

The Interplay Between Atrial Fibrillation and Heart Failure on long-term Mortality and Length of Stay: Insights from the United Kingdom ACALM Registry

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Abstract

Background: There is concern that the development of heart failure and atrial fibrillation has a detrimental influence on clinical outcomes. The aim of this study was to assess all-cause mortality and length of hospital stay in patients with chronic and new-onset concomitant AF and HF.

Methods: Using the ACALM registry, we analysed adults hospitalised between 2000 - 2013 with AF and HF and assessed prevalence, mortality and length of hospital stay. Patients with HF and/or AF at baseline (study-entry) were compared with patients who developed new-onset disease during follow-up.

Results: Of 929,552 patients, 31,695 (3.4%) were in AF without HF, 20,768 (2.2%) had HF in sinus rhythm, and 10,992 (1.2%) had HF in AF. Patients with HF in AF had the greatest all-cause mortality (70.8%), followed by HF in sinus rhythm (64.1%) and AF alone (45.1%, $p < 0.0001$). Patients that developed new-onset AF, HF or both had significantly worse mortality (58.5%, 70.7% and 74.8% respectively) compared to those already with the condition at baseline (48.5%, 63.7% and 67.2% respectively, $p < 0.0001$). Patients with HF in AF had the longest length of hospital stay (9.41 days, 95% CI 8.90-9.92), followed by HF in sinus rhythm (7.67, 95% CI 7.34-8.00) and AF alone (6.05, 95% CI 5.78-6.31).

Conclusions: Patients with HF in AF are at a greater risk of mortality and longer hospital stay compared to patients without the combination. New-onset AF or HF is associated with significantly worse prognosis than long-standing disease.

Introduction

Heart failure (HF) and atrial fibrillation (AF) are two common and important cardiovascular disease entities of the 21st century. Despite considerable advances in management for both conditions, there remains debate regarding widely used therapies, including rate versus rhythm control [1], beta-blockers [2] and cardiac glycosides [3] with recent meta-analyses demonstrating limited prognostic impact. In the United Kingdom (UK), HF affects 900,000 patients and has an estimated 10-year mortality of 42.8% [4], with an associated economic burden on the National Health Service (NHS), contributing to 2% of all NHS in-patient bed days and 5% of hospital admissions [5, 6]. Aside from the financial impact, the length of stay (LoS) also has important implications on clinical outcomes and is associated with increased readmission and greater mortality [7]. Additionally, AF is the most common cardiac arrhythmia, with increasing prevalence [8, 9]. If left untreated, AF is a significant risk factor for systemic thromboembolism and cardiomyopathy, placing patients at risk of death [10].

The presence of AF or HF increases the likelihood of the other, with HF being the strongest risk factor for the development of AF. Similarly, AF precipitates and exacerbates LV dysfunction, giving rise to AF-induced cardiomyopathy [11]. In the Framingham Heart Study (1980-2012), among 1737 individuals with new AF, 37% had HF, and among 1166 individuals with new HF, 57% had AF [12]. Prevalence rates of AF in patients with HF and vice versa is dependent upon the disease severity, for example, AF prevalence increased from 4 to 40% as New York Heart Association (NYHA) functional class increased from I to IV [13]. The mechanisms behind these associations is likely mediated by multiple factors: abrupt changes in heart rate and an irregular rhythm may compromise cardiac output; persistent tachycardia may precipitate tachycardia-mediated cardiomyopathy; loss of atrial

systole impairs optimal ventricular filling; left atrial stretch; and activation of neurohumoral factors hastens maladaptive responses.

With regard to survival, most observational analyses that have assessed the impact of concomitant AF and HF were performed over a decade ago, which raised concern that the combination is an independent predictor of mortality [14-19]. Accordingly, the aim of this study was to provide an up to date analysis of prevalence, mortality and length of stay in patients with HF and/or AF in a large robust database of patients admitted to hospitals in England. Additionally, we investigate the clinical consequence of developing new onset AF or HF during long-term follow-up.

