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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 is 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 (52%) than female participants, with a mean (SD) 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 among 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 antiarrhythmic medications for the heart cluster. Women were more likely to have the heart symptom cluster than men were. Individuals with all of the symptoms in the heart cluster were younger (69.6 vs 73.7 years; $P = .029$) than those with none of the symptoms in the heart cluster and were more likely to be on antiarrhythmic medications.

CONCLUSION: Three unique atrial fibrillation symptom clusters were identified in this study population.

Keywords

Adult, Aged, Aged, 80 and over, Atrial Fibrillation, Australia, Chronic Disease, Cluster Analysis, Cross-Sectional Studies, Female, Humans, Male, Middle Aged, Socioeconomic Factors, Symptom Assessment

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Symptom Clusters in Adults with Chronic Atrial Fibrillation

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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

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Conflicts of Interest
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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 preexisting 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 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.

Symptom Clusters

The dendrogram, pseudo-F and pseudo-T indicated that a three cluster solution was the optimal solution (Figure 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). Over half with the tired cluster (n=24) also experienced the heart cluster (Table 3).

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 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.

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 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]

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.[37] 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.[38,39] It is possible that BMI may also influence heart cluster membership via altered cardiac interoception,[40] or as the result of perceived differences in symptom burden and severity.[41]

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.[42,43]

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.[44-46] 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.[47] 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),[48,49] 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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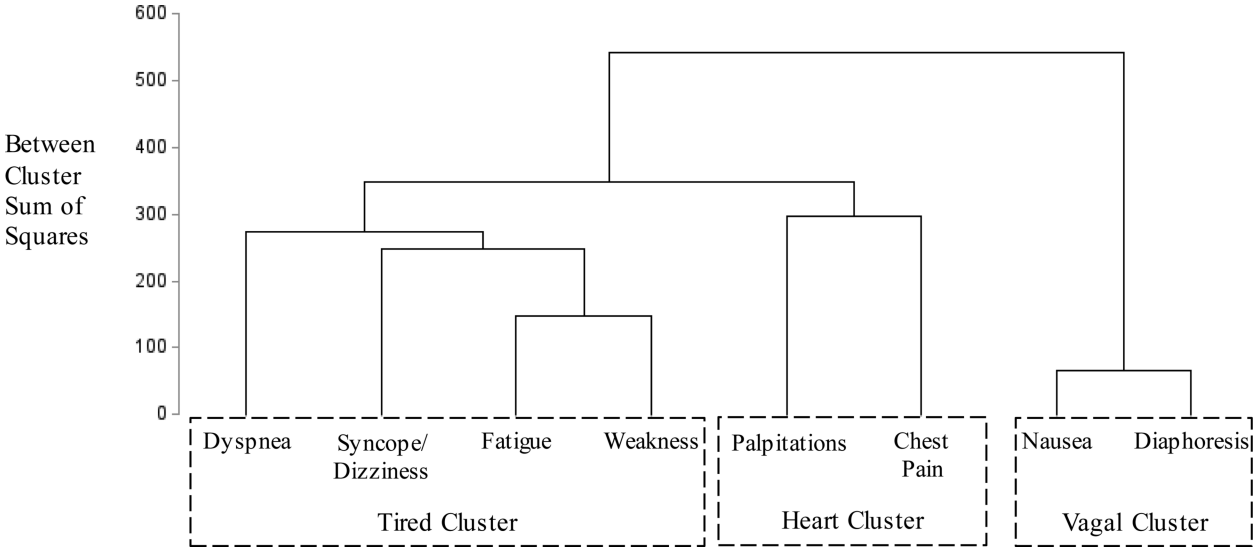

Figure 1.

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

Table 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 $p<0.001$

Table 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 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%)

Table 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 (%).

Table 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)	