ORIGINAL RESEARCH

Association Between High-Sensitivity C-Reactive Protein and Total Stroke by Hypertensive Status Among Men

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***Background*—**High-sensitivity C-reactive protein (hsCRP), a marker of systemic inflammation, may promote atherosclerosis, particularly among adults with elevated blood pressure; however, data are sparse. We examined the association between hsCRP concentrations and risk of total stroke by hypertension status (normotension, prehypertension, and hypertension) among men in the Physicians' Health Study (PHS).

***Methods and Results*—**Blood samples were collected (1996–1997) and assayed for hsCRP among 10 456 initially healthy men from PHS I and PHS II and followed from 1997 to 2012. Self-reported hypertension status, cardiovascular risk factors, lifestyle, and alcohol consumption were obtained from the baseline questionnaire prior to randomization in PHS II. Strokes were updated approximately annually and confirmed by medical records according to the National Survey of Stroke criteria. Multivariable Cox models were used. We observed 395 incident total strokes over 115 791 person-years. In analyses adjusted for potential confounders and stroke risk factors, clinically elevated hsCRP (>3 mg/L) was associated with a 40% significantly greater hazard of total stroke compared with hsCRP <1 mg/L (hazard ratio 1.40, 95% CI 1.06 to 1.87; P_{trend}=0.01). Additional adjustment for blood pressure and biomarkers associated with cardiovascular risk marginally attenuated the estimates. Results were similar by hypertension status, although not statistically significant among normotensive and prehypertensive participants due to limited events.

***Conclusions*—**Elevated hsCRP levels were associated with a greater risk of total stroke, even after adjustment for potential confounders and cardiovascular risk factors. Risk of total stroke was significantly higher among hypertensive men with elevated hsCRP compared with normotensive men with low hsCRP. **(*J Am Heart Assoc*. 2015;4:e002073 doi: 10.1161/JAHA.115.002073)**

Key Words: high-sensitivity C-reactive protein • hypertension • ischemic stroke • prehypertension

Elevated blood pressure (BP) is a powerful risk factor for both ischemic and hemorrhagic stroke.[1,2] Stroke risk increases monotonically across the range of systolic BP (SBP), with an 8% increase in risk of stroke for each 10-mm Hg increase in SBP among white adults and a 24% greater risk among black adults.[3] Hypertension (SBP ≥140 mm Hg and/or diastolic BP [DBP] ≥90 mm Hg) is the most common major modifiable risk factors for stroke in the United States, with a prevalence of nearly 30% among adults.[4] In addition, the prevalence of prehypertension among US adults is 36% (SBP 120 to <140 mm Hg, DBP 80 to <90 mm Hg, no current or past history of antihypertensive medication use) and has been consistently associated with greater risk of total incident and fatal stroke. Stroke risk has been shown to increase with the severity of prehypertensive status[5] and is intermediate among the associations observed for optimal BP and hypertensive status.[6] Prehypertension and hypertension status cluster with stroke risk factors, such as high-sensitivity C-reactive protein (hsCRP), elevated body mass index, and glucose.[7]

C-reactive protein (CRP), a marker of low-grade systemic inflammation, has been associated with greater risk and severity of total and ischemic stroke in healthy populations.[8,9] Among 22 676 Japanese men and women, hsCRP above the median was associated with >2-fold increased risk of ischemic stroke among prehypertensive participants and >3-fold risk among hypertensive participants compared with

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Received June 10, 2015; accepted August 10, 2015.

those with optimal BP.[9] Elevated hsCRP concentrations have also been associated with endothelial dysfunction, differentiation of macrophages, and smooth muscle cell proliferation.[10] Moreover, elevated inflammation among prehypertensive and hypertensive adults may exacerbate and accelerate the atherogenic process. Hence, to understand the relationship between inflammation and stroke among persons with elevated BP, we examined the association between hsCRP concentrations and stroke by hypertension status in a large prospective cohort.

Materials and Methods

Physicians' Health Study

We used data from the follow-up cohorts of the Physicians' Health Study (PHS) I[11,12] and PHS II randomized trials.[13] Participants included 11 754 men who continued follow-up in the PHS starting in 1995 and 14 641 participants randomized into PHS II starting in 1997. Analyses were restricted to the 17 176 of 26 395 active participants who provided blood samples starting in 1995. Annual mailed questionnaires regarding trial adherence, adverse events, disease end points, and lifestyle and behavioral risk factors were collected.