Methods

Study population

We examined the prevalence and impact of concomitant AF and HF on all-cause mortality and LoS using an entirely anonymous database of adult patients compiled using the ACALM Algorithm of Comorbidities, Associations, Length of stay and Mortality (ACALM) study protocol, which has been previously used and described by our group [20-23]. The ACALM study protocol used International Classification of Diseases and Related Health Problems, revision 10 (ICD-10) and Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4 (OPCS-4) codes to identify patients from completely anonymous electronic hospital records. Mortality status at the end of the study period was determined by record linkage to the National Health Tracing Services (NHS strategic tracing service) which utilises data from the Office for National Statistics (ONS).

The study population consisted of all 929,552 adult patients admitted to seven hospitals in North of England, UK, between 1st January 2000 and 31st March 2013. Patients under the age of 18 were excluded. Follow-up of individual patients began at their first hospitalisation during this study period. This start date was selected because it is when ICD-10 coding started being used widely in the hospitals included in the study. HF and/or AF was diagnosed according to NICE guidelines [6, 24], and given an ICD-10 code for HF or AF. Data on LoS, age, gender, ethnicity, mortality and co-morbidities were available from the local health authority computerised hospital activity analysis register for all patients. The ACALM study protocol was subsequently applied to transfer this raw data into a useful search database. Prevalence rates for comorbidities presented refer to coding at any point during the study timeframe (at baseline or follow-up). We do not have access to any laboratory results or drug

information. The final diagnoses, comorbidities and procedural codes at discharge were entered for each patient in the hospital electronic diagnosis database that eliminates the possibility of duplicating patients.

Data analyses

Using this dataset both cross-sectional and longitudinal analyses were performed for patients admitted with a diagnosis of HF and/or AF. In the cross-sectional analysis, disease groups (AF without HF [AF alone]; HF in SR; HF in AF) were compared to the control group composed of the remainder of the study population without a HF or AF diagnosis. Kaplan-Meier curves were used to illustrate the effect of the disease on survival and the time variable was the period from first admission to death with time zero defined as the date the patient was admitted to hospital for the first time within the study period. To determine the influence of developing new-onset AF \pm HF on mortality we performed a longitudinal analysis. Patients were categorised into baseline (if the disease was present at study-entry) and developed groups (if new-onset disease was identified during follow-up) for all patients with AF, HF and the combination.

Unadjusted crude mortality rates were expressed as a percentage and unadjusted odds ratio (calculated according to Altman [25]). Adjusted mortality rates were utilised in the cross-sectional analysis and were performed by multivariate logistic analysis accounting for variations in gender, ethnic group and other cardiovascular comorbidities (ischaemic heart disease, cerebrovascular disease, hypertension, chronic kidney disease, hyperlipidaemia, type 1 diabetes mellitus, type 2 diabetes mellitus, peripheral vascular disease, prior angioplasty, prior coronary artery bypass graft, prior myocardial infarction). The multivariate logistic

regression was modelled and performed in SPSS version 21.0 (SPSS Inc. Chicago, IL). P values <0.05 were taken as statistically significant.

LoS was defined as the number of inpatient days during the index hospitalisation. For patients with several hospitalisations, only the LoS data for their first hospitalisation was included in the study. LoS was calculated from the admission and discharge dates and included both of these days. LoS was treated as a continuous variable and since it was normally distributed a Student's t test was applied comparing the mean LoS in each of the three experimental groups (AF alone; HF in SR; HF in AF) in turn compared to the control group. A Levene's test for equality of variances was applied prior to the t-test. P values were calculated two-tailed and $p < 0.05$ was taken as significant.

Research governance

The data used in this study was completely anonymous, non-identifiable and non-traceable conforming to local research ethics policies. Appropriate ethics and research and development approvals were sought and obtained. Access to the ACALM database was limited to members of the ACALM study unit (PC, HU, SC, RP). Confidentiality of information was maintained in accordance with the UK Data Protection Act.

Results

Baseline demographics are shown in Table 1. In general, patients with HF in AF were older (76.9 vs 71.9 years) and had more comorbidities [hypertension, peripheral vascular disease (PVD), chronic kidney disease (CKD) and ischaemic heart disease (IHD)] compared to HF in SR and AF alone. Male gender accounted for around half of the study population and the majority were of Caucasian origin. Out of 929,552 patients admitted during the study period, at baseline or follow-up 31,760 patients had HF (3.42%) and 42,687 had AF (4.59%). Of the HF group, 20,768 were in sinus rhythm (SR, 65.4%) and 10,992 were in AF (34.6%). Of the AF group, 31,695 (74.2%) had AF without HF (AF alone).

