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## Introduction

In contrast to previous trials of AF treatment, EAST-AFNET 4 suggests the superiority of early rhythm control compared to rate control in patients with atrial fibrillation (AF). It is unclear whether this result is attributable to earlier timing of intervention, or other factors, such as improved therapeutic options for rhythm control.

## Objectives

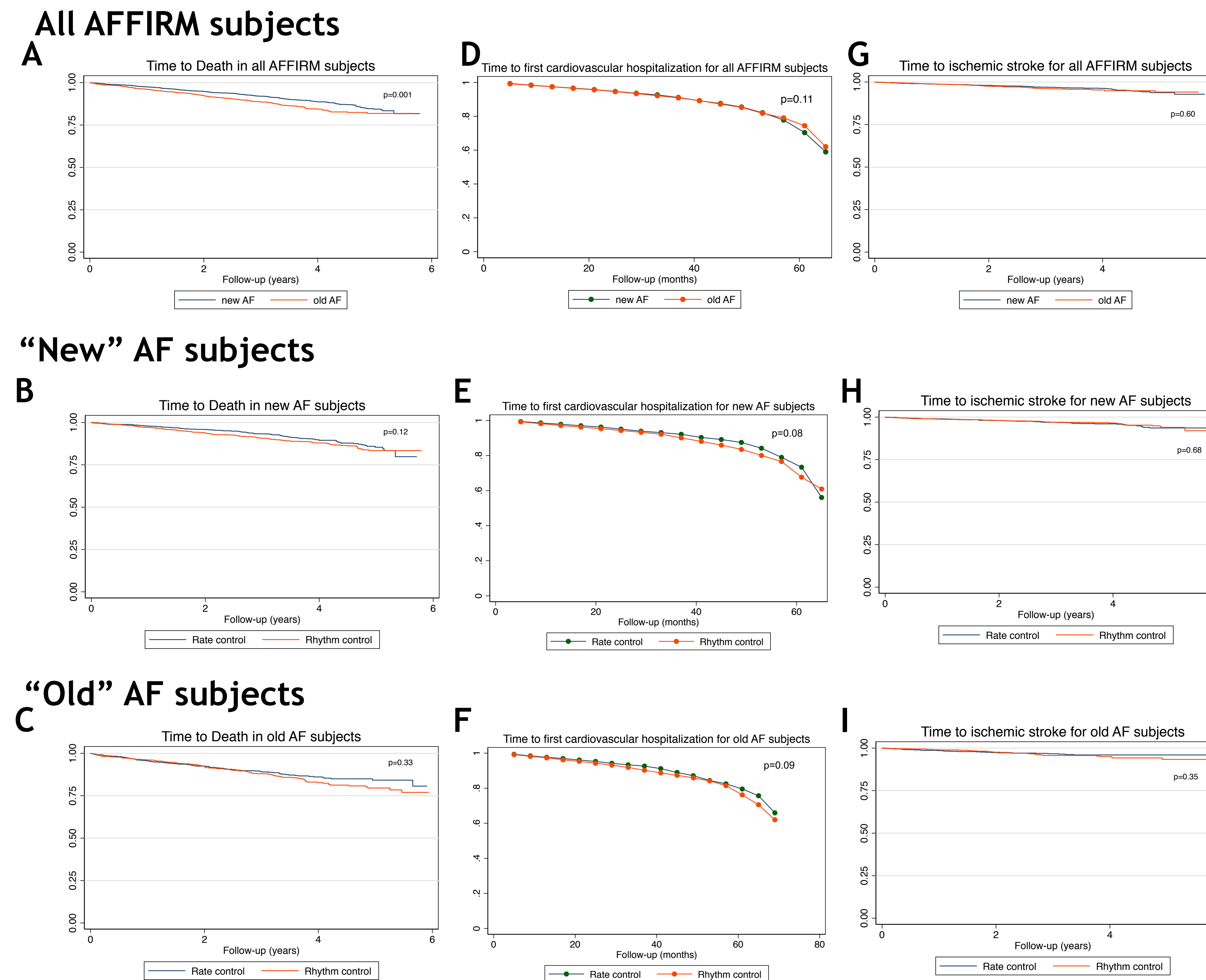
This study aimed to isolate the assessment of early intervention on AF from temporal changes in AF treatments through a secondary analysis of AFFIRM subjects.

