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Research Article

Antihypertensive Use and the Effect of a Physical Activity Intervention in the Prevention of Major Mobility Disability Among Older Adults: The LIFE Study

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Abstract

Background: This subgroup analysis of the Lifestyle Intervention and Independence for Elders trial evaluates the impact of a long-term physical activity (PA) intervention on rates of major mobility disability (MMD) among older adults according to their antihypertensive medication use.
Methods: Lifestyle Intervention and Independence for Elders study participants were randomized to center-based PA or health education for a median of 2.7 years. Participants were sedentary men and women aged 70–89 years with objectively measured physical limitations. This analysis evaluated rates of MMD and persistent MMD among 1,633 participants, according to antihypertensive medication use. Participants were designated as either (i) an angiotensin-converting enzyme (ACE) inhibitor user (ACEi+), (ii) a user of other antihypertensives not including ACEi (ACEi–), or (iii) nonusers of antihypertensive medications (AHT–). Interactions were explored between antihypertensive use and randomized arm.
Results: Interaction terms for MMD (p = .214) and persistent MMD (p = .180) did not reach statistical significance. For MMD, PA displayed marginal effects among ACEi+ (hazard ratio [HR] = 0.76; 95% confidence interval [CI] = 0.57, 1.02) and ACEi– (HR = 0.76; 95% CI = 0.60, 0.97) but not AHT– (HR = 1.19; 95% CI = 0.75, 1.87). For persistent MMD, the effect of PA was greatest among ACEi+ (HR = 0.57; 95% CI = 0.39, 0.84) when compared to ACEi– (HR = 0.76; 95% CI = 0.55, 1.06) or AHT– (HR = 1.18; 95% CI = 0.59, 2.36).
Conclusions: The effects of long-term PA on the incidence of MMD and persistent MMD were similar among three subgroups of older adults stratified by their antihypertensive medication use. However, though statistical interactions did not reach significance, several findings may warrant future study in other cohorts given the post hoc nature of this study.

Keywords: Clinical trials—Exercise—Physical function—Physical activity

The maintenance of physical independence among older adults is an important public health challenge as the inability to perform basic physical tasks increases risk of hospitalization (1) and death (2). Some investigators have suggested that angiotensin-converting enzyme (ACE) inhibitors may attenuate age-related declines in physical function (3,4) as epidemiologic studies have suggested that use of ACE inhibitors may indeed slow functional decline (5,6), possibly by increasing muscle mass and strength (6,7). However, the results

of randomized controlled trials were mixed, with studies reporting that ACE inhibitors may (8,9) or may not (10,11) improve physical performance.

Although it remains possible that the efficacy of ACE inhibitors as a therapeutic for physical function may vary by drug and/or patient population, recent evidence from our group suggests that the greatest benefit of ACEi may be observed when combined with regular physical activity (PA) (12,13)—though conflicting reports exist (14). We previously reported that participants in the Lifestyle Interventions and Independence for Elders (LIFE) pilot study who used ACE inhibitors and participated in a 1-year PA intervention displayed robust improvements in objective measures of physical function compared to ACE inhibitor users who participated in a health education intervention. In contrast, these improvements among PA participants were not observed among individuals taking other antihypertensive medications or persons not taking antihypertensive medications. These data suggested that ACE inhibitor use, and not antihypertensive therapy per se, may facilitate functional responses to structured PA—though additional data are needed to confirm this hypothesis.

The objective of the present study was to evaluate the incidence of major mobility disability (MMD) among participants in each arm of the main LIFE trial according to their antihypertensive medication use. The LIFE study was an eight-site, phase 3, randomized clinical trial, which demonstrated that long-term (median 2.7 years), structured PA reduced the incidence of MMD among older adults at high risk for becoming disabled (15). In addition to MMD, a key outcome of the trial was persistent MMD, defined as the observation of MMD at two consecutive follow-up assessments or MMD followed by death. Here, we examine the potential influence of ACE inhibitors and other antihypertensive medications on the incidence MMD and persistent MMD among older adults participating in the LIFE study. We hypothesized that, among ACE inhibitor users, participants randomized to the PA arm would display reduced rates of MMD and persistent MMD compared to those in the health education arm. In addition, we hypothesize that no differences will be observed between intervention arms among individuals taking antihypertensive medications but not taking ACE inhibitors or among individuals not taking any antihypertensive medications.

