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Predictors of mortality in patients with lacunar stroke in the Secondary Prevention of Small Subcortical Strokes trial

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Abstract

Background and Purpose—The Secondary Prevention of Small Subcortical Stroke trial (SPS3) recruited participants meeting clinical and radiologic criteria for symptomatic lacunes. Individuals randomized to dual antiplatelet therapy with clopidogrel and aspirin had an

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unanticipated increase in all-cause mortality compared with those assigned aspirin. We investigated the factors associated with mortality in this well characterized population.

Methods—We identified independent predictors of mortality among baseline demographic and clinical factors by **Cox regression** analysis in participants of the SPS3 trial. Separately, we examined the effect on mortality of non-fatal bleeding during the trial.

Results—During a mean follow-up of 3.6 years, the mortality rate was 1.78%/yr for the 3020 participants, mean age 63 years. Significant independent predictors of mortality at study entry were age, diabetes, history of hypertension, systolic blood pressure (HR = 1.3 per 20 mmHg increase), serum hemoglobin < 13 g/dl (HR = 1.6), renal function (HR = 1.3 per eGFR decrease of 20 mL/min), and body mass index (HR = 1.8 per 10kg/m^2 decrease). Participants with ischemic heart disease (p=0.01 for interaction) and normotensive/pre-hypertensive participants (p=0.03 for interaction) were at increased risk if assigned to dual antiplatelet therapy. Non-fatal major hemorrhage increased mortality in both treatment arms (HR 4.5, 95% CI 3.1, 6.6, p <0.001).

Conclusions—Unexpected interactions between assigned antiplatelet therapy and each of ischemic heart disease and normal/pre-hypertensive status accounted for increased mortality among patients with recent lacunar stroke given dual antiplatelet therapy. Despite extensive exploratory analyses, the mechanisms underlying these interactions are uncertain.

Keywords

lacunar stroke; mortality; antiplatelet therapy; clinical trials

Background

Lacunar infarcts, or small subcortical strokes, represent 25% of all ischemic strokes, are associated with cognitive and functional impairment, and are frequently discovered on brain imaging without a prior clinical presentation (i.e. covert infarcts). (1-4) Hypertension is associated, and the pathology is often in the small penetrating arteries of the brain (5) (6). Little is known about the predictors of mortality in those with lacunar infarcts. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial tested two levels of blood pressure control and dual antiplatelet therapy (aspirin plus clopidogrel) vs. monotherapy (aspirin plus placebo) in patients with a recent symptomatic lacunar stroke verified by MRI. All-cause mortality was increased in those assigned dual antiplatelet therapy with higher mortality for vascular and nonvascular causes of death. (7) A meta-analysis of trials of dual antiplatelet therapy vs. aspirin monotherapy did not show a similar association suggesting that the SPS3 results were unique. (8) While fatal hemorrhage was more common in the dual antiplatelet arm (9 cases vs. **4**), the number of fatal bleeds was insufficient to explain the difference in mortality. (7) We sought to determine the predictors of mortality in this population and hypothesized that the increased mortality might be the result of higher rates of non-fatal hemorrhage in the dual antiplatelet therapy group.

Methods

The rationale, design, participant characteristics, and main results of the SPS3 trial have been reported elsewhere. (7, 9-11) In brief, SPS3 was a randomized, multicenter clinical trial

conducted in 81 clinical centers in North America, Latin America, and Spain. Patients >30 years with a recent (<180 days) symptomatic lacunar stroke who were without surgically-amenable ipsilateral carotid artery disease (hemispheral infarcts) or major-risk cardioembolic sources (all infarcts) were eligible and randomized simultaneously in a 2-by-2 factorial design, either to single or dual antiplatelet therapy (aspirin + placebo vs. aspirin + clopidogrel, double-blind) and to one of two target levels of systolic blood pressure control (130-149 mmHg vs. <130 mmHg, open-label). Participants with a clinical lacunar syndrome were required to meet MRI criteria. (7) MRI eligibility was determined by local investigators, with images submitted for central interpretation by a neuroradiologist. Disabling strokes (modified Rankin Scale ≥4) were excluded.