## Materials and Methods

We performed a secondary analysis of subjects enrolled in the **Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM Study, NCT 0000556)**. AFFIRM subjects were stratified into two subgroups: (1) subjects with “new” AF defined as participants whose enrollment-qualifying episode of AF was their first clinically documented episode of AF and (2) subjects with “old” AF defined as participants who had been diagnosed with AF prior to their study-qualifying AF episode(s). The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular hospitalizations, ischemic stroke, days of hospitalization, and days requiring ICU care.

After tabulating simple summary statistics, survival analysis of time to death or administrative censoring was performed using continuous time-to-event analysis, with unadjusted findings depicted using Kaplan-Meier graphs and log-rank testing. We constructed a multivariable clinical risk model with stepwise forward Cox regression. Discrete time-to-event analysis was performed with life-table analysis for binned event-time intervals, with complementary log-log multivariable regression.

## Results



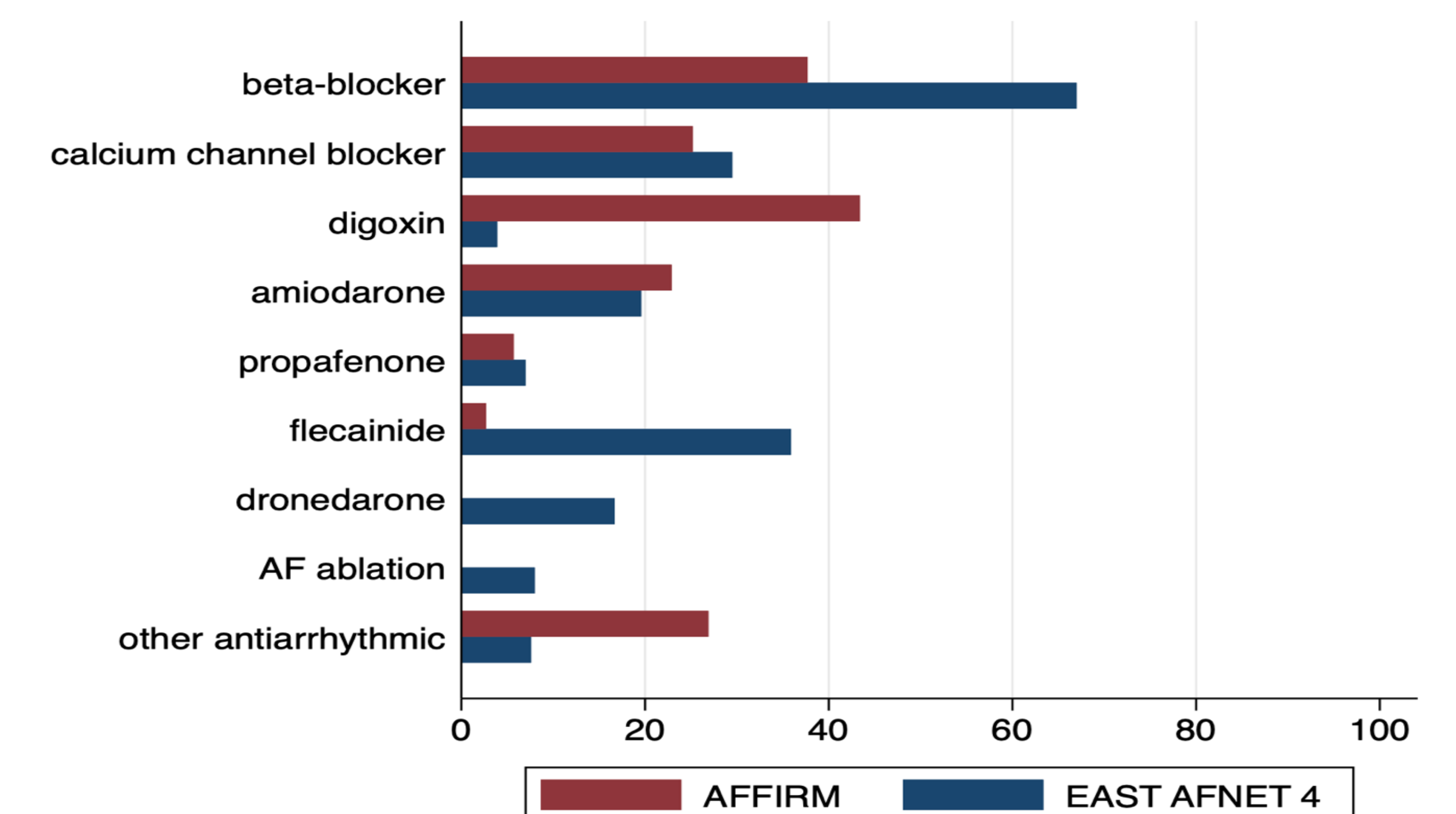
**Figure 1: Time-to-event analysis for A-C: All cause mortality, D-F: Cardiovascular hospitalization, and G-I: Ischemic stroke.** The first column depicts A: Kaplan Meier curves comparing new and old AF subgroups, showing significantly reduced survival in those with pre-existing AF prior to enrollment. B: Comparison of rate and rhythm control treatment arms in newly diagnosed AF subgroup demonstrated no significant difference in survival between treatment arms. C: No significant difference between rate versus rhythm control strategies in individuals with old AF. The y-axis represents proportion of subjects alive at any given timepoint listed on the x-axis. The second column depicts discrete time to first cardiovascular hospitalization, using life table graphs depicting time to first cardiovascular hospitalization comparing D: new and old AF subgroups, E: rate versus rhythm control in new AF subgroup, and F: rate versus rhythm control in old AF subgroup. The right-most column depicts Kaplan Meier analysis of time to ischemic stroke between G: new and old AF subgroups, and compares rate versus rhythm control strategies in the H: “new” AF subgroup and I: “old” AF subgroup. The y-axis represents the proportion of subjects who have not yet had an event at any given timepoint listed on the horizontal axis.

