RESARCH TITLE: Polypharmacy, statin use and 6-month dyspnea trajectories among older adults with serious, life-limiting diseases.

BACKGROUND: Dyspnea is common amongst patients with serious, life-limiting medical conditions including cardiovascular disease, pulmonary disease and cancer. Dyspnea affects patients with advanced cardiopulmonary disease and is one of the indications for referral to palliative care services according to the most recent heart failure guidelines. Between 27-61% of COPD patients experience moderate-to-severe dyspnea. One-quarter of patients with advanced cancer have moderate-to-severe dyspnea during their last 6 months of life with 70% of patients in one series reporting episodic dyspnea crises. In addition to the distress experienced during periods of acute or chronic dyspnea for these patients, dyspnea also exacerbates other symptoms such as pain, fatigue, anxiety and depression.

Polypharmacy is associated with falls, hospitalization and mortality in older persons. Targeting which medications are preferred for discontinuation remains a challenge. Statins are common in older patients and are prescribed to reduce risk for poor cardiovascular outcomes. Statins have also been associated with improvements in exercise capacity and reduced exacerbations for patients with chronic obstructive pulmonary disease (COPD) and pulmonary hypertension. However, statins are also associated with muscle inflammation, aching and pain. Animal models have suggested that statins could accelerate aging-related decline in diaphragmatic mitochondria in mice. There is at least one case report of restrictive pulmonary disease from diaphragmatic paralysis leading to dyspnea associated with statin use in humans. However, there are currently no data exploring the potential impact of statins on dyspnea for patients with life limiting disease.

Given the high personal costs for patients and their caregivers, dyspnea is an important target for improving patient-centered care for patients with serious, life-limiting diseases. In addition to advancing clinicians' awareness of dyspnea symptoms, new strategies need to be developed to decrease the burden of dyspnea for patients living with these conditions over time. Latent class, group-based trajectory analyses seek to understand how distinct groups behave over time and what variables are contributing to the differences observed differences within each group. Trajectory analyses could improve our understanding of what patterns of dyspnea over time are experienced by patients and what factors are associated with the different patterns. Repeated measures for symptoms over time using a validated instrument would be an essential first step to better understanding how to develop palliative interventions to help patients living with dyspnea.

To begin to address these gaps, we propose a trajectory analysis to determine the optimal number of different trajectories for dyspnea in older patients with serious diseases. As an informal validation step, we will then describe hospitalization and mortality outcomes associated with the different groups. Finally, we will determine what impact polypharmacy, in general, and statin use, specifically, have on dyspnea trajectory. These pilot data will begin to develop a foundation to inform future intervention work focusing on de-prescribing medications for patients with dyspnea in the setting of serious life-limiting medical diseases that will include detailed outcomes including dyspnea assessments and performance measurements such as 6-minute walk distances. Our specific aims are to:

Aim 1. Evaluate the optimal number of trajectories of dyspnea amongst older patients with life-limiting diseases in the statin discontinuation trial using trajectory modeling.
H1. At least 3 trajectories of dyspnea are optimal to identify groups of older adults with serious, life-limiting conditions: worsening, stable and improving.
Aim 2. Describe outcomes associated with 6-month dyspnea trajectories.
H2. Worsening dyspnea trajectory is associated with all cause and cardiovascular-specific

hospitalization risk and mortality.
Aim 3. Determine the associations between polypharmacy (binary variable) and medication count (continuous variable) and dyspnea trajectories.
Subaim 3. Explore associations between statin use and dyspnea trajectories.
H3a. Polypharmacy and medication count are associated with increased 6-month dyspnea burden trajectory.
H3b. Statin discontinuation is associated with improving dyspnea trajectory.

Study Design: Longitudinal data analysis using PCRC data repository: Statin Discontinuation.

Major inclusion and exclusion criteria: English-speaking patients ≥18 years and older who received a statin for at least three months prior to enrollment and who have a life-limiting disease determined by the surprise question, life-expectancy of more than one month and functional decline in the previous 3 months.

Patient population: We will include patients enrolled in the Statin Discontinuation trial (n=381); specifically, this includes patients enrolled from 15 PCRC sites and randomized to statin discontinuation or usual care. Approximately half of these patients (mean age=74 years) had malignant tumor and 58% had cardiovascular disease. Median survival was 31 weeks.

Study procedures and data collection: To develop dyspnea trajectories, we will first use data collected from the Edmonton Symptom Assessment System (ESAS) item that explores dyspnea symptoms at the time of the interview. Patient-reported dyspnea is gauged as 0=no shortness of breath and 10=worst possible shortness of breath. ESAS are administered up to 8 times for study participants (enrollment and then weeks 2, 4, 8, 16, 20 and 24). As a form of internal validation, we will compare individual results from the ESAS dyspnea item with self-reported troublesome symptom frequency and severity for dyspnea from the McGill Quality of Life Questionnaire. To define the trajectories, we will use semi-parametric, group-based modeling described in Jones 2001. We will evaluate trajectories to minimize variance within each group while maintaining group distinction (Aim 1). For patient outcomes (Aim 2), we will use hospitalization and mortality as previously described in the parents study. For factors associated with each dyspnea trajectory, we will compare baseline demographic characteristics stratified by statin discontinuation.

Outcomes: For Aims 1 and 3, dyspnea trajectories are the primary outcomes. Aim 2 includes patient outcomes (all-cause and cardiovascular-specific hospitalization and mortality).

Statistical Analysis: We will describe trajectories as the primary outcomes for Aims 1 and 3. For Aim 2, we will use Cox time-to-event analyses. Categorical variables will be described using frequency distributions, and continuous variables will be described using appropriate summary statistics for central tendency (mean, median), and variability. We will use PROC TRAJ to discover distinct groups over time and TRAJPLOT to illustrate dyspnea trajectories over time. All calculations will be done during the analysis stage using SAS software.

Future directions: This project will serve as an essential first step to successfully submit and compete for R01-equivalent funding to identify and test de-prescribing strategies for patients living with serious life-limiting diseases who experience moderate-to-severe dyspnea.

Budget: We request $16,000 to cover 12% effort for PhD-level biostatistician (JP Tate) who is expert in longitudinal data analysis. We also request $11,000 to cover 5% effort plus fringe and indirects for PI support (K Akgün) and $1500 for travel to the NPCRC Annual Meeting.

Timeline: Submit the necessary paperwork and data use agreements (Month 1). Data cut and analyses (months 2-6); finalize models (end of month 7). Prepare and submit a peer-review manuscript (months 8-10) and begin submit R01-level grant submission (months 10-12).