All-cause mortality

Follow-up was 100% complete, and all 929,552 patients could be analysed. During a follow-up period of 13.25 years 137,054 (14.7%) of patients died in the whole database. 45.1% of AF patients and 66.5% of HF patients died. Compared to the control group, mortality was greater in patients with AF alone (OR 6.16, 95% CI 6.02-6.31); HF in SR (OR 13.4, 95% CI 13.0-13.8); and HF in AF (OR 18.2, 95% CI 17.5-19.0; Table 2; Figure 1). HF patients in AF had a higher crude mortality compared to those in SR (70.8% vs 64.1%; $p < 0.0001$).

In the multivariate model, although attenuated, the same pattern persisted with adjusted OR for mortality being 3.73 for AF alone (95% CI 3.62-3.84); 6.51 for HF in SR (95% CI 6.27-6.76); and 8.76 for HF in AF (95% CI 8.31-9.23) in comparison to the control group. Other comorbidities that remained significantly associated with increased mortality included hypertension, CKD, IHD, diabetes, PVD, stroke and MI. In contrast, the baseline presence of hyperlipidaemia, prior PCI or CABG was associated with an advantageous prognosis.

Longitudinal analysis

Of 42,687 patients with AF at any point during the study, 29,164 (68.3%) had AF at baseline (study-entry) and 13,523 (31.7%) developed new-onset AF during follow-up. The incidence of ischaemic and haemorrhagic stroke in this population has previously been reported. {Sangha, 2015 #47} Mortality was significantly greater with developed AF than baseline AF (58.5% vs 48.5%, $p<0.0001$). Of 31,760 patients with HF, 19,474 (61.3%) had HF at baseline and 12,286 (38.7%) developed new-onset HF during follow-up. Mortality was significantly greater with developed HF than baseline HF (70.7% vs 63.7%, $p<0.0001$). Of 10,992 patients with HF in AF, 5,728 (52.1%) had the combination at baseline and 5,264 (47.9%) developed HF in AF during follow-up. Mortality was significantly greater in the developed group than the baseline group (74.8% vs 67.2%, $p<0.0001$; Supplemental Table 1; Figure 2).

Length of stay

A similar pattern to the influence of AF and HF on mortality was identified with length of hospital stay. Mean LoS was significantly longer in patients with AF alone (mean 9.4 days); HF in SR (mean 11.0 days); and HF in AF (mean 12.8 days) compared with controls (3.2 days, $p<0.0001$). The mean difference in hospital stay compared to controls was 6.05 days for AF alone (95% 6.02-6.31, $p<0.0001$); 7.67 days for HF in SR (95% CI 7.34-8.00, $p<0.0001$); and 9.41 days for HF in AF (95% CI 8.90-9.92, $p<0.0001$, Table 2).

Discussion

In a comprehensive long-term registry of almost 1,000,000 patients, we found patients with HF in AF are at greater risk for all-cause mortality and longer LoS compared to patients with either condition alone. Moreover, we were able to show that patients who develop new-onset AF and/or HF exhibit a higher risk of all-cause mortality compared to chronic disease. Based on our analysis, adjustment for differences in baseline characteristics did attenuate the association with mortality however the HF patients in AF remained at greater risk of adverse clinical outcomes. This highlights the need to explore evidence-based therapeutics in order to aid in optimal decision making strategies to enhance clinical outcome.

The heavy burden of HF and AF as disease entities often co-exist, yet the clinical and prognostic impact is largely unknown [14-19, 26]. The present study supports the notion that the concomitant development of this combination impacts prognosis, compared to patients with either condition alone. The presence of combined AF and HF remained an independent predictor of mortality following adjustment for comorbidities. After exploring chronic from new-onset AF or HF, it became apparent that the development of AF or HF was associated with significantly worse survival. The specific cause of this excess mortality with new-onset disease may be partly explained by an increase in HF progression and a 3-fold increase in sudden cardiac death [27]. We have highlighted the vulnerability of this cohort by demonstrating a similar pattern regarding length of hospital stay. The increase in LoS seen with concomitant HF and AF may be explained by a marked increase in clinical HF progression that accompanies new-onset AF [28].