Prior lacunar stroke or TIA was identified only when a clinical episode antecedent to the qualifying event consistent with a classic subcortical ischemic stroke syndrome was documented and was not based solely on neuroimaging findings. Severity of hypertension was determined from the systolic blood pressure at entry adjusted by the number of antihypertensive medications. Specifically, the average of two screening systolic blood pressure measurements (3 measurements each visit) taken at least one week apart, were adjusted by adding 5 mmHg for each antihypertensive medication (up to a maximum of 4) at the time of the measurement. Normotensive was defined as <120 mmHg, pre-hypertensive as 120-<140 mmHg, stage I hypertension as 140-<160 mmHg, and stage II hypertension as ≥160 mmHg. For these analyses, we combined normotensives and pre-hypertensives into one group. Participants with a history of myocardial infarction, angina pectoris as well as those who had undergone coronary artery bypass, coronary angioplasty or stenting were identified as having ischemic heart disease (IHD). Estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation. (12)

Hemorrhage during the trial was defined as major if serious or life-threatening if it met any of the following criteria: urgent hospitalization or emergency medical treatment, transfusion of red blood cells (excluding that associated with coronary artery bypass graft, open-heart, or elective surgery), residual functional sequelae, or surgical therapy for bleeding.

The antiplatelet arm of SPS3 was stopped on recommendation of the data and safety monitoring committee after a planned interim analysis when 2/3 of the primary events had occurred due to futility and evidence of harm (increased mortality in patients assigned dual antiplatelet therapy). For this analysis, we considered deaths that occurred until the time that the antiplatelet trial was terminated; 16 additional deaths that occurred during continuation of the blood pressure trial were not considered. One additional death was discovered after reporting of the main results. (7) The cause of death was adjudicated by a central events committee blinded to treatment assignment and classified as vascular cerebral, vascular non-cerebral, probable vascular, nonvascular, or uncertain. Disagreements were resolved by consensus.

All analyses followed **the** intention to treat principle. Patient demographic and clinical characteristics were summarized by treatment group using proportions for categorical variable and means and standard deviations (SD) for continuous. The distributions of the

continuous variables were assessed for normality and found to be approximately normally distributed with the exception of the body mass index (BMI). BMI was further classified as: < 18.5 kg/m^2 (underweight), 18.5–24.9 (normal), 25–29.9 (overweight), and ≥30 (obese). Crude (univariate) hazard ratios (HR) and the 95% confidence intervals (CI) for each of the patient demographic and clinical characteristics were computed separately by assigned antiplatelet treatment groups. To determine independent predictors of mortality, variables univariately associated with **increased risk of death** ($p < 0.05$) in one or both treatment groups along with assigned antiplatelet treatment group were then considered in a multivariable Cox proportional hazards regression model. Forward stepwise regression was used to identify independent predictors, and interaction terms between assigned antiplatelet treatment and patient characteristic were investigated if the main effect term for the patient characteristic was statistically significant. **HR** estimates and 95% CIs were reported for variables independently predictive of mortality. Mortality and other event rates were computed by dividing the total number of deaths (or other event) by the total number of patient years of exposure for each assigned treatment group. Confidence intervals for event rates were computed assuming a Poisson distribution. The time to major hemorrhage was calculated as the time to the first one in the case of multiple hemorrhages and analyzed as a time dependent variable. Exposure for patients without a major hemorrhage was censored at the time of termination of study participation or at death. Statistical significance was accepted at the 0.05 level, and all tests were two-sided. Analyses were done using SPSS 20.0 (Armonk, NY).

