ATRIAL FIBRILLATION SYMPTOM CLUSTERS

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DEDICATION

To my husband Caleb, for always believing in me, giving me confidence, and encouraging me to pursue my dreams.

To my daughters Adeline and Fiona, for being a constant source of inspiration, joy, and loving kindness.

To my parents, for providing me with so many opportunities to learn and explore the world.

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ABSTRACT

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Background: Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. The majority of adults with AF are symptomatic, and symptoms are major determinants of quality-of-life. We proposed a theoretical model of symptom perception that involves both symptom detection and symptom interpretation. In order to better understand AF symptom perception, the aim of this body of work was to identify AF-specific symptom clusters, characterize individuals within clusters based on sociodemographic and clinical variables, and determine whether symptom cluster membership was associated with healthcare utilization (AF-related emergency department visits and hospitalizations).

Methods/Results: Data sets from the Standard versus Atrial Fibrillation spEcific managemenT strategY (SAFETY) Trial (n=355) and Vanderbilt Atrial Fibrillation Registry (VAFR, n=1,501) were used to conduct cross-sectional secondary data analyses of adults with clinically verified AF. Symptom clusters were identified using self-reported symptoms and two statistical approaches: hierarchical cluster analysis and latent class analysis. Regression analyses were performed with VAFR to determine associations with healthcare utilization. Three symptom clusters were found using cluster analysis and SAFETY participants, 2 symptom clusters using cluster analysis and VAFR participants, and 4 symptom clusters using latent class analysis and VAFR participants. Symptom cluster membership was associated with gender, age, AF type, BMI, heart failure, coronary artery disease, current use of anti-arrhythmic medication, and history of ablation. Although the clusters differed between studies, when the results from the different studies were compared the results were complimentary. The symptom clusters found with VAFR were associated with an increased rate of AF-related emergency department visits and hospitalizations, either when compared to all individuals without that specific cluster (hierarchical

cluster analysis), or when compared to an Asymptomatic cluster of patients (latent class analysis).

Conclusions: Clinically meaningful symptom clusters were identified that were associated with increased rates of healthcare utilization. Both modifiable and non-modifiable sociodemographic and clinical characteristics are associated with cluster membership.

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CHAPTER 1: INTRODUCTION

Introduction to the Problem

Atrial fibrillation (AF) symptoms are intrusive, emotionally distressing, and functionally limiting, with a resultant negative impact on quality-of-life.[1,2] Healthcare providers use the presence of symptoms to determine the appropriate treatment strategy (rate versus rhythm control) and to evaluate treatment effectiveness.[3,4] While the majority of individuals with AF experience symptoms, the type and number of symptoms can vary significantly between individuals.[4-7] Even among typically symptomatic individuals, the presence and type of symptoms can fluctuate from one episode of AF to the next.[8,9] The most common symptoms of AF include palpitations, shortness of breath, chest pain, dizziness, and fatigue.[5]

Symptom perception involves both the detection of physical sensations and the interpretation of meaning.[10-13] Symptom detection is the awareness of abnormal bodily sensations, while interpretation encompasses the cognitive and emotional meaning of the detected sensations.[10-13] It is unclear whether the reported variation in AF symptom perception is the result of differences in detection, interpretation, or both. Multiplicative effects from co-occurring detected symptoms likely impacts symptom interpretation, and as such would influence an individual's response to symptoms.

The perception of isolated symptoms is likely distinct from that of interacting groups of symptoms.[10,14] The Symptoms Experience Model[10] delineates that individual symptoms, and the interactions between symptoms, influence the overall meaning of the symptom experience and influence a variety of health outcomes. The presence of multiple symptoms adds to the complexity of the symptom perception process. Symptom clusters are groups of symptoms that co-occur and are related to each other, either due to a shared underlying mechanism, a shared covariance, or through a unique effect on patient outcomes.[14-16] Exploring AF symptom clusters will advance our understanding of the complex interactions and associations between AF

symptoms.[14] While the frequency of individual AF symptoms have been described,[5] this body of work is the first that examined symptom clusters among adults with AF.

It is evident that variability in AF symptom perception exists both between and within individuals. However, there remains a paucity of knowledge regarding the symptoms and symptom clusters perceived by individuals with AF. Research examining the presence of AF symptom clusters and the impact on outcomes is an important first step towards understanding the importance of AF symptom variability. This dissertation is the starting point of a research trajectory that explores AF symptoms and symptom variability. This study increases knowledge of detected symptoms and symptom clusters, and the role they play in healthcare utilization decisions, thereby generating hypotheses for future studies on AF symptom perception and self-care.

Background and Significance

AF is an emerging cardiovascular epidemic. The current prevalence of AF in the United States (US) is nearly 3 million and is projected to rise to 8 million by the year 2050 due to the aging population and improved survival from cardiovascular disease.[17] AF disproportionately impacts older adults, affecting only 0.1% of adults younger than 55 years, but 3.8% of adults 60 years or older, and 9% of adults 80 years or older.[18] The financial burden of AF is significant, with a direct cost of 7 billion dollars annually in the US, the majority of which is attributable to hospitalizations.[19] The cost of AF-related hospitalizations is projected to increase 55% by 2020 as compared to 2010.[20] Symptoms are a major predictor of hospitalization among adults with AF.[21]

A strong correlation exists between AF symptoms and profound quality-of-life impairments.[22] Prior qualitative research suggests that impaired quality-of-life may be related to the unpredictable and functionally limiting nature of AF symptoms.[2] Interestingly, objective measures of disease, such as ejection fraction, are poorly correlated with quality-of-life measures.[23] Furthermore, compared to patients with a greater extent of structural heart disease, adults with symptomatic AF have similar, and sometimes worse, impairment of quality-of-life.[1]

Because symptoms affect approximately 70-90% of individuals with AF, symptom alleviation is a critical aspect of AF management.[6,24]

Symptomatic episodes of AF are erratic and can recur despite lifestyle modifications and medical interventions.[4] Individuals with symptomatic AF often feel unprepared to manage the unpredictable and functionally limiting symptoms of AF.[2] AF symptoms are typically managed with either a rate control or a rhythm control strategy; however both approaches can fail to fully eradicate the symptoms associated with AF.[4]

Complicating AF symptom management is the fact that symptoms may correlate poorly with objectively assessed arrhythmia episodes.[8,9,25,26] Objective assessment with telemetry reveals that individuals with AF may experience symptoms with some episodes of AF, while other AF episodes do not result in symptoms.[9] Similarly, some individuals may perceive a symptomatic episode of AF when in fact they are in sinus rhythm.[8,26] For example, when a group of adults with symptomatic AF were monitored with continuous home electrocardiography, 42% of reported symptomatic AF episodes were actually sinus rhythm.[8] Another study found that device-detected arrhythmia events accounted for only 8% of the unique variance in AF symptom scores.[25] An individual patient's ability to accurately perceive AF ranges from 0% to 100%.[8] These findings highlight our limited understanding of AF symptoms and suggest that factors other than arrhythmia occurrence alone are involved in the perception of symptoms. An unexplored area of research that may influence whether a person interprets symptoms as being related to AF is the number, type, and co-occurrence of symptoms experienced.

Prior research suggests that a number of factors influence symptom perception, including: age,[3,27] gender,[5,24,27,28] negative emotions,[25] personality,[28] type of AF (i.e. paroxysmal versus permanent),[5,6] and conditions such as myocardial infarction[27] and heart failure.[29] For instance, research suggests that women have more frequent and severe AF symptoms,[24,28] although not a greater number of symptoms.[25] Advanced age has also been shown to reduce perception of AF symptoms,[27] although evidence remains somewhat contradictory.[25]

Understanding the multi-faceted nature of AF symptom perception is critical to the advancement and improvement of AF symptom management. Unfortunately, our ability to improve AF symptom management is hindered by limited knowledge of AF symptom perception. Symptom perception varies dramatically among individuals with AF, ranging from no symptoms to severe symptoms that markedly impair quality-of-life and functional status.[24] To better understand symptom perception, we must first define two important concepts: symptoms and symptom clusters.

Symptoms

Symptoms are subjective bodily sensations that individuals recognize within themselves and consider a departure from normal function.[10,13,30] Innumerable somatic stimuli occur every day, only a fraction of which reach conscious awareness.[13] Bodily sensations are a result of detected somatic stimuli, and bodily sensations are considered symptoms if an individual considers the sensation abnormal.[13] Of note in this definition is that symptoms do not necessarily indicate an illness or disease, just the subjective evaluation of the sensation as abnormal. This aspect of the definition is important since subjective reports of AF symptoms do not always correlate well with objective measurement of heart rhythm.[8,9,25,26]

Symptom Clusters

Groups of related symptoms, or symptom clusters, likely influence symptom perception in unique ways compared to isolated symptoms.[15] For this study, symptom clusters are defined as two or more co-occurring and related symptoms, although some authors consider three symptoms the minimum requirement for a symptom cluster.[15,31] Symptoms may be related for a variety of reasons, including a shared underlying mechanism, a shared covariance, or through a unique effect on patient outcomes.[14-16,31]

A wide range of methods are used to quantify symptom clusters, including correlation analysis, graphical modeling, path analysis, latent class analysis, structural equation modeling, factor analysis, and cluster analysis.[14,32] Some of these methods rely on the assumption of underlying latent factors relating the symptoms within clusters, while others rely on either

correlation or measurements of dissimilarity (e.g. Euclidean distance) between symptoms.[14,32] Symptoms can be clustered by symptom variables or by individuals, resulting in either groups of symptoms or groups of individuals with similar symptom patterns.[15] When clustering groups of symptoms, a certain degree of correlation between all concurrent symptoms is to be expected, but the correlation of symptoms within clusters should be greater than the correlation of symptoms across different clusters.[31] Many of the quantitative methods used to identify symptom clusters require a degree of subjectivity in determining the presence and number of clusters, which may be considered a weakness of symptom cluster research in general.[32] However, a critical component of symptom cluster research is evaluation of the theoretical and clinical meaningfulness of statistically identified symptom clusters, making subjective evaluation acceptable for this line of inquiry.[31,32]

Although it is unlikely that AF symptoms occur in isolation, the concept of symptom clusters has not previously been explored in AF patients. Symptom clusters warrant analysis among adults with AF because of the known impact symptom clusters have on patient outcomes in other cardiovascular diseases. For example, symptom clusters have been shown to influence mortality and event-free survival among individuals with acute coronary syndrome and heart failure.[33,34] Specific symptom clusters may also have a unique effect on quality-of-life.[35] Further, symptom clusters may result from a shared underlying mechanism,[36,37] making symptom cluster analysis an appealing approach to the exploration of symptom variability among individuals with AF. This dissertation is an important contribution to AF symptom research because it examines both the presence of symptom clusters, and the consequence of identified clusters on patient reported outcomes. By increasing knowledge of AF symptoms and symptom clusters, this body of work will contribute to hypothesis generation and suggestions for potential areas of exploration in future AF symptom research.

Theoretical Model

We define symptom perception as a process of detecting symptoms and interpreting symptom meaning.[10-13] The process of symptom perception is influenced by a variety of factors

including prior experience, demographic, cultural, clinical, physiological and psychological characteristics.[10] As previously noted, a number of factors have been identified that influence the perception of AF symptoms including age,[27] gender,[5,24,27,28] negative emotions,[25] personality,[28] type of AF (i.e. paroxysmal versus permanent),[5,6] baseline functional status,[3] and comorbid cardiovascular conditions.[27,29] The type, number, and frequency of symptoms detected influences the individual patient's interpretation of the symptom(s) meaning, which results in several potential consequences. Some of the potential consequences of AF symptom perception include healthcare utilization for symptom management (emergency services, hospitalizations, clinic appointments), reduced quality of life, and impaired functional status. The complexity of symptom perception is illustrated in Figure 1.1, modified from the Symptoms Experience Model[10] and the Symptom Interpretation Model.[12]

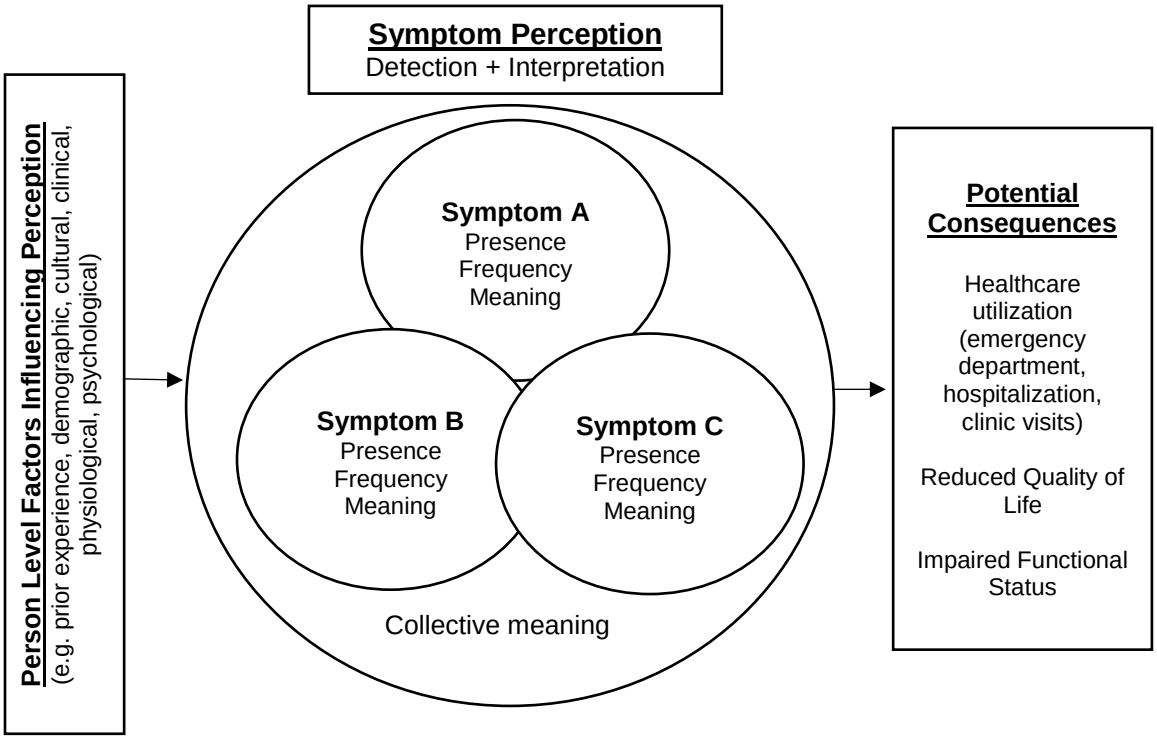

Figure 1.1: Theoretical model. Symptom perception involves detection and interpretation. Detection is described in terms of presence and frequency. Interpretation is described in terms of symptom meaning. Groups of symptoms (i.e. clusters) result in collective meaning.

Symptom detection is defined as the awareness of abnormal bodily sensations.[10-13] Symptom detection can be described in terms of symptom presence and frequency.[10] Other terms used in the literature to describe detected symptoms include intensity, quality, burden, severity, and distress;[10,30,38] however these terms suggest a cognitive or emotional appraisal of the detected symptom and are therefore excluded from our definition of symptom detection.

Symptom interpretation is defined as the emotional and cognitive process whereby each individual symptom is assigned meaning, and co-occurring related symptoms (symptom clusters) have a collective meaning.[10,12] The interpretation of symptom meaning encompasses both symptom attribution and the implications the symptom has for the person's life. The interpretation of meaning is subjective, and may or may not result in the attribution of the detected symptom to the appropriate source. For example, a person experiencing fatigue related to AF may attribute the symptom to normal aging, rather than considering it a symptom of AF. Likewise, a person experiencing palpitations may attribute the symptom to AF, when in fact they are experiencing sinus tachycardia. Symptoms may have a variety of personal meanings or implications. For example, symptoms may impact daily activities, relationships, or an individual's sense of mortality,[10] each of which would have a unique meaning for the patient. Further, symptom clusters likely influence symptom meaning in unique ways due to the multiplicative effect of co-occurring symptoms.[10] In our model collective meaning represents the meaning that results from the occurrence of symptom clusters.

The detection and interpretation of symptoms influences an individual's response to the symptoms. Potential consequences of AF symptoms include healthcare utilization for symptom management (emergency services, hospitalizations, clinic appointments), reduced quality of life, and impaired functional status. If an individual interprets a symptom as life-threatening, it is likely they would seek immediate medical attention, whereas if they interpret a symptom as a normal result of aging, then they may not seek medical attention. As a result, an individual's ability to accurately attribute and interpret the meaning of a symptom will influence their response to the

symptom. In this manner, symptom perception plays an important role in self-care decisions (e.g. the decision to seek medical attention).

Gaps in the Literature

This dissertation uses a theoretically based approach to examine gaps in the literature related to AF symptom perception. To our knowledge this body of work is the first to describe AF symptom clusters and to evaluate the impact of symptom clusters on healthcare utilization. This work uses cross-sectional secondary data analyses to answer new and meaningful research questions, reducing the burden of research participation by capitalizing on existing data. Identifying symptom clusters and determining their association with healthcare utilization has the potential to improve risk stratification for patients with AF, and will be beneficial for the future development of interventions aimed at improving symptom management and self-care for individuals with AF.