In the multivariate model for the effect of comorbidities, although the majority were associated with worse mortality outcomes, hyperlipidaemia, prior PCI and CABG were favourable predictors. These associations have been identified previously in this cohort and may be explained by being a healthier subgroup that is more amenable to improved prognostic interventions [20, 22]. The prevalence of these comorbidities were significantly different between groups, with the HF in AF group being older and more likely to have a history of hypertension, CKD, IHD and stroke. HF patients with these significant comorbidities may be predestined to acquire AF, which subsequently predisposes them to HF advancement, as well as having more limited reserve to counter the adverse haemodynamic effects of AF [29]. Therefore, it is likely that the presence of AF in HF is an indirect surrogate marker of increasing LV dysfunction and cardiac decompensation. However, there is likely a direct impact of this combination, acting as a trigger for HF progression, as these patients appear unable to fully compensate for the loss of atrial contraction.

Although previous studies have assessed the impact of AF and HF on survival (which have been meta-analysed by Mamas et al [26]), many of these studies were small post-hoc analyses of randomised trials, with relatively short follow-up. Of 16 studies included in the meta-analysis, only 3 studies observed no increase in mortality with HF patients in AF [14, 30, 31] with the pooled analysis demonstrating a significant association with mortality (observational studies OR 1.14, 95% CI 1.03-1.26; post-hoc studies OR 1.40, 95% CI 1.32-1.48) compared to HF in SR [26]. Despite this analysis being performed 8 years ago, they support our findings that concomitant AF and HF are associated with increased mortality.

Importantly, studies that investigate HF in the presence of chronic AF are subject to ascertainment bias, since the HF in AF cohort represent a selected, survivor population. In

contrast, new-onset AF identified in a prospective registry eliminates the bias of not including AF patients who have died prior to the observation period.

Our finding that patients with new-onset AF or HF have worse outcomes was supported by other prospective epidemiological studies [32-34]. Patients with HFrEF who developed new-onset AF were found to exhibit a 2-fold increase in mortality and a 4.5-fold increase in hospitalisation [35]. However, this is in contrast to the report by Crijns et al, who studied patients with moderate-severe HF, and demonstrated no association between new-onset AF and a poorer outcome [18].

Limitations

This analysis was a prospective follow-up of a registry from a limited number of hospitals in the north of England. In order to establish whether the combination of AF and HF is related to poor outcomes, it is essential that the disease group can be compared to a comparable comparator group. To attempt to achieve this, we have performed statistical adjustment. However, removing all confounding bias is extremely difficult, since important confounders can be unknown or masked. This is in part because both AF and HF precipitate pathological and haemodynamic abnormalities, such as reduced LVEF, raised pulmonary capillary wedge pressure and changes to systemic blood pressure, leading to worse symptoms and reduced exercise capacity [36, 37]. The presence of these conditions also leads to clinicians prescribing guideline recommended therapies, which may impact on clinical outcomes [3, 6, 24, 38]. Even with a reasonable selection of adjustment variables, when treatment and control groups differ vastly in characteristics, reliable effect estimates are not possible without breaching the assumptions of the statistical model [39]. Therefore even after

statistical adjustment, residual confounding can remain. Subsequently, observational data is hypothesis generating, rather than definitive.

In this database, we did not have access to therapeutic data for individual patients. Data on cardioversion attempts, rate-controlling agents, anticoagulation and HF therapies does impinge on prognosis and we therefore cannot exclude that these may account for some of the associations observed. Furthermore, we relied on the accuracy of ICD-10 coding for collecting data on comorbidities and we were unable to elicit the severity and types of these comorbidities. {O'Malley, 2005 #46} Of great importance to determining clinical outcomes is differentiating between subtypes of AF (paroxysmal, persistent, long-standing and permanent) and HF (HFrEF and HFpEF), however this data was not available. Additionally, we cannot exclude that differences in clinical outcomes between patients with incident AF and/or HF compared to that of prevalent disease are due to survivor bias.

