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Association Between Age and Outcomes of Catheter Ablation Versus Medical Therapy for Atrial Fibrillation: Results From the CABANA Trial

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BACKGROUND: Observational data suggest that catheter ablation may be safe and effective to treat younger and older patients with atrial fibrillation. No large, randomized trial has examined this issue. This report describes outcomes according to age at entry in the CABANA trial (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation).

METHODS: Patients with atrial fibrillation ≥65 years of age, or <65 with ≥1 risk factor for stroke, were randomly assigned to catheter ablation versus drug therapy. The primary outcome was a composite of death, disabling stroke, serious bleeding, or cardiac arrest. Secondary outcomes included all-cause mortality, the composite of mortality or cardiovascular hospitalization, and recurrence of atrial fibrillation. Treatment effect estimates were adjusted for baseline covariables using proportional hazards regression models.

RESULTS: Of 2204 patients randomly assigned in CABANA, 766 (34.8%) were <65 years of age, 1130 (51.3%) were 65 to 74 years of age, and 308 (14.0%) were ≥75 years of age. Catheter ablation was associated with a 43% reduction in the primary outcome for patients <65 years of age (adjusted hazard ratio [aHR], 0.57 [95% CI, 0.30–1.09]), a 21% reduction for 65 to 74 years of age (aHR, 0.79 [95% CI, 0.54–1.16]), and an indeterminate effect for age ≥75 years of age (aHR, 1.39 [95% CI, 0.75–2.58]). Four-year event rates for ablation versus drug therapy across age groups, respectively, were 3.2% versus 7.8%, 7.8% versus 9.6%, and 14.8% versus 9.0%. For every 10-year increase in age, the primary outcome aHR increased (ie, less favorable to ablation) an average of 27% (interaction *P* value=0.215). A similar pattern was seen with all-cause mortality: for every 10-year increase in age, the aHR increased an average of 46% (interaction *P* value=0.111). Atrial fibrillation recurrence rates were lower with ablation than with drug therapy across age subgroups (aHR 0.47, 0.58, and 0.49, respectively). Treatment-related complications were infrequent for both arms (<3%) regardless of age.

CONCLUSIONS: We found age-based variations in clinical outcomes for catheter ablation compared with drug therapy, with the largest relative and absolute benefits of catheter ablation in younger patients. No prognostic benefits for ablation were seen in the oldest patients. No differences were found by age in treatment-related complications or in the relative effectiveness of catheter ablation in preventing recurrent atrial arrhythmias.

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Key Words: age groups ■ anti-arrhythmia agents ■ atrial fibrillation ■ catheter ablation ■ pulmonary veins

Editorial, see p 805

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Clinical Perspective

What Is New?

- This is the first complete report of the age subgroup analysis from the CABANA trial (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation).
- The relationships between key mortality inclusive study outcomes and atrial fibrillation recurrence outcomes and patient age are reported using age as a continuous variable.
- A clear relationship between age and select CABANA outcomes was identified whereby the relative benefit of catheter ablation compared with drug therapy was greatest for younger patients and declined with advancing age; catheter ablation was superior to drug therapy to reduce atrial fibrillation recurrence across age groups.

What Are the Clinical Implications?

- The evidence for a prognostic benefit from catheter ablation in atrial fibrillation was strongest in younger patients.
- Regardless of age, in patients with symptomatic atrial fibrillation for whom a rhythm control strategy is preferred and who have drug intolerance or inefficacy, catheter ablation is a reasonable treatment strategy.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
aHR	adjusted hazard ratio
CABANA	the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation trial
HR	hazard ratio

Initial randomized trials of catheter ablation for atrial fibrillation (AF) focused on relatively young patients and reported that ablation was superior to drug therapy for reducing or eliminating AF and improving quality of life.[1,2] Subsequent observational reports of catheter ablation suggested that the relative benefits of catheter ablation to prevent AF recurrences extended to older age groups, in association with reasonably low complication rates.[3–5] However, no large randomized controlled trial data have examined whether, and in what ways, the long-term clinical outcomes of catheter ablation, compared with medical therapy, vary as a function of patient age.

The CABANA trial (Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation) was the first large prospective randomized trial with extended follow-up to compare catheter ablation with drug therapy regarding mortality-inclusive outcomes in a diverse patient population that included a broad spectrum of ages and all AF types.[6] As previously reported, the trial showed that catheter ablation had an inconclusive effect on the primary composite study outcome (a composite of death, disabling stroke, serious bleeding, or cardiac arrest) and on all-cause mortality.[7] The secondary outcomes of AF recurrence, quality of life, and the composite of mortality and cardiovascular hospitalization showed clinically consequential benefits of catheter ablation compared with drug therapy.[8,9]

Prespecified subgroup analyses revealed ≈50% reduction in the primary outcome with catheter ablation relative to drug therapy in the patients who were <65 years of age at enrollment but showed a diminishing benefit in older patients.[7] This report provides a more comprehensive description of the relationship of patient age with the benefits and risks of catheter ablation in CABANA.

