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General Information

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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: The Texas Health Resources Clinical Scholars Program
How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_0.pdf
https://yoda.yale.edu/system/files/scan_feb_20_2020_at_4.12_pm.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT01032629 - 28431754DIA3008 - A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Validation of a Machine Learning-based Model to Predict the Risk of Heart Failure among Patients with Diabetes Mellitus: the WATCH-DM Risk Score

Narrative Summary:

For this analysis, we will 1) use the CANVAS trial dataset to externally validate the WATCH-DM risk score and 2) evaluate the effect of canagliflozin across quintiles of the WATCH-DM risk groups.

Scientific Abstract:

Background:
We have previously developed a novel approach leveraging machine learning methods, which can handle high-dimensional data, to predict incident HF in patients with T2DM (type 2 diabetes mellitus). The WATCH-DM risk score (Weight [BMI], Age, hyperTension [SBP and DBP], Creatinine, High Density Lipoprotein, Diabetes [HbA1c], MI and CABG) integrates readily available clinical, laboratory, and electrocardiographic variables to efficiently predict incident HF risk among high-risk patients with T2DM.
Objective:
For this analysis, we will 1) use the CANVAS trial dataset to externally validate the WATCH-DM risk score and 2) evaluate the effect of canagliflozin across quintiles of the WATCH-DM risk groups.
Study Design:
We will calculate the WATCH-DM score for each participant in the CANVAS dataset.
Participants:
All patients. We will exclude those patients with existing heart failure (HF) at baseline or those with sub-clinical HF/symptoms at baseline.
Main Outcomes Measures:
We will use the baseline characteristics data and the 5-year follow-up. Our outcome of interest is Incident HF hospitalization.
Statistical Analysis:
We will first remove those participants with a baseline diagnosis of clinical or subclinical HF. Participants will also be removed if they contain WATCH-DM variables with missing data. We will then calculate the WATCH-DM score for each participant in the CANVAS dataset. Using the observed incident HF (heart failure), we will calculate the Harrel's C-statistic to evaluate the predictive ability of our model.

Brief Project Background and Statement of Project Significance:

The sodium-glucose cotransporter 2 inhibitors (SGLT2i), a class of glucose-lowering therapies, have been shown to reduce risk of HF in at-risk patients with T2DM (type 2 diabetes mellitus), and are now supported as second-line therapies (after metformin) in patients with T2DM and cardiovascular risk factors or with prevalent ASCVD (atherosclerotic cardiovascular disease). However, limited guidance is available regarding targeted introduction of these therapies in patients with T2DM at heightened risk of HF (heart failure). Importantly, current risk prediction models with traditional risk factors incompletely capture HF risk in T2DM.
As such, we developed a novel approach leveraging machine learning methods, which can handle high-dimensional data, to predict incident HF in patients with T2DM. Specifically, we developed and internally validated a novel risk prediction model for incident HF in patients with T2DM at high cardiovascular risk enrolled in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial (ClinicalTrials.gov Identifier NCT00000620). Using over 8,200 patients and 66 covariates from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, we used a random survival forest (RSF), a nonparametric decision tree machine learning approach, to identify predictors of incident HF. We externally validated our model using data from the ALLHAT trial. Calibration using the validation dataset was acceptable as shown with Hosmer-Lemeshow statistics (chi-square=9.63, p=0.29). The

WATCH-DM risk score demonstrated good discrimination with an overall C-index of 0.70 (95% CI 0.67-0.72). However, given the increased importance of SGLT2i medications, we would like to evaluate the association with WATCH-DM scores in patients who have received these medications. We hope to find an interaction between treatment effect and WATCH-DM risk scores for the risk of incident HF.

Specific Aims of the Project:

For this analysis, we will 1) use the CANVAS trial dataset to externally validate the WATCH-DM risk score and 2) evaluate the effect of canagliflozin across quintiles of the WATCH-DM risk groups.

What is the purpose of the analysis being proposed? Please select all that apply.
Research on clinical prediction or risk prediction

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

All patients will be included. We will exclude those patients with existing heart failure (HF) at baseline or those with sub-clinical HF/symptoms at baseline.

Main Outcome Measure and how it will be categorized/defined for your study:

Our main outcome of interest is incident heart failure (HF) hospitalization at 5 years.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

From the WATCH-DM risk score previously developed, we will stratify participants based on age, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), hemoglobin A1c (Hb A1c), high-density lipoprotein (HDL-C), serum creatinine, a history of previous MI (myocardial infarction), a history of previous CABG (coronary artery bypass graft).

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

We will also evaluate the association sex, race, smoking history, natriuretic peptide levels, and (if available) echocardiographic parameters across quintiles of the WATCH-DM risk score.

Statistical Analysis Plan:

We will first remove those participants with a baseline diagnosis of clinical or subclinical HF. Participants will also be removed if they contain WATCH-DM variables with missing data. We will then calculate the WATCH-DM score for each participant in the CANVAS dataset. Using the observed incident HF (heart failure), we will calculate the Harrel's C-statistic to evaluate the predictive ability of our model.
Next, we will use the WATCH-DM risk score to categorize the CANVAS participants into quintiles of HF risk. Baseline characteristics will be calculated for each quintile. The unadjusted observed risk of incident HF across the quintiles of WATCH DM risk score will be compared using KM curves and log rank method. The WATCH-DM risk calibration capability will be tested by plotting the observed HF risk versus predicted HF risk across the quintiles of WATCH DM Risk score categories. The WATCH-DM risk score calibration capability will be assessed both visually and using the Nam-D'Agostino ?2 goodness-of-fit test; a non-significant ?2 (p-value>0.05) indicates good calibration.
Finally, using Cox proportional hazard models, we will compare the risk of incident HF across quintiles of WATCH-DM risk score. We will also test for an interaction between the treatment effect and WATCH-DM risk score for the risk of incident HF.
Software Used:
R
Project Timeline:

2/01-4/30/2020 Data acquisition

5/1-5/31/2020 Data extraction
6/1-6/30/2020 Data analysis
7/1-7/31/2020 Drafting manuscript
8/1-8/30/2020 Manuscript draft shared with YODA project for approval
8/2020 First submitted for publication
9/1/2020 Results reported back to the YODA Project

Dissemination Plan:

This research results are planned to published to the journal Diabetes Care.

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