Results

Among the 3,020 participants with recent lacunar stroke, the mean age was 63 years and the frequencies of hypertension, diabetes and ischemic heart disease were 80%, 37% and 10% respectively. During 10,758 years of follow-up for the antiplatelet trial (mean 3.6 years, range 0-8.2 years), there were 191 deaths (annualized rate 1.78%). All-cause mortality was increased in the group assigned dual antiplatelet therapy compared with those assigned aspirin monotherapy (113 deaths vs. 78, HR 1.5, 95% CI 1.1 to 2.0). Mortality did not vary by assigned blood pressure target at the time the antiplatelet trial was terminated. Major bleeding was increased in the dual antiplatelet therapy arm but was not affected by blood pressure target assignment. (Table 1)

Factors at study entry associated with mortality

Patient demographic and clinical characteristics examined for an association with mortality are shown in Table 2. Participants in either assigned antiplatelet group who were older (an average of 7 years), had lower body mass index, were diabetic, a history of hypertension or reduced renal function had increased risk of death. Those assigned to dual antiplatelet therapy with a history of ischemic heart disease, lower diastolic blood pressure, less severe hypertension, aspirin use at the time of the qualifying event, and lower hemoglobin were **also at higher risk.**

By multivariable analysis, independent predictors at study entry of death were increasing age, lower body mass index, history of hypertension, higher systolic blood pressure,

diabetes, hemoglobin <13g/dL, and lower eGFR with no statistically significant interaction between any of these factors and antiplatelet therapy assignment. (Table 3) However, patients assigned to dual antiplatelet therapy with ischemic heart disease (p=0.01 for interaction), and normotensive/prehypertensive patients (p=0.03 for interaction) were at increased risk of death. (Table 3, Figure 1) For the 71% of participants who were stage I or stage II hypertensive but without ischemic heart disease, the mortality rates were equal between antiplatelet arms. There was no significant imbalance in these factors between the antiplatelet assignments. Estimates of HRs were not appreciably changed by the exclusion of history of hypertension as a variable.

Nonfatal hemorrhage and mortality

We hypothesized that nonfatal major hemorrhage would be associated with death and that assignment to dual antiplatelet therapy would be associated with a higher rate of nonfatal major hemorrhage. A major hemorrhage during the study period was independently predictive of mortality (HR 4.5, 95% CI 3.1, 6.6, p <0.001) when added to the model with patient characteristics at study entry **(Table 3)**. No important effect on hazard ratio estimates in that model was observed, and the increased risk of death with major hemorrhage was not increased for patients assigned dual antiplatelet therapy (p = 0.7 for interaction). Of the 161 patients who had a major hemorrhage, the first was fatal for 13 patients (9 assigned dual antiplatelet therapy). Those assigned dual vs. monotherapy had a higher rate of non-fatal major hemorrhage (n=96, 1.9% /pt-yr vs. n=52, 1.0%, p < 0.001). Regardless of assigned antiplatelet treatment, the mortality rate was higher for patients with a non-fatal major hemorrhage compared to those with no major hemorrhage (dual: 4.2%/pt-yr vs. 1.8%, p=0.002; mono: 3.1% vs. 1.3%, p=0.03). (Table 4)

Discussion

The observation of increased mortality in individuals with lacunar stroke assigned dual antiplatelet therapy was unexpected

We undertook data-driven analyses to assess the differential mortality observed with dual antiplatelet therapy in SPS3. Participants with a history of ischemic heart disease had a significantly higher mortality rate when assigned to dual antiplatelet therapy compared to those assigned to aspirin, despite evidence that dual antiplatelet therapy prevents myocardial infarction better than aspirin in populations with vascular disease. (8) Those assigned dual antiplatelet therapy were at increased risk of death if they were normotensive/pre-hypertensive and had no history of ischemic heart disease. While this may be a chance association, the definition of lacunar stroke in SPS3 was rigorous, requiring MRI confirmation, and may have selected for a unique mixture of vascular pathology with an unexpected response to the trial interventions.