METHODS

Overview

CABANA is an National Institutes of Health/National Heart, Lung, and Blood Institute–sponsored trial, and the trial data sets will be made public through the National Institutes of Health website BioLINCC.[7]

CABANA enrolled 2204 patients with untreated or undertreated AF (patients were excluded if >1 membrane-active antiarrhythmic drug prescribed for them had failed). Patients ≥18 years of age were eligible regardless of the type of AF (paroxysmal, persistent, or long-standing persistent) as long as treatment of AF was clinically indicated in the judgment of the treating physician.[6,7] Eligibility further required that those <65 had additional comorbidities that conferred increased risk of stroke (hypertension, heart failure, history of stroke, diabetes, or other heart problems).[6]

Patients were randomly assigned 1:1 to the treatment strategy of catheter ablation versus drug therapy. Catheter ablation included pulmonary vein isolation confirmed with a circular mapping catheter, and additional ancillary ablation was permitted at the discretion of operators.[6] Patients randomly assigned to drug therapy could undergo sequential antiarrhythmic drug or rate control therapies, directed by the judgment of the treating physicians, with the majority of patients receiving rhythm control therapy with antiarrhythmic drugs.[7] Additional details about the randomized treatment strategies have been previously reported.[6] Median follow-up in CABANA was 48.5 months. Each site's institutional review board or ethics committee approved the study, and written informed consent was obtained from all patients.

CABANA Trial Outcomes

The CABANA primary outcome was a composite of death, disabling stroke, serious bleeding, or cardiac arrest.[6] Secondary outcomes included all-cause mortality, the composite of death or cardiovascular hospitalization, and recurrent AF. Recurrent AF

was recorded using a proprietary monitoring system (CABANA Box) available at 86% of enrolling sites.[9] Recurrent AF was defined as an episode of atrial arrhythmia outside the 90-day blanking period lasting ≥30 seconds, and AF recurrences were adjudicated by the CABANA ECG Core Laboratory.

Statistical Analysis

This age subgroup analysis of the CABANA population was prespecified.[6] Patients were aggregated into age groups for descriptive purposes using CHA_2DS_2-VASc cut points of <65, 65 to 74, and ≥75 years of age.[7] Primary analyses used age as a continuous variable in prognostic models.

For descriptive statistics, we used medians (25th, 75th percentiles) for continuous variables and counts (percentages) for categorical variables. Treatment comparisons were performed using intention to treat to define treatment assignment. Kaplan-Meier estimation was used to construct survival curves on the basis of time-to-event analysis.[10]

Unadjusted and adjusted Cox proportional hazards models were used to estimate average relative treatment effect hazard ratios (HRs) with associated 95% CIs.[11] The effect of age on the ablation:drug therapy HR was estimated by including age and an age×treatment interaction term in the models, with age as a continuous variable. Adjusted Cox models included the following variables: treatment, age, age×treatment interaction, sex, race and ethnicity, AF type, years since onset of AF, history of heart failure, structural heart disease (mitral regurgitation, left ventricular hypertrophy, and increased left atrial diameter), CHA_2DS_2-VASc score, history of coronary artery disease, and hypertension. These models were used to produce graphical descriptive representations of the relationship between age and estimated treatment effect and to calculate the relative increase in the HR associated with a 10-year increase in age.

To avoid dropping the few patients who had ≥1 missing baseline covariates from the Cox model analyses, the main analyses used a single-imputation method using either the median (continuous variables) or the mode (categorical variables). Estimates generated without any imputed data were almost identical (data not shown).

Recurrent AF (AF/atrial flutter/atrial tachycardia) cumulative incidence rates were estimated using a proportional hazards (Fine-Gray) model assuming death as a competing risk and adjusting for the covariables enumerated earlier.[12] Only the 1240 patients who used the proprietary CABANA-Box recorder and provided postblanking period recordings were included in this portion of the analysis.[9]

P values, where provided, are intended as adjunctive interpretive aids reflecting the unexpectedness of the observed effects or differences under the assumption that the null hypothesis is true.[13] Treatment×covariable interaction *P* values are commonly used to probe for the presence of consequential treatment interactions. However, given the poor statistical power these tests typically have in this context, we also examined the relative and absolute effects of age variations on treatment outcomes and used graphical displays to supplement numeric estimates in providing a comprehensive examination of the relevant relationships.[14] No adjustments were made for multiple comparisons. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

RESULTS

Baseline Characteristics

Age was equally distributed by treatment group in CABANA. Within each age subgroup, major demographic and clinical characteristics were reasonably well balanced by randomized treatment assignment (Table). However, many baseline factors varied as a function of age. Patients ≥75 had a higher proportion of women, lower proportions of racial or ethnic minorities and diabetes, and greater proportions had CHA_2DS_2-VASc >2 or previous revascularization compared with younger age groups (Table S1). The proportion of patients with paroxysmal or persistent/long-standing persistent AF did not differ significantly between age groups (Table S1). Median duration of AF before study enrollment was 1.2 years, 1.1 years, and 0.8 years for the <65 years, 65 to 74 years, and ≥75 years age group, respectively.