Participants were excluded if they were missing data on hsCRP (n=5157), had a prior history of chronic disease (stroke [n=17]; cancer [except nonmelanoma skin cancer; n=1192]; cardiovascular disease, including myocardial infarction, coronary artery bypass graft surgery, and angioplasty [n=108]), or were missing data on BP or reported implausible values (DBP ≤40 or SBP ≥300; n=246). The final baseline population for analysis consisted of 10 456 participants (61% of those who provided blood samples; 3701 in PHS I cohort and 6755 in PHS II).

High-Sensitivity C-Reactive Protein Assay

Participants were asked to have their blood drawn into provided Vacutainer tubes (Becton Dickinson), centrifuged, and returned on cold packs by prepaid overnight courier. On receipt, samples were immediately aliquoted and stored at −80°C in liquid nitrogen freezers. The hsCRP levels (in mg/L) were measured by enzyme-linked immunosorbent assay based on purified protein and polyclonal antibodies (Calibiochem) and standardized to the World Health Organization First International Reference Standard.[14] As reported previously, the assay had sensitivity of 0.08 μg/mL with a mean intra-assay coefficient of variation of 4.2%. CRP has also been shown to remain relatively stable over 5 years (age-adjusted correlation coefficient 0.6, P=0.001).[15] Total and high-density lipoprotein cholesterol was measured using standard laboratory assays, as described previously.[14]

Stroke Assessment

All incident nonfatal and fatal strokes diagnosed after blood draw through the end of follow-up in 2012 were included in these analyses. Men (or next of kin for decedents) reporting stroke on follow-up questionnaires were asked for permission to review medical records. Deaths were detected through information provided by the next of kin and postal authorities and were verified by medical records and death certificates. Follow-up of morbidity and mortality in the PHS is >99% complete. Documentation of stroke events required evidence of a cerebrovascular event obtained from all available sources, including death certificates (for fatal events) and hospital records. Stroke was classified according to criteria established by the National Survey of Stroke[16] requiring evidence of a focal neurological deficit with sudden or rapid onset that persisted for >24 hours or until death. Strokes were classified as ischemic, hemorrhagic (including subarachnoid and intraparenchymal hemorrhage), and stroke of unknown subtype. We counted only stroke diagnoses that were confirmed after review of all medical records and reports of brain imaging by an end points committee of physicians, with excellent interobserver agreement.[17] Interrater reliability was also high for ischemic stroke (96.4%, κ=0.84) and hemorrhagic stroke (97.1%, κ=0.87).[17] The primary end points for this study were total stroke (ischemic, hemorrhagic, and strokes of unknown subtype), with ischemic and hemorrhagic stroke as secondary end points.

Statistical Analysis

Distributions of baseline characteristics were compared by clinical categories of hsCRP.[18] Partial Spearman correlation coefficients for hsCRP and cardiovascular risk factors were adjusted for age. Multivariable Cox models estimated the association between hsCRP and risk of total stroke presented by hazard ratios (HRs) and corresponding 95% CIs. In addition, hsCRP was modeled as continuous after log transformation, according to clinically defined categories (<1, 1 to ≤3, >3 mg/L), and dichotomized at >3 mg/L. Furthermore, we considered the 95th percentile of hsCRP as an upper threshold (<1, 1 to ≤3, >3 to <5.6, ≥5.6). Linear trend was assessed by modeling the median value of each category as ordinal.