Conclusion

Concomitant AF and HF is independently associated with a marked increase in mortality and longer hospital stay, compared to patients with HF or AF alone. The development of new-onset AF or HF leads to significantly worse survival compared to patients with chronic disease. Although the development of AF in HF patients may be a surrogate indicator of HF progression alone, we still found the combination was independently associated with adverse outcome. Still, future analyses of HF patients in AF are required to confirm the vulnerability of these patients. This type of information is vital if we are to defend against the enormous healthcare burden posed by these two conditions.

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Figure Legends

Figure 1: Kaplan Meier Survival curves for patients with AF (n=31,695), HF in SR (n=20,768), and HF in AF (10,992)

Figure 2: Comparison of study-entry (baseline) with new-onset (developed) atrial fibrillation or heart failure on mortality

Unadjusted odds ratio with 95% confidence intervals.

Tables

Table 1: Baseline demographics of patients admitted during the study period

Characteristic	Control	AF alone	HF in SR	HF in AF	P value
n (%)	866,097 (93.17%)	31,695 (3.41%)	20,768 (2.23%)	10,992 (1.18%)	
Mean Age (years ± SD)	48.1±19.9	73.3±12.9	71.9±14.5	76.9±11.0	<0.001
Male gender %	43.3	52.1	51.0	48.9	<0.001
Caucasian %	76.5	89.1	82.9	89.3	<0.001
South Asian %	8.2	1.7	5.4	1.9	<0.001
Afro-Caribbean %	3.0	0.6	1.7	0.9	<0.001
Oriental %	0.7	0.3	0.2	0.2	<0.001
Mixed %	0.8	0.1	0.2	0.1	<0.001
Other %	10.8	8.3	9.7	7.6	<0.001
Hypertension %	16.1	47.6	42.2	45.9	<0.001
PVD %	0.9	4.5	5.9	6.2	<0.001
CKD %	1.3	6.8	14.4	17.3	<0.001
IHD %	7.6	28.9	42.8	43.2	<0.001
CABG %	0.5	3.5	1.4	1.3	<0.001
PCI %	1.3	1.4	2.8	1.1	<0.001
MI %	2.1	6.8	16.0	12.2	<0.001
Stroke %	1.9	12.0	7.0	10.9	<0.001
T1DM %	1.1	1.1	2.7	1.5	<0.001
T2DM %	6.5	16.2	22.6	21.1	<0.001
Hyperlipidaemia %	5.2	13.5	12.0	10.5	<0.001

P value represents one-way ANOVA comparison for differences between all 4 groups. AF, atrial fibrillation; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; HF in AF, heart failure in atrial fibrillation; HF in SR, heart failure in sinus rhythm; IHD, ischaemic heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Table 2: All-cause mortality and length of stay

Group	Total Sample	Crude Mortality n (%)	Unadjusted mortality OR (95% CI)	Adjusted mortality OR (95% CI)	Length of stay (mean days ± SD)	Length of stay mean difference (95% CI)
Control	866,097	101,684 (11.7)			3.2 ± 13.5	
AF alone	31,695	14,280 (45.1)	6.16 (6.02-6.31)	3.73 (3.62-3.84)	9.4 ± 19.8	6.05 (6.02-6.3)
HF in SR	20,768	13,305 (64.1)	13.4 (13.0-13.8)	6.51 (6.27-6.76)	11.0 ± 20.0	7.67 (7.34-8.0)
HF in AF	10,992	7,785 (70.8)	18.2 (17.5-19.0)	8.76 (8.31-9.23)	12.8 ± 22.0	9.41 (8.90-9.9)

Table 3: Multivariate model for the effect of comorbidities at baseline on mortality

Variable	Odds ratio	95% CI	P value
Hypertension	1.51	1.48-1.54	<0.0001
CKD	3.96	3.83-4.15	<0.0001
IHD	2.51	2.46-2.57	<0.0001
Hyperlipidaemia	0.39	0.37-0.40	<0.0001
T1DM	1.59	1.50-1.68	<0.0001
T2DM	1.62	1.58-1.66	<0.0001
PVD	2.82	2.68-2.97	<0.0001
Prior PCI	0.12	0.12-0.13	<0.0001
Stroke	5.66	5.47-5.86	<0.0001
Prior CABG	0.30	0.27-0.33	<0.0001
Prior MI	2.79	2.68-2.90	<0.0001