Methods

LIFE Study Overview

The LIFE study was a multicenter, single-blind, parallel randomized trial conducted at eight centers across the United States between February 2010 and December 2013. Details of the study design (16) and participant recruitment/characteristics (17) were detailed previously. The study protocol was approved by the institutional review boards at all participating sites. Written informed consent was obtained from all study participants. The trial was monitored by a data and safety monitoring board appointed by the National Institute on Aging. The LIFE study was registered with www.clinicaltrials.gov prior to participant enrollment in the trial (NCT01072500).

Medical Screening and Medication Assessment

Participants were assessed every 6 months at clinic visits. Home, telephone, and proxy assessments were attempted if participants could not come to the clinic. The assessment staff was blinded to the intervention and remained separate from the intervention team. Participants were asked not to disclose their assigned intervention arm or talk about their interventions during the assessment.

Baseline data included demographic information, medical history, medication inventory, body mass index, cognitive status via the Modified Mini-Mental State Examination (18), lower-extremity function, measured via Short Physical Performance Battery (SPPB) (18), and PA, assessed with the Community Healthy Activities Model Program for Seniors (CHAMPS) PA questionnaire (19) and accelerometry over a 7-day period (Actigraph, Inc., Pensacola, FL) (20). Baseline medication use was assessed by visual inspection of all prescription and nonprescription medications taken in the previous 2 weeks. Drug names and whether the medication was prescribed were recorded. Medications were later coded to reflect their function (eg, antihypertensive) and drug class (eg, ACEi, diuretic, β-blocker). Medication usage was reassessed in the same manner during the participant's 12-month follow-up visit.

Randomization and Interventions

Participants were randomized to PA or health education via a secure, web-based data management system using a permuted block algorithm (with random block lengths) stratified by field center and sex. Both arms received an initial individual 45-minute face-to-face introductory session by a health educator who described the intervention, communicated expectations, and answered questions.

Details of the study interventions were published previously (21). Briefly, the PA intervention involved walking, with a goal of 150 min/week, strength, flexibility, and balance training. The intervention included attendance at two center-based visits per week and home-based activity three to four times per week for the duration of the study. The PA sessions were individualized and progressed toward a goal of 30 minutes of walking daily at moderate intensity, 10 minutes of primarily lower-extremity strength training by means of ankle weights (2 sets of 10 repetitions), 10 minutes of balance training, and large muscle group flexibility exercises.

The health education intervention included weekly educational workshops during the first 26 weeks, and then monthly sessions thereafter. Workshops included topics relevant to older adults, such as how to effectively negotiate the health care system, how to travel safely, preventive services and screenings recommended at different ages, where to go for reliable health information, nutrition, etc. The workshops did not include any PA topics. The program also included a 5- to 10-minute instructor-led program of gentle upper extremity stretching or flexibility exercises.

Outcome Assessments

Details of MMD ascertainment were reported previously (15). Briefly, participants were asked to walk 400 m at their usual pace, and MMD was defined as the inability to complete the walk within 15 minutes without sitting and without the help of another person or walker. When MMD could not be objectively measured because of the inability of the participant to come to the clinic and absence of a suitable walking course at the participant's home, institution, or hospital; an alternative adjudication of the outcome was based on objective inability to walk 4 m in less than 10 seconds, or self-, proxy-, or medical record–reported inability to walk across a room. If participants met these alternative criteria, they would not be able to complete the 400-m walk within 15 minutes. Two consecutive MMD assessments or MMD followed by death defined persistent MMD.

Statistical Analyses

For this analysis, participants were categorized by antihypertensive medication status as either nonusers of antihypertensive medications (AHT−), users of ACE inhibitors (ACEi+), or users of other

antihypertensive medications (ACEi–). If an individual used both ACE inhibitor and another antihypertensive medication, they were considered to be an ACE inhibitor user. Our prior analysis of the LIFE pilot study (13) indicated that the use of angiotensin receptor blockers was not associated with differential effects of PA, so these medications were not segregated for the primary analysis here.