Bleeding was associated with mortality in the SPS3 cohort. There were more fatal and non-fatal major bleeds in the dual treatment arm and major nonfatal bleeds correlated with mortality. The association between non-fatal major bleeding and mortality is plausible as it may lead to physician discontinuation of medications and/or nonadherence by patients. (13)The proportion of patients with non-fatal major bleeding in SPS3 was 6.3% in the dual

antiplatelet group and 3.5% in the monotherapy group over a mean follow up of 43 months. These rates are similar to those observed in the CHARISMA trial which compared dual therapy to aspirin in individuals at high vascular risk. (14)

We lacked detailed data on exposure time for non-assigned treatments in participants who withdrew permanently from assigned antiplatelet therapy and cannot exclude antiplatelet non-adherence as an explanation of the excess mortality associated with nonfatal major hemorrhage. Non-adherence is unlikely though to be the complete explanation for the difference in mortality as the increase in vascular mortality in those assigned dual antiplatelet therapy was insufficient to explain the mortality difference between antiplatelet arms. (Table 5)This likely reflects an overlap of factors which affect vascular and non-vascular mortality. In addition, the assignment of cause of death by record review is inherently imprecise and a limitation of our analysis.

In general populations, obese individuals experience significantly higher all-cause mortality when compared to normal weight individuals while those overweight have significantly lower mortality suggesting a J shaped relationship. (15) In SPS3 we found a linear, inverse relationship between BMI and mortality with no interaction with treatment assignment. This may be partially explained by confounding due to smoking or pre-existing disease. (16) While we cannot exclude pre-existing disease, adjustment for smoking did not weaken the association between lower body mass index and mortality. A similar association has been observed in recent observational studies of stroke cohorts. (17, 18) The mechanism for this observation, termed the obesity paradox, remains unexplained.

The overall mortality rate in SPS3 (1.78%/yr) is lower than in other recent trials of secondary prevention. (PRoFESS 3%/yr, VITATOPS **4.7%/yr**, PERFORM **2.6%/yr**, ESPRIT 2.3%/yr) which may be explained by a distinctive type of vascular disease underlying stroke or younger participant age. (19-22) Mortality risk following lacunar infarct was 8% in the first year in a recent systematic review (N = 544). (23)While this is substantially higher than we observed there are several limitations in the observational cohorts which include relatively small numbers, poor and variable definition of lacunar stroke, variable follow up and a mean age of 71 (SPS3 mean age 63). Our analyses have been done in a population which met trial inclusion criteria with aggressive management of blood pressure and high prevalence of statin therapy which likely contributed to lower mortality than found in the systematic review. Independent predictors of mortality in patients with MRI defined lacunar infarcts have not been previously defined. We identified seven independent predictors at study entry of mortality: age, lower body mass index, hemoglobin <13 g/dL, lower eGFR, history of hypertension, increased systolic blood pressure, and diabetes. Nonfatal major hemorrhage during the course of the trial was also associated with increased mortality.

A systematic review and meta-analysis of the effect of the addition of clopidrogel to aspirin on mortality identified SPS3 results as an outlier and noted that overall adding clopidogrel to aspirin does not increase mortality. (8) An interaction between dual therapy and mortality has been observed though in the asymptomatic and primary prevention subsets of the CHARISMA population with increased mortality risk in those assigned dual therapy. (24)

The SPS3 population behaves similar to the low risk population in CHARISMA suggesting that individuals with lacunar infarct form a distinct subset of those with established vascular disease and have increased risk of mortality on dual antiplatelet therapy.

Our study has several limitations. The population included in the study was relatively healthy stroke survivors recruited a median of 62 days after the qualifying stroke. Classification of death as vascular or nonvascular was dependent on the narrative supplied by the trial sites. We did not correct for multiple comparisons and the results must be interpreted with caution.