Treatment Data

Of the 766 patients who were <65 years of age at baseline, 375 (49.0%) were randomly assigned to the ablation group and 391 (51.0%) to the drug therapy group (Table). In the 1130 patients who were 65 to 74 years of age, 577 (51.1%) were randomly assigned to ablation and 553 (48.9%) to drug therapy. For the 308 patients who were ≥75 years of age, 156 (50.6%) were randomly assigned to ablation and 152 (49.4%) to drug therapy.

Of the 375 patients in the ablation arm who were <65 years of age, 345 (92.0%) had their assigned ablation procedure at a median of 32 days (25th, 75th percentile, 10, 60). The corresponding values for the 577 patients 65 to 74 years of age were 522 (90.5%) at a median of 28 days (25th, 75th percentile, 14, 51), and for the 156 patients ≥75 years of age the corresponding values were 139 (89.1%) at a median of 30 days (25th, 75th percentile, 17, 58). There were 145 (43.2%), 232 (45.8%), and 59 (43.7%) patients in the ablation arm on a rhythm control drug at some point during the postblanking period, and 78 (23.2%), 143 (28.3%), and 40 (29.6%) patients on a rhythm control drug at the last available follow-up contact.

Of the 391 patients in the drug therapy arm <65 years of age, 113 (28.9%) patients crossed over to ablation at a median of 381 days. The corresponding values for the 553 patients 65 to 74 years of age were 157 (28.4%) at a median of 369 days, and for the 152 patients ≥75 years of age, the corresponding values were 31 (20.4%) at a median of 282 days. A rhythm control drug was being used in 310 (80.7%), 468 (87.0%), and 118 (83.7%) patients at some point during the postblanking period, and 201 (52.3%), 285 (53.0%), and 73 (51.8%) patients at the last available follow-up.

Table. Baseline Characteristics by Age Group and Treatment

Characteristics	Age: <65 y (N=766)		Age: 65–74 y (N=1130)		Age: ≥75 y (N=308)	
	Ablation (N=375)	Drug (N=391)	Ablation (N=577)	Drug (N=553)	Ablation (N=156)	Drug (N=152)
Age						
N	375	391	577	553	156	152
Median (Q1, Q3)	59.2 (54.3, 62.1)	59.4 (55.7, 62.6)	69.3 (67.3, 71.8)	69.3 (67.2, 71.9)	77.6 (76.5, 80.0)	77.3 (76.0, 79.4)
Female sex	94/375 (25.1)	104/391 (26.6)	234/577 (40.6)	234/553 (42.3)	85/156 (54.5)	68/152 (44.7)
Minorities*	54/375 (14.4)	51/389 (13.1)	47/574 (8.2)	49/553 (8.9)	12/155 (7.7)	12/152 (7.9)
History of cerebrovascular accident or transient ischemic attack	48/375 (12.8)	32/390 (8.2)	50/577 (8.7)	52/553 (9.4)	19/156 (12.2)	19/152 (12.5)
History of heart failure	64/375 (17.1)	68/389 (17.5)	80/577 (13.9)	74/553 (13.4)	30/156 (19.2)	21/152 (13.8)
New York Heart Association class II or greater	130/373 (34.9)	154/388 (39.7)	184/569 (32.3)	179/551 (32.5)	64/155 (41.3)	67/150 (44.7)
CHA_2DS_2-VASc > 2	117/375 (31.2)	113/391 (28.9)	359/577 (62.2)	364/553 (65.8)	151/156 (96.8)	141/152 (92.8)
Type of atrial fibrillation at enrollment						
Paroxysmal	159/375 (42.4)	155/390 (39.7)	247/577 (42.8)	263/553 (47.6)	64/156 (41.0)	58/152 (38.2)
Persistent and longstanding persistent	216/375 (57.6)	235/390 (60.3)	330/577 (57.2)	290/553 (52.4)	92/156 (59.0)	94/152 (61.8)
Mitral valve regurgitation	129/304 (42.4)	127/296 (42.9)	210/426 (49.3)	191/362 (52.8)	66/109 (60.6)	53/99 (53.5)
Diastolic dysfunction	30/243 (12.3)	41/255 (16.1)	43/308 (14.0)	39/308 (12.7)	15/84 (17.9)	21/80 (26.3)
Left ventricular hypertrophy	145/314 (46.2)	166/304 (54.6)	143/436 (32.8)	121/374 (32.4)	46/114 (40.4)	41/102 (40.2)
Previous use of antiarrhythmic drug	174/355 (49.0)	183/368 (49.7)	249/547 (45.5)	289/534 (54.1)	68/145 (46.9)	79/146 (54.1)
Previous revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery)	29/375 (7.7)	41/390 (10.5)	65/577 (11.3)	69/553 (12.5)	37/156 (23.7)	23/152 (15.1)
Diabetes	111/375 (29.6)	117/390 (30.0)	139/577 (24.1)	131/553 (23.7)	30/156 (19.2)	33/152 (21.7)
Previous stroke	26/375 (6.9)	17/390 (4.4)	33/577 (5.7)	33/553 (6.0)	9/156 (5.8)	8/152 (5.3)
Previous use of direct oral anticoagulants	231/375 (61.6)	259/391 (66.2)	364/577 (63.1)	325/553 (58.8)	94/156 (60.3)	104/152 (68.4)
Hypertension	305/375 (81.3)	344/390 (88.2)	440/577 (76.3)	434/553 (78.5)	131/156 (84.0)	122/152 (80.3)
Body mass index						
N	374	384	560	548	152	152
Median (Q1, Q3)	31.9 (27.6, 36.4)	31.7 (28.2, 36.6)	29.7 (26.7, 33.7)	30.0 (26.4, 34.6)	27.6 (24.7, 31.3)	27.6 (25.2, 31.1)
Left atrial diameter						
N	210	228	270	258	72	70
Median (Q1, Q3)	4.6 (4.1, 5.1)	4.6 (4.2, 5.2)	4.4 (4.0, 4.9)	4.3 (3.9, 4.8)	4.4 (3.8, 4.6)	4.5 (4.0, 4.9)
Left atrial volume index						
N	75	66	104	105	23	17
Median (Q1, Q3)	41.0 (32.0, 50.0)	40.4 (35.3, 48.0)	39.0 (29.9, 48.7)	36.0 (27.7, 44.2)	42.0 (30.7, 56.0)	34.0 (33.0, 47.0)
Years since onset of atrial fibrillation						
N	373	383	576	551	151	151
Median (Q1, Q3)	1.3 (0.4, 4.3)	1.1 (0.3, 3.7)	1.0 (0.3, 3.9)	1.1 (0.3, 3.8)	0.8 (0.2, 4.1)	0.8 (0.2, 3.5)