Self-reported hypertension status, cardiovascular and lifestyle factors, and alcohol consumption were obtained from the last questionnaire for those not randomized into PHS II or from the baseline questionnaire prior to randomization in PHS II. Hypertension status was defined as normotension (SBP <120 and DBP <80 and no current or past history of treatment for hypertension), prehypertension (SBP 120 to <140 mm Hg or DBP 80 to <90 mm Hg and no current or

past history of antihypertensive medication use), or hypertension (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg or current or past history of antihypertensive medication use). Self-reports of BP among a similar population of male health professionals demonstrated high agreement between reported and confirmed hypertension status.[19] Self-reported physical activity, diet, hormonal status, and chronic disease outcomes (hypertension, diabetes, and heart disease) have been validated previously in similar populations.[20–23] We considered 3 multivariable models. Model 1 adjusted for potential confounders (age, smoking status, physical activity, aspirin use, and PHS cohort). Model 2 (primary model) further adjusted for chronic disease factors associated with stroke risk (body mass index; antihypertensive medication; cholesterol medication; history of hypertension, atrial fibrillation, and diabetes). Model 3 further adjusted for markers of stroke risk (SBP, DBP, total and high-density lipoprotein cholesterol). Indicator variables were assigned for missing values of physical activity (n=36, <1%), antihypertensive medication (n=97, <1%), alcohol (n=47, <1%), and cholesterol medication (n=270 <3%). The HR (95% CI) of total, ischemic, and hemorrhagic stroke by prehypertension and hypertension status was calculated.

Effect modification of hsCRP (≤3 or >3 mg/L) and total stroke was evaluated by selected stroke risk factors (age, hypertension status, SBP, DBP, use of hypertension medication, cholesterol medication, body mass index, history of diabetes, atrial fibrillation, and smoking status). The likelihood ratio test comparing a multivariable model adjusted for main effects to a model including interaction terms was used to test for significant interactions. All *P* values were 2-sided. Analyses were conducted with SAS (version 9.2; SAS Institute).

Statement of Ethics

This study was approved by the institutional review board of Brigham and Women's Hospital, and all procedures followed were in accordance with institutional guidelines. Participants provided written informed consent to participate.

Results

All baseline risk factors varied significantly across categories of hsCRP ($P<0.05$) except for aspirin use and alcohol consumption (Table 1). Men with elevated hsCRP (>3 mg/L) were significantly more likely to be older, current users of antihypertensive medication and/or cholesterol medication, and current smokers and to have a history of diabetes and atrial fibrillation. We observed moderately strong, significant, positive, age-adjusted Spearman correlations ($P<0.001$) for hsCRP and body mass index ($r=0.32$) and modest, significant, positive correlations with SBP ($r=0.12$), DBP ($r=0.09$), and total cholesterol ($r=0.04$). Modest, significant, negative correlations ($P<0.001$) were observed with high-density lipoprotein ($r=-0.22$) and alcohol ($r=-0.05$).

Over 15 years of follow-up (median 11.8 years, interquartile range 10.8 to 13.3 years), there were 395 confirmed total stroke events (338 ischemic, 56 hemorrhagic, and 1 unknown). There were 21 total strokes among normotensive men (12 per 10 000 person-years), 110 among prehypertensive men (22 per 10 000 person-years), and 264 among those with hypertension (52 per 10 000 person-years). In multivariable analyses, men with elevated hsCRP (>3 mg/L) had significantly greater risk of total stroke compared with those with low hsCRP concentrations (<1 mg/L; $P_{trend}=0.01$) (Table 2, model 2), and risk associated with hsCRP exhibited monotonic log-linear association (HR 1.18, 95% CI 1.07 to 1.29). Estimates were only slightly attenuated and remained statistically significant after adjusting for BP and biomarkers of stroke risk. When we considered a value of hsCRP ≥95th percentile (≥5.6 mg/L), results were materially unchanged (data not shown).

Elevated hsCRP (>3 mg/L) among hypertensive men was associated with a significantly greater risk of total stroke, similar to the association in the population overall. Among prehypertensive men, hsCRP >3 mg/L was associated with an elevated but nonsignificant increased risk of total stroke. Estimates for normotensive men were unstable due to few events (n=21), of which only 4 events were among those with hsCRP ≥1 mg/L. Findings were unaltered after restriction to hsCRP concentrations <10 mg/L.

When ischemic and hemorrhagic stroke were examined separately (Table 3), hsCRP >3 mg/L was associated with significantly greater risk of ischemic stroke; estimates for hemorrhagic stroke were elevated but not statistically significant due to a limited number of incident events (n=56). Among hypertensive men, hsCRP >3 mg/L was associated with a significantly greater risk of ischemic stroke compared with hsCRP <1 mg/L. Among normotensive and prehypertensive men, elevated hsCRP was not significantly associated with risk of ischemic stroke.