Purpose and Specific Aims

The overarching purpose of this body of work was to better understand AF symptom perception by examining detected AF symptoms, identifying symptom clusters, and exploring the relationship between clusters and healthcare utilization. To achieve these aims we utilized two existing data sets from the Standard versus Atrial Fibrillation spEcific managemenT strategY (SAFETY) Trial[39] and the Vanderbilt Atrial Fibrillation Registry (VAFR).[40]

The first aim was to examine symptoms detected by adults with AF and identify symptom clusters. Self-reported survey data on symptom presence and frequency were used for the identification of symptom clusters. We used both data sets and two statistical approaches (hierarchical cluster analysis and latent class analysis) for the identification of symptom clusters (Table 1.1). To our knowledge, this body of work represents the only research to date that addresses AF-specific symptom clusters.

The second aim was to characterize individuals within symptom clusters based on demographic and clinical characteristics. There is currently a paucity of knowledge regarding the

inter-individual variability in AF symptoms. By increasing our understanding of the differences in symptoms between individuals with specific characteristics, this aim improves our ability to design tailored interventions for AF symptom management and self-care.

The third aim was to determine whether symptom cluster membership is associated with healthcare utilization (AF-related hospitalizations and emergency department visits). We hypothesized that distinct AF-specific symptom clusters could be identified that were associated with AF-related hospitalizations and ED utilization. For this aim we used regression analysis to determine whether individuals within identified cluster were more likely to be hospitalized or use the emergency department for AF. Self-reported AF-related hospitalizations and emergency department visits from VAFR[40] were used to achieve this aim. Theoretically, both AF-related hospitalizations and emergency department utilization could be reduced via improved symptom management and self-care. Therefore, the results of this aim will be used to determine potential outcomes for future self-care interventions for individuals with AF.

Table 1.1 Specific Aims with Corresponding Data-set(s) and Chapters

Specific Aim	**Data-Set**	**Chapter**
Aim 1: Examine symptoms detected by adults with AF and identify symptom clusters	SAFETY and VAFR	II, III, IV
Aim 2: Characterize individuals within symptom clusters based on demographic and clinical characteristics	SAFETY and VAFR	II, III, IV
Aim 3: Determine whether symptom cluster membership is associated with healthcare utilization (AF-related hospitalizations and emergency department visits)	VAFR	III, IV

Summary

This dissertation explores the poorly understood and under-researched topic of AF symptom perception. Specifically, this theoretically based body of work identifies AF-specific symptom clusters, characterizes individuals within symptom clusters, and determines the association between symptom clusters and AF-related healthcare utilization. The knowledge gained from this dissertation was used to develop future recommendations for research and clinical practice in relation to AF symptom management and self-care.

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CHAPTER 2: SYMPTOM CLUSTERS IN ADULTS WITH CHRONIC ATRIAL FIBRILLATION

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Abstract

Background: Symptom clusters have not previously been explored among individuals with atrial fibrillation of any type. **Objective:** The purpose of this study was to determine the number of symptom clusters present among adults with chronic atrial fibrillation and to explore sociodemographic and clinical factors potentially associated with cluster membership. **Methods:** This was a cross-sectional secondary data analysis of 335 Australian community-dwelling adults with chronic (recurrent paroxysmal, persistent, or permanent) atrial fibrillation. We used self-reported symptoms and agglomerative hierarchical cluster analysis to determine the number and content of symptom clusters present. **Results:** There were slightly more male participants (52%) than female, with a mean age of 72 (±11.25) years. Three symptom clusters were evident, including a vagal cluster (nausea and diaphoresis), a tired cluster (fatigue/lethargy, weakness, syncope/dizziness, and dyspnea/breathlessness), and a heart cluster (chest pain/discomfort and palpitations/fluttering). We compared patient characteristics between those with all the symptoms in the cluster, those with some of the symptoms in the cluster, and those with none of the symptoms in the cluster. The only statistically significant differences were in age, gender, and the use of anti-arrhythmic medications for the heart cluster. Women were more likely to have the heart symptom cluster than men. Individuals with all of the symptoms in the heart cluster were younger (69.6 versus 73.7, p=0.029) than those with none of the symptoms in the heart cluster, and were more likely to be on anti-arrhythmic medications. **Conclusion:** Three unique atrial fibrillation symptom clusters were identified in this study population.

Keywords: atrial fibrillation, adult, cardiovascular disease, symptom cluster

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, with an estimated global prevalence of 2.8%.[1] AF affects more than 3 million individuals in the United States (US) alone.[2] Emergency department visits and hospitalizations for AF are costly and rising both in the US and globally. In the US, emergency department visits for AF increased by 88% between 1993 and 2004.[3] Approximately 64% of those seen in US emergency departments for AF are subsequently hospitalized.[3] The direct cost of AF in the US is nearly 7 billion dollars annually, which is primarily attributable to hospitalizations.[4] Globally, the proportion of healthcare spending attributable to the direct costs of AF ranges from 0.28 to 1.01%.[1] By 2020 the cost of AF-related hospitalizations is predicted to increase by 55% compared to 2010.[5] Symptoms are a main predictor of hospitalizations among individuals with AF.[6]

Symptoms are an important but under-researched aspect of AF. A wide spectrum of symptom experiences occur among AF patients, with some experiencing multiple, severe symptoms and others experiencing no, few, or vague symptoms.[7,8] The goals of AF management are to prevent severe complications associated with AF and reduce or eliminate symptoms. There are three primary strategies to achieve these goals: prevention of thromboembolism, heart rate control, and restoration of sinus rhythm.[8] Preventing thromboembolism and rate-control are goals regardless of symptom status. AF symptoms, which negatively impact functional status and quality of life,[9,10] are a primary consideration when determining whether to attempt restoration of sinus rhythm for longer-term management of recurrent paroxysmal or persistent AF.[8] Unfortunately, little is understood regarding AF symptom variability and the mechanisms of AF symptoms,[11] which may hamper our ability to make effective treatment decisions.

While the frequency of individual AF symptoms has been described,[7] it is likely that AF symptoms co-occur as symptom clusters; groups of two or more related and co-occurring symptoms.[12,13] Symptom clusters occur as the result of a shared etiology, a shared covariance, or a shared effect on outcomes.[12-15] Symptom clusters could help explain the variability of AF symptoms experienced and may be associated with treatment outcomes. Furthermore, AF-

specific symptom clusters may be associated with underlying physiologic processes related to clinical variables, the sub-type of AF, or the etiology of AF. Understanding the physiology underlying symptom clusters may assist clinicians to better individualize treatment. If associations between symptom clusters and outcomes exist, providers could use symptom cluster assessment as a method of risk stratification. Thus, the purpose of this study was to determine the number of symptom clusters present among adults with chronic AF and to explore sociodemographic and clinical factors potentially associated with cluster membership.

Methods

This study was a cross-sectional secondary data analysis of data from a randomized controlled pragmatic clinical trial conducted in Australia between 2010 and 2014; the Standard versus Atrial Fibrillation spEcific managemenT strategY (SAFETY) Trial.[16] Applicable ethics board approvals were obtained as required for the original trial[16] and through the University of Pennsylvania Institutional Review Board for this secondary data analysis. The methods and results of the trial have been reported previously.[16,17] Methods are summarized briefly here:

A total of 335 individuals were included in the SAFETY Trial. Participants were eligible if they had a diagnosis of chronic AF, lived independently within the community following their index hospital admission (within a radius of 40km), and provided informed consent. Chronic AF was defined as recurrent paroxysmal, persistent, or permanent AF. Exclusion criteria included a primary diagnosis of valvular heart disease, a scheduled catheter ablation procedure, a pre-existing diagnosis of heart failure (all patients were subject to echocardiography to exclude this diagnosis), transient AF (i.e. AF associated with acute myocardial infarction, pericarditis, recent cardiac surgery, sepsis, or excessive alcohol), or a terminal disorder or malignant disease that required palliative care.[17] All participants in the original cohort were included in this cross-sectional secondary data analysis.

Measurement of Variables

Atrial Fibrillation Symptoms

Symptoms were measured using an AF profiling tool developed specifically for the SAFETY Trial. For this cluster analysis we used self-reported symptoms collected during the index hospitalization (Appendix 1). Each symptom was reported on a binary (yes/no) scale. Participants were instructed to report all symptoms previously or currently experienced in association with AF. Six common symptoms of AF were measured: dyspnea/breathlessness, syncope/dizziness, fatigue/lethargy, palpitations/fluttering, chest pain/discomfort, and weakness. Participants could report other symptoms via free-text response. Nausea and diaphoresis were commonly reported using the other option, and were therefore included in this analysis. Participants also reported if they did not experience symptoms when in AF, which was recorded as a binary yes/no response.

Clinical and Demographic Variables

All participants were comprehensively profiled upon enrollment in the study. All clinical and demographic variables used for this analysis were obtained during the baseline assessment. Variables were collected by trained study personnel via medical record review and patient self-report.

Statistical Analysis

All data analysis was conducted in SAS version 9.4 (Cary, North Carolina). Descriptive statistics were used to describe the data. Symptom clusters were identified with agglomerative hierarchical cluster analysis, because of our goal to create mutually exclusive groups of symptoms.[14,18,19] Cluster analysis maximizes both the homogeneity within clusters and the heterogeneity between clusters.[18,19] We used Ward's method with Euclidean distance as the dissimilarity measure.[18,20] The ideal number of clusters was determined using a combination of dendrograms, pseudo F, and pseudo T.[18,21] Additionally, we compared the results of the cluster analysis with exploratory factor analysis to validate our findings.

After identifying symptom clusters, we compared characteristics of individuals with each cluster to those without the cluster in order to understand the potential factors associated with cluster membership. To do this, we divided participants into three groups for each symptom cluster: those with all the symptoms in the cluster, those with some of the symptoms in the cluster (one or more, but not all, of the symptoms), and those with none of the symptoms in the cluster. Next, we used Fisher's exact test, chi-square test, and Kruskal-Wallis one-way analysis of variance to determine the statistical significance of 13 factors to determine if these factors were associated with symptom cluster membership. We used a broad range of demographic and clinical characteristics, specifically age, gender, ethnicity, body mass index (BMI), Charlson Comorbidity Index,[22] cardiovascular comorbidities, and cardiac medications. We considered these factors as potentially associated with cluster membership based on the results of prior research (e.g. the influence of age and gender), due to similarity of symptom profiles with selected comorbidities,[8,11] and because of our assumption that certain medications may contribute to certain symptoms (e.g. beta-blockers and fatigue). Statistical significance was determined using the predetermined value of $p<0.05$.

Results

Sample Characteristics

The mean age of participants was 72 (±11.25), with a range of 40 to 93 years (Table 2.1). Participants were predominantly European/Caucasian (96%), and there were slightly more male participants (52%) than female. The majority considered themselves symptomatic (83%), with only 17% (n=57) reporting themselves as asymptomatic. Dyspnea/breathlessness was the most common symptom, affecting 56% of participants despite the absence of underlying heart failure.

Table 2.1: Baseline Characteristics and Symptoms of the SAFETY Trial Cohort

	All (N=335)	**Female (N=161, 48%)**	**Male (N=174, 52%)**
Sociodemographic Profile			
Age (years)#	72 (±11.3)	74 (±10.3)	69 (±11.6)
Ethnicity			
European/Caucasian	323 (96.4%)	156 (96.9%)	167 (96.0%)
Aboriginal/Torres Strait Islander	4 (1.2%)	1 (0.6%)	3 (1.7%)
Asian	5 (1.5%)	3 (1.9%)	2 (1.2%)
Middle Eastern	3 (0.9%)	1 (0.6%)	2 (1.2%)
Living Alone#	132 (39.4%)	82 (50.9%)	50 (28.7%)
Clinical Profile			
AF Sub-Type			
Recurrent Paroxysmal	9 (2.7%)	4 (2.5%)	5 (2.9%)
Persistent	293 (87.5%)	140 (87.0%)	153 (87.9%)
Permanent	33 (9.9%)	17 (10.6%)	16 (9.2%)
Body Mass Index*	29.6 (±6.7)	30.5 (±7.9)	28.8 (±5.3)
Charlson Comorbidity Index	4.9 (±2.6)	5.1 (±2.4)	4.7 (±2.7)
Hypertension	240 (71.6%)	123 (76.4%)	117 (67.2%)
Coronary Artery Disease*	112 (33.4%)	40 (24.8%)	72 (41.4%)
Valve disease	12 (3.6%)	7 (4.4%)	5 (2.9%)
History of Cardiac Revascularization Surgery#	68 (20.3%)	18 (11.2%)	50 (28.7%)
Beta Blocker	165 (49.3%)	77 (47.8%)	88 (50.6%)
Calcium Channel Blocker	74 (22.1%)	39 (24.2%)	35 (20.1%)
Digoxin	117 (34.9%)	64 (39.8%)	53 (30.5%)
Anti-Arrhythmic	101 (30.2%)	51 (31.7%)	50 (28.7%)
Symptom Profile			
Asymptomatic (self-reported)	57 (17.0%)	21 (13.0%)	36 (20.7%)
Dyspnea/Breathlessness	186 (55.5%)	93 (57.8%)	93 (53.5%)
Fatigue/Lethargy*	168 (50.2%)	91 (56.5%)	77 (44.3%)
Palpitations/Fluttering#	169 (50.5%)	102 (63.4%)	67 (38.5%)
Weakness*	122 (36.4%)	70 (43.5%)	52 (29.9%)
Chest Pain/Discomfort	136 (40.6%)	70 (43.5%)	66 (37.9%)
Syncope/Dizziness	119 (35.5%)	65 (40.4%)	54 (31.0%)
Nausea	21 (6.3%)	12 (7.5%)	9 (5.2%)
Diaphoresis	15 (4.5%)	8 (5.0%)	7 (4.0%)

Data are mean (± standard deviation) or number of patients (%). Characteristics that were significantly different between females and males are marked with an asterisk (*) for $p<0.05$, and with a pound sign (#) for $p<0.001$

Symptom Clusters

The dendrogram, pseudo-F and pseudo-T indicated that a three cluster solution was the optimal solution (Figure 2.1). We labeled the symptom clusters the *vagal cluster* (nausea and diaphoresis), *tired cluster* (fatigue/lethargy, weakness, syncope/dizziness, and dyspnea/breathlessness), and *heart cluster* (chest pain/discomfort and palpitations/fluttering). Both vagal cluster symptoms occurred in only 3 participants. The heart cluster was the most common, with all symptoms occurring in 26% (n=88) of participants. All tired cluster symptoms were present in 14% (n=47) of participants (Table 2.2). Over half with the tired cluster (n=24) also experienced the heart cluster (Table 2.3).

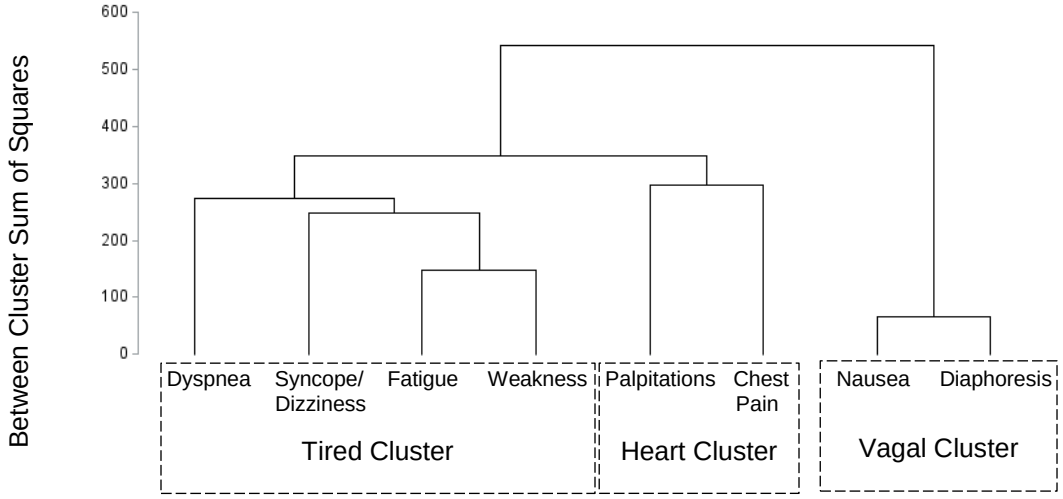

Figure 2.1: Dendrogram of atrial fibrillation symptom clusters. All symptoms were self-reported at baseline

Table 2.2: Symptom Cluster Membership

Cluster Membership	
Vagal Cluster (diaphoresis and nausea)	**N (%)**
None of the symptoms	302 (90%)
Some of the symptoms	30 (9%)
All of the symptoms	3 (1%)
Tired Cluster (weakness, fatigue, syncope/dizziness, dyspnea)	
None of the symptoms	95 (28%)
Some of the symptoms	193 (58%)
All of the symptoms	47 (14%)
Heart Cluster (chest pain and palpitations)	
None of the symptoms	118 (35%)
Some of the symptoms	129 (39%)
All of the symptoms	88 (26%)

Table 2.3: Cluster Co-occurrence within the SAFETY Trial Cohort

Cluster Combinations			
	Vagal	**Heart**	**Tired**
Vagal	3 (0.9%)	2 (0.6%)	2 (0.6%)
Heart		88 (26%)	24 (7%)
Tired			47 (14%)

Characteristics of Symptom Cluster Groups

There were no statistically significant differences in patient characteristics for the vagal or tired cluster. In the heart cluster, statistically significant differences were found in age, gender, AF sub-type, and use of anti-arrhythmic medications (Table 2.4). The mean age progressively declined for individuals with none (73.7 years, n=118) versus some (71 years, n=129) versus all (69.6 years, n=88) of the heart cluster symptoms. Participants with all the heart cluster symptoms were 4 years younger on average than individuals with none of the heart cluster symptoms (69.6 versus 73.7 years, p=0.029). Women were significantly more likely to have the heart cluster than men (p=0.0015), with 20% of men (n=35) and 33% of women (n=53) having both of the heart cluster symptoms. Heart cluster membership varied by AF sub-type (p=0.042). Among participants with permanent AF, 55% had none, 30% had some, and 15% had all of the heart cluster symptoms. In contrast, 27% of participants with persistent and 33% with paroxysmal AF

had all of the heart cluster symptoms. In comparison, 18% of individuals with permanent AF had all the tired cluster symptoms, compared to 14% with persistent and 11% with paroxysmal AF, although not statistically significant. Participants with the heart cluster were more likely to take anti-arrhythmic medication as part of rhythm-control therapy than individuals without the heart cluster (p=0.002). Among participants with both heart cluster symptoms, 40% were on anti-arrhythmics, compared to 34% for participants with one of the heart symptoms and 19% for participants with none of the heart symptoms. Comparatively, only 26% of participants with all the tired cluster symptoms were on anti-arrhythmics. Interestingly, we did not find a statistically significant relationship between the tired cluster and use of rate-control medications, even though rate-control medications have side-effect profiles similar to tired cluster symptoms.