In conclusion, participants in SPS3, while experiencing a lower mortality rate than previously reported lacunar stroke populations, had higher mortality when assigned dual antiplatelet therapy which was not explained by fatal hemorrhage. It is unlikely to be explained by non-adherence to antiplatelet therapy as vascular mortality did not differ significantly between groups. Unexpected interactions were observed between dual antiplatelet therapy and absence of hypertension and history of ischemic heart disease with increased mortality in both subgroups. This observation, if confirmed in other datasets, has implications for the design of trials testing combination antiplatelet therapy and its broader use in stroke populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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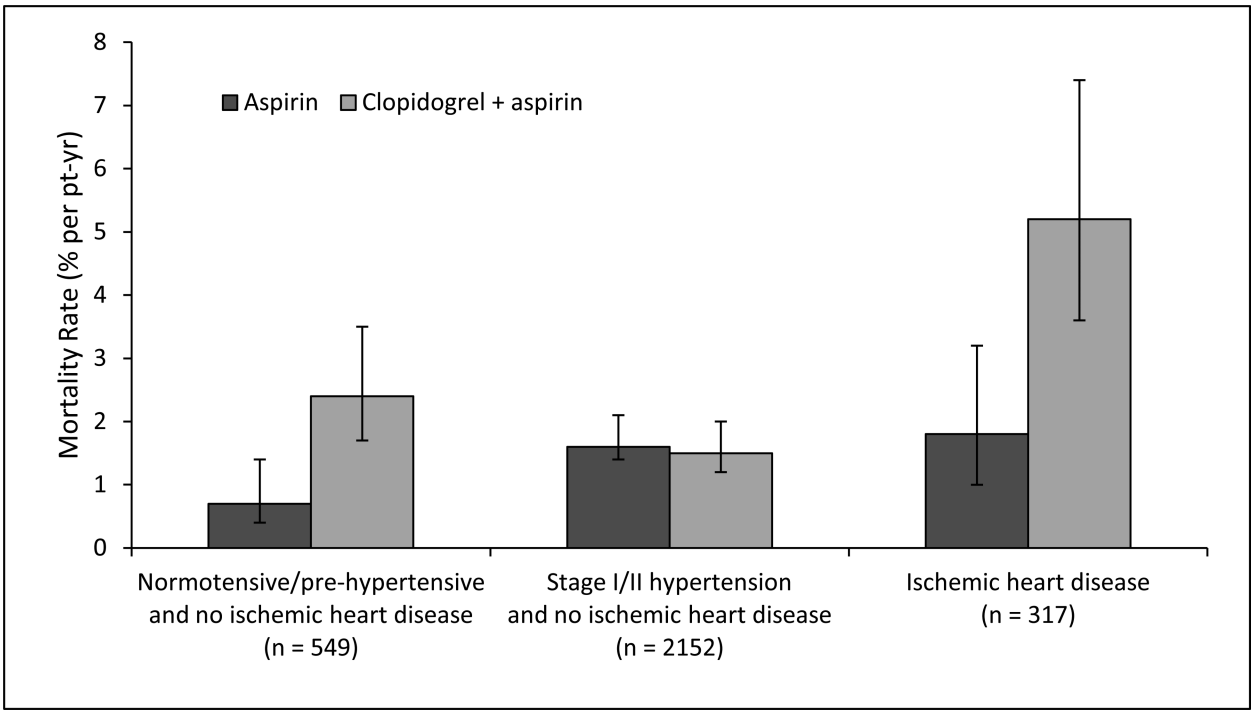

Figure 1.

Mortality rates with bars for 95% confidence intervals by hypertension and ischemic heart disease status and assigned antiplatelet group.

Table 1

Mortality and major bleeding by assigned interventions. The 3020 participants were randomized in a 2 × 2 factorial design to aspirin and higher systolic blood pressure target, n = 755; aspirin and lower target, n = 748; clopidogrel + aspirin and higher target, n = 764, and clopidogrel + aspirin and lower target, n = 753.

		Higher systolic blood pressure target	Lower systolic blood pressure target	Overall
Death, n	Aspirin	37	41	78
	Clopidogrel + aspirin	51	62	113*
	Overall	88	103^	
Major Bleed, n	Aspirin	26	30	56
	Clopidogrel + aspirin	50	55	105
	Overall	76	85	

*Hazard ratio 1.5 for clopidogrel plus aspirin vs. aspirin monotherapy; 95% CI, 1.1 to 2.0, $p = 0.006$.