There was no evidence to suggest that the association between hsCRP and total stroke varied significantly by any a priori stroke risk factors (Table 4) ($P_{interaction}>0.05$).

Discussion

In this population of >10 000 men free of known cardiovascular disease at baseline, elevated hsCRP (>3 mg/L) was associated with a significantly greater risk of total stroke compared with low hsCRP (<1 mg/L). This association did not

Table 1. Baseline Characteristics by Categories of High-Sensitivity CRP

Characteristics	Total	CRP (mg/dL)			*P* Value
		<1	1 to ≤3	>3	
Participants, % (n)	10 456	55 (5781)	33 (3412)	12 (1263)	
Age, y	65±8.9	64±8.4	66±8.9	68±9.0	<0.0001
White, % (n)	92 (9648)	92 (5300)	93 (3170)	93 (1178)	0.03
CRP, mg/dL	0.9 (0.4 to 1.8)	0.5 (0.3 to 0.7)	1.6 (1.2 to 2.1)	4.9 (3.7 to 7.5)	<0.0001
Systolic blood pressure, mm Hg	128.2±12.5	126.6±12.1	130±12.5	131.6±13.0	<0.0001
Diastolic blood pressure, mm Hg	78.2±7.5	77.6±7.4	78.8±7.4	79.3±8.0	<0.0001
Hypertension medication, % (n)					<0.0001
Never	70 (7218)	75 (4285)	66 (2216)	57 (717)	
Past	4 (459)	4 (245)	4 (149)	5 (65)	
Current	26 (2682)	21 (1206)	30 (1010)	37 (466)	
Smoking, % (n)					<0.0001
Never	55 (5700)	58 (3333)	53 (1814)	44 (553)	
Past	42 (4431)	40 (2331)	43 (1474)	50 (626)	
Current	3 (319)	2 (114)	4 (123)	7 (82)	
Exercise ≥1 days/week, % (n)	63 (6605)	67 (3878)	60 (2022)	56 (705)	<0.0001
Aspirin, % (n)*					0.29
0 to 13 days	32 (3366)	33 (1885)	31 (1064)	33 (417)	
Any use	68 (7081)	67 (3892)	69 (2345)	67 (844)	
Alcohol, % (n)					0.09
Rarely	17 (1781)	17 (955)	17 (582)	19 (244)	
Monthly	7 (728)	7 (386)	8 (255)	7 (87)	
2/day to daily	76 (7900)	77 (4414)	75 (2558)	74 (928)	
BMI, kg/m^2	25.8±3.5	25.0±3.0	26.5±3.7	27.1±4.2	<0.0001
History of diabetes, % (n)	6 (591)	4 (244)	7 (233)	9 (114)	<0.0001
Atrial fibrilatiion, % (n)	7 (766)	6 (347)	8 (281)	11 (138)	<0.0001
Total cholesterol, mg/dL	203 (180 to 227)	202 (180 to 225)	205 (182 to 231)	201 (175 to 225)	<0.0001
HDL cholesterol, mg/dL	42.1 (34 to 52)	44 (36 to 55)	40 (32 to 50)	38 (30 to 48)	<0.0001
Cholesterol medication use, % (n)					0.04
Never	80 (8148)	79 (4454)	80 (2675)	83 (1019)	
Past	2 (248)	2 (136)	2 (80)	3 (32)	
Current	18 (1790)	18 (1032)	17 (578)	15 (180)	

Values are mean±SD, median (interquartile range), or frequency (%). BMI indicates body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein.
*Nonuser=0 to 13 days; any use ≥14 days.

significantly differ by hypertension status or other stroke risk factors; however, only 21 stroke events were observed among normotensive participants, underscoring the role of elevated BP in stroke risk. Furthermore, men with elevated hsCRP (>3 mg/dL) exhibited a similarly increased risk of both ischemic and hemorrhagic stroke.