Table 2.4: Comparison of Heart Cluster Groups

Characteristic	**None of the symptoms N=118**	**Some of the symptoms N=129**	**All of the symptoms N=88**	**p-value**
Gender				**0.002**
Male (%)	76 (64.4%)	63 (48.8%)	35 (39.8%)	
Female (%)	42 (35.6%)	66 (51.2%)	53 (60.2%)	
Age (years)	73.7 (±10.7)	71 (±11.6)	69.6 (±11.1)	**0.029**
European/Caucasian Ethnicity (%)	115 (97.5%)	124 (96.1%)	84 (95.5%)	0.759
AF Sub-Type				**0.042**
Recurrent Paroxysmal	5 (4.2%)	1 (0.8%)	3 (3.4%)	
Persistent	95 (80.5%)	118 (91.5%)	80 (90.9%)	
Permanent	18 (15.3%)	10 (7.8%)	5 (5.7%)	
Body Mass Index	29.9 (±7.6)	29.9 (±6.5)	28.8 (±5.4)	0.710
Charlson Comorbidity Index	5.2 (±2.4)	4.8 (±2.6)	4.5 (±2.6)	0.108
Hypertension (%)	87 (73.7%)	95 (73.6%)	58 (65.9%)	0.381
Coronary Artery Disease (%)	49 (41.5%)	37 (28.7%)	26 (29.6%)	0.068
Valve Disease (%)	6 (5.1%)	6 (4.7%)	0 (0%)	0.079
Cardiac Surgery (%)	26 (22%)	23 (17.8%)	19 (21.6%)	0.672
Beta Blocker (%)	66 (55.9%)	57 (44.2%)	42 (47.7%)	0.173
Calcium Channel Blocker (%)	31 (26.3%)	26 (20.2%)	17 (19.3%)	0.392
Digoxin (%)	37 (31.4%)	49 (38%)	31 (35.2%)	0.550
Anti-Arrhythmic (%)	22 (18.6%)	44 (34.1%)	35 (39.8%)	**0.002**

Statistically significant differences (p<0.05) are shown in bold. Data are mean (± standard deviation) or number of patients (%).

Discussion

This is the first study to establish the presence of AF symptom clusters in individuals with chronic forms of AF. We identified three distinct clusters; a *vagal cluster* (nausea and diaphoresis), *tired cluster* (fatigue, weakness, syncope/dizziness, and dyspnea), and *heart cluster* (palpitations and chest pain). These clusters are unique compared to symptom clusters identified among other cardiovascular patient populations (Table 2.5).[23-25] The AF cluster that shares the most similarities with other cardiovascular clusters is the tired cluster, which shares some symptoms with heart failure physical symptom clusters. However, it is important to note that patients with heart failure were specifically excluded from this study cohort. Further, the AF tired cluster is unique because dizziness/syncope is included in our cluster. AF patients may have disease-specific mechanisms for dizziness/syncope, such as tachycardia, bradycardia or post-conversion pause, which cause this symptom to cluster with fatigue, weakness, and dyspnea. Alternately, these symptoms are potentially pharmacologically based given the fine line between benefit and risk of adverse events in those being treated for AF.[17]

Table 2.5: Cardiovascular Symptom Clusters

	Symptom Cluster			
Acute Coronary Syndrome (ACS)[1]	Classic ACS Cluster (chest pain)	Pain Cluster (arm, back, shoulder, neck, throat, and jaw pain)	Stress Cluster (shortness of breath, sweating, nausea, indigestion, dread, and anxiety)	Diffuse Cluster (multiple symptoms present but with low representation of any particular symptom)
Heart Failure[2]	Physical Cluster (dyspnea, fatigue/increase need to rest, fatigue/low energy, and sleep disturbances)		Emotional/Cognitive Cluster (worrying, feeling depressed, and cognitive problems)	
Heart Failure[3]	Physical Capacity Cluster (dyspnea, difficulty walking or climbing, fatigue/increased need to rest, fatigue/low energy, and sleep difficulties)		Emotional/Cognitive Cluster (worrying, feeling depressed, and cognitive problems)	

The vagal cluster was quite rare (n=3) in our sample. However, the fact that symptoms associated with vasovagal response cluster together is interesting due to the well-recognized

occurrence of vagally-mediated AF.[8,26]. It is interesting to note that syncope/dizziness were measured as a single item in this study and clustered with the tired symptoms, rather than the vagal cluster. Future studies of AF symptom clusters should measure dizziness and syncope as distinct symptoms to determine whether one or the other may cluster differently if measured independently.

The tired cluster might be considered vague or non-specific[11] and therefore not easily attributable to AF. However, dyspnea was the most frequently reported AF symptom in our sample (56%), followed closely by fatigue (50%), which occurred at the same frequency as palpitations (50%). These findings are in contrast to the large study by Levy et al.[7] which found palpitations were the most common symptom of AF (54%), followed by dyspnea (44%) and fatigue (14%). The Levy[7] study examined outpatients whereas our symptom data are from index hospital admissions, which may explain the difference in reported symptoms. AF results in loss of atrio-ventricular synchrony and often in tachycardia and/or bradycardia, which can adversely affect hemodynamic status through impaired diastolic filling and impaired left ventricular systolic function.[11] Hemodynamic changes associated with AF are a plausible mechanism for the clustering of fatigue, weakness, dyspnea, and syncope/dizziness.

The heart cluster consists of the symptoms that may be the most readily attributed to AF, palpitations and chest pain. Certain individuals may be more prone to perceive sensations in the chest due to differences in afferent neural stimulation or central nervous system functioning.[11,27] A study of heart transplant patients showed that despite cardiac denervation one-third of participants could still perceive their heartbeat, suggesting the perception of palpitations is unrelated to cardiac mechanoreceptors.[28] Similarly, chest pain often occurs during AF despite the absence of acute coronary syndrome.[29] Numerous studies reveal that neuropsychiatric variables influence the perception of AF symptoms,[30-32] and palpitations in particular.[33,34] Taken together, these findings support the idea that a mechanism outside the myocardium is responsible for the heart cluster symptoms. Further research is needed to elucidate the precise mechanisms of these

symptoms. Interestingly, the heart cluster was the only cluster with significant differences in patient characteristics between those with versus without the cluster.

Our results indicate that membership in the heart symptom cluster is associated with younger age, female gender, AF sub-type, and anti-arrhythmic use. Gender-based differences in the SAFETY cohort have been described previously: women in the cohort were older, more likely to experience symptomatic AF (especially fatigue, palpitations, and weakness), and presented with a unique clinical profile characterized by higher BMI, less coronary artery disease/revascularization, and more depression.[35] Our study furthers these findings by revealing that symptom cluster membership also varies by gender. Previous reports indicate younger age and female gender are associated with an increased frequency and severity AF symptoms.[31,36] However, Sears et al.[32] found that age and gender were not significantly associated with the number of AF symptoms reported. Our results indicate that age and gender are indeed non-modifiable characteristics that influence certain aspects of symptom perception, specifically symptom clustering. While age and gender may not influence the number of symptoms reported, these characteristics do influence other aspects of symptom perception such as the type of symptoms experienced, and their perceived frequency and severity.

Gender differences in the SAFETY Trial may have contributed to the greater number of women who experienced the heart cluster. Depression was more common in women ($p=0.017$)[35] and may be an important factor effecting symptom perception. Higher levels of negative emotions are associated with a greater number of AF symptoms, influencing the number of symptoms experienced more than objectively measured episodes of AF.[32] Similarly, increased severity of depression and anxiety are associated with increased AF symptom severity ($p<0.001$).[31] Palpitations were significantly more common among the women in our study, and are known to be influenced by neuropsychiatric variables.[34] It is plausible that differences in neuropsychiatric variables influenced the number of men versus women that experienced the heart cluster. BMI also varied by gender in our study. Elevated BMI is a well-documented risk factor for AF development.[37,38] It is possible that BMI may also influence heart cluster membership via altered

cardiac interoception,[39] or as the result of perceived differences in symptom burden and severity.[40]

Heart cluster membership varied based on sub-type of AF. The results are difficult to interpret for participants with paroxysmal AF due to small numbers (n=9). However, our results indicate that permanent AF has a unique symptom presentation. Individuals with permanent AF were least likely to have all of the symptoms in the heart cluster. In contrast, these individuals were most likely to have all the tired cluster symptoms. These differences in symptom profile are important factors to consider in terms of clinical decision making related to symptom-management. Unfortunately, symptom-management options are limited for individuals with permanent AF: Guidelines recommend against rhythm-control, and therefore symptoms are primarily managed through rate-control.[8] Alternative therapies, such as yoga and biofeedback, can reduce AF symptoms and may be the most beneficial in individuals with permanent AF, but these methods are understudied in this population.[41,42]

It is possible the large proportion of participants in the SAFETY cohort with persistent AF (87.5%) influenced the association between the heart cluster and anti-arrhythmic medication. However, the proportion of individuals with persistent AF was high both among individuals with all the heart cluster symptoms (90.9%) and all the tired cluster symptoms (85.1%), yet a statistically significance association with anti-arrhythmics was only found in the heart cluster. Another possible explanation is that patients and/or providers are more likely to consider palpitations and chest pain as symptoms of AF, or as more severe symptoms of AF, compared to the vague symptoms in the tired cluster, subsequently resulting in selection of a rhythm-control strategy. In fact, prior research indicates patients often erroneously attribute AF symptoms such as dyspnea and fatigue to ageing, deconditioning, or poor sleep, and that these erroneous attributions result in treatment-seeking delay prior to AF diagnosis.[43-45] Further research is warranted to explore whether symptom attribution influences treatment decisions post-diagnosis among individuals with chronic forms of AF.

Limitations

This study has several limitations. First, we used symptom data collected with a survey that was not validated psychometrically, which could influence the cluster solution. Second, high levels of cognitive impairment (approximately two-thirds of participants) have been reported for this cohort, which likely influenced the ability of participants to recall and accurately report symptoms.[46] However, the SAFETY cohort typifies patients with AF (minus individuals with concurrent heart failure), so we consider this an acceptable limitation for this study. Third, our findings are based on self-reported symptoms which were not correlated objectively with heart rhythm monitoring. Fourth, the symptoms reported in this study may not represent all possible symptoms of AF (e.g. emotional and cognitive symptoms),[47,48] and as a result important clusters or components of clusters may be missing from this report. While we recognize the limitations of our study, we consider this work an important first step towards understanding symptom clusters and factors associated with cluster membership among adults with chronic AF.

Conclusions

We identified three symptom clusters among adults with chronic AF, demonstrating that AF symptoms do not always occur in isolation. Cluster membership is associated with two non-modifiable patient characteristics; age and gender. We also demonstrated that the combination of chest pain and palpitations is more likely to be associated with clinical factors including AF sub-type and the use of anti-arrhythmic medications. Additional studies are warranted to replicate these findings and explore the impact of symptom clusters on patient treatment and outcomes.

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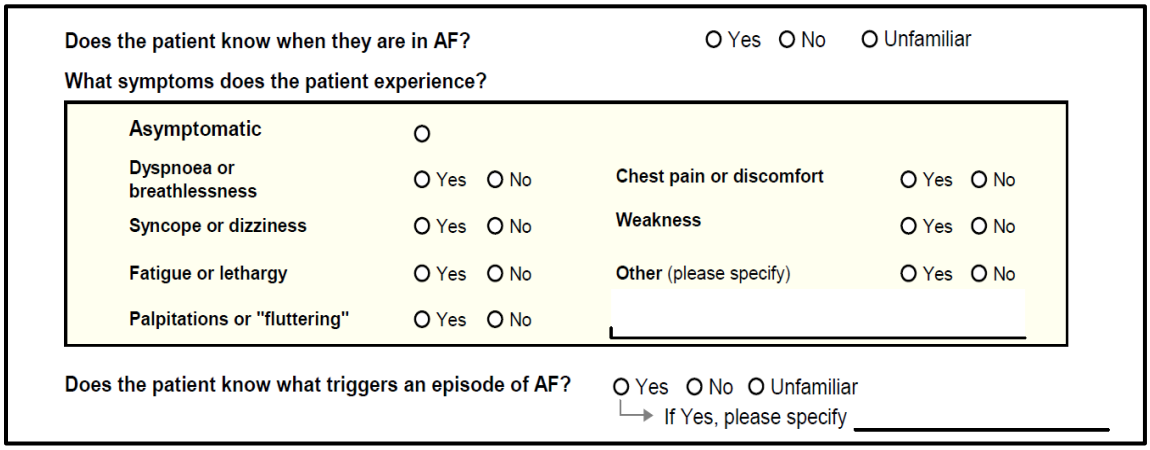
Appendix 1: Profiling tool developed to assess AF symptoms in SAFETY Trial



CHAPTER 3: SYMPTOM CLUSTERS INCREASE RATE OF HOSPITALIZATIONS AND EMERGENCY DEPARTMENT VISITS IN ADULTS WITH ATRIAL FIBRILLATION

Abstract

Background: Symptom clusters among adults with atrial fibrillation have previously been identified but not verified with follow-up studies. No study to date has examined the relationship between symptom clusters and outcomes in adults with atrial fibrillation. **Objective:** The purpose of this study was to identify AF-specific symptom clusters, characterize individuals within each cluster, and determine whether symptom cluster membership is associated with AF-related hospitalizations and ED visits. **Methods:** This was a secondary data analysis of the 1,501 adults from the Vanderbilt Atrial Fibrillation Registry with clinically verified paroxysmal, persistent, or permanent atrial fibrillation. Self-reported symptoms were used to determine symptom clusters with hierarchical cluster analysis (Ward's method). We used dendrograms, pseudo F, and pseudo T to determine the ideal number of clusters. Next, we then used regression analyses to examine the association between cluster membership and healthcare utilization. **Results:** Males predominated (67%) and the average age was 58.4 years. Two symptom clusters were identified, an At Rest cluster (3.7%, n=56, fatigue at rest, shortness of breath at rest, chest pain, and dizziness) and With Activity cluster (32.7%, n=491, shortness of breath with activity and exercise intolerance). Experiencing all the symptoms in the At Rest cluster resulted in nearly triple the rate of ED utilization (incident rate ratio 2.8, $p<0.0001$) and nearly twice the rate of hospitalizations (incident rate ratio 1.9, $p<0.0001$) compared to individuals with none of the At Rest symptoms. **Conclusion:** The At Rest symptom cluster is associated with significant increases in emergency department visits and hospitalizations.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. More than 33 million individuals are estimated to have AF globally.[1] In the United States (US) alone more than 3 million people are currently affected by AF, with a projected increase to 8 million by the year 2050.[2] Individuals with AF utilize a wide variety of inpatient and outpatient healthcare services. Globally and across studies, inpatient services account for the majority of AF spending.[3,4] The direct cost of AF treatment in the US is 6.65 billion dollars annually, and hospitalizations with a principle discharge diagnosis of AF account for the majority of spending (2.93 billion dollars, 44%).[4] Ambulatory and outpatient treatment costs an estimated 1.76 billion annually, 17% of which is attributable to emergency department (ED) visits.[4] Symptoms are a major predictor of hospitalizations among individuals with AF.[5]

Given the substantial cost of AF treatment, it is crucial to ensure adequate outpatient symptom management for AF, which could reduce hospitalizations and ED visits. Unfortunately, AF symptoms are poorly understood and little is known regarding the mechanisms of AF symptoms.[6] For instance, AF symptoms do not always correlate with episodes of arrhythmia,[7-9] making it challenging to know the best approach to symptom management for some patients. The scant research on AF symptoms provides does not provide specific information regarding which symptoms, or combinations of symptoms, are the most likely to result in healthcare utilization.

The examination of symptom clusters is a previously unexplored area of AF symptom research that may help us better understand the relationship between symptoms and healthcare utilization.[10] Symptom clusters are groups of 2 or more symptoms that are related due to shared mechanisms, covariance, or effect on outcomes. For this study, we define symptom clusters as two or more co-occurring symptoms.[20,21] If symptom clusters can be identified that are associated with healthcare utilization, we can use that information to develop tailored interventions aimed at reducing unnecessary ED visits and avoidable hospitalizations. As such, the purpose of this study was three-fold: 1) to identify AF-specific symptom clusters, 2) to characterize individuals within

each identified symptom cluster, and 3) to determine whether symptom cluster membership is associated with healthcare utilization (AF-related hospitalizations and ED visits).