^Hazard ratio 1.1 for lower vs. higher blood pressure target, 95% CI 0.86 to 1.5, $p = 0.4$.

Table 2

Baseline features associated with all cause death by assigned antiplatelet

	Prevalence, % or mean (sd)		Crude Hazard Ratio (95% CI)	
	aspirin + clopidogrel	aspirin + placebo	aspirin + clopidogrel	aspirin + placebo
Age, years	63 (11)	63 (11)	1.8 (1.5, 2.1)* per 10 year increase	1.8 (1.4, 2.2)* per 10 year increase
Male	62	64	1.1 (0.73, 1.6)	1.2 (0.75, 2.0)
Race/ethnic group				
Non-Hispanic White	51	51	reference group	reference group
Hispanic	30	30	1.0 (0.66, 1.6)	0.60 (0.33, 1.1)
Black	16	16	0.79 (0.46, 1.3)	0.64 (0.34, 1.2)
Other/multiple	3	2	0.81 (0.25, 2.6)	0.86 (0.21, 3.5)
Region				
United States or Canada	65	65	reference group	reference group
Latin America	23	23	1.5 (0.94, 2.3)	0.70 (0.36, 1.4)
Spain	12	12	1.4 (0.74, 2.7)	0.90 (0.38, 2.1)
Body mass index, kg/m^2	29 (6)	29 (6)	2.1 (1.5, 3.1)* per 10 unit increase	1.7 (1.1, 2.6)* per 10 unit increase
Body mass index, kg/m^2			*	*
< 25#	24	23	reference group	reference group
25-29.9	41	41	0.66 (0.44, 1.0)	0.60 (0.36, 1.0)
≥ 30	35	36	0.44 (0.27, 0.71)	0.41 (0.23, 0.72)
Current tobacco smoker	20	21	0.75 (0.45, 1.2)	1.4 (0.85, 2.4)
Alcohol use (≥7 drinks/week)	12	13	0.70 (0.37, 1.3)	1.2 (0.64, 2.3)
History of hypertension	76	74	1.7 (1.0, 2.8)*	2.7 (1.3, 5.7)*
Screening blood pressure, mmHg				
Systolic	143 (19)	143 (19)	1.1 (0.98, 1.2) per 10 unit increase	1.2 (1.1, 1.3)* per 10 unit increase
Diastolic	78 (11)	78 (11)	1.3 (1.1, 1.6)* per 10 unit decrease	1.1 (0.86, 1.3) per 10 unit decrease
Severity of hypertension^			*	
normotensive	2	2	reference group	reference group
pre-hypertensive	18	18		
stage I	40	42	0.55 (0.33, 0.91)	1.3 (0.67, 2.5)
stage II	39	38	1.2 (0.77, 1.9)	1.8 (0.93, 3.3)

	Prevalence, % or mean (sd)		Crude Hazard Ratio (95% CI)	
	aspirin + clopidogrel	**aspirin + placebo**	**aspirin + clopidogrel**	**aspirin + placebo**
Diabetes	35	38	2.0 (1.3, 2.8)*	1.6 (1.0, 2.5)*
Ischemic heart disease	10	11	2.9 (1.9, 4.4)*	1.2 (0.65, 2.3)
Prior symptomatic lacunar stroke or transient ischemic attack	15	15	1.3 (0.82, 2.1)	1.9 (1.1, 3.3)*
Aspirin use at time of qualifying event	30	29	1.5 (1.1, 2.2)*	0.93 (0.57, 1.5)
Statins at time of randomization	68	69	0.91 (0.62, 1.3)	0.69 (0.44, 1.1)
Hemoglobin (g/dL)	14 (2)	14 (2)	0.75 (0.67, 0.84)* per 1 unit decrease	0.92 (0.80, 1.1) per 1 unit decrease
Hemoglobin < 13 g/dL	34	33	2.4 (1.7, 3.5)*	1.6 (1.0, 2.4)*
HbA1c (%) (n = 987 of 1105 diabetics)	8.2 (2)	8.4 (3)	1.0 (0.92, 1.2) per 1 unit increase	1.0 (0.86, 1.2) per 1 unit increase
eGFR (ml/min/1.73m^2)	81 (20)	82 (20)	1.2 (1.1, 1.4)* per 10 unit decrease	1.4 (1.2, 1.5)* per 10 unit decrease
LDL-c (mg/dL)	113 (40)	112 (39)	1.0 (0.98, 1.1) per 10 unit decrease	1.1 (1.0, 1.1) per 10 unit decrease
Assigned intensive blood pressure control	50	50	1.1 (0.82, 1.7)	1.1 (0.70, 1.7)