Values displayed are n/N (%) unless mentioned otherwise. Q1 indicates 1st quartile; and Q3, 3rd quartile.

*Hispanic or Latino or non-White race. Minority status was determined by the site investigator in conjunction with the patient based on predefined categories as required by the National Institutes of Health (NIH) using NIH-specified categories.

Treatment-Related Complications

Treatment-related adverse events were uncommon in both arms and showed no evident association with age (Table S2). For patients in the ablation arm who received an ablation, hematoma and pericardial effusion not requiring intervention were the most common procedure-related adverse events and occurred in <3%. Among patients receiving drug therapy, thyroid dysfunction was the most common adverse event and occurred in <2%.

Clinical Outcomes by Intention to Treat

CABANA Primary Outcome

For the CABANA primary composite outcome, the ablation:drug therapy HR varied continuously with age,

with the largest estimated relative benefits for ablation occurring in the youngest portion of the cohort and an HR of 1 (consistent with no difference in treatment effects) or above occurring at ≈78 years of age (Figure 1). For every 10-year increase in age, the adjusted hazard ratio (aHR) increased (became less favorable for ablation) an average of 27% (interaction *P* value=0.215). When patients were grouped into 3 prespecified age subgroups, the ablation:drug aHR for the primary outcome was 0.57 (95% CI, 0.30–1.09) for <65 years of age, 0.79 (95% CI, 0.54–1.16) for 65 to 74 years of age, and 1.39 (95% CI, 0.75–2.58) for ≥75 years of age (interaction *P* value=0.134; Figure 2). Corresponding 4-year Kaplan-Meier primary composite event rates were (Figure 2): for <65 years of age, ablation 3.2%, drug therapy 7.8%; for 65 to 74 years of age, ablation 7.8%, drug therapy 9.6%; and for ≥75 years of age, ablation 14.8%, drug therapy 9.0%. The Kaplan-Meier primary composite event rate age subgroup plots are shown in Figure S1.

Total Mortality

A similar pattern of results was obtained for the estimated treatment effect on total mortality alone as a function of age at enrollment (interaction *P* value=0.111; Figure 3). For every 10-year increment in age, the ablation:drug therapy aHR increased an average of 46%. The ablation:drug therapy aHR was 0.46 (95% CI, 0.21–1.00) for <65 years of age, 0.72 (95% CI, 0.44–1.18) for 65 to 74 years of age, and 1.92 (95% CI, 0.88–4.17) for ≥75 years of age (interaction *P* value=0.031; Figure 2). Kaplan-Meier total mortality age subgroup plots are shown in Figure S2.