Methods

We conducted a cross-sectional secondary data analysis using de-identified data from the Vanderbilt Atrial Fibrillation Registry (VAFR).[11] VAFR is a single center clinical biorepository that prospectively enrolled AF patients and their family members beginning in October 2002. The registry was approved by the Vanderbilt University Institutional Review Board (IRB), and this secondary data analysis was approved by the University of Pennsylvania IRB.

Study Population

Consecutively enrolled patients from Vanderbilt cardiology clinics, ED, and in-patient services are captured in VAFR[11-13]. Inclusion requirements were documented AF or atrial flutter and age of 18 years or greater. AF was documented on an electrocardiogram (ECG), Holter monitor, rhythm strip, or event recorder. AF was defined as replacement of p-waves with rapid oscillations that varied in size, shape, and timing and were accompanied by irregular ventricular response when atrioventricular conduction was intact. Patients were excluded from VAFR if AF was only present within the first 90 days after cardiac surgery or were unable/unwilling to provide written informed consent.

Our sample for this study consists of the 1,501 adults in the VAFR clinical registry with a confirmed diagnosis of AF and a completed baseline symptom survey. We excluded from our analysis individuals who had atrial flutter but not AF, and individuals who did not complete a baseline symptom survey.

Measurement of Variables

Demographic and Clinical Characteristics

Upon enrollment in VAFR, a detailed sociodemographic, medical, and drug history was obtained for all participants using an investigator designed form in RedCap[14] to standardize data collection. Data were collected by trained study personnel (registered nurses) using a

combination of patient-report and medical record review. We used the following variables to characterize participants in our study: age at consent, gender, ethnicity, body mass index (BMI), ejection fraction, left atrial diameter, AF type (paroxysmal, persistent, or permanent), age of AF onset, current use of anti-arrhythmic medication, current use of other cardioactive medications, history of ablation, history of coronary bypass, heart failure, coronary disease, valve disease, hypertension, and CHADS2 score. The CHADS2 score is commonly used to estimate stroke risk; scores range from 0 (least risk) to 6 (most risk) and are calculated by assigning one point each for the presence of heart failure (C), hypertension (H), age 75 or older (A), or diabetes (D), and two points for prior stroke/transient ischemic attack (S).[15] We calculated AF duration by subtracting age of AF onset from age at consent. Paroxysmal AF was defined as AF that lasted for at least 30 seconds and terminated spontaneously. Persistent AF was defined as AF that lasted for 7 days or longer and required electrical or chemical cardioversion. Permanent AF was defined as continuous AF for which the decision was made not to restore sinus rhythm. Left atrial diameter and ejection fraction were recorded on all participants from the echocardiogram or magnetic resonance imaging performed closest to the time of enrollment.

Atrial Fibrillation Symptoms

Participants completed the University of Toronto AF Severity Scale (AFSS) upon enrollment.[11,16,17] The AFSS is a 19-item survey composed of three sections: The first measures general life satisfaction and the global frequency, duration, and severity of AF episodes, the second measures healthcare utilization, and the third is a symptom subscale that measures the presence and frequency of seven of the most common AF symptoms (palpitations, shortness of breath at rest, shortness of breath with activity, exercise intolerance, dizziness, fatigue at rest, and chest pain).[17] Specifically, the following is asked of each specific symptom: how often have you been bothered by (palpitations) in the past 4 weeks. Subjects respond on a 6 point Likert scale ranging from none (1) to a great deal (6), and total scores for the symptom subscale range from 0 to 35. The internal consistency (Cronbach's α) for AF burden is 0.94.[18] Internal consistency and test-retest reliability for the symptom subscale have not been reported, however

the AFSS has been used in the validation of other AF-specific disease severity and quality of life scales, including the Canadian Cardiovascular Society Severity in AF scale (CCS-SAF).[19] CCS-SAF is a physician-rated measure of symptom severity, documented correlation between arrhythmia and symptoms, and AF-related functional impairment with scores ranging 0-4. Between CCS-SAF class 0 and 4, there was more than a four-fold increase in the AFSS symptom subscale scores, demonstrating the ability of this subscale to discern clinically meaningful differences in symptoms. We used the symptom subscale of the AFSS as our measure for the symptom cluster analysis.

Healthcare Utilization

The second section of the AFSS[11,16] measures participants' utilization of healthcare services. Specifically, participants report whether they have ever been cardioverted and how many times, along with how many hospitalizations, ED visits, and specialist clinic visits they have had within the past 12 months related to their AF. The AFSS was collected by the study nurses either by telephone or during clinic visits. We examine two of these variables, hospitalizations and ED visits, because they represent AF-specific healthcare utilization that could potentially be reduced with improved symptom management and self-care. The healthcare utilization section of the AFSS has a low but acceptable 3-month test-retest reliability of 0.71 and internal consistency (Cronbach's α) of 0.67.[18]

Statistical Analysis

All analyses were conducted using SAS version 9.4 (Cary, North Carolina). Standard descriptive statistics were used to describe the data. Symptom clusters were identified with agglomerative hierarchical cluster analysis, using Ward's method and Euclidean distance as our dissimilarity measure.[22-25] Cluster analysis maximizes the heterogeneity between clusters while simultaneously minimizing the homogeneity within clusters.[23,24] To determine the ideal number of clusters we used dendrograms, pseudo F, and pseudo T.[23,26]

Once symptom clusters were identified, we looked for associations between cluster membership and sociodemographic and clinical variables. To do this, we first dichotomized the

symptom variables: if a symptom was rated no (1), very little (2), or a little (3) it was dichotomized as no/inexistent, whereas if a symptom was rated a fair amount (4), a lot (5), or a great deal (6) it was dichotomized as yes/existent. Next, we divided participants into three groups for each symptom cluster: those with none, some, or all of the symptoms in the cluster. Next, we compared characteristics of the individuals within each group (none/some/all) for each of the identified symptom clusters. Comparisons were made with Fisher's exact or chi-square tests for categorical variables and Kruskal-Wallis one-way analysis of variance for continuous and ordinal variables. We compared a broad range of sociodemographic and clinical characteristics and a p-value of < 0.05 was considered statistically significant.

Our next step was to conduct two separate regression analyses to determine the association between 1) symptom clusters and number of AF-related hospitalizations, and 2) symptom clusters and number of AF-related ED visits. We used Poisson regression to model both of our outcome variables, AF-related hospitalizations and AF-related ED visits. Sociodemographic and clinical variables that were significant when comparing characteristics between individuals with none/some/all symptoms in a cluster were entered into our adjusted analyses as independent variables. Additionally, other potential confounders were included in the adjusted model if they were known *a priori* to be associated with healthcare utilization or if they changed the strength of the association between the symptom clusters and the response variable by more than 10%.

Results

Sample Characteristics

The mean age of participants was 58.4 years (±12.2), ranging between 18.1 and 88.5 years (Table 3.1). Participants were predominantly Caucasian (96%) and primarily male (67%). Exercise intolerance was the most common symptom, affecting 42% of participants, followed by shortness of breath with activity (40%) and palpitations (33%). The majority of the sample had paroxysmal (51%) or persistent (42.5%) AF, with only a small portion having permanent AF

(6.5%). Average AF duration was 4.5 (± 5.8) years. Approximately half the sample was on an anti-arrhythmic medication (55%) and/or had a prior catheter or surgical ablation (52%).

Table 3.1: Demographic and Clinical Profile of VAFR Participants

	All (N=1,501)	Female (N=497, 33%)	Male (N=1,004, 67%)
Demographic Profile			
Age (years)	58.4 (±12.2)	60.9 (±12.8)	57.1 (±11.7)
Ethnicity			
Caucasian	1,436 (95.7%)	473 (95.2%)	963 (95.9%)
Asian	4 (0.3%)	0 (0%)	4 (0.4%)
Black	53 (3.5%)	23 (4.6%)	30 (3%)
Hispanic	6 (0.4%)	1 (0.2%)	5 (0.5%)
Native American	2 (0.1%)	0 (0%)	2 (0.2%)
Clinical Profile			
AF Sub-Type			
Paroxysmal	765 (51.1%)	308 (62.1%)	457 (45.6%)
Persistent	636 (42.5%)	164 (33.1%)	472 (47.1%)
Permanent	97 (6.5%)	24 (4.8%)	73 (7.3%)
AF Duration	4.5 (±5.8)	4.3 (±5.3))	4.6 (±6.0)
Body Mass Index	31.1 (±6.6)	30.8 (±7.5)	31.2 (±6.1)
CHADS2 score	1.1 (±1.0)	1.2 (±1.0)	1.0 (±1.0)
Left Atrial Diameter	42 (±7.8)	43.1 (±7.7)	39.8 (±7.6)
Heart Failure	216 (14.4%)	69 (13.9%)	147 (14.7%)
Hypertension	927 (62.0%)	313 (63.1%)	614 (61.5%)
Coronary Artery Disease	317 (21.3%)	73 (14.8%)	244 (24.5%)
Valve disease	391 (26.8%)	165 (34.0%)	226 (23.2%)
History of AF ablation	771 (52.4%)	253 (52.1%)	518 (52.5%)
History of Cardiac Bypass Surgery	109 (7.3%)	14 (2.9%)	95 (9.5%)
Digoxin	213 (14.4%)	78 (16.0%)	135 (13.6%)
Calcium Channel Blocker	468 (31.6%)	165 (33.7%)	303 (30.5%)
Beta Blocker	730 (49.2%)	241 (49.2%)	489 (49.2%)
Anti Lipidemic	630 (42.5%)	191 (39.1%)	439 (44.1%)
Ace/Angiotensin Blocker	591 (39.8%)	187 (38.2%)	404 (40.6%)
Anti-Arrhythmic	817 (55.1%)	274 (56.0%)	543 (54.6%)
Symptom Profile			
Chest Pain	206 (13.7%)	95 (19.1%)	111 (11.1%)
Dizziness	289 (19.3%)	140 (28.2%)	149 (14.8%)
SOB at Rest	297 (19.8%)	127 (25.6%)	170 (16.9%)
SOB with Activity	599 (39.9%)	239 (48.1%)	360 (35.9%)
Exercise Intolerance	623 (41.5%)	259 (52.1%)	364 (36.3%)
Fatigue at Rest	359 (23.9%)	159 (32.0%)	200 (19.9%)
Palpitations	494 (32.9%)	221 (44.5%)	271 (27.2%)

Symptom Clusters

A three cluster solution was indicated as the optimal solution based on the dendrogram, pseudo-F, and pseudo-T (Figure 3.1). One of the clusters in the three cluster solution consists of a single symptom (palpitations), and therefore does not meet our definition of a symptom cluster (two or more co-occurring symptoms).[20,21] We labeled the two clusters that met our definition of a symptom cluster the *At Rest cluster* (fatigue at rest, shortness of breath at rest, chest pain, and dizziness) and the *With Activity cluster* (shortness of breath with activity and exercise intolerance). The With Activity symptom cluster was the most common, with all symptoms being experienced in 32.7% (n=491) of participants. All the At Rest cluster symptoms occurred in 3.7% (n=56) of participants (Table 3.2). There was significant co-occurrence of the two clusters, with 51 of the 56 participants who had the At Rest cluster also having the With Activity cluster (Table 3.2).

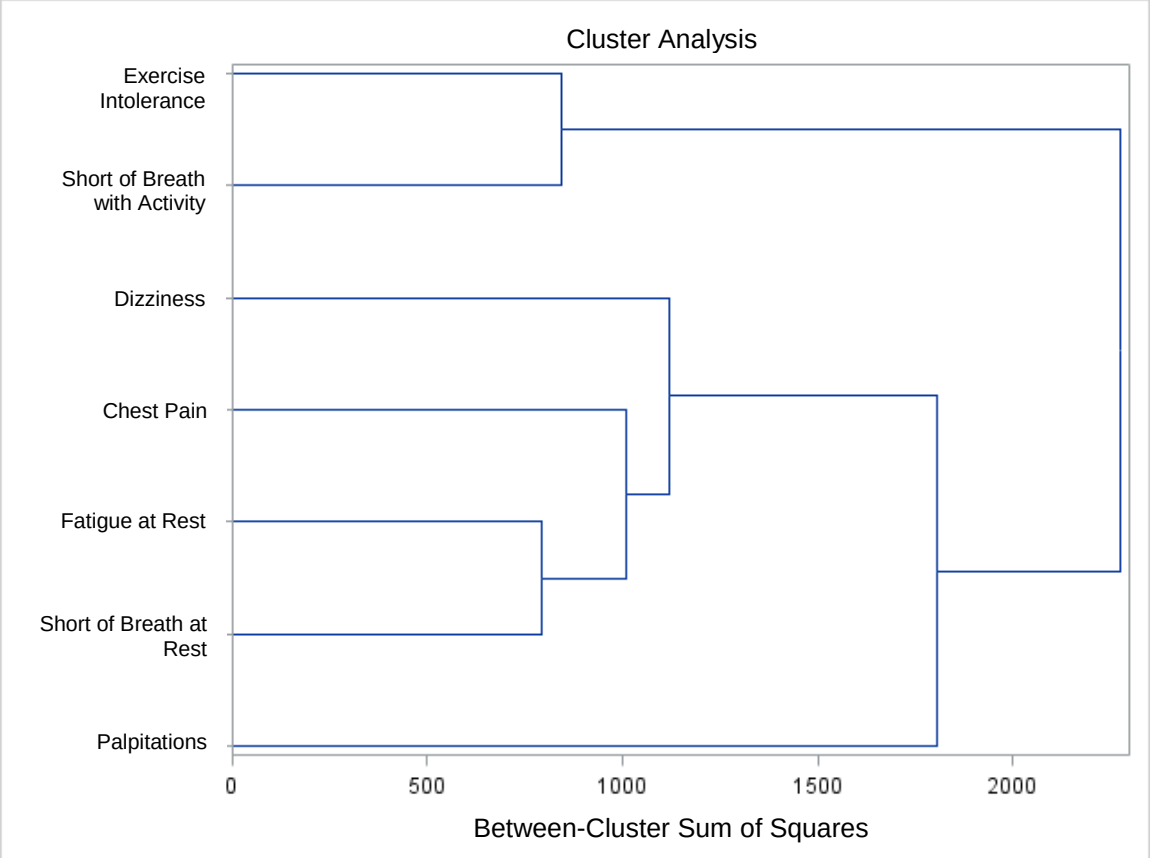


Figure 3.1: Dendrogram of symptom clusters. Symptoms were self-reported at baseline

Table 3.2: Cluster Co-occurrence within VAFR

	Palpitations	At Rest	With Activity
Palpitations	494 (32.9%)	47 (3.1%)	268 (17.8%)
At Rest		56 (3.7%)	51 (3.4%)
With Activity			491 (32.7%)

Characteristics by Symptom Cluster Membership

Several sociodemographic and clinical characteristics varied by cluster membership. Women comprised the greatest proportion of the group that had all symptoms in the At Rest cluster (52% women versus 48% men, $p<0.0001$), even though the overall sample was two thirds male. Statistically significant differences in ethnicity, body mass index, coronary disease, heart failure, current use of anti-arrhythmic medication, and history of ablation were also apparent. Table 3.3 provides full details regarding the differences in sociodemographic and clinical characteristics between participants with all, some, and none of the symptoms in the At Rest cluster.

For the With Activity cluster, women were again more likely than men to have all of the symptoms in the cluster. Among the group with all of the With Activity symptoms, 59% were male and 41% were female ($p<0.0001$), but due to the larger proportion of men in the study this represents 3% of all men and 6% of all women. Participants with none of the With Activity symptoms were approximately 2 years younger on average than individuals with all of the symptoms (57.5 years versus 59.5 years, $p=0.01$). AF type varied between individuals with none, some, or all of the symptoms in the With Activity cluster ($p<0.0001$). Additional sociodemographic and clinical factors that showed statistically significant variance by cluster membership included body mass index, ejection fraction, coronary disease, heart failure, current use of anti-arrhythmic medication, and history of ablation (Table 3.3).