Baseline characteristics were summarized by baseline medication subgroup using means (*SD*) and proportions. Differences in characteristics between subgroups were tested using parametric or nonparametric analysis of variance or chi-square tests. For MMD and persistent MMD within each baseline medication subgroup, the number of participants experiencing events was divided by the time until the initial event or time until last follow-up to obtain the number of events per person year by intervention arm. Censoring time was defined as the time from randomization until the last ascertainment of the each type of event, or death. Cumulative incidence curves by baseline medication subgroup and intervention arm were obtained using the Nelson–Aalen estimator. To compare intervention effects within baseline medication subgroups, we estimated hazard ratios (HRs) with 95% confidence intervals using Cox regression models. Models used sex and field center as stratifying factors for the underlying hazards. Two base models were fit for each outcome. Model 1 only included the effects previously mentioned as stratifying factors; whereas Model 2 controlled for baseline SPPB score and a composite index of comorbid conditions published previously (13,22). To each of these models, we added factors representing the effect of the intervention, the baseline medication subgroup and the interaction between the intervention effect and the baseline medication subgroup. Based on results observed from key outcomes in primary study analyses, three-way interactions were explored between baseline medication subgroup, the intervention effect, and both baseline SPPB and sex. We also defined the medication variables as a time-dependent variable and refit the models allowing for medication use as a time-dependent covariate. The baseline medication was used to predict the occurrence of the event during baseline to 12 months, and 12-month medication was used to predict the occurrence of the event after 12 months. To look at individual medication class effects, we defined six indicator variables identifying whether a participant was on ACE, alpha blockers, angiotensin receptor blockers, beta blockers, calcium channel blockers, or diuretics at baseline. A model was fit adding each of these six variables and then interactions between each medication type and the intervention effect were investigated by rerunning models adding only the single interaction term. All analyses were completed using SAS™ 9.4.

Results

A total of 1,633 of 1,635 participants were included in this analysis because medication information was unavailable for two participants. Participants' baseline demographic characteristics are listed in Table 1 stratified by antihypertensive medication use status. The mean age of the 1,633 evaluable participants was 79 years (*SD* = 5 years); 67% were women, 24% were racial and/or ethnic minorities, and 45% had an SPPB score ≤7. Eighty-one percent (n = 1,325) of study participants were taking at least one antihypertensive drug at baseline, and 32% (n = 515) were using an ACE inhibitor. Baseline characteristics stratified by medication use and randomized study arm are shown in the Supplementary Material in Supplementary Table S1.

Median attendance to the PA intervention (65%; 25th–75th percentiles = 31–79) was similar among medication subgroup (p = .47). Over the course of the study, median session attendance was 61% (33–76) for ACEi+, 65% (33–79) for ACE–, and 66% (25–82) for AHT–. No difference was observed among medication subgroup for the total volume of walking (center + home based) performed during the course of the study (p = .44). Median walking time was 115 (71–168) min/week for ACEi+, 114 (71–159) min/week for ACEi–, and 118 (72–182) min/week for AHT–. Median attendance to the health education intervention was 84% (71–92) and did not differ among medication subgroup (p = .51).

Rates of MMD events are shown in Table 2 by antihypertensive medication use status. In general, rates were highest among ACE inhibitor users, with highest rates observed among those assigned to the health education intervention. Lowest rates were generally observed among antihypertensive nonusers.

Results of the Cox regression analyses containing main effects for intervention and medication are shown in Table 3. A significant main effect for intervention was observed for MMD (p < .05) by both Model 1 (unadjusted) and Model 2 (adjusted for baseline function and comorbidity) indicating a beneficial effect of PA. Both models similarly indicated a significant, beneficial intervention effect for persistent MMD (p < .05). A significant main effect for medication use was also observed in Models 1 and 2 for both MMD (p < .05) and persistent MMD (p < .01).

Results of the Cox regression analyses containing the interaction effect between intervention and medication are shown in Table 4. The interaction term did not reach statistical significance in either model for MMD or persistent MMD (p > .05). Cumulative incidence curves are shown in Figures 1 and 2 depicting the difference in rates of outcome events between PA and health education intervention arms within each medication subgroup. Analyses incorporating medication use as a time-dependent covariate provided similar conclusions (see Supplementary Material).

The three-way interactions among intervention arm, medication use, and baseline function (SPPB score) were not statistically significant for either MMD (p = .48) or persistent MMD (p = .29). Similar results were observed for the three-way interaction including sex for MMD (p = .67); however, the three-way interaction for persistent MMD was statistically significant (p = .008). For males, HRs for the effect of PA relative to health education were 0.34 (0.17, 0.66) for ACEi+, 1.36 (0.71, 2.58) for ACEi–, and 4.06 (0.46, 36.33) for AHT–. For females, HRs were 0.79 (0.49, 1.29) for ACEi+, 0.60 (0.40, 0.89) for ACEi–, and 0.99 (0.46, 2.11) for AHT–.