Patients in the ablation arm showed the expected monotonic increase in mortality as a function of increasing age (Figure 2). Four-year mortality was 2.2% in the patients <65 years of age, 4.7% in the 65 to 74 group, and 11.7% in the ≥75 group. In the ablation arm, no deaths occurred during the first 6 months of follow-up, regardless of age. In the drug therapy arm, the corresponding 4-year mortality estimates were 5.8%, 5.3%, and 3.8%, respectively.

This pattern of divergent relationship between age and total mortality by treatment group was also seen for the primary composite outcome (Figure 2) and for cardiovascular mortality (data not shown).

Mortality or Cardiovascular Hospitalization

For the composite outcome of death or cardiovascular hospitalization, a similar inverse age gradient of the benefit of ablation was found, but the treatment effect size was substantially larger and had better precision (narrower CIs; interaction *P* value=0.031; Figure 2, Figure S3).

AF Recurrence

In the subset of patients who used the CABANA recording system, freedom from recurrent AF (AF/atrial flutter/atrial tachycardia) was consistently improved by catheter ablation relative to drug therapy across the age spectrum: aHR, 0.47 (95% CI, 0.35–0.62) for <65 years of age; aHR, 0.58 (95% CI, 0.48–0.70) for 65 to 74 years of age; and aHR, 0.49 (95%, CI 0.34–0.70) for ≥75 years of age (Figure 2, Figure S4).

In the ablation arm, patients <65 years of age had a 4-year AF recurrence rate of 48% versus 57% and 52% for patients 65 to 74 and ≥75 years of age, respectively (Figure 2). In the drug therapy arm, the corresponding 4-year AF recurrence rates were 69%, 72%, and 78%, respectively (Figure 2).

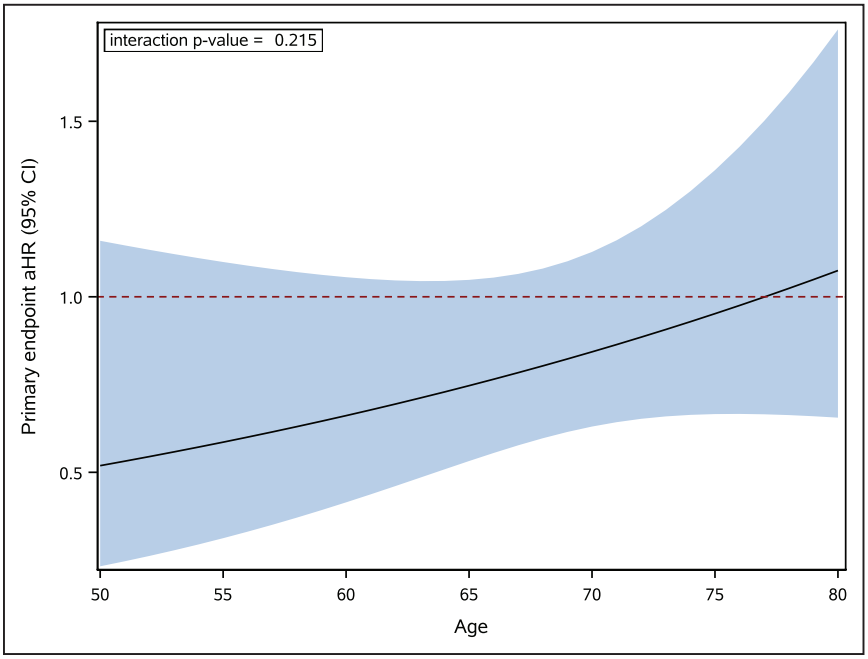

Figure 1. Treatment effect on primary outcome as a function of age as a continuous variable.
The relative risk reduction with catheter ablation vs drug therapy as a function of age as a continuous variable for the primary composite outcome of death, disabling stroke, serious bleeding, or cardiac arrest. The figure shows the adjusted hazard ratio as a solid black line with the 95% CIs represented as the shaded area. The drug arm is used as reference group. aHR indicates adjusted hazard ratio.

