 27.7–32.0% of patients did not use any LLT after ASCVD diagnosis. The majority of ASCVD patients were treated with statin monotherapy.

Adherence and persistence were similar across drug classes but declined over a 24-month period across all LLTs. The persistence across drug classes was found to be longer among monotherapies than combination therapies. About a third of ezetimibe and a quarter of PCSK9i users discontinued treatment during 24-months of follow-up.

2.10. Efficacy and Safety of Finerenone in Patients with CKD and T2D by Baseline Insulin Treatment

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Purpose: Finerenone is a novel, selective, nonsteroidal mineralocorticoid receptor antagonist that significantly reduced the risk of kidney and CV outcomes in patients with CKD and T2D in the FIDELIO-DKD trial, with no effect on blood glucose. In advanced T2D, insulin is often used to control glycemia; this analysis will report outcomes from the FIDELIO-DKD trial by baseline insulin treatment.

Methods: In FIDELIO-DKD (NCT02540993), 5734 patients with T2D, UACR 305,000 mg/g, eGFR 25 < 75 mL/min/1.73 m² and treated with optimized RAS blockade were randomized to oral finerenone or placebo. The primary outcome was a composite of kidney failure, a sustained 40% eGFR decline from baseline, or renal death. The key secondary outcome was a composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure.

Results: Of the 5674 patients analyzed, 3637 (64.1%) were treated with insulin or insulin analogues at baseline. Patients treated with insulin at baseline had a higher A1C and a longer duration of diabetes, with higher proportions of statin and GLP-1RA use, and lower use of other anti-hyperglycemic agents than those who were not. Finerenone did not affect A1C during the trial. The primary and key secondary CV outcome occurred in fewer patients treated with finerenone, with no between-group interaction (primary outcome: HR 0.85, 95% CI 0.73 0.98 with insulin; HR 0.79, 95% CI 0.64 0.96 without insulin; *p*-value for interaction 0.56; CV outcome: HR 0.82, 95% CI 0.69 0.97 with insulin; HR 0.95, 95% CI 0.74 1.23 without insulin; *p*-value for interaction 0.33). Hyperkalemia events were similar between groups (mean treatment difference between finerenone and placebo for

treatment-emergent serum potassium >5.5 mmol/L, 11.1% with insulin and 13.4% without insulin), with a low incidence of hyperkalemia-related treatment discontinuation

Conclusions: Finerenone has a beneficial effect on kidney and CV outcomes in patients with CKD and T2D, irrespective of insulin use at baseline

2.11. FIDELIO-DKD Study Analysis of Effects of Finerenone by Baseline HbA1C

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Purpose: Patients with CKD and T2D are at high risk of morbidity and mortality despite the use of guideline-directed therapies. Finerenone, a novel, selective, nonsteroidal mineralocorticoid receptor antagonist, reduced the risk of adverse kidney and CV outcomes in patients with CKD and T2D; here we report outcomes by baseline A1C.

Methods: FIDELIO-DKD (NCT02540993) randomized 5734 patients from 48 countries to receive oral finerenone or placebo. Eligible patients had T2D, with a UACR of 30–5000 mg/g, eGFR < 75 mL/min/1.73 m² and received optimized RAS blockade. Patients with A1C > 12% at screening were excluded. The primary outcome was a composite of kidney failure, sustained 40% decrease in eGFR from baseline, or renal death. The key secondary outcome was a composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure.

Results: In the 5674 patients analyzed, the mean baseline A1C was 7.7% and mean diabetes duration was 16.6 years; finerenone did not affect A1C during the trial. Overall, 2948 patients had A1C = 7.5% and 2715 patients had A1C > 7.5% at baseline. Patients with higher A1C levels were more likely to use insulin and had a longer duration of diabetes. After a median follow-up of 2.6 years, the primary outcome occurred in fewer patients treated with finerenone compared with placebo, this was observed in both the A1C 7.5% and > 7.5% groups (18.7% vs. 21.5% patients with A1C of 7.5% [HR 0.86; 95% CI 0.73–1.01]; 16.9% vs. 20.7% patients with A1C > 7.5% [HR 0.79; 95% CI 0.66–0.94]; P-interaction 0.47). Finerenone also reduced the incidence of the key secondary CV outcome compared with placebo regardless of baseline A1C (HR 0.88; 95% CI 0.71–1.07 for A1C ≤ 7.5% and HR 0.83; 95% CI 0.69–1.01 for A1C > 7.5%; P-interaction 0.73). Reduction in UACR was consistent across subgroups. Overall, hyperkalemia events were independent of the A1C level.

Conclusions: In patients with CKD and T2D, treatment with finerenone reduced the risk for developing adverse kidney and CV outcomes independent of baseline A1C.