Table 3.3: Demographic and Clinical Characteristics by VAFR Cluster Membership

	At Rest			
	None of the Symptoms N=892	**Some of the Symptoms N=553**	**All of the Symptoms N=56**	**p-value**
Gender				**<0.0001**
Male	664 (74%)	313 (57%)	27 (48%)	
Female	228 (26%)	240 (43%)	29 (52%)	
Age (years)	58.2 (12.4±)	58.9(12±)	55.8 (10.1±)	0.09
Caucasian Ethnicity	851 (95%)	535 (97%)	50 (89%)	**0.03**
AF Duration (years)	4.6 (6.1±)	4.3 (5.3±)	4.1 (4.4±)	0.95
AF Sub-Type				0.49
Paroxysmal	457 (51%)	284 (51%)	24 (43%)	
Persistent	371 (42%	235 (43%)	30 (54%)	
Permanent	62 (7%)	33 (6%)	2 (4%)	
Body Mass Index	30.5 (6.2±)	31.8 (7.1±)	32.4 (7.2±)	**0.003**
Ejection Fraction	55.6 (9.9±)	54.7 (10.5±)	54.8 (9.8±)	0.24
Coronary Disease	156 (18%)	148 (27%)	13 (23%)	**0.0002**
Heart Failure	99 (11%)	101 (18%)	16 (29%)	**<0.0001**
Anti-Arrhythmic	435 (49%)	344 (63%)	38 (67%)	**<0.0001**
History of Ablation	417 (48%)	313 (58%)	41 (75%)	**<0.0001**
	With Activity			
	None of the Symptoms N=770	**Some of the Symptoms N=240**	**All of the Symptoms N=491**	**p-value**
Gender				**<0.0001**
Male	569 (74%)	146 (61%)	289 (59%)	
Female	201 (26%)	94 (39%)	202 (41%)	
Age (years)	57.5 (12.5±)	58.9 (12.1±)	59.5 (11.8±)	**0.01**
Caucasian Ethnicity	734 (95%)	231 (96%)	471 (96%)	0.78
AF Duration	4.6 (6.2±)	4.6 (5.6±)	4.3 (5.1±)	0.89
AF Sub-Type				**<0.0001**
Paroxysmal	445 (58%)	120 (50%)	200 (41%)	
Persistent	272 (35%)	107 (45%)	257 (52%)	
Permanent	50 (7%)	13 (5%)	34 (7%)	
Body Mass Index	30 (6±)	30.8 (6.5±)	32.7 (7.2±)	**<0.0001**
Ejection Fraction	55.9 (9.1±)	55.4 (10.4±)	54.2 (11.3±)	**0.03**
Coronary Disease	121 (16%)	59 (25%)	137 (28%)	**<0.0001**
Heart Failure	65 (8%)	36 (15%)	115 (23%)	<**0.0001**
Anti-Arrhythmic	375 (49%)	145 (61%)	297 (62%)	**<0.0001**
History of Ablation	334 (44%)	135 (58%)	302 (63%)	**<0.0001**

Statistically significant p-values (p<0.05) are shown in bold. Data are mean (± standard deviation) or number of patients (%).

Impact of Symptom Clusters on Healthcare Utilization

Emergency Department Utilization

In unadjusted analyses, experiencing all the symptoms in the At Rest cluster more than tripled the rate of ED utilization (incident rate ratio 3.6, p<0.0001, Table 3.4), while having all the

symptoms in the With Activity cluster resulted in more than one and a half times the rate of ED utilization (incident rate ratio 1.6, p<0.0001). In the adjusted model, the With Activity cluster no longer had a statistically significant association with ED utilization (incident rate ratio 0.96, p=0.6604). Experiencing all the symptoms in the At Rest cluster had the strongest association with ED utilization of all variables in the model, resulting in nearly triple the rate of ED utilization compared to individuals with none of the At Rest symptoms (incident rate ratio 2.8, p<0.0001). The symptom 'palpitations' did not cluster with other symptoms, but on its own did result in a slightly increased rate of ED utilization in the adjusted model (incident rate ratio 1.17, p=0.046). We did an exploratory analysis of interactions between AF type and both history of ablation and current use of anti-arrhythmic medication and none were statistically significant. However, individuals with permanent AF and a history of ablation had nearly twice the rate of ED utilization as individuals with paroxysmal AF (incident rate ratio 1.8, p=0.45).

Table 3.4: At Rest Cluster Emergency Department Utilization

At Rest Cluster	**Unadjusted** IRR/p-value	**Adjusted*** IRR/p-value
None	(ref)	(ref)
Some	1.663/<0.0001	1.423/<0.0001
All	3.643/<0.0001	2.767/<0.0001
*adjusted for gender, age, AF type, history of ablation, current AAD, heart failure, palpitations, body mass index, coronary disease, left ventricular ejection fraction, AF duration		

Hospitalizations

Experiencing all the symptoms in the At Rest cluster nearly tripled the rate of hospitalizations in unadjusted analyses (incident rate ratio 2.8, p<0.0001), whereas having all symptoms in the With Activity cluster corresponded with more than one and a half times the rate of hospitalizations (incident rate ratio 1.7, p<0.0001, Table 3.5). In the adjusted model, the With Activity cluster no longer had a statistically significant association with hospitalizations (incident rate ratio 0.98, p=0.85). Among the retained variables, having all symptoms in the At Rest cluster was the most strongly associated with hospitalizations, resulting in almost twice the rate of hospitalizations compared to individuals with none of the At Rest symptoms (incident rate ratio

1.9, p<0.0001). Palpitations also increased the rate of hospitalizations in the adjusted model (incident rate ratio 1.27, p=0.002). Exploratory testing of interactions between AF type and both history of ablation and current use of anti-arrhythmic medication resulted in no statistically significant interactions. However, individuals with permanent AF and current use of anti-arrhythmic medications had over twice the rate of hospitalization as individuals with paroxysmal AF (incident rate ratio 2.2, p=0.24).

Table 3.5: At Rest Cluster Hospitalizations

At Rest Cluster	**Unadjusted** IRR/p-value	**Adjusted*** IRR/p-value
None	(ref)	(ref)
Some	1.719/<0.0001	1.340/ 0.0001
All	2.799/<0.0001	1.904/<0.0001
*adjusted for gender, age, ethnicity, AF type, history of ablation, current AAD, heart failure, palpitations, body mass index, coronary disease, left ventricular ejection fraction, AF duration		

Discussion

Using a large sample of adults with clinically verified AF, we identified two AF-specific symptom clusters: The *At Rest cluster* (fatigue at rest, shortness of breath at rest, chest pain, and dizziness) and the *With Activity cluster* (shortness of breath with activity and exercise intolerance). Experiencing all symptoms in the At Rest cluster conferred significant risk for both ED utilization and hospitalization. These findings are consistent with prior research which shows that severe European Heart Rhythm Association (EHRA) symptom scores (defined as symptoms that effect daily activities) are a major predictor of incident hospitalizations in patients with AF.[5] Recent research also indicates that individuals who experience AF symptoms that are readily attributable to cardiac causes (i.e. chest pain or dizziness) are more likely to seek treatment in a timely manner (<24 hours).[27] This offers a logical explanation as to why the At Rest cluster of symptoms is more likely to result in ED utilization than others.

The clusters identified in this study differ from the previously reported AF-specific symptom clusters identified using participants in the SAFETY trial.[10,28] The symptom clusters identified with SAFETY included a *vagal cluster* (nausea and diaphoresis), *tired cluster* (fatigue,

weakness, syncope/dizziness, and dyspnea), and *heart cluster* (palpitations and chest pain).[10] Differences between the VAFR and SAFETY recruitment strategies, inclusion criteria, and approach to symptom measurement likely account for the differences between the symptom clusters found in these studies. Participants in VAFR were recruited from both inpatient and outpatient settings, whereas SAFETY participants were all recruited during an inpatient admission. The symptom profiles of individuals requiring inpatient management likely differ from those of individuals in an outpatient environment.[5] This discrepancy could account for differences in symptom profiles that potentially affected the symptom cluster results. A second important difference between VAFR and SAFETY participants is that individuals with heart failure were excluded from SAFETY but were included in VAFR. Comorbid heart failure likely impacts symptoms and symptom clusters, by affecting either the severity or the type of symptoms reported.[29] Another important difference between the two studies was the method of symptom measurement. Both studies used parsimonious symptom scales, but the specific symptoms measured varied. The differences in the inclusion criteria and symptoms measured likely impacted the results of the symptom cluster analyses.

The symptom of palpitations did not cluster with other symptoms in the present study. However, palpitations independently increased the risk of both ED utilization and hospitalization. Recent studies reveal that approximately 75% of patients presenting to the ED for AF report palpitations.[30,31] In a prior study of AF symptom clusters using SAFETY[28] trial participants, palpitations clustered with chest pain.[10] It is possible that if a comprehensive rather than parsimonious symptom scale were used, that palpitations would cluster with other symptoms. Regardless of clustering, palpitations should be considered a symptom that increases a patient's risk for ED utilization and hospitalization, and therefore patients may benefit from symptom management and self-care strategies.

Several statistically significant differences were noted in the sociodemographic and clinical characteristics of individuals with the At Rest and With Activity symptom clusters. Individuals with all of either the At Rest or With Activity symptom clusters were more likely to be

on anti-arrhythmic therapy, have a history of ablation, be female, have an elevated BMI, and have heart failure. Consistent with clinical recommendations,[32] our findings indicate that rhythm control strategies (anti-arrhythmic medications and ablation) were more commonly used for individuals with significant symptom burden.

Our finding that women are more likely to experience both the At Rest and With Activity symptom clusters is consistent with prior research related to AF symptom clusters, which similarly found that women were more likely to experience a cluster of palpitations and chest pain.[10] In fact, the majority of AF symptom literature indicates that women report more frequent and severe symptoms than men.[33-35]

Obesity is a known risk factor for increased AF burden and symptom severity,[36,37] and our findings provide further evidence of the relationship between obesity and AF symptoms. The association between obesity and AF symptom severity may be confounded by physical inactivity and depression,[38] indicating two modifiable factors that could be targeted in interventions aimed at improving AF symptom management and self-care.

AF and heart failure have many symptoms in common (e.g. shortness of breath, fatigue), so it is not surprising that individuals with heart failure were more likely to experience both symptom clusters. Concomitant heart failure and AF may further exacerbate each other due to the effects of each on hemodynamic function,[32] making symptomatic management of both conditions more challenging. Pre-existing heart failure is a primary predictor for hospitalization among patients with AF (hazard ratio 1.57),[5] indicating symptomatic AF patients with heart failure may benefit the most from interventions designed to improve AF symptom management and self-care.

Our findings reveal that individuals with all the symptoms in the With Activity cluster tend to be older and have persistent or permanent AF. This information is useful for clinical evaluation, suggesting the importance of careful assessment in this patient population for these intermittent and vague symptoms which prior research indicates are often attributed to other causes (e.g. aging, deconditioning).[27]

To date, symptom management for AF has largely been focused on rate and/or rhythm control strategies via medical or surgical management.[32] Studies of self-care strategies to improve symptom management are largely lacking, and the few studies published are in the early stages of intervention development.[39-41] Self-care is defined as the decision making processes that individuals use to maintain health and manage illness, with symptom perception acknowledged as having a profound impact on self-care outcomes.[42] Health-promoting lifestyle choices are an important component of self-care (e.g. nutritious diet, exercise) which are beginning to be explored as options for AF symptom management.[36,37,43,44] Additional research is warranted to explore the effect of self-care interventions on AF symptoms and healthcare utilization.

Limitations

There are several important limitations to our study. First, our study lacks both psychological comorbidities (e.g. depression, anxiety) and symptoms (e.g. worry, fear). Psychological comorbidities have been shown to influence both the number and severity of AF symptoms.[8,35] Psychological symptoms may be important components of symptom clusters, but we were unable to examine this possibility since they are not measured with the AFSS. Future prospective studies of AF symptom clusters should include psychological covariates. Second, it may be beneficial to use a more comprehensive symptom scale for future AF symptom cluster studies (e.g. the Symptom Checklist[45,46]). The AFSS is a parsimonious, validated symptom scale which is appropriate for clinical practice and certain research questions. However, a more comprehensive scale could provide clarity regarding the different clusters found in this study and our prior work.[10] Third, our sample was primarily Caucasian and male, however AF is more common in this demographic[47,48] and as such does not necessarily limit the generalizability of our findings. Finally, the healthcare utilization outcome variables were self-reported. The variables were collected with the validated AFSS healthcare utilization subscale, and participants were only asked to recall hospitalizations and ED visits within the past 12 months, therefore we believe

participants recall is likely accurate. However, future studies using medical record review or claims data should be conducted to confirm our findings.

Conclusion

This study provides evidence of two AF-specific symptom clusters. The At Rest cluster of symptoms increases a patient's risk for healthcare utilization. These results should be confirmed with additional studies. Symptom are quick and easy to assess, and therefore our results offer a useful tool that can aid in clinical decision making and risk-stratification for patients with AF.

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CHAPTER 4: LATENT CLASS REGRESSION ANALYSIS IDENTIFIES SYMPTOM CLUSTERS AMONG ADULTS WITH ATRIAL FIBRILLATION THAT INCREASES HOSPITALIZATIONS AND EMERGENCY DEPARTEMENT VISITS

Abstract

Background: Symptom clusters among adults with atrial fibrillation may influence healthcare utilizations. This is the first study to use latent class analysis to evaluate symptom clusters among adults with atrial fibrillation. **Objective:** The purpose of this study was to: 1) identify clusters of patients with similar symptom profiles, 2) characterize the individuals within each cluster, and 3) determine whether specific symptom profiles are associated with healthcare utilization (AF-related hospitalizations and ED visits). **Methods:** This was a cross-sectional secondary data analysis of 1,291 adults from the Vanderbilt Atrial Fibrillation Registry with clinically verified paroxysmal, persistent, or permanent atrial fibrillation. We used self-reported symptoms and latent class analysis to determine symptom clusters, with clinical and demographic variables included as covariates. We then conducted regression analyses to examine the association between latent class membership and healthcare utilization (atrial fibrillation related emergency department visits and hospitalizations). **Results:** Participants were predominantly male (67%) and ranged in age from 18.9 and 88.5 years, with a mean of 58.4 years (±11.9). Four latent classes were evident, including 1) Asymptomatic cluster (N=487, 38%), 2) Highly Symptomatic cluster (N=142, 11%), 3) With Activity cluster (N=326, 25%), and 4) Mild Diffuse cluster (N=336, 26%). Membership in the Highly Symptomatic and With Activity clusters resulted in significantly increased rates of both emergency department visits and hospitalizations. **Conclusion:** Clinically meaningful atrial fibrillation symptom clusters were identified that increase both emergency department visits and hospitalizations.

Introduction

The perception of symptoms is a major factor in the decision to utilize healthcare services. Symptom perception refers to both the detection of symptoms and the interpretation of symptom meaning.[1-4] For individuals with atrial fibrillation (AF), symptoms may be interpreted as relatively harmless, resulting in a 'wait and see' approach, or might be interpreted as life-threatening and prompt a decision to seek immediate medical attention.[5,6]

Limited data is available regarding the relationship between AF symptoms and healthcare utilization outcomes.[7] Between 1993 and 2004 emergency department (ED) visits for AF increased 88%, and almost 64% of ED visits for AF resulted in a subsequent hospitalization.[8] Two studies using the Outcomes Registry for Better Informed Treatment of AF found that symptoms rated as severe with the European Heart Rhythm Association classification system were a major predictor of hospitalizations.[9,10] However, the relationship between specific AF symptoms and healthcare utilization outcomes has not been reported. There are a wide range of symptoms experienced by individuals with AF including palpitations, chest pain, shortness of breath, dizziness, exercise intolerance, and fatigue.[11] It is likely that distinct AF symptoms are interpreted differentially, resulting in disparate utilization of healthcare services depending on the specific symptoms present.

Symptom clusters are groups of 2 or more co-occurring symptoms that are related due to a shared mechanism, covariance, or effect on patient outcomes.[12-15] Symptom clusters likely have a unique impact on healthcare utilization due to the multiplicative effect of co-occurring symptoms.[1] There are two basic approaches to symptom cluster research: 1) clustering symptom variables and 2) clustering individuals into mutually exclusive groups with similar symptom profiles.[14,16] Our prior work on AF symptom clusters used the approach of identifying clusters of symptoms.[17] To our knowledge, no previous study has sought to identify clusters of AF patients who have similar symptom profiles. Understanding the symptom profiles that are associated with higher rates of healthcare utilization could improve our ability to risk stratify patients and provide individualized support to patients at higher risk for ED visits or hospitalization. The purpose of this

study was to: 1) identify clusters of patients with similar symptom profiles, 2) characterize the individuals within each cluster, and 3) determine whether specific symptom profiles are associated with healthcare utilization (AF-related hospitalizations and ED visits).

Methods

This was a cross-sectional secondary data analysis using de-identified data from the Vanderbilt Atrial Fibrillation Registry (VAFR),[18] a single center clinical biorepository. VAFR prospectively enrolled AF patients and their family members beginning in October 2002. Institutional Review Board (IRB) approval was obtained from Vanderbilt University for the registry, and from the University of Pennsylvania for this secondary data analysis. All VAFR participants provided written informed consent.

Study Population

Patients from Vanderbilt cardiology clinics, ED, and in-patient services were consecutively enrolled in VAFR[18-20]. Inclusion requirements were age of 18 years or greater and AF or atrial flutter documented with an electrocardiogram (ECG), Holter monitor, rhythm strip, or event recorder. AF was defined as replacement of p-waves with rapid oscillations that varied in size, shape, and timing and were accompanied by irregular ventricular response when atrioventricular conduction was intact. Patients were excluded from VAFR if AF was only present within the first 90 days after cardiac surgery. For this study, we included in our sample the 1,501 adults from the VAFR clinical registry with a confirmed diagnosis of AF and a completed baseline symptom survey. We excluded individuals who had atrial flutter but not AF.

Measurement of Variables

Demographic and Clinical Characteristics

Participants in VAFR had a detailed sociodemographic, medical, and drug history taken upon enrollment. An investigator designed REDCap[21] form was used to standardize data collection. A combination of patient-reported and medical record review data were collected by trained study personnel (registered nurses). We used the following variables to characterize

participants in our study: age at consent, gender, ethnicity, body mass index (BMI), ejection fraction, AF type (paroxysmal, persistent, or permanent), AF duration, current use of anti-arrhythmic medication, history of ablation, history of coronary bypass, heart failure, and coronary disease. We determined AF duration by subtracting the reported age of AF onset from age at consent. Paroxysmal AF was defined as lasting for at least 30 seconds and terminating spontaneously, persistent AF as lasting for 7 days or longer and requiring electrical or chemical cardioversion, and permanent AF as continuous AF for which a decision was made not to restore sinus rhythm. The echocardiogram or magnetic resonance imaging performed closest to the time of enrollment was used to record the ejection fraction for all participants.