Models fit to investigate the effect of individual medication classes (controlling for the main effect of other classes) revealed a significant two-way interaction (p = .049) between medication use and intervention arm indicating a potentially beneficial effect of PA within those taking calcium channel antagonists/blockers (CCBs) on the incidence of MMD, as the HR for those taking CCBs (n = 476) was 0.64 (0.47, 0.86) compared to 0.93 (0.75, 1.14) for those not taking CCBs. No other statistically significant interactions of individual drug classes were observed (data not shown).

Discussion

To our knowledge, this study is the first to report findings indicating the potential effects of antihypertensive medications on the incidence of MMD among older adults randomized to long-term PA or health education interventions. In contrast to our hypotheses, we did not observe statistically significant differences in the effect of randomization to PA versus health education among antihypertensive medication subgroups (ACE+, ACEi–, and AHT–). Despite the lack

Table 1. Baseline Characteristics of Lifestyle Intervention and Independence for Elders Study Participants by Baseline Antihypertensive Medication Use

Antihypertensive Status	AHT– (*n* = 308)	ACEi+ (*n* = 515)	ACEi– (*n* = 810)	*p* Value
Age, y	78.6 ± 5.3	78.9 ± 5.3	79.0 ± 5.1	.5623
≥80 y	131 (42.5%)	226 (43.9%)	345 (42.6%)	.8841
Female	227 (73.7%)	292 (56.7%)	577 (71.2%)	<.0001
Race				<.0001
White	263 (85.4%)	397 (77.1%)	578 (71.4%)	
African American/black	28 (9.1%)	81 (15.7%)	178 (22.0%)	
Other	17 (5.5%)	37 (7.2%)	54 (6.7%)	
Education—college or above	209 (68.3%)	324 (63.0%)	510 (63.1%)	.2304
Systolic blood pressure, mmHg	125.4 ± 16.5	127.2 ± 18.8	128.4 ± 17.9	.0387
Diastolic blood pressure, mmHg	69.3 ± 9.8	67.0 ± 10.4	68.6 ± 10.2	.0039
Body mass index, kg/m^2	28.3 ± 6.1	30.7 ± 5.7	30.6 ± 6.0	<.0001
Fair to poor health, self-rated	29 (9.4%)	100 (19.5%)	141 (17.5%)	.0006
Health conditions, number	0.9 ± 0.9	2.1 ± 1.0	1.9 ± 1.1	<.0001
Hypertension	32 (10.5%)	459 (89.8%)	658 (82.0%)	<.0001
Diabetes	35 (11.4%)	192 (37.5%)	187 (23.1%)	<.0001
Osteoarthritis	57 (18.7%)	90 (17.6%)	171 (21.2%)	.2435
Lung disease	43 (14.1%)	73 (14.3%)	137 (17.0%)	.2980
Myocardial infarction	9 (2.9%)	51 (10.0%)	69 (8.6%)	.0010
Stroke	10 (3.3%)	43 (8.4%)	56 (6.9%)	.0161
Heart failure	3 (1.0%)	26 (5.1%)	42 (5.2%)	.0056
Cancer	59 (19.3%)	117 (22.8%)	194 (24.0%)	.2393
Hip fracture	21 (6.8%)	21 (4.1%)	28 (3.5%)	.0447
Liver disease	4 (1.3%)	4 (0.8%)	14 (1.7%)	.3367
Baseline SPPB score, points	7.5 ± 1.5	7.3 ± 1.6	7.4 ± 1.6	.1432
Score ≤ 7	132 (42.9%)	236 (45.8%)	362 (44.7%)	.7093
Physical activity, steps/d*	2,513 ± 1,498		2,595 ± 1,369	<.0001
Median (IQR)	2,833 (1,843–3,849)	2,194 (1,523–3,146)	2,384 (1,655–3,237)	

Notes: ACE = angiotensin-converting enzyme; ACEi+ = taking ACE inhibitors; ACEi– = taking antihypertensive medications excluding ACE inhibitors; AHT– = not taking antihypertensive medications; IQR = interquartile range; SPPB = Short Physical Performance Battery. Values are expressed as means ± *SD* or *n* (%) unless otherwise noted.

*Measured via triaxial accelerometry as reported previously (20).