## Conclusion

AFFIRM subjects diagnosed with atrial fibrillation within 6 months of study enrollment showed no difference in survival, cardiovascular hospitalization, or ischemic stroke between rate and rhythm control strategies. Superiority of rhythm control strategies reported by newer AF trials may be more attributable to the refinement of AF therapies and less related to timing of intervention.

	“Old” AF (n=1391)	“New” AF (n=2526)	p-value
Age	71 [65, 76]	71[65, 76]	0.24
Sex	37.5%	40.2%	0.10
Race	13.9%	10%	0.001
BMI	28.4 [25.1, 32.5]	28.9 [24.5, 31.6]	0.06
Randomized to rhythm control treatment arm	49.7%	50.0%	0.87
EF	54.7%	56.4%	0.07
Died	18.8%	14.6%	0.004
CAD	37.6%	39.0%	0.38
MI	19.8%	16.4%	0.006
CABG	12.2%	12.9%	0.50
PCI	8.7%	9.4%	0.50
LA Diameter	4.4 [3.9, 4.9]	4.3 [3.9, 4.8]	0.26
Mitral regurgitation	21.9%	18.7%	0.03
HTN	71.3%	71.2%	0.98
PAD	7.1%	7.1%	0.93
DM	23.0%	18.9%	0.002
Hepatic or renal Comorbidities	6.9%	4.9%	0.008
Pulmonary disease	14.9%	14.8%	0.97
Active Smoker	14.2%	11.0%	0.003
History of Stroke	14.4%	12.1%	0.03

**Table 1: Baseline demographics and clinical findings stratified by AF subgroup** Race (% non-Caucasian); BMI (body mass index, kg/m<sup>2</sup>); EF (left ventricular ejection fraction); LA Diameter (left atrial diameter, cm); HTN (hypertension); PAD (peripheral arterial disease); DM (diabetes mellitus); MI (myocardial infarction); CABG (history of coronary artery bypass graft surgery); PCI (history of percutaneous coronary intervention). Entries are listed as median values with interquartile range. Continuity corrected  $\chi^2$ -testing was performed for covariates with non-normal distributions identified using Shapiro-Wilks testing. Categorical variables reported as percentage (number of subjects/ total subjects observed in AF subcategory). \*p-values based on unequal variance t-test for continuous variables and Chi-square testing or Fisher’s exact test for categorical variables.



**Figure 2: Comparison of initial rate and rhythm control strategies upon enrollment in AFFIRM and EAST-AFNET 4 trials.**