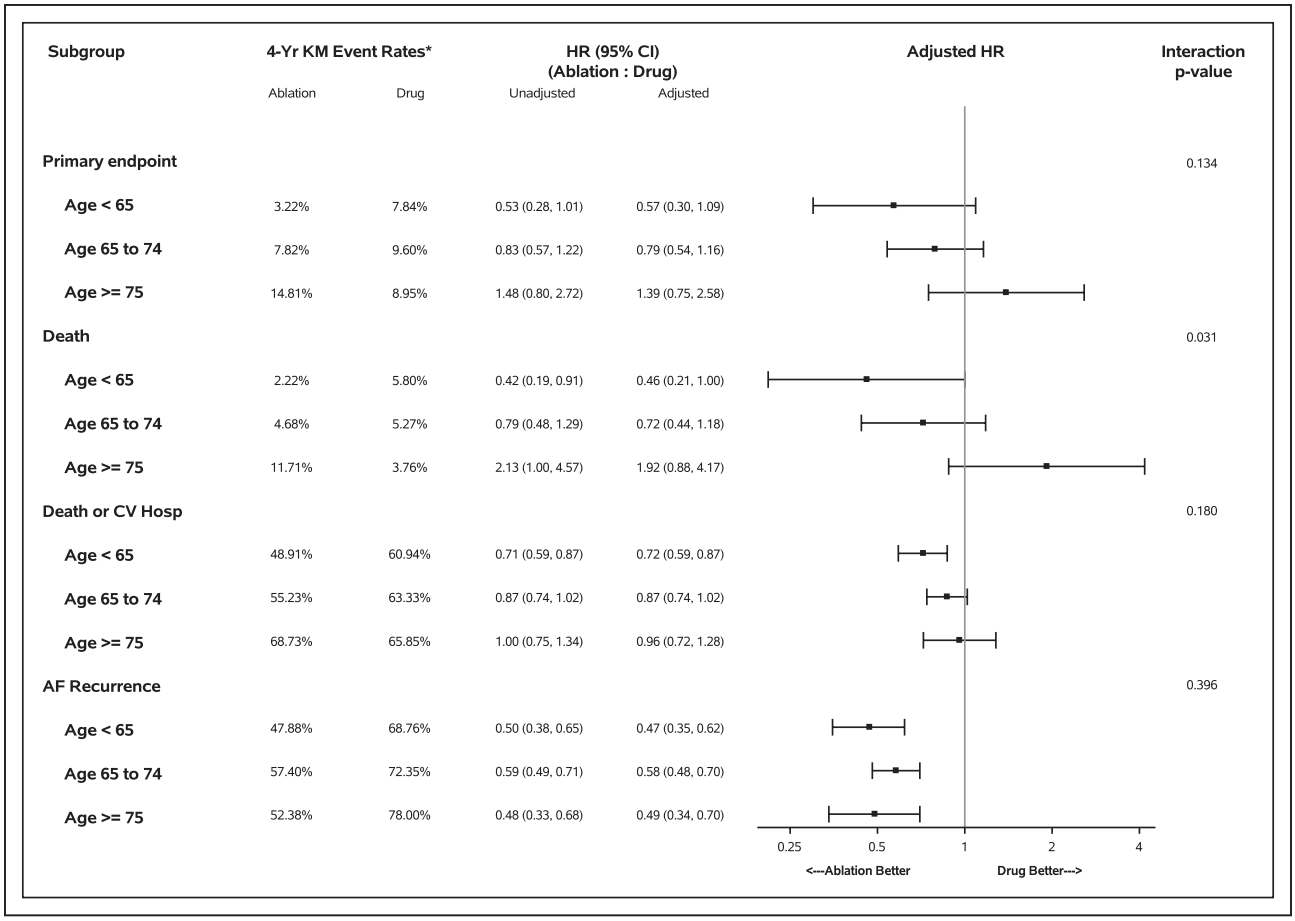

Figure 2. Four-year Kaplan-Meier event rates and unadjusted and adjusted hazard ratios by intention-to-treat age subgroups.
AF indicates atrial fibrillation; CV, cardiovascular; HR, hazard ratio; and KM, Kaplan-Meier.

DISCUSSION

Primary Findings

As part of the prespecified subgroup analyses in the CABANA trial, we previously reported that the effect of ablation on the primary outcome varied by age. Specifically, patients receiving ablation who were <65 years of age showed benefit compared with patients receiving drug therapy (HR, 0.52 [95% CI, 0.27–1.00]), but the older age groups did not.[7] The purpose of the present report is to examine this result in greater depth. The primary findings of this investigation confirm that treatment benefit assessed on both relative and absolute scales varied as a function of age, with older patients having progressively smaller incremental prognostic benefits from catheter ablation. Among the oldest patients (≥75 years), our analyses include a possibility of worse outcomes with ablation, although such inferences must be tempered by an appreciation of the increased uncertainty in this age range attributable to the smaller numbers of such patients (308/2204, 14%) enrolled in the trial. Similar variations by age were seen for the primary outcome and for all-cause mortality. Although age was a prespecified subgroup in CABANA, the observed age-based variation in relative treatment effectiveness was not expected.