Table 2. Events, Person-Years of Follow-up and Events/Person-Years by Medication Use for Each Outcome

	Physical Activity			Successful Aging Health Education		
Outcome	Events/*N*	PY	Events/100 PY	Events/*N*	PY	Events/100 PY
MMD*						
ACE inhibitor use	86/260	556.65	15.45	105/255	522.55	20.09
Other antihypertensive use	120/401	904.22	13.27	149/409	887.02	16.80
No antihypertensive use	40/156	360.74	11.09	36/152	362.90	9.92
Persistent MMD†						
ACE inhibitor use	41/260	575.35	7.13	68/255	541.39	12.56
Other antihypertensive use	62/401	930.20	6.67	79/409	920.16	8.59
No antihypertensive use	17/156	366.15	4.64	15/152	370.74	4.05

Notes: ACE = angiotensin-converting enzyme; MMD = major mobility disability; PY = person-years.

*Defined by the inability to complete a 400-m walk test within 15 min without sitting and without the help of another person or walker.

†Defined by two consecutive MMD assessments separated by 6 months or MMD followed by death. 100 PY = 100 person-years.

of statistical significance, several findings may have clinical significance and warrant future study in other cohorts. For instance, HRs suggest that the PA intervention was particularly effective in preventing MMD outcomes for those taking antihypertensive medications. In particular, the most beneficial effect of PA appeared to be among ACEi users for the prevention of persistent MMD. Second, these data did identify a significant three-way interaction suggesting the combined effects of the intervention and medication use may differ by sex. Third, to our knowledge, this study is the first to report data suggesting a potential benefit of combining PA with calcium channel antagonists.

Our prior findings from the LIFE pilot study (13) were in line with evidence from aged rats indicating that combining exercise with systemic ACE inhibition improved exercise tolerance significantly more than exercise alone (12,23). Similar studies also reported that combining the ACE inhibitor perindopril with treadmill running resulted in significantly greater increases in muscle capillary density and the proportion of type I fibers among older rats (24,25). One possible explanation for

Table 3. Cox Regression Results Indicating Main Effects for Intervention and Medication

Outcome	Model 1*		Model 2*,†	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
MMD				
Intervention (PA vs HE)	0.81 (0.69, 0.97)	.019	0.84 (0.71, 1.00)	.049
Medication use		<.001		.048
ACEi use versus no use	1.77 (1.35, 2.32)		1.43 (1.07, 1.91)	
Other use versus no use	1.46 (1.12, 1.88)		1.26 (0.96, 1.65)	
Persistent MMD				
Intervention (PA vs HE)	0.72 (0.57, 0.91)	.006	0.75 (0.59, 0.95)	.017
Medication use		<.001		.004
ACEi use versus no use	2.36 (1.58, 3.52)		2.00 (1.31, 3.04)	
Other use versus no use	1.77 (1.20, 2.61)		1.56 (1.04, 2.34)	

Notes: ACE = angiotensin-converting enzyme; CI = confidence interval; HE, health education; HR = hazard ratio; MMD = major mobility disability; PA = physical activity.
*Hazards for disability outcomes stratified by sex and clinical site.
†Includes adjustment for baseline covariates including Short Physical Performance Battery score and a composite index of comorbid conditions reported previously (13,22).

Table 4. Cox Regression Results Indicating Interaction Effect Between Intervention and Medication

Outcome	Model 3*		Model 4*,†	
	PA to HE HR (95% CI)	*p* for Interaction	PA to HE HR (95% CI)	*p* for Interaction
MMD				
ACEi use	0.76 (0.57, 1.02)	.214 (2 *df*)	0.80 (0.59, 1.07)	.175 (2 *df*)
Other antihypertensive use	0.76 (0.60, 0.97)		0.78 (0.61, 0.99)	
No antihypertensive use	1.19 (0.75, 1.87)		1.25 (0.80, 1.98)	
Persistent MMD				
ACEi use	0.57 (0.39, 0.84)	.180 (2 *df*)	0.58 (0.39, 0.86)	.127 (2 *df*)
Other antihypertensive use	0.76 (0.55, 1.06)		0.79 (0.56, 1.11)	
No antihypertensive use	1.18 (0.59, 2.36)		1.31 (0.65, 2.63)	

Notes: ACE = angiotensin-converting enzyme; CI = confidence interval; *df* = degrees of freedom; HE, health education; HR = hazard ratio; MMD = major mobility disability; PA = physical activity.
*Hazards for disability outcomes stratified by sex and clinical site.
†Includes adjustment for baseline covariates including Short Physical Performance Battery score and a composite index of comorbid conditions reported previously (13,22).

the discrepancy between our previous and present findings may be inadequate power in this secondary analysis to detect modest interactions between medication use and intervention for dichotomous clinical outcomes. Still, though the interactions did not reach statistical significance, the data for MMD and persistent MMD are generally consistent with our prior work and encourage further follow-up study.