We are aware of only 2 studies that have examined hsCRP and the risk of developing stroke by hypertensive status, with only 1 specifically examining prehypertensive participants. Among a population of middle-aged Japanese adults,[9] in analyses that directly compared CRP across hypertension status, prehypertension status was associated with a non-significantly elevated risk of ischemic stroke (HR 1.72, 95% CI 0.93 to 3.18) compared with normotension. Moreover, prehypertensives with elevated CRP and hypertensives with low CRP (population median: men ≥0.5 mg/L, women ≥0.4 mg/L) exhibited a similarly increased risk of ischemic stroke compared with normotensive participants with low CRP

Table 2. Multivariable Association Between High-Sensitivity CRP and Risk of Total Stroke

	Categories of CRP			
	<1	1 to ≤3	>3	P_{trend}
All men, % (n)*	55 (5781)	33 (3412)	12 (1263)	
Events (n=395)†	176	143	76	
Incidence rate‡	27	38	58	
Age adjusted	1.00	1.20 (0.96 to 1.50)	1.61 (1.23 to 2.11)	<0.001
Model 1	1.00	1.18 (0.94 to 1.47)	1.54 (1.17 to 2.02)	0.002
Model 2	1.00	1.12 (0.89 to 1.41)	1.41 (1.06 to 1.87)	0.01
Model 3	1.00	1.14 (0.90 to 1.44)	1.40 (1.05 to 1.88)	0.02
Normotension, % (n)	67 (997)	26 (381)	7 (109)	
Events (n=21)	17	2	2	
Incidence rate‡	15	5	17	
Model 1	1.00	0.25 (0.06 to 1.07)	0.82 (0.18 to 3.66)	0.49
Model 2	1.00	0.24 (0.05 to 1.04)	0.86 (0.19 to 4.01)	0.55
Model 3	1.00	0.22 (0.05 to 0.97)	0.85 (0.18 to 4.09)	0.49
Prehypertension, % (n)	60 (2575)	31 (1314)	10 (409)	
Events (n=110)	55	39	16	
Incidence rate‡	19	26	36	
Model 1	1.00	1.16 (0.77 to 1.76)	1.39 (0.79 to 2.45)	0.25
Model 2	1.00	1.14 (0.75 to 1.75)	1.36 (0.76 to 2.42)	0.29
Model 3	1.00	1.13 (0.74 to 1.73)	1.36 (0.76 to 2.45)	0.30
Hypertension, % (n)	47 (2209)	37 (1717)	16 (745)	
Events (n=264)	104	102	58	
Incidence rate‡	43	56	79	
Model 1	1.00	1.20 (0.91 to 1.58)	1.50 (1.09 to 2.09)	0.02
Model 2	1.00	1.22 (0.92 to 1.61)	1.50 (1.08 to 2.10)	0.02
Model 3	1.00	1.16 (0.88 to 1.54)	1.42 (1.01 to 1.99)	0.05

Data for models are shown as hazard ratio (95% CI). Model 1 was adjusted for age, smoking status, physical activity, aspirin use, alcohol consumption, and Physicians' Health Study cohort. Model 2: Model 1 plus body mass index; antihypertensive medication; cholesterol medication; history of hypertension, atrial fibrillation, and diabetes. Model 3: Model 2 plus systolic blood pressure, diastolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol. P=0.72 for interaction between CRP and total stroke by hypertension status. CRP indicates C-reactive protein.

*The category *all men* includes normotensive, prehypertensive, and hypertensive men.

†Normotensive estimates should be interpreted with caution due to limited number of events.

‡Incidence rate per 10 000 person-years.

(HR 2.63 [95% CI 1.11 to 6.24] and HR 2.64 [95% CI 1.13 to 6.16], respectively). Ischemic stroke risk was highest among those with hypertension and elevated CRP (HR 3.47, 95% CI 1.54 to 7.79). In contrast, due to the limited number of events among normotensive men, we were unable to directly compare the risk of stroke among prehypertensive and hypertensive men to normotensive men. We observed that the risk of stroke among hypertensive men increased across levels of hsCRP, and the risk of stroke among prehypertensive men was consistently intermediate among normotensive and hypertensive men. Nevertheless, there was no indication that the association between CRP and stroke differed significantly due to hypertension status, suggesting that the role of CRP in stroke pathophysiology may not be significantly altered by hypertension status.