Age-Related Variation in Outcomes With Ablation Versus Drug Therapy: Possible Explanations

Several explanations can be proposed for why the observed outcomes of catheter ablation relative to drug therapy in AF might vary as a function of age. First, older subjects might reasonably be expected to face higher short-term procedural risks, which could cancel out some longer-term benefits from more effective AF suppression. However, in CABANA, no procedural mortality occurred in any patients randomly assigned to the ablation strategy, and significant nonfatal complications were infrequent in both arms. Second, older patients with AF could have more advanced, established disease, with more atrial myopathy and remodeling. The implications of this possibility are that AF in older patients would be harder to treat effectively to achieve sustained suppression of AF, and, thus, the magnitude of any benefit associated with the suppression of AF would be smaller. However, there is little evidence that older subjects in CABANA actually had more severe or

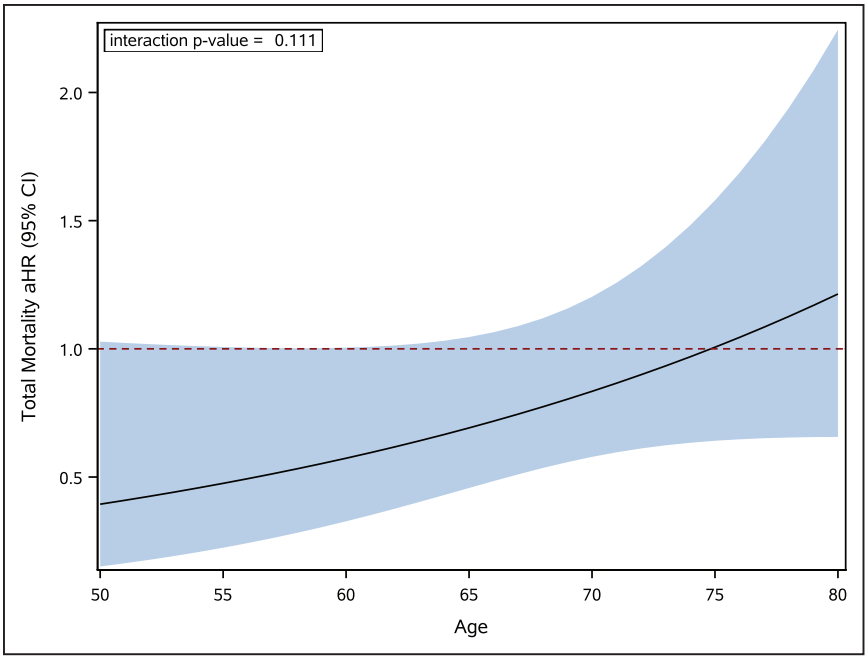

Figure 3. Treatment effect on total mortality as a function of age as a continuous variable.
The relative risk reduction with catheter ablation vs drug therapy as a function of age as a continuous variable for total mortality. The figure shows the adjusted hazard ratio as a solid black line with the 95% CIs represented as the shaded area. The drug arm is used as reference group. aHR indicates adjusted hazard ratio.

advanced stage AF. No differences were seen across age subgroups in the proportion of subjects with persistent AF at baseline (Table S1). The median time from AF onset to enrollment was not longer for older subjects. In the subset of subjects with baseline imaging data, left atrial diameter and volume did not consistently increase as a function of age (data not shown). Therefore, older age in CABANA was not clearly a marker for more advanced atrial myopathy, at least by these measures.

A third potential explanation for the age-related variation in the CABANA ablation treatment effect is the possibility that the crossover rate from drug therapy to ablation varied by age. If ablation actually lowers the risk of the primary outcome (mostly mortality), then more crossovers from the drug arm should narrow the difference in the primary event rates between the 2 arms and reduce the treatment effect size. Crossovers in the age ≥75 drug therapy subgroup were lower (20% crossover rate) than in the younger patients (28%–29% crossover rate), so crossover differences do not appear to be a sufficient explanation for the observed long-term treatment differences.

A fourth possibility is that the observed age-related treatment effect variation is a marker for some important, but as yet unrecognized, variation in the causal relationships between AF and adverse clinical outcomes. AF is well-known to be associated with increased mortality in both clinical cohorts and populations.[15,16] Whether the AF is a fully modifiable cause of that increased risk, an unmodifiable risk indicator (like age itself), or a combination of both is unsettled. In other words, it is possible that the modifiable risk associated with AF is more prevalent in younger patients with AF, whereas AF in older patients may be associated more often with unmodifiable risk. An example of this in a very different context can be found in the case of ventricular arrhythmias leading to sudden death. In the SCD-HeFT trial (Sudden Death in Heart Failure), we observed that primary prevention implantable cardioverter defibrillator therapy was beneficial in reducing mortality in New York Heart Association class II patients, but not in New York Heart Association class III.[17] The explanation appears to be that, in the context of more advanced heart failure, the proportion of arrhythmic deaths that are potentially preventable with appropriate implantable cardioverter defibrillator therapy is substantially less than in New York Heart Association class II (a competing risks problem) and that, even when the mechanism of death is a ventricular tachyarrhythmia, the implantable cardioverter defibrillator more often fails to restore a stable heart rhythm (possibly an effectiveness of therapy problem).[18,19] The competing risks possibility seems unlikely in CABANA given that the mortality rate we observed in the patients ≥75 years of age randomly assigned to drug therapy was quite low, much lower in fact than the overall mortality rates from recent large observational studies of AF that included many subjects >75 years.[20,21] The dissociation in the oldest patients in the drug therapy arm between poor maintenance of sinus rhythm/AF recurrence (worse than in younger patients receiving drug therapy and patients in the ablation arm at all ages) and their very low mortality favors a non-AF explanation.