The data for persistent MMD are particularly intriguing. Our analysis suggests that PA was particularly effective among persons who were taking ACE inhibitors. However, the three-way interaction for sex indicates that this finding was driven primarily by a greater effect in men. It is unclear why such an effect might exist. Women did account for a smaller proportion of ACE inhibitor users compared to the other two medication subgroups, consistent with prior evidence that women are less likely than men to be prescribed ACE inhibitors (26). However, the proportions of women randomized to the two intervention arms were similar for each medication subgroup (Supplementary Table S1). Though evidence is sparse to suggest sex-based physiologic differences in the effects of antihypertensive medications, this sex-based finding could be related to preclinical evidence indicating that female rats have higher renal and circulating levels of the vasodilatory peptide angiotensin (1–7) and other "nonclassical" components of the renin–angiotensin system (27,28). It is important to note, however, that the three-way interaction analyses were purely exploratory and should be interpreted cautiously and should serve as a potential basis for identifying an association of interest for further evaluation. Future studies are likely warranted to fully evaluate the possibility for such an interaction to truly exist.

Recently, Sumukadas et al. (14) reported that random assignment to perindopril did not improve distance walked on the 6-minute walk test compared to placebo alone. However, this prior trial included only 10 weeks of supervised exercise and had a significant proportion of participants (31%) who either refused or discontinued medication—possibly limiting any potential medication effects. The study also differed from the present study as it did not incorporate dichotomous, adjudicated clinical outcomes or compare different antihypertensive classes. The latter point is particularly important given the finding here that use of calcium channel antagonists was associated with a reduction in MMD events among those in the PA compared to the health education intervention. To our knowledge, this is the first report of this association. Subsequent randomized trials are needed to definitely determine if antihypertensive choice influences rates incidence of mobility disability outcomes among older adults.