2.12. The Role of Leptin and Inflammatory Related Biomarkers in Individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Purpose: Leptin is a member of the cytokine family; its receptor (LEPR-b) is the longest form receptor expressed in cells of the immune system; wherein LEPR-b deficiency causes a decrease in CD4+ cells. LEPR-b is located in hypothalamic and brain stem nuclei, and it primarily regulates energy status. As well, leptin indirectly regulates widespread pain and exercise tolerance by decreasing circulating cortisol. Hyperinsulinemia increases leptin production in adipocytes on a diurnal rhythm; however, the precise relationship between insulin, leptin and pro-inflammatory markers remains uncertain. In clinical settings, high-sensitivity C-reactive protein (hsCRP) has been widely used, as an inflammatory predictor for leptin-related cardiometabolic outcomes and chronic inflammatory symptoms. Leptin-related metabolic and inflammation dysregulations have been clinically reported in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), but not fully elucidated. We examined the association of plasma insulin, leptin, and hsCRP levels with ME/CFS self-reported symptom severity.

Methods: Prospective analyses were conducted on ME/CFS patients who met Fukuda/CDC criteria at Birmingham hospital, Alabama, U.S.A. The independent variables were hyperinsulinemia ($>174 \text{ } \mu\text{IU/mL}$), hyperleptinemia/hypoleptinemia ($>18.3/<3.3 \text{ ng/mL}$), residual inflammation risk (hsCRP $\hat{\alpha}\% \pm 2$ and $\hat{\alpha}\% \pm 26.2 \text{ mg/L}$) and within-individual-variability (WIV) for each biomarker. WIV was defined for each individual as standard deviation/sample residuals adjusting for time and calculated from once-daily random plasma samples over 10–12 weeks. The primary outcomes were: (1) ME/CFS symptom score trends [generalized pain, persistent fatigue, sleep disturbance, impairment of concentration and memory (brain fog), and post-exertional malaise (PEM)] calculated from the MFI-20 questionnaire with anchors from 0 to 100 and recorded once daily over a matching 12–14 weeks, and (2) dichotomized symptom severity, with severe symptoms defined as scores $> 60/100$. After adjusting for age and time, we reported: (1) standard errors (SEM) and p -values for symptom trends using multivariable mixed-effect linear regression models, and (2) odds ratios for severe symptoms using multivariable alternating logistic regression models.

Results: We included 29 ME/CFS patients. All were females and >18 years old. Hyperinsulinemia, hyperleptinemia/hypoleptinemia, and residual inflammation risk were 7%, 80%/7%, and 74%, respectively. The medians of insulin-WIV, leptin-WIV and hsCRP-WIV were [(0.24; IQR 0.15–0.38), (0.25; IQR 0.15–0.40), (0.33; IQR 0.18–0.51)] respectively. On average, hyperleptinemic patients had the highest leptin-WIV and 50% of them had residual inflammation risk. Severe (fatigue, pain, brain fog, sleep disturbance, and PEM) were reported in 50%, 29%, 41%, 30%, and 57% of patients, respectively. In the adjusted analysis, worse fatigue scores (7.49; SEM, 2.23; $p = 0.002$) were associated with higher insulin-WIV. Hyperleptinemia (OR 1.54; 95% CI 1.13–2.09) compared to hypoleptinemia, and residual inflammation risk (OR 1.65; 95% CI 1.21–2.25) were associated with higher odds of severe fatigue. Worse pain scores (7.17; SEM, 2.30; $p = 0.005$) were associated with higher leptin-WIV, and (8.45; SEM, 2.25; $p = 0.0009$) higher hsCRP-WIV, and residual inflammation risk (OR 1.75; 95% CI 1.34–2.29) was associated with higher odds of severe pain. Severe brain fog scores (9.20; SEM, 2.44; $p = 0.0008$) were associated with higher insulin-WIV, higher leptin-WIV (4.73; SEM, 2.12; $p = 0.03$). Residual inflammation risk (OR 1.40; 95% CI 1.16–1.77) was associated with higher odds of severe brain fog. Hyperleptinemia (OR 0.60; 95% CI 0.43–1.19) was associated with lower odds of severe PEM compared to hy-

poleptinemia, and better sleep quality was associated (6.07; SEM, 1.70; $p = 0.001$) with higher insulin-WIV, and (3.37; SEM, 1.47; $p = 0.03$) higher leptin-WIV.

Conclusions: In patients with ME/CFS, symptoms severity was associated with hyperleptinemia, inflammation and within-individual-variability of these biomarkers. Leptin and hsCRP may be clinically useful in predicting symptom severity. Larger clinical trials are needed to further examine the prediction and causality of these biomarkers in the development of ME/CFS diagnosis. The efficacy and safety of anti-inflammatory therapies may be evaluated in sub-clusters of ME/CFS with metabolic responses and inflammation dysregulations to improve patient-reported symptoms.

3. Perspectives

On 11–14 October 2023, CMHC will host its 18th Annual CMHC meeting, held in Boston, MA, USA. During this three-and-a-half-day conference, world-renowned experts will present on the latest developments in cardiovascular disease, chronic kidney disease, obesity and lifestyle, type 2 diabetes, lipids, and more. The meeting will include extensive expert panel discussions and debates, as well as ample opportunities for audience Q and A, with the goal of enhancing the interactions with thought leaders and to help clinicians walk away with practical advice to apply directly to patient care.

For more information about this meetings and future activities from CMHC, please visit: <https://www.cardiometabolichealth.org/> (accessed on 17 November 2022).

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