A final possibility to consider, therefore, is that the absence of an age-related gradient in mortality in the drug therapy arm, and the resulting variation in the relative treatment benefits of ablation, reflects "the play of chance." Randomization only guarantees treatment group balance, or exchangeability, in expectation, but does not guarantee that every potentially relevant characteristic is completely balanced in both arms in a specific trial cohort. When subgroups are examined, the possibilities for imbalances become greater and if these affect unmeasured factors

with causal/prognostic importance, unexpected patterns in treatment-related outcomes may be created.

AF Ablation and Mortality Outcomes

The CABANA trial was originally designed to test the AF-mortality connection by hypothesizing that catheter ablation would reduce AF and thereby would reduce all-cause mortality relative to drug therapy.[6] The primary mechanisms that are presumed to connect AF with mortality are large strokes and progressive heart failure. The stroke risk is mitigated primarily with effective oral anticoagulation. Whether rhythm control adds stroke protection to anticoagulation is still unsettled. Progressive heart failure now appears to be the greatest prognostic threat from AF, particularly among older patients.[20] In a large cohort of older subjects with implanted cardiac devices and nonpermanent AF, greater AF burden was associated with increased risk for new-onset heart failure and for all-cause mortality.[22] This is consistent with evolving thinking regarding the importance of atrial cardiomyopathies and inflammation in advancing AF.

The first trial-based evidence that more effective suppression of AF with catheter ablation relative to drug therapy produced a mortality benefit came from the CASTLE-AF trial (Catheter Ablation versus. Standard Conventional Treatment in Patients with LV Dysfunction and AF) that enrolled patients with AF and systolic heart failure (New York Heart Association class ≥II) with an ejection fraction ≤35%.[23] In CASTLE-AF, the relative benefits of ablation versus medical therapy on mortality were somewhat larger in patients <65 years of age (HR, 0.48 [95% CI, 0.27–0.85]) than in patients ≥65 years of age (HR, 0.79 [95% CI. 0.50–1.23]).[23]

Noseworthy et al[21] reported on 135 688 CABANA-eligible patients treated with catheter ablation or drug therapy in an administrative database of subjects with health insurance coverage and found that patients <65 years of age had the greatest relative benefit of catheter ablation on the primary CABANA outcome (HR, 0.57 [95% CI, 0.47–0.69]), with somewhat less benefit in older patients (HR 0.77 for ages 65–74 years [95% CI, 0.66–0.90]; HR, 0.73 for ≥75 [95% CI, 0.62–0.87]). The discrepancies for the oldest subgroup (age ≥75) between randomized trial data (CABANA) and observational registry data together with the absence of any good causal explanation for the lack of treatment benefit for the oldest patients in CABANA suggest that older patients with AF who are otherwise appropriate candidates for ablation should not be denied the choice of ablation on the basis of these results.

Limitations

Several important caveats should be considered in interpreting our results. First, single-variable subgroup analyses of clinical trials, even when prespecified, should be interpreted with substantial caution. The CABANA trial results showed that, for the overall population intention-to-treat comparison, catheter ablation had an indeterminate effect on the primary outcome and on all-cause mortality, further reinforcing the need for caution in interpreting outcome variations in subgroup data. In CABANA, we had no reason based on experience and on the published literature available at the time our analyses plans were finalized to expect a major variation in the effects of the treatment assignment on the primary outcome of CABANA by age. Second, large efficacy trials are almost never powered for subgroup analyses, and that was clearly true in the case of CABANA. Last, cutting the trial cohort into subgroups even when analysis is done by intention to treat creates the possibility for complex, difficult to detect biases to influence observed results. Such concerns may be particularly relevant in procedure-based trials when treatment assignment masking is infeasible. Nonetheless, subgroup analyses, when performed carefully and presented with appropriate caveats, can provide useful supplemental data in helping to understand the complex interplay between patients and the treatment being studied. If unusual patterns are found, independent replication is an important step in assessing their credibility.

Conclusions

In patients with AF enrolled in the CABANA trial, prespecified subgroup analyses showed an age-based variation in clinical outcomes for catheter ablation relative to drug therapy, such that younger patients had the largest relative and absolute clinical outcome benefits with ablation. For the oldest patients enrolled in CABANA, relative and absolute treatment estimates did not show any prognostic advantages of ablation. No differences were found by age in treatment safety or in the advantage of catheter ablation in preserving freedom from recurrent atrial arrhythmias.

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Supplemental Material

Tables S1 and S2

Figures S1–S4

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