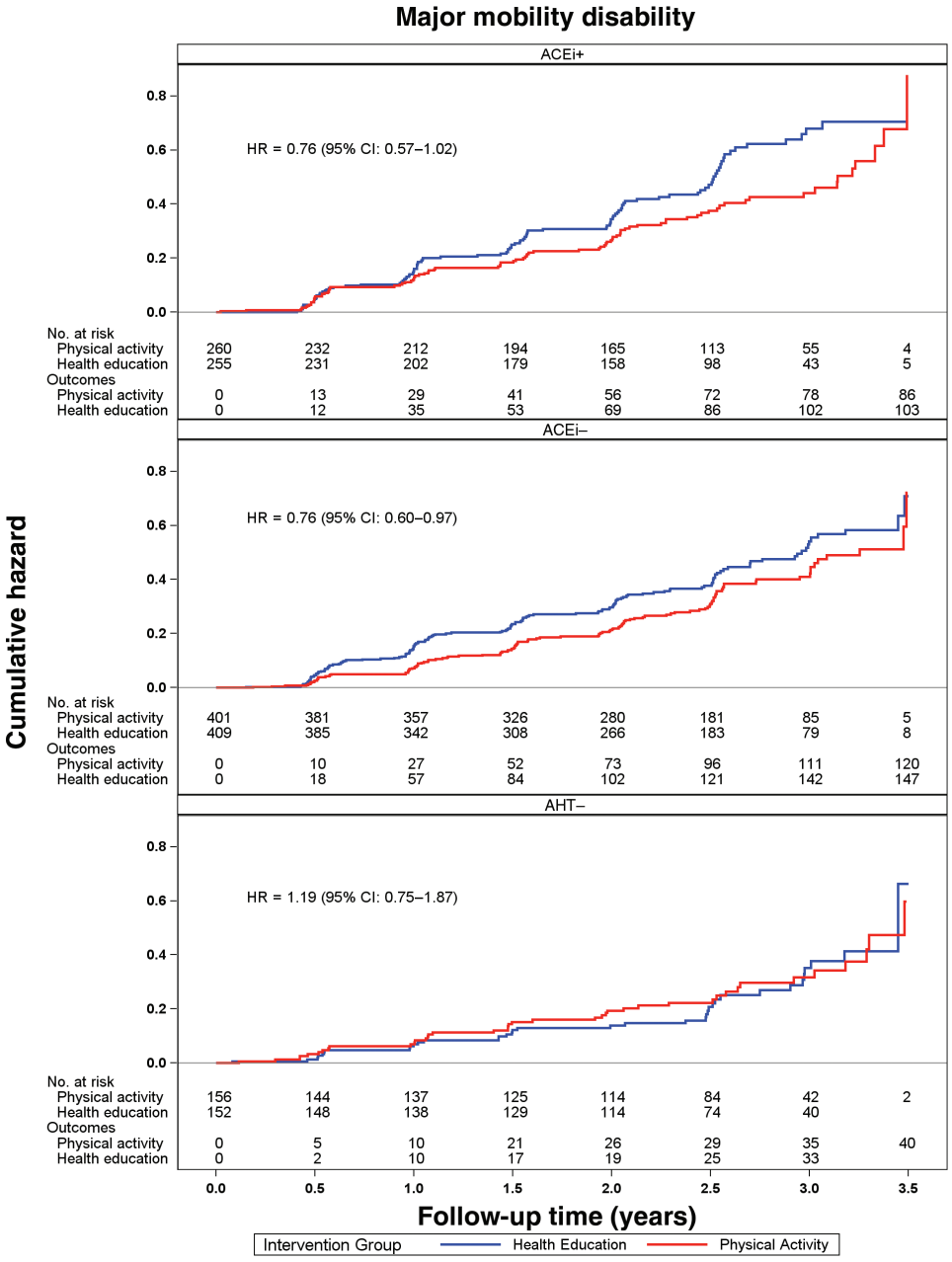

Figure 1. Cumulative hazard plot for time to major mobility disability in each intervention arm by baseline medication usage. Hazard ratio and confidence intervals based on Model 3, Table 4. ACE = angiotensin-converting enzyme; ACEi+ = taking ACE inhibitors; ACEi– = taking antihypertensive medications excluding ACE inhibitors; AHT– = not taking antihypertensive medications.

Given the post hoc nature of this study, there are several points related to the analytic approach and interpretation that require mention. For instance, it should be noted that the AHT– consists of both nonhypertensive individuals and hypertensive individuals not requiring active drug treatment. We explored the potential to evaluate outcome rates among only those persons with untreated hypertension; however, the prevalence of untreated hypertension (2.8% of total study sample) was insufficient to make meaningful comparisons using this group. Moreover, it is critical to note that the objective of this analysis was to evaluate differences in the effects of the PA and health education interventions within each of the subgroups rather than to directly compare outcome rates among medication subgroups. As noted in Table 1, direct comparison among the medication subgroups is significantly confounded by several differences (both observed and unobserved) in baseline characteristics. Thus, future studies with more appropriate study designs are required to evaluate questions related to medication use per se—for example, the potential sources of differences in overall outcome rates across medication subgroups (Table 2). In contrast, the focus of the present analysis is on the effect of randomization within each of these subgroups—a question that can be directly addressed with these data given the randomized design and large subgroup sample sizes ($n > 300$ in all subgroups).

The primary strengths of this study include the clinically relevant population, large sample size, multisite design, rigorous procedures to ascertain and adjudicate outcome events, excellent retention, and well-tracked PA participation over a long-term period. Still, the results of