P value represents **XXX**. CABG, coronary artery bypass grafting; CKD, chronic kidney disease; IHD, ischaemic heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Table 4: Comparison of study-entry (baseline) with new-onset (developed) atrial fibrillation and/or heart failure on mortality

Group		Total Sample (% of group)	Crude Mortality n (%)	Odds ratio for mortality (95% CI)
AF (n 42,687)	Baseline	29,164 (68.3%)	14,150 (48.5%)	7.08 (6.92-7.26)
	Developed	13,523 (31.7%)	7,915 (58.5%)	10.61 (10.25-10.99)
HF (n 31,760)	Baseline	19,474 (61.3%)	12,400 (63.7%)	13.18 (12.79-13.58)
	Developed	12,286 (38.7%)	8,690 (70.7%)	18.17 (17.46-18.90)
HF+AF (n 10,992)	Baseline	5,728 (52.1%)	3,848 (67.2%)	15.39 (14.56-16.27)
	Developed	5,264 (47.9%)	3,937 (74.8%)	22.30 (20.95-23.74)

Figures

Figure 1.

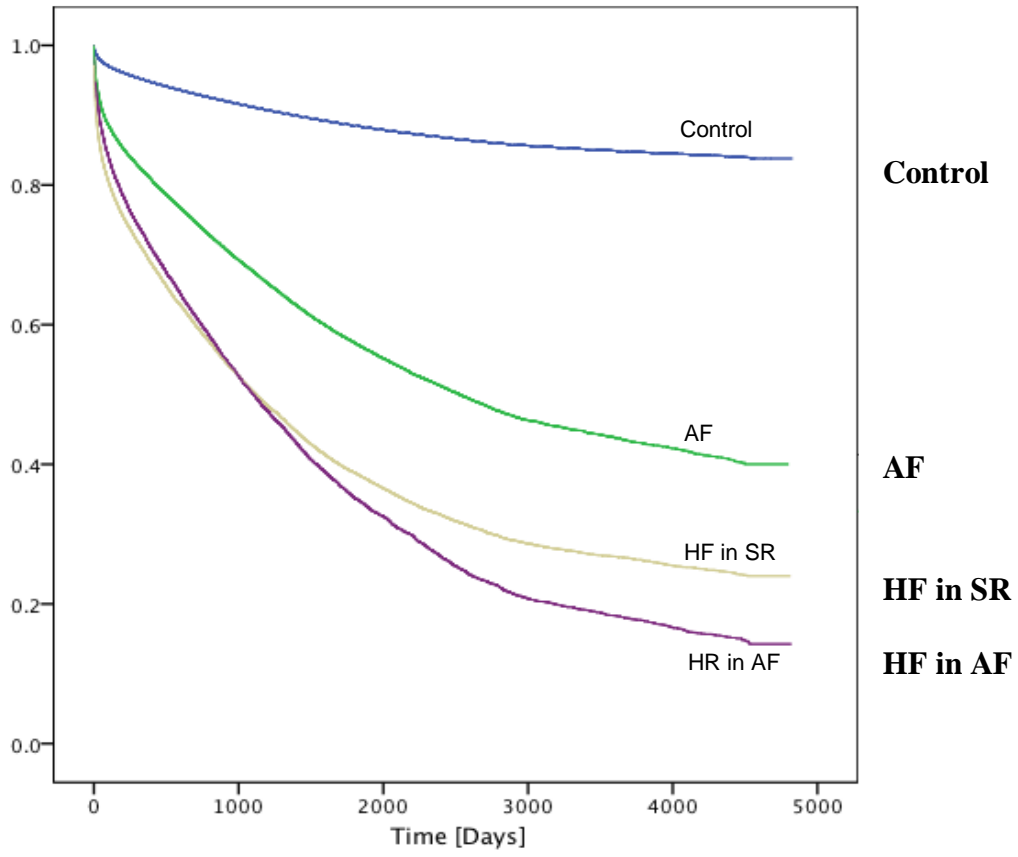


Figure 2.