Atrial Fibrillation Symptoms

All participants were asked to complete a symptom survey upon enrollment in VAFR, specifically the 19-item University of Toronto AF Severity Scale (AFSS).[18,22,23] To measure symptoms we used the third section of the AFSS, which is a symptom subscale that provides information regarding the presence and frequency of 7 common AF symptoms (palpitations, shortness of breath at rest, shortness of breath with activity, exercise intolerance, dizziness, fatigue at rest, and chest pain).[23] Specifically, participants are asked how often they have been bothered by (palpitations) in the past 4 weeks. Subjects respond separately for each symptom on a 6 point Likert scale ranging from none (1) to a great deal (6). Total scores for the symptom subscale range from 0 to 35. Internal consistency and test-retest reliability for the symptom subscale have not been reported. However, the AFSS has been used to validate the Canadian Cardiovascular Society Severity in AF scale (CCS-SAF),[24] which is a physician-rated measure of symptom severity, correlation between arrhythmia and symptoms, and functional impairment, with scores ranging 0-4. Between CCS-SAF class 0 and 4, the AFSS symptom subscale scores increased more than four-fold, demonstrating the ability of this subscale to discern clinically meaningful differences in symptoms.

Healthcare Utilization

The second section of the AFSS[18,22] measures if and how often participants were

cardioverted, hospitalized, visited the ED, and/or had specialist clinic appointments in the past 12 months related to their AF. Trained study nurses collected the AFSS either by telephone or during clinic visits. We examine two of these healthcare utilization variables, hospitalizations and ED visits, because we believe they could be safely reduced with interventions aimed at improving symptom management and self-care. The AFSS healthcare utilization section has low but acceptable 3-month test-retest reliability (0.71) and internal consistency (Cronbach's α, 0.67).[25]

Statistical Analysis

Clusters were identified using latent class analysis, a type of finite mixture model.[26] Latent class analysis allows for the simultaneous examination of relationships between multiple variables, covariates, and outcomes.[16,26] The goal of latent class modeling is to stratify categorical observed (manifest) variables by an unobserved (latent) variable, eliminating confounding between the observed variables. The latent class model probabilistically groups every observation (patient) into a latent class, which also results in expectations regarding how that patient responds to each observed variable in the model. A latent class regression model extends the basic latent class model and allows for the inclusion of covariates (independent variables), which predict latent class membership.[26]

We conducted a latent class regression analysis in R 3.3.0 using the poLCA package.[26-28] We used the 7 symptoms on the AFSS subscale as our manifest (observed) variables. We included 11 sociodemographic and clinical covariates (independent variables) in our latent class model that were known *a priori* to be associated with AF symptoms.[11,17,24,29-32] Covariates were retained in our final adjusted model if they were statistically significant ($p < 0.05$) or if their removal changed the strength of the association between covariates and the latent classes by more than 10%. The poLCA package estimates the model by maximizing the log-likelihood function. To ensure we found the global maximum of the log-likelihood, we conducted 100 random start repetitions of our final model. The ideal number of latent classes is not pre-determined, but is determined using statistical fit indices combined with evaluation of the model for theoretical and clinical meaningfulness. The two most widely used fit indices are the Bayesian

information criterion (BIC) and Akaike information criterion (AIC), which we used in combination with the Pearson's χ^2 statistical test to evaluate our model.[26] For each test, lower values equate to a better fitting model. The poLCA package provides probabilities by class for each manifest variable entered into the model. We define probabilities >0.5 as high, probabilities between 0.2 and 0.5 as moderate, and probabilities <0.2 as low.

Our final step was to conduct two separate regression analyses that used measures of healthcare utilization as the dependent variables and latent class membership as the independent variable. The first regression analysis used AF-related ED visits as the dependent variable, and the second regression used AF-related hospitalizations as the dependent variable. Because sociodemographic and clinical covariates that potentially affect symptoms and healthcare utilization (e.g. age, comorbidities) were already entered into the latent class regression analysis as covariates, we did not use them again in these regression analyses. The healthcare utilization regression analyses and standard descriptive statistics were conducted in SAS version 9.4 (Cary, North Carolina). We considered p-values of <0.05 statistically significant.

Results

Sample Characteristics

Participants were predominantly male (67%) and ranged in age from 18.9 and 88.5 years, with a mean of 58.4 years (±11.9). The sample primarily consisted of individuals with paroxysmal (51.1%) and persistent (43.6%) AF. Our analytic sample size was reduced to 1,291 for our final model because poLCA automatically excludes observations with missing values on any covariate. We used the chi-square test to compare symptom severities of individuals that were and were not included in the analytic sample and found no statistically significant differences (p<0.05) in symptoms. Sample characteristics are further detailed in Table 4.1.

Table 4.1: Sample Characteristics

Variable	N=1,291
Sociodemographic Profile	
Age (years)	58.4 (±11.9)
Male	861 (67%)
Female	430 (33%)
Caucasian	1,239 (96%)
Clinical Profile	
AF Sub-Type	
Paroxysmal	660 (51.1%)
Persistent	563 (43.6%)
Permanent	68 (5.3%)
AF Duration	4.4 (±5.5)
Body Mass Index	30.9 (±6.4)
CHADS2 score	1.1 (±1.0)
Left Atrial Diameter	41.7 (±7.7)
Left Ventricular Ejection Fraction	55.5 (±9.9)
Heart Failure	177 (13.7%)
Hypertension	800 (62.2%)
Coronary Artery Disease	270 (20.9%)
History of AF ablation	713 (55.2%)
Anti-Arrhythmic Medication	750 (58.1%)

Latent Class Regression Analysis

Model Selection

Our analyses indicated that the optimal solution consisted of four classes (Figure 4.1). In the initial unadjusted model, fit statistics indicated that either a 3 or 4 class solution could be selected. Therefore, we analyzed both the 3 and 4 class solutions when removing covariates to adjust the model. In the final 4 class model, 9 of the 11 covariates were retained (only AF duration and ethnicity were removed). The fit statistics for the final model did not precisely indicate which solution was most appropriate (Table 4.2). The BIC treats Type I and Type II errors as equally undesirable, whereas the AIC treats Type II errors as the most undesirable. As a result, the AIC is more likely to indicate an overfit model;[33] therefore we chose the model indicated by the BIC. The symptom profiles of the various solutions were compared, and the 4

class solution also made the most theoretical and clinical sense, and as such is considered our optimal solution.

Table 4.2: Statistical Fit Indices

Number of Classes	AIC	BIC	χ^2
3	23668.95	24314.34	**353461.8**
4	23435.95	**24313.4**	497686.1
5	**23208.67**	24318.75	530398.5

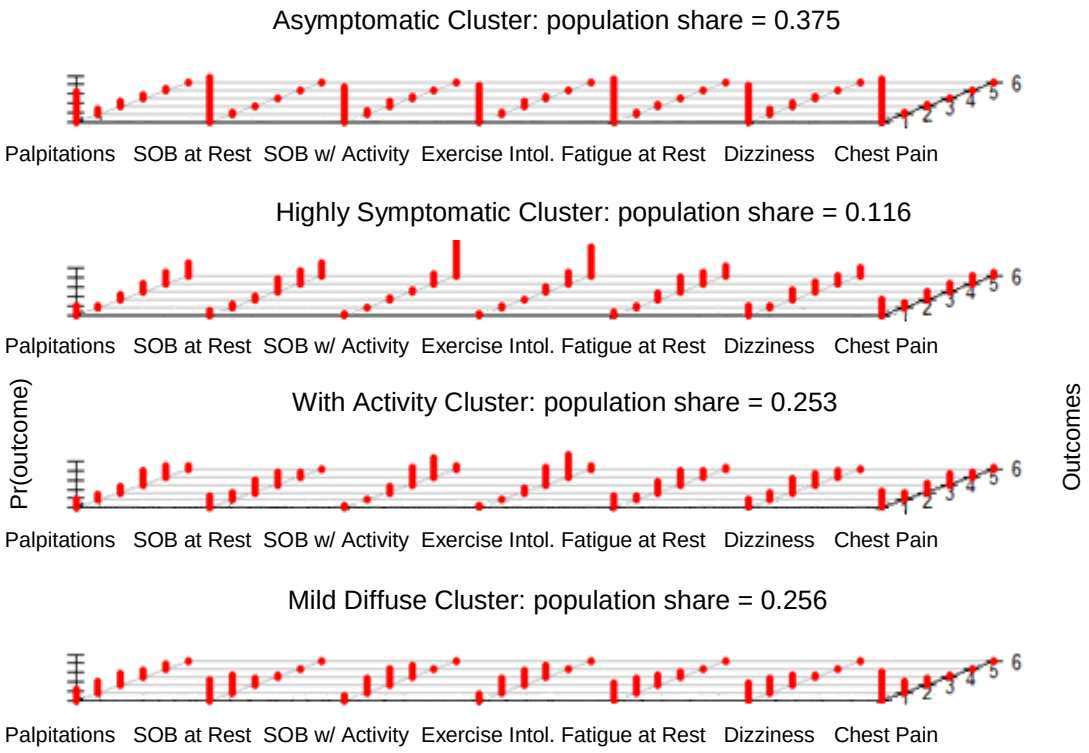

Figure 4.1: Graphical representation of latent class membership and probability of manifest variables

Latent Class Symptom Characteristics by Cluster Membership

The Asymptomatic cluster consisted of individuals with a high probability of responding "none" for every symptom (Table 4.3). This cluster had the highest membership (N=487, 38%). The Highly Symptomatic cluster (N=142, 11%) is characterized by a high probability to answer "a great deal" for the symptoms of shortness of breath with activity and exercise intolerance, along

with a moderate probability of experiencing a “fair amount” to “a great deal” of palpitations, shortness of breath at rest, and fatigue at rest. The With Activity cluster (N=326, 25%) is characterized by a moderate probability of experiencing most symptoms in the “a little” to “a lot” range. However, the most probable symptoms/symptom ratings in the With Activity cluster are shortness of breath with activity and exercise intolerance rated as “a fair amount” and “a lot”. The Mild Diffuse cluster (N=336, 26%) is characterized by a moderate probability of experiencing most of the symptoms “none”, “very little” or “a little”, and a high probability to report “none” for chest pain. In every class, chest pain was highly or moderately likely to be reported as “none”.

Table 4.3: Symptom Probabilities by Cluster Membership

	Likert Rating Probabilities					
Cluster Membership	None	Very Little	A Little	Fair Amount	A Lot	Great Deal
Asymptomatic Cluster (N=487, 38%)						
Palpitations	**0.6362**	0.1209	0.1230	0.0677	0.0364	0.0158
Shortness of Breath at Rest	**0.9426**	0.0344	0.0176	0.0054	0.0000	0.0000
Shortness of Breath with Activity	**0.7509**	0.0722	0.1182	0.0348	0.0157	0.0082
Exercise Intolerance	**0.7654**	0.0519	0.1185	0.0352	0.0252	0.0039
Fatigue at Rest	**0.9073**	0.0230	0.0361	0.0253	0.0083	0.0000
Dizziness	**0.7866**	0.1018	0.0676	0.0411	0.0028	0.0000
Chest Pain	**0.9120**	0.0455	0.0298	0.0094	0.0033	0.0000
Highly Symptomatic Cluster (N=142, 11%)						
Palpitations	0.1872	0.0387	0.1008	0.1655	*0.2347*	*0.2731*
Shortness of Breath at Rest	0.0800	0.0578	0.0493	*0.2655*	*0.2741*	*0.2733*
Shortness of Breath with Activity	0.0099	0.0000	0.0179	0.0364	0.1939	**0.7418**
Exercise Intolerance	0.0153	0.0139	0.0087	0.1104	*0.2533*	**0.5984**
Fatigue at Rest	0.0718	0.0249	0.1332	*0.2987*	*0.2536*	*0.2179*
Dizziness	0.1990	0.0359	*0.2078*	0.1999	0.1835	0.1738
Chest Pain	*0.3408*	0.0936	0.1528	0.1698	0.1780	0.0650
With Activity Cluster (N=326, 25%)						
Palpitations	0.1891	0.1013	0.1329	*0.2802*	*0.2357*	0.0609
Shortness of Breath at Rest	*0.2393*	0.1466	*0.2405*	*0.2697*	0.1039	0.0000
Shortness of Breath with Activity	0.0615	0.0180	0.1166	*0.3691*	*0.3849*	0.0499
Exercise Intolerance	0.0325	0.0189	0.0920	*0.3463*	*0.4632*	0.0471
Fatigue at Rest	*0.2348*	0.0983	*0.2289*	*0.2811*	0.1375	0.0194
Dizziness	0.1972	0.1518	*0.2930*	*0.2292*	0.1288	0.0000
Chest Pain	*0.3555*	0.1356	0.1935	*0.2076*	0.0917	0.0161
Mild Diffuse Cluster (N=336, 26%)						
Palpitations	*0.2310*	*0.2436*	*0.2388*	0.1571	0.1006	0.0289
Shortness of Breath at Rest	*0.4378*	*0.3772*	0.1530	0.0320	0.0000	0.0000
Shortness of Breath with Activity	0.0942	*0.2997*	*0.3507*	*0.2366*	0.0113	0.0074

Exercise Intolerance	0.1384	*0.3132*	*0.3003*	*0.2461*	0.0021	0.0000
Fatigue at Rest	*0.3888*	*0.2993*	0.1991	0.0975	0.0154	0.0000
Dizziness	*0.3815*	*0.3137*	*0.2191*	0.0554	0.0184	0.0119
Chest Pain	**0.5973**	*0.2348*	0.1376	0.0280	0.0023	0.0000

High probabilities (>0.5) are in bold, moderate probabilities (0.2-0.5) are in italics.

Latent Class Covariates by Cluster Membership

Eleven sociodemographic and clinical variables that are known to influence AF symptoms (e.g. age, gender, comorbidities, AF type, ablation)[11,17,24,29-32] or were theoretically likely to influence AF symptoms (e.g. ejection fraction)[7] were entered into our initial latent class model as covariates. Nine of these covariates were retained in the final model, several of which had statistically significant variation from the reference class (Asymptomatic cluster). Across each cluster, gender and history of ablation were the most consistently associated with cluster membership (Table 4.4). Males made up the majority (77%) of the Asymptomatic cluster, whereas the male/female split was 50/50 in the Highly Symptomatic cluster, and close to equally divided in the With Activity cluster (54.6% male/45.4% female), despite the fact that the overall study population was 67% male and 33% female. The Asymptomatic cluster had the lowest percentage of patients with prior ablation. Individuals in the Highly Symptomatic cluster were less likely than those in the Asymptomatic cluster to have paroxysmal AF (32.4% versus 54.4%), and more likely to have persistent AF (61.3% versus 38%), a higher BMI (mean 33.8 versus 30), heart failure (33.8% versus 9.2%), and coronary disease (35.9% versus 17.3%). Individuals in the With Activity cluster were more likely than those in the Asymptomatic cluster to have a higher BMI (mean BMI 32 versus 30), be on anti-arrhythmic medication (69% versus 51%), and have coronary disease (28.2% versus 17.3%). The Mild Diffuse cluster was the only group that differed significantly by age, with a younger mean age of 56.9 compared to 58.6 for the Asymptomatic cluster.

Table 4.4: Latent Class Regression Model Covariates by Cluster Membership

Covariate	**Asymptomatic Cluster** (N=487)	**Highly Symptomatic Cluster** (N=142)	**With Activity Cluster** (N=326)	**Mild Diffuse Cluster** (N=336)
Gender		#	#	*
Male	377 (77.4%)	71 (50%)	178 (54.6%)	235 (69.9%)
Female	110 (22.6%)	71 (50%)	148 (45.4%)	101 (30.1%)
Age	58.6 (±12.4)	59.8 (±10.5)	59.1 (±12.2)	56.9 (±11.6) *
AF Type		#		*
Paroxysmal	265 (54.4%)	46 (32.4%)	181 (55.5%)	168 (50%)
Persistent	185 (38%)	87 (61.3%)	135 (41.4%)	156 (46.4%)
Permanent	37 (7.6%)	9 (6.3%)	10 (3.1%)	12 (3.6%)
Ejection Fraction	56.1 (±9)	52.8 (±12.1)	56.3 (±9.7)	54.8 (±10)
BMI	30 (±5.7)	33.8 (±7.3) #	32 (±6.9) *	30 (±5.9)
Anti-arrhythmic	251 (51.5%)	91 (64.1%)	225 (69%) *	183 (54.5%)
Heart Failure	45 (9.2%)	48 (33.8%) *	46 (14.1%)	38 (11.3%)
Coronary Disease	84 (17.3%)	51 (35.9%) *	92 (28.2%) #	43 (12.8%)
Ablation	202 (41.5%)	89 (62.7%) #	220 (67.5%) #	202 (60.1%) #

Values are expressed as N (%) or Mean (±SD). Covariates that are significantly different from reference (Asymptomatic Cluster) are marked with an asterisk (*) for $p<0.05$, and with a pound sign (#) for $p<0.001$.