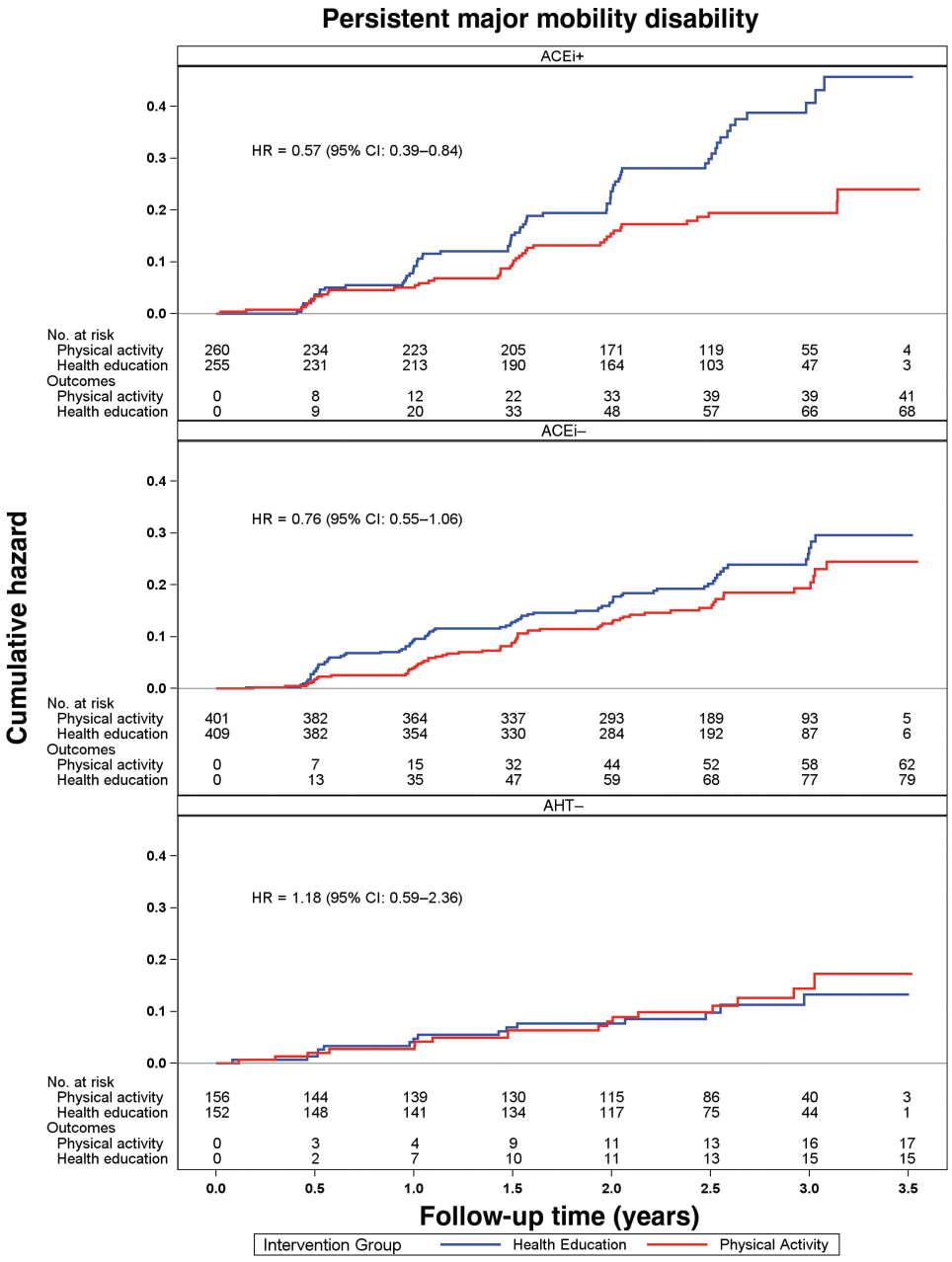

Figure 2. Cumulative hazard plot for time to persistent major mobility disability in each intervention arm by baseline medication usage. Hazard ratio and confidence intervals based on Model 3, Table 4. ACE = angiotensin-converting enzyme; ACEi+ = taking ACE inhibitors; ACEi– = taking antihypertensive medications excluding ACE inhibitors; AHT– = not taking antihypertensive medications.

this study are not conclusive because our findings are based on post hoc subgroup analyses and addressed a number of outcomes. Thus, the potential for a type I error is higher than is suggested by the use of a nominal p value of .05. Second, the trial was not powered to detect interactions with medication use so modest interactions cannot be ruled out. It should also be noted that participants were not randomly assigned to medication usage; thus, the comparisons observed here reflect the effects of PA within each medication subgroup rather than a direct comparison of the effects of differing medication usage. Additional studies that randomly assign patients to medication use are needed to appropriately address this latter question.

In conclusion, the present study is the first to report subgroup findings from a phase 3 trial indicating the potential effects of antihypertensive medications on the incidence of mobility disability outcomes among older adults randomized to long-term PA or health education interventions. These data do not indicate a significant influence of differing antihypertensive medication use on the effect of a PA intervention on the rate of functional outcome events among older adults. However, several findings may warrant further follow-up study. Potentially promising follow-up paths include the differential effects between sexes, the association of calcium channel antagonist use with MMD outcomes, and encouraging results suggesting a benefit of PA among persons taking antihypertensive medications. Future investigations designed specifically to address these newly identified hypotheses may be warranted.

Supplementary Material

Please visit the article online at http://gerontologist.oxfordjournals.org/ to view supplementary material.

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