*Indicates a significant increase in mortality risk ($p < 0.05$)

#13 patients had body mass index < 18.5 kg/m^2

^See Methods section for definition of severity of hypertension.

Table 3
Multivariable predictors of all cause death - final model

Variables considered for MV model were those in Table 1 with $p \leq 0.05$ for one or both treatment groups. If main effect term was significant, then an interaction term with assigned AP was investigated.

	Hazard Ratio (95% CI)	Statistical significance
Age, per 10 y increase	1.6 (1.3, 1.8)	< 0.001
Body mass index per 10 kg/m^2 decrease	1.8 (1.4, 2.4)	< 0.001
History of hypertension	1.7 (1.1, 2.7)	0.02
Systolic blood pressure per 20 mmHg increase	1.3 (1.1, 1.5)	0.003
Diabetes	2.0 (1.5, 2.7)	< 0.001
Hemoglobin < 13 g/dL	1.6 (1.2, 2.1)	0.001
eGFR per 20 mL/min/1.73m^2 decrease	1.3 (1.1, 1.5)	0.02
Normotensive/pre-hypertensive		*
assigned mono antiplatelet therapy	1.0 (0.56, 2.0)	
assigned dual antiplatelet therapy	2.5 (1.5, 4.0)	
Ischemic heart disease		**
assigned mono antiplatelet therapy	0.99 (0.53, 1.8)	
assigned dual antiplatelet therapy	2.7 (1.8, 4.1)	

Abbreviations: eGFR = estimated glomerular filtration rate

* p = 0.03 for interaction

** p = 0.01 for interaction

Table 4

Relationship of severity of first bleeding event during trial and death according to antiplatelet assignment

	Aspirin		Clopidogrel + aspirin	
	# Deaths / n	**Rate (% per pt-yr)**	**# Deaths / n**	**Rate (% per pt-yr)**
Fatal hemorrhage	4/4		9/9	
Non-fatal major hemorrhage	8/52	3.1	18/96	4.2
No major hemorrhage	66/1447	1.3	86/1412	1.8

Table 5

Cause of death by treatment assignment

	Number of deaths		Hazard ratio (95%CI)
	Aspirin	Clopidogrel + aspirin +	
All participants			
All deaths	78	113	1.5 (1.1, 2.0)
Vascular*	25	45	1.9 (1.1, 3.0)
Non-vascular	31	39	
Uncertain cause	22	29	
Ischemic heart disease ± stage I/ II hypertension at entry			
All deaths	11	30	2.9 (1.4, 5.8)
Vascular*	4	14	3.8 (1.2, 12)
Non-vascular	4	9	
Uncertain cause	3	7	
Normotensive/pre-hypertensive and no ischemic heart disease at entry			
All deaths	8	28	3.3 (1.5, 7.3)
Vascular*	0	11	>60 (0.51,> 1000)
Non-vascular	6	9	
Uncertain cause	2	8	
Stage I/II hypertension and no ischemic heart disease at entry			
All deaths	59	55	0.98 (0.68, 1.4)
Vascular*	21	20	1.0 (0.54, 1.8)
Non-vascular	21	21	
Uncertain cause	17	14	

*Includes definite and probable vascular deaths (defined in supplementary appendix)