Impact of Symptom Clusters on Healthcare Utilization

Emergency Department Utilization

After the latent class regression analysis was complete we conducted our next regression analysis, which used latent class membership as the independent variable and AF-related ED visits as the dependent variable. We used the Asymptomatic cluster as the reference. Membership in the Highly Symptomatic cluster was associated with nearly two and a half times the rate of AF-related ED visits as the Asymptomatic cluster (incident rate ratio 2.37, $p<0.0001$). The With Activity cluster also had an elevated rate of ED visits, with more than one and a half times the ED visits compared to the Asymptomatic cluster (incident rate ratio 1.7, $p<0.0001$). The Mild Diffuse cluster was not associated with a significantly increased rate of ED visits compared to individuals in the Asymptomatic cluster (Table 4.5).

Table 4.5: Incident Rate Ratios for AF-related ED Visits and Hospitalizations

	Emergency Visits		**Hospitalizations**	
Cluster Membership	IRR	p-value	IRR	p-value
Asymptomatic	Reference	Reference	Reference	Reference
Highly Symptomatic	2.37	<0.0001	2.36	<0.0001
With Activity	1.7	<0.0001	1.67	<0.0001
Mild Diffuse	1.03	0.76	1.22	0.03

IRR: incident rate ratio

Hospitalizations

Next, we conducted a regression with latent class membership as the independent variable and AF-related hospitalizations as the dependent variable. The Asymptomatic cluster was again used as the class of reference. Results are very similar to those for ED visits. Membership in the Highly Symptomatic cluster was associated with nearly two and a half times the rate of AF-related hospitalizations compared to the Asymptomatic cluster (incident rate ratio 2.36, p<0.0001). The With Activity cluster had over one and a half times the rate of hospitalizations as the Asymptomatic cluster (incident rate ratio 1.67, p<0.0001). Mild Diffuse cluster membership also increased the rate of hospitalizations, although to a lesser degree than the other clusters. Mild Diffuse cluster membership resulted in 1.22 times the rate of hospitalizations (p=0.03) compared to the Asymptomatic cluster (Table 4.5).

Discussion

We discovered 4 clusters of patients with unique symptom and covariate profiles, specifically, the: 1) Asymptomatic, 2) Highly Symptomatic, 3) With Activity, and 4) Mild Diffuse symptom clusters. When we examined the 4 clusters for differences in rates of healthcare utilization, the results revealed that individuals in the Highly Symptomatic and With Activity clusters had significantly higher rates of both ED visits and hospitalizations compared to the Asymptomatic cluster. Our results confirm prior research, which shows that generalized symptom severity is a major predictor of hospitalization among adults with AF.[9] Our results expand on this prior knowledge by demonstrating that individuals with specific symptom and covariate profiles are at particular risk for ED visits and hospitalizations.

The individuals most at risk for both ED visits and hospitalizations belong to the Highly Symptomatic cluster. Individuals in this cluster are likely to experience multiple symptoms, in particular shortness of breath with and without activity, exercise intolerance, palpitations, and fatigue at rest. These individuals are more likely to be obese and have persistent AF, heart failure, and coronary disease when compared to individuals in the Asymptomatic cluster. These results are congruent with prior research that identifies heart failure,[32] coronary disease,[30] and obesity[34] as a risk factors for AF symptoms. Heart failure has also previously been shown to increase the risk of hospitalizations among patients with AF.[9] Our results augment current knowledge by providing a comprehensive and specific symptom and clinical profile of patients with an elevated rate of AF-related ED visits and hospitalizations.

The Highly Symptomatic cluster was equally split between males and females despite the fact that the overall study population was 67% males and 33% female. The With Activity cluster similarly had a greater proportion of females than the overall study population. These results are consistent with prior research which shows that women are more likely than men to experience a significant level of symptoms, negatively impacting their quality of life.[35]

The goal of self-care is for patients to adequately monitor, maintain, and manage their health.[36] For individuals in the Highly Symptomatic or With Activity cluster, self-care interventions have the potential to improve AF symptoms and reduce ED visits and hospitalizations. For example, weight reduction, cardio-respiratory fitness, and cardiometabolic risk factor management reduce AF symptom burden, symptom severity, and arrhythmia recurrence[37-39] making weight reduction and physical activity meaningful self-care goals for individuals with symptomatic AF. The standard versus AF specific management strategy (SAFETY) trial[40] compared standard care to nurse managed home and telephone-based follow up for hospitalized patients with AF, which included elements related to self-care such as patient/caregiver education and medication management, and resulted in an increased proportion of days alive and out of the hospital.[40] Another important component of AF-specific self-care is heart rate monitoring, which can help patients identify the presence of AF when symptoms are vague or non-specific.[6]

Individuals with clinical profiles placing them at risk for increased rates of healthcare utilization (i.e. those with heart failure, obesity, and/or coronary disease who are highly symptomatic) are ideal candidates for AF-specific self-care interventions. However, to date there are no studies reported of comprehensive self-care measures or interventions specific to individuals with AF.

Age was not a factor that influenced membership in the Highly Symptomatic or With Activity symptom clusters, although members of the Mild Diffuse cluster were approximately 2 years younger than Asymptomatic cluster members. Consistent with our findings, prior research on AF symptom clusters showed that age may vary for some, but not all, symptom clusters.[17] In that study, AF patients with the cluster of chest pain and palpitations were younger than members of other clusters.

Chest pain and palpitations were uncommon symptoms in this sample, despite prior reports indicating they are common symptoms of AF.[11,17] Chest pain was likely to be reported as absent or infrequent by members of every symptom cluster in our study. Palpitations, a symptom commonly associated with AF, had only a low to moderate probability in every cluster we identified. These findings are important since chest pain and palpitations are classic cardiac symptoms and patients may have difficulty interpreting the less cardiac-specific symptoms in this study (e.g. shortness of breath, fatigue). Lack of accurate symptom interpretation influences the response to symptoms, possibly delaying early intervention and prompt treatment.[5,6] Prompt recognition of symptoms and treatment in a non-urgent outpatient setting has the potential to reduce utilization of the ED and subsequent hospitalizations. Education for people at-risk for AF and with AF should include a focus on the non-specific symptoms that often occur with AF.[6,41]

Using the same data set (VAFR), we previously identified 2 AF-specific symptom clusters (the At Rest and With Activity clusters) using cluster analysis, an approach that clustered symptoms rather than individuals, and resulted in mutually exclusive clusters of symptom variables (Streur, unpublished data). In the present latent class analysis, our approach was to cluster individuals, therefore the same symptom may be present in multiple clusters, but differ based on the probability of each Likert scale rating. The results of these two studies are

complimentary, with both having a With Activity cluster, which is marked by the symptoms shortness of breath with activity and exercise intolerance. Further, the At Rest cluster from the cluster analysis is similar to the Highly Symptomatic cluster from the latent class analysis, with both including individuals who experience shortness of breath at rest, fatigue at rest, chest pain, and dizziness. The Highly Symptomatic cluster is additionally marked by shortness of breath with activity and exercise intolerance, which is congruent with our prior cluster analysis findings, given that 51 out of the 56 individuals with the At Rest cluster also had the With Activity cluster. Similar to our cluster analysis with VAFR (Streur, unpublished data), the clusters identified in the present latent class analysis do not align with the cluster analysis we conducted using SAFETY trial participants.[17,40] Reasons for the discrepancy have been previously discussed (Streur, unpublished data), and include differences in sample recruitment (SAFETY[17,40] recruited only from inpatient setting), inclusion criteria (SAFETY[17,40] excluded patients with heart failure), and the symptom measurement.

Limitations

There are important limitations of our work worth noting. First, our healthcare utilization outcomes variables (AF-related ED visits and hospitalizations) from AFSS are self-reported and were not verified with medical records. However, the AFSS was obtained by a trained study registered nurse either by telephone or in person. Consequently, patients with questions regarding their history of AF-related ED visits and hospitalizations had access to study nurses for clarification regarding how to accurately complete the AFSS. Second, history of ablation was increased for all latent classes (in comparison to the asymptomatic class). Because of limitations related to our cross-sectional study design and our de-identified data set, we do not know the timing of ablations and what proportion of the hospitalizations reported on the AFSS may be for these (typically) planned admissions.

Conclusion

We identified 4 AF-specific symptom clusters using latent class analysis and showed that membership in specific clusters is associated with an increased rate of ED visits and

hospitalizations. Cluster membership is associated with several sociodemographic and clinical factors, most notably gender, AF type, heart failure, coronary disease, and BMI. Additional research is warranted to verify if these symptom clusters can be used clinically to identify patients at an elevated risk for ED visits or hospitalizations, and whether self-care interventions targeted towards these patients could reduce the rate of ED visits and unplanned hospitalizations.

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CHAPTER 5: CONCLUSION

Introduction

Major gaps in the literature exist in relation to the causes, consequences, and perception of AF symptoms.[1] AF symptoms negatively impact several important patient outcomes, including healthcare utilization rates, quality of life, and functional status. Improved symptom management has the potential to positively impact these outcomes. Self-care is an important component of chronic disease management that is under-researched among patients with AF, yet has strong potential to improve AF symptom management and related outcomes.[5] Symptom perception is a primary factor influencing self-care decisions.[6,7] This body of work focused on AF symptom perception and consequences of AF symptoms. The theoretical framework for this work was a modification of the Symptoms Experience Model[8] and the Symptom Interpretation Model.[9] Our definition of symptom perception combined detection and interpretation, with co-occurring symptoms theorized as having a unique effect on the interpretation and consequent response to symptoms.

The overarching goal of these studies was to better understand AF symptom perception by examining detected symptoms, identifying symptom clusters, and exploring the relationship between clusters and healthcare utilization. The specific aims were to: 1) examine symptoms detected by adults with AF and identify symptom clusters, 2) characterize individuals within symptom clusters based on demographic and clinical characteristics, and 3) determine whether symptom cluster membership was associated with healthcare utilization (AF-related hospitalizations and ED visits). The purpose of this final chapter is to summarize the results and discuss the implications of each specific aim, relate the findings to the underlying theoretical model, then provide recommendations for future research and implications for clinical practice.

Discussion of Principle Findings

Identification of Symptom Clusters

The first aim was to examine symptoms detected by adults with AF and identify symptom clusters. This aim was addressed in each of the three manuscripts comprising this work, using two data sets (SAFETY[10,11] and VAFR[12,13]) and two different analytic methods (cluster analysis and latent class analysis). An overview of the principal findings is contained in Table 5.1. In summary, we found 3 symptom clusters using cluster analysis and the SAFETY participants, 2 symptom clusters using cluster analysis and the VAFR participants, and 4 symptom clusters using latent class analysis and the VAFR participants. The clusters found among the SAFETY participants differed significantly from those found in the VAFR participants, a thorough discussion of which follows. When comparing the results from the two analytic techniques used among the VAFR participants, the clusters differ, yet the results are complimentary. The major difference was that cluster analysis resulted in 2 clusters and latent class analysis in 4 clusters, the additional clusters consisting of an asymptomatic group of participants and a mildly symptomatic group of participants.

Table 5.1 Principal Findings of Specific Aim 1

Specific Aim 1: Examine symptoms detected by adults with AF and identify symptom clusters		
Study	**Analytic Technique**	**Principal Findings**
Symptom Clusters in Adults with Chronic Atrial Fibrillation	Cluster analysis (SAFETY[10,11])	3 clusters identified: 1) Vagal (nausea and diaphoresis), 2) Tired (fatigue/lethargy, weakness, syncope/dizziness, and dyspnea/breathlessness), and 3) Heart (chest pain/discomfort and palpitations/fluttering)
Symptom Clusters Increase Rate of Hospitalizations and Emergency Department Visits in Adults with Atrial Fibrillation	Cluster analysis (VAFR[12,13])	2 clusters identified: 1) At Rest (fatigue at rest, shortness of breath at rest, chest pain, and dizziness), and 2) With Activity (shortness of breath with activity and exercise intolerance)
Latent Class Regression Analysis Identifies Symptom Clusters among Adults with Atrial Fibrillation that Increase Hospitalizations and Emergency Department Visits	Latent class analysis (VAFR[12,13])	4 clusters identified: 1) Asymptomatic (unlikely to experience any symptoms), 2) Highly Symptomatic (likely to experience most of the symptoms), 3) With Activity (most likely to experience shortness of breath with activity and exercise intolerance), and 4) Mild Diffuse (experience symptoms but only infrequently)

The symptom clusters identified with SAFETY[10,11] and VAFR[12,13] differ as detailed in Table 5.1. There are several probable explanations for these differential results, including: 1) sample recruitment (SAFETY recruited only from inpatient setting whereas VAFR recruited from both inpatient and outpatient settings), 2) inclusion criteria (SAFETY excluded patients with heart failure whereas VAFR included participants both with and without heart failure), 3) demo-graphic characteristics (SAFETY patients were 14 years older on average, were evenly split between males and females, and primarily had persistent AF (88%), whereas VAFR patients were younger, primarily (67%) male, and only 43% had persistent AF), and 4) symptom measurement (SAFETY used a study-specific tool whereas VAFR used the psychometrically validated AFSS). Individuals admitted to the hospital for AF likely differ in symptoms and other aspects of their clinical profile compared to individuals being seen for AF in an outpatient environment, making this an important distinction between the two samples.[3] Similarly, comorbid heart failure is known to influence AF symptoms,[14] therefore this difference in participant profiles could have impacted the symptom clusters identified. The most important factor in the different cluster results was likely the approach to symptom measurement. First, the symptoms measured in each study were different, making it improbable that the clusters identified in each study would be identical. Even symptoms that were included in both studies were worded differently (e.g. fatigue/lethargy versus fatigue at rest, syncope/dizziness versus dizziness), which could influence whether a participant identifies as having that particular symptom. Additionally, participants in VAFR were instructed to report symptoms that occurred during the past 4 weeks, whereas SAFTEY participants were asked what symptoms they previously or currently experienced with AF, with no time-limitation applied. An additional distinction between the two measures was that SAFETY participants recorded yes/no responses, whereas VAFR participants could rank the frequency of symptoms on a 6-point Likert scale. Finally, SAFETY participants could list “other” symptoms as free-text, whereas VAFR participants had no “other” option and could only report the frequency of the symptoms listed. The vagal cluster from the SAFETY cluster analysis was composed entirely of symptoms reported as “other”. Combined, these differences in the symptom measures likely account for the differences between the clusters identified using each respective data set.

Results from the two studies that used VAFR data differ but are complimentary. Participants with the At Rest cluster (cluster analysis) experienced fatigue at rest, shortness of breath at rest, chest pain, and dizziness. Of the 56 participants with the At Rest cluster, 51 also had the With Activity cluster (shortness of breath with activity and exercise intolerance). Similarly, participants in the Highly Symptomatic cluster (latent class analysis) were likely to experience shortness of breath at rest, fatigue at rest, shortness of breath with activity, and exercise intolerance, while also having the probability of experiencing chest pain and dizziness although to a lesser degree.

There are no published studies of AF symptom clusters with which to compare this body of work. However, the clusters identified were unique compared to clusters reported in other cardiovascular patient populations.[15] For instance, Riegel[16] found three clusters, plus a chest pain only group, among patients with acute coronary syndrome. The clusters included a Pain cluster (arm, back, shoulder, neck, throat, and jaw pain), a Stress cluster (shortness of breath, sweating, nausea, indigestion, dread, and anxiety, and a Diffuse cluster (characterized by multiple low frequency symptoms).[16] We similarly found a Mild Diffuse cluster (characterized by multiple low frequency symptoms) using latent class analysis, although the symptoms reported were different, making these clusters unique from one another. Other studies of individuals with acute coronary syndrome[17] and acute myocardial infarction[18] had similar but different results from the study by Riegel,[16] indicating that precise replication of results has been an issue in other cardiac populations as well. Two studies with heart failure patients identified nearly identical clusters,[19,20] which were labeled as a Physical cluster (dyspnea, difficulty walking/climbing, fatigue, and sleep problems) and an Emotional/Cognitive cluster (worry, depressed feelings, and cognitive problems), neither cluster clearly resembling any of the clusters we identified among patients with AF. However, these studies are not truly comparable with our results since neither of the symptom measures we used included any sleep, cognitive, or emotional symptoms, which are key components of the heart failure symptom clusters.

The use of different symptom measures was the primary weakness of these studies in collectively addressing Aim 1. Unfortunately, the lack of comparability between studies is a problem in AF symptom research in general, as there is no accepted standard for patient-reported measurement of symptoms.[1] Furthermore, the most commonly used patient-reported symptom measures have sparse information published in regards to their development and psychometric validation.[1,21-25] Several AF symptom scales have recently been developed that address this concern, but it is yet to be determined if these newer scales will be widely adopted for use.[26,27] Additionally, many symptom scales are parsimonious, retaining only those symptoms that are the most common,[27] or that have the most impact on quality of life.[26] However, the objectives of symptom cluster research are such that it is better to comprehensively measure symptoms rather than using a parsimonious scale.[28] For instance, if the goal is to determine 1) the underlying mechanism of the cluster, or 2) the patient profile most at risk for an outcome, a scale that is too parsimonious could result in the loss of valuable information, as we saw with the SAFETY trial data.

The primary strength of the Aim 1 results is that they address the gap in the AF literature related to symptom clusters. The National Institute of Nursing Research considers symptom cluster research an innovative and priority topic for symptom science.[29] Numerous theoretical conceptualizations of the symptom perception process exist, some of which discuss the impact of symptom clusters on the perception process.[8,9,30-33] We defined symptom perception as a complex process that involves the detection and interpretation of symptoms, with clusters of symptoms having a unique impact on the interpretation of symptom meaning. The fact that we were unable to replicate the symptoms clusters is an indication that additional work is needed to understand AF-specific symptom clusters. Failure to precisely replicate clusters has occurred in numerous other disease processes, and reflects the need for improved and consistent methods for determining symptom cluster occurrence and composition.[34] Accordingly, these studies can be used for guidance in the design of future research related to AF symptoms and symptom clusters.