The mechanisms underlying the association between CRP and stroke are not well defined, although atherosclerotic pathways are hypothesized. CRP may induce atherogenesis by activating the inflammatory cascade and interacting with endothelial and smooth muscle cells, resulting in foam cell formation, endothelial dysfunction, and plaque destabilization.[24] In a randomized clinical trial comparing rosuvastatin with placebo, there was a significant reduction in fatal (HR 0.52, 95% CI 0.33 to 0.80) and nonfatal (HR 0.49, 95% CI 0.30 to 0.81) stroke among participants with low low-density lipoprotein and hsCRP >2 mg/L, supporting the role of CRP in

Table 3. Multivariable Association Between High-Sensitivity CRP and Risk of Ischemic and Hemorrhagic Stroke

	Categories of CRP			
	<1	1 to ≤3	>3	P_{trend}
Ischemic stroke*				
All men†				
Events (n=338)	148	126	64	
Age adjusted	1.00	1.25 (0.99, 1.59)	1.60 (1.19 to 2.16)	0.002
Model 1	1.00	1.22 (0.96, 1.55)	1.51 (1.12 to 2.04)	0.01
Model 2	1.00	1.23 (0.95 to 1.57)	1.41 (1.03 to 1.93)	0.04
Model 3	1.00	1.16 (0.90 to 1.49)	1.33 (0.97 to 1.83)	0.08
Prehypertension				
Events (n=85)	44	30	11	
Model 1	1.00	1.12 (0.70 to 1.79)	1.24 (0.63 to 2.42)	0.51
Model 2	1.00	1.06 (0.66 to 1.71)	1.16 (0.59 to 2.30)	0.67
Model 3	1.00	1.02 (0.63 to 1.65)	1.14 (0.57 to 2.28)	0.71
Hypertension				
Events (n=234)	89	94	51	
Model 1	1.00	1.28 (0.95 to 1.71)	1.51 (1.07 to 2.15)	0.03
Model 2	1.00	1.30 (0.97 to 1.75)	1.51 (1.06 to 2.16)	0.03
Model 3	1.00	1.22 (0.91 to 1.64)	1.41 (0.98 to 2.03)	0.07
Hemorrhagic stroke*				
All men†				
Events (n=56)	28	16	12	
Age adjusted	1.00	0.86 (0.47 to 1.60)	1.66 (0.84 to 3.29)	0.14
Model 1	1.00	0.88 (0.47 to 1.63)	1.71 (0.86 to 3.41)	0.12
Model 2	1.00	0.91 (0.49 to 1.72)	1.84 (0.90 to 3.73)	0.09
Model 3	1.00	0.96 (0.51 to 1.81)	1.88 (0.92 to 3.83)	0.08
Prehypertension				
Events (n=25)	11	9	5	
Model 1	1.00	1.30 (0.54 to 3.17)	1.89 (0.63 to 5.66)	0.26
Model 2a	1.00	1.46 (0.59 to 3.60)	2.33 (0.78 to 6.96)	0.13
Model 3a	1.00	1.58 (0.64 to 3.91)	2.46 (0.81 to 7.43)	0.11
Hypertension				
Events (n=29)	15	7	7	
Model 1	1.00	0.63 (0.25 to 1.54)	1.49 (0.60 to 3.70)	0.36
Model 2	1.00	0.62 (0.25 to 1.55)	1.48 (0.58 to 3.79)	0.35
Model 3	1.00	0.65 (0.26 to 1.62)	1.53 (0.59 to 3.94)	0.32

Data for models are shown as hazard ratio (95% CI). Models 1 to 3 are described in Table 2. Model 2a: Adjusted for covariates in Model 2 excluding history of atrial fibrillation, diabetes, and hypertension medication, due to model stability. Model 3a: Model 2a plus systolic blood pressure, diastolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol. P=0.45 for interaction between CRP and ischemic stroke by hypertension status. P=0.47 for interaction between CRP and hemorrhagic stroke by hypertension status. CRP indicates C-reactive protein.
*Stratum-specific estimates for normotensive not included due to limited number of events either overall or in exposed categories (ischemic stroke: 4 events for CRP ≥1; hemorrhagic stroke: 2 events total).
†The category *all men* includes normotensive, prehypertensive, and hypertensive men.