Clinical and Demographic Characterization of Individuals within Symptom Clusters

The second aim was to characterize individuals within symptom clusters based on demographic and clinical characteristics. This aim was achieved in each of the manuscripts within this body of work. For both approaches using cluster analysis, comparisons were made between individuals with none, some, and all symptoms in each cluster. For the latent class analysis, we included demographic and clinical covariates in the latent class regression model, which means that the covariates help predict class membership.[35] An overview of the principal findings for Aim 2 is available in Table 5.2.

Across the studies, certain characteristics consistently varied based on cluster membership, specifically gender, age, AF type, and rhythm management therapies (anti-arrhythmic medication and history of ablation). Other characteristics varied by cluster membership in some but not all of the studies, specifically BMI, coronary disease, and heart failure. The first analysis conducted was the cluster analysis using SAFETY[10,11] participants, and BMI was not included as a covariate. We recognized this as a weakness while planning the studies that used VAFR[12,13] participants, therefore BMI was included as a covariate in the subsequent studies. BMI did prove to be an important characteristic, with elevated BMI being associated with the majority of symptom clusters in both subsequent studies. Although coronary disease did not show statistically significant variation in the SAFETY cluster analysis, it did in both VAFR studies. Individuals with heart failure were not included in SAFETY, however, heart failure proved to be an important covariate in predicting membership in the Highly Symptomatic cluster in the VAFR latent class analysis.

Table 5.2 Principal Findings of Specific Aim 2

Specific Aim 2: Characterize individuals within symptom clusters based on demographic and clinical characteristics	
Study	**Principal Findings**
Symptom Clusters in Adults with Chronic Atrial Fibrillation	Heart cluster membership was associated with younger age, female gender, anti-arrhythmic medication use, and paroxysmal and persistent AF type.
Symptom Clusters Increase Rate of Hospitalizations and Emergency Department Visits in Adults with Atrial Fibrillation	Female gender, anti-arrhythmic medication use, history of ablation, elevated BMI, coronary disease, and heart failure were associated with both the At Rest and With Activity clusters. Older age, AF type (persistent and permanent), and slightly lower ejection fraction were associated with the With Activity (but not At Rest) cluster. Non-Caucasian ethnicity was associated with the At Rest cluster.
Latent Class Regression Analysis Identifies Symptom Clusters among Adults with Atrial Fibrillation that Increase Hospitalizations and Emergency Department Visits	Gender and history of ablation were consistently associated with cluster membership (female gender increased the likelihood of being symptomatic). Members of the Highly Symptomatic cluster were more likely to have persistent AF, higher BMI, heart failure, and coronary disease compared to Asymptomatic cluster members. Members of the With Activity cluster were more likely to have higher BMI, be on anti-arrhythmic medication, and have coronary disease compared to Asymptomatic cluster members. Members of the Mild Diffuse cluster were more likely to have persistent AF and be younger compared to Asymptomatic cluster members.

The variables associated with cluster membership in this work are consistent with prior research related to AF symptoms. Female gender has consistently been shown to be associated with increased symptom severity and frequency.[36-39] Our results provide additional support for the association between female gender and symptom frequency and severity. Several factors could be involved in the gender-based differences in symptom perception. Females may be more willing than males to report symptoms, may evaluate the symptoms differently in terms of severity, and may experience or interpret the symptoms differently based on physiological differences between males and females (i.e. hormone differences). Additionally, heart failure,[40] coronary disease,[41] and obesity[42-45] have previously been demonstrated as factors influencing AF symptom burden, symptom severity, and arrhythmia recurrence. The hemodynamic changes that accompany heart failure and coronary disease help to explain the importance of these comorbidities on AF symptom presence and severity.[1] For example, reduced cardiac output or impaired myocardial perfusion would increase a patient's chance of experiencing reduced exercise capacity, shortness of breath, or fatigue. However, AF patients without these

comorbidities also experience these symptoms, so it is important to recognize the symptoms may be present even in the absence of overt structural heart disease.[46] The relationship between elevated BMI and the presence of symptom clusters could be due to obesity-related reductions in exercise capacity or physical activity, or to other confounding factors such as depression.[42,44] The With Activity cluster was associated with older age, whereas other clusters were associated with younger age (Heart cluster and Mild Diffuse cluster), which helps to explain the previous lack of consistent findings in relation to age-related differences in AF symptoms.[41,47] Differences in cognition, interoceptive ability, and emotional response to symptoms are a likely cause for age related differences in symptom cluster experience.[48-50] Collectively, these results strengthen the evidence base regarding which patients are most at risk for specific symptom profiles.

Determining Associations Between Symptom Clusters and Healthcare Utilization

The third aim of this body of work was to determine whether symptom cluster membership was associated with healthcare utilization (AF-related hospitalizations and ED visits). This aim was accomplished using the VAFR[12,13] dataset, and was assessed with two different analytic approaches: cluster analysis and latent class analysis. An overview of the principal findings is contained in Table 5.3. In summary, we found that certain symptom clusters were associated with an increased rate of AF-related hospitalizations and ED visits, either when compared to all individuals without that specific cluster (cluster analysis), or when compared to an Asymptomatic cluster of patients (latent class analysis).

The rate of AF-related ED visits and hospitalizations was greatest among those individuals in the most symptomatic clusters (At Rest and Highly Symptomatic), while the With Activity cluster identified with latent class analysis also demonstrated a statistically significant increase in healthcare utilization, although to a lesser degree. These results confirm the hypothesis that distinct AF-specific symptom clusters could be identified that were associated with AF-related hospitalizations and ED visits.

Table 5.3 Principal Findings of Specific Aim 3

Specific Aim 3: Determine whether symptom cluster membership was associated with healthcare utilization (AF-related hospitalizations and ED visits)		
Study	**Analytic Technique**	**Principal Findings**
Symptom Clusters Increase Rate of Hospitalizations and Emergency Department Visits in Adults with Atrial Fibrillation	Cluster analysis (VAFR[12,13])	Patients with all symptoms of the At Rest cluster had 2.8 times the rate of AF-related ED visits and 1.9 times the rate of AF-related hospitalizations compared to those with none of the symptoms.
Latent Class Regression Analysis Identifies Symptom Clusters among Adults with Atrial Fibrillation that Increase Hospitalizations and Emergency Department Visits	Latent class analysis (VAFR[12,13])	Compared to patients in the Asymptomatic cluster, those in the Highly Symptomatic cluster had 2.4 times the rate of AF-related ED visits and hospitalizations, while those in the With Activity cluster had 1.7 times the rate of ED visits and hospitalizations.

Two prior studies from a large-scale observational AF registry reveal that more severe European Heart Rhythm Association (EHRA) symptom classification is associated with increased rates of hospitalization among patients with AF.[3,51] The EHRA score is a physician-assessed AF symptom severity scale which rates symptoms as none (1), mild (2), severe (3), or disabling (4).[52] Freeman[51] and colleagues found that patients with EHRA scores of greater than or equal to 2 had a greater risk of hospitalization (hazard ratio 1.23). Steinberg[3] and colleagues found that severe symptoms (EHRA score = 3) were predictive of all-cause hospitalizations (hazard ratio 1.37). The same authors found that significant comorbid heart failure (rated as New York Heart Association class II-IV) was the greatest predictor of all-cause hospitalization (hazard ratio 1.57).[3] Our results confirm these prior studies in that the clusters with the most severe symptom profiles were associated with increased rates of hospitalization. Further, heart failure was a predictive covariate for membership in our Highly Symptomatic cluster. Unlike prior studies, our results identify specific clusters of symptoms that could be used to identify patients at higher risk for ED visits and hospitalizations.

Haworth[33] proposed that effectively meeting a patient's needs and negotiating a symptom management plan requires that healthcare providers understand the meaning patients associate with symptoms. A theoretical assumption underlying our hypothesis that AF-specific symptom

clusters could be identified that were associated with healthcare utilization was that symptom clusters would have a unique impact on symptom meaning compared to the meaning associated with individual symptoms. The findings presented here support this assumption, suggesting through the impact of symptom clusters on healthcare utilization that symptom clusters likely influence the interpretation of symptom meaning. Additional research is warranted to further test and confirm the influence of symptom clusters on self-care and symptom management decisions.

Summary

This body of work represents a significant, theoretically based contribution to the AF symptom literature, providing evidence that: 1) AF-specific symptom clusters exist, 2) gender, age, BMI, heart failure, coronary disease, AF-type, and rhythm control treatment strategies are associated with membership in specific clusters, 3) specific symptom clusters and patient profiles are associated with AF-related ED visits and hospitalizations. These studies used existing data sets to answer new and meaningful questions related to AF symptom perception. The theoretical model used to guide these studies posited that: 1) symptom perception is the combination of detection and interpretation, 2) demographic and clinical variables influence symptom perception, 3) co-occurring groups of symptoms (symptom clusters) uniquely influence symptom meaning/interpretation, and 4) healthcare utilization is a consequence of differences in symptom perception.

The results are congruent with the theoretical model, indicating that evaluation of patients' symptom detection, demographic, and clinical profile can provide valuable information regarding their risk of visiting an ED or being hospitalized for AF. For example, the symptoms shortness of breath at rest and fatigue at rest were features of both the At Rest and Highly Symptomatic clusters, the two clusters we identified that were associated with the greatest increase in rate of ED visits and hospitalizations. Consistent with prior research,[3,43] our results indicate that heart failure and elevated BMI are clinical factors that may be particularly useful as indicators of risk for more severe symptoms and increased rate of ED visits and hospitalizations. Clinically, symptom cluster profiling augments prior knowledge and could be combined with other

measures (i.e. EHRA[52]) to identify patients most at risk for AF-related ED visits and hospitalizations.

One limitation of this work is the cross-sectional study design. Additionally, the theoretical model used for this work did not depict changes in symptoms over time. Incorporating the temporal dimensions of symptoms into symptom theories and research is an ongoing challenge.[30,31,53] Examining temporal aspects of symptoms may be important for determining underlying physiological or psychological mechanisms, predicting responses, designing interventions, and improving outcomes. In the present studies, the nature of our data sets meant that we could not examine if or how certain time-specific variables (i.e. ablation) changed symptom cluster trajectories. Brant[30] suggests latent growth curve models that include multiple symptoms as well as time-invariant antecedents and outcomes as one potential approach for examining changes in symptoms over time.[30] Understanding how symptoms change over time and relate to each other temporally could improve our ability to design interventions tailored to a patient's specific symptom trajectory and clinical profile.[30] Future prospectively designed symptom and symptom cluster studies, both observational and interventional, should use theoretical models that incorporate temporal dimension and should aim to include temporal dimensions in the study design when appropriate.

Implications for Future Research

Additional studies are warranted to validate the symptom clusters identified in this body of work. It would be preferable to use a widely accepted symptom measure in order to improve comparability (e.g. AFSS[25,54] or Symptom Checklist[21-23]). However, it may also be warranted to use a comprehensive rather than parsimonious symptom measure for future studies. Using a more comprehensive measure of symptoms may help clarify which clusters are reproducible in other AF samples, and would ensure valuable information on less common symptoms is gathered (e.g. nausea and diaphoresis, which comprised the Vagal cluster). It is warranted to use a symptom measure that includes sleep, cognitive, and emotional symptoms, as these types of symptoms do occur in AF patients.[22,27] In patients with heart failure, a cognitive/emotional

symptom cluster increased the risk for shorter event-free survival more than the physical symptom cluster, indicating the potential importance of these symptoms in the AF population as well.[19]

This work focused on AF symptom clusters, but there has been limited research to date describing the AF symptom experience in general,[55-57] or the experience and influence of individual AF symptoms. For example, studies have documented the poor correlation between symptoms and actual arrhythmia occurrence,[47,58,59] and it would be beneficial to know if certain symptoms are more likely than others to correlate with arrhythmia. Research on individual AF symptoms is still warranted and should not be neglected.

A limitation of quantitative symptom cluster research in general is related to the use and timing of symptom scales. A defining characteristic of symptom clusters is that they are groups of co-occurring symptoms.[28,60] For quantitative symptom cluster research, using a scale with a time-limitation on when the symptoms occurred (i.e. the last 4 weeks) should increase the chance that the clusters identified are characterized by co-occurring symptoms. However, even symptoms that occurred in the past 4 weeks may not occur concomitantly. An alternative approach would be the use of innovative qualitative, mixed-method, or technology-based approaches to symptom cluster identification.[61-65] For example, MacPherson[64] and colleagues developed a computerized symptom capture tool (C-SCAT), which is an iPad application that was originally designed to assess 30 common cancer symptoms using a combination of graphical images and free text responses to capture the symptom experience. This innovative C-SCAT technology has subsequently been used to heuristically examine symptom clusters in adolescents and young adults with cancer and mid-life women experiencing menopause.[62,65]

Quantitative research is generally considered the standard for symptom cluster research.[34,66,67] Three quantitative approaches have typically been identified as the ideal methods for symptom cluster research: cluster analysis, factor analysis, and latent class analysis.[15,34,66] Despite the general consensus that each method is appropriate for identifying clusters, questions remain regarding the *best* approach for statistical determination of symptom clusters. For

instance, Chen[68] compared hierarchical cluster analysis, principal component analysis, and exploratory factor analysis and found that each technique produced different, albeit similar, results. This is consistent with the findings of the present dissertation, where cluster analysis and latent class analysis produced different although complimentary results. Chen[68] concluded that a key factor in attaining replication of symptom clusters would be for the research community to consistently utilize a common analytical method, and suggested using the approach that results in the most clinically meaningful results. Henoch's[69] approach to the problem with consistency was to use multiple questionnaires and multiple analytic techniques, then to report the findings that were consistently found across different instruments and analytic techniques. A similar approach was used in the present study with the SAFETY data, by comparing the hierarchical cluster analysis results with exploratory factor analysis in order to validate our findings.[70] Alternatively, although quantitative methods are generally considered superior in the symptom cluster literature, qualitative and mixed-methods research would be an ideal methodological approach for determining which statistical technique provides the most clinically meaningful results. Qualitative research could be used to independently explore symptom clusters, while mixed-methods would be useful for triangulating qualitative and quantitative data in order to confirm symptom clusters determined with statistical methods. Further, mixed-methods could be beneficial in determining which statistical methods produce clusters that patients themselves recognize and consider clinically meaningful.

We have already discussed two ways in which qualitative research could be beneficial to advance symptom cluster research. A third benefit of qualitative research is the avoidance of interoceptive bias, or misrepresentation. Interoception refers to an individual's ability to perceive internal bodily sensations.[50,71] Once an individual believes a bodily sensation is abnormal, it is considered a symptom.[72] Interoceptive accuracy varies significantly between individuals and is influenced by cognitive and emotional factors that are not yet fully understood.[50] When bodily sensations are categorized as symptoms (as is done with quantitative symptom measures), the mere process of categorization may result in interoceptive bias, making the patient more likely to interpret something as a symptom.[73] While quantitative methodologies certainly are appropriate, it

is important to recognize the weaknesses of quantitative methods in relation to symptom cluster research, and to augment quantitative methods and advance symptom science through the use of qualitative and mixed-methods approaches.

Hospitalizations and ED visits for AF are on the rise,[74] costly,[74] and negatively impact quality of life.[75,76] The findings from these studies will be useful for designing interventions aimed at safely reducing healthcare utilization among individuals with AF. Appropriate interventions include those aimed at improving self-care. Symptom perception is a vital component of self-care due to its influence on decisions to seek care.[7] Knowledge deficits regarding appropriate self-care for AF have been documented[77-81] and addressed[10,82,83] in a limited number of studies to date. While knowledge is an important contributor to self-care, knowledge alone is insufficient to ensure an appropriate response to symptoms, and as such self-care interventions should aim to also improve skills, confidence, compatibility with patient values, and accurate symptom interpretation.[7] Nurse-led AF programs in Australia and the Netherlands that included self-care elements and were designed to engage patients and improve knowledge have been successful at reducing hospitalizations and prolonging survival.[10,83] The body of work reported here improves our ability to build on and replicate these studies with interventions targeted to those patients who are at the most risk.

Implications for Clinical Practice

Patients with AF are often symptomatic and symptoms are typically treated with a medical and/or procedural rate and/or rhythm control strategy. These studies revealed one modifiable clinical characteristic, BMI, which is associated with more severe symptom clusters. In line with other recent research,[43-45] this finding supports that weight reduction and exercise could be appropriate strategies to employ clinically as an approach to AF symptom management.

Most importantly, this work identifies specific clusters of patients most at risk for ED visits and hospitalizations based on symptoms, demographic, and clinical variables. These results should be used clinically as an additional form of risk stratification. While education is generally provided for all patients, it is often rushed, or assumed to have been covered at previous

appointments. These higher risk patients should be provided adequate time for education (and re-education) at follow up appointments. Topics covered should include concerning signs or symptoms to report, the importance of medication adherence and reasons for each medication, signs and symptoms to monitor in relation to comorbid heart failure, and the warnings signs of stroke. Additionally, these patients may benefit from telephone based follow up with a nurse or nurse practitioner, at least until their heart rate and other treatment parameters are stabilized.

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