stroke pathophysiology.[25] Moreover, elevated CRP concentrations may exacerbate the underlying proatherothrombotic environment of hypertension.[26] CRP has been independently associated with increases in BP[27] and incident hypertension,[28–30] although these associations may be confined to older populations.[31] Whether CRP plays a causal role or

Table 4. Multivariable* Association Between High-Sensitivity CRP and Total Stroke by Key Cardiovascular Risk Factors

Characteristic	CRP ≤3 mg/L	CRP >3 mg/L, HR (95% CI)	$P_{interaction}$
Age			0.26
Events	80	16	
<65	1.00	1.79 (1.03 to 3.11)	
Events	239	60	
≥65	1.00	1.32 (0.99 to 1.77)	
Hypertension status*			0.90
Events	19	2	
Normotension	1.00	1.23 (0.27 to 5.53)	
Events	94	16	
Prehypertension	1.00	1.29 (0.75 to 2.21)	
Events	206	58	
Hypertension	1.00	1.38 (1.02 to 1.86)	
Systolic blood pressure			0.82
Events	197	42	
<140	1.00	1.67 (1.19 to 2.35)	
Events	122	34	
≥140	1.00	1.47 (1.00 to 2.18)	
Diastolic blood pressure			0.10
Events	283	60	
<90	1.00	1.46 (1.10 to 1.95)	
Events	36	16	
≥90	1.00	2.43 (1.31 to 4.50)	
Hypertension medication†			0.17
Events	176	27	
Never	1.00	1.06 (0.70 to 1.60)	
Events	28	10	
Past	1.00	3.04 (1.30 to 7.13)	
Events	107	38	
Current	1.00	1.56 (1.07 to 2.28)	
Cholesterol medication use			
Events	274	66	0.16
Nonusers	1.00	1.28 (0.97 to 1.69)	
Events	45	10	
Current	1.00	1.71 (0.85 to 3.47)	
BMI			0.75
Events	152	29	
<25	1.00	1.39 (0.92 to 2.10)	
Events	167	47	
≥25	1.00	1.30 (0.93 to 1.82)	
History of diabetes			0.11
Events	284	69	
No	1.00	1.45 (1.10 to 1.90)	
Events	35	7	
Yes	1.00	0.87 (0.38 to 2.01)	
History of atrial fibrillation			0.82
Events	283	63	
No	1.00	1.30 (0.98 to 1.72)	
Events	36	13	
Yes	1.00	1.63 (0.84 to 3.17)	
History of smoking			0.20
Events	144	33	
Never	1.00	1.76 (1.20 to 2.60)	
Events	175	43	
Ever	1.00	1.24 (0.88 to 1.75)	

BMI indicates body mass index; CRP, C-reactive protein; HR, hazard ratio.
*Adjusted for covariates listed for model 2 in Table 2.
†Missing data for 97 participants and 9 events regarding antihypertensive medication.

serves as a marker of subclinical disease remains under debate.[26] Our data indicate that CRP does not influence risk of stroke through hypertension and is not modified by hypertension status, suggesting an independent role for CRP in stroke risk, potentially through other pathways.

It is unclear whether CRP significantly improves long-term prediction of stroke. Current guidelines do not support CRP measurement for stroke risk assessment in healthy or high-risk populations[24]; however, our data suggest that elevated CRP concentrations (>3 mg/L), regardless of hypertension status, were associated with greater risk of total stroke. Persons with prehypertension and elevated CRP may represent an intermediate-risk group that might be targeted for early intervention or clinical trials.[1] Given the high prevalence of prehypertension and hypertension in the United States, with higher estimates among men and particular racial/ethnic minorities,[32] even modest elevations of risk in this group may have a substantial public health impact.

We were unable to examine ischemic stroke subtypes for which atherosclerotic mechanisms may play a more prominent role. These analyses used a single baseline measurement of hsCRP, which may be subsequently influenced by subclinical disease and medication use, particularly statins, for which use increased considerably during follow-up. In analyses excluding those on cholesterol medication at baseline,

however, the association between elevated hsCRP (>3 mg/L) and total stroke was materially unchanged compared with the full cohort analysis (Table 4). Furthermore, previous work by our group has demonstrated long-term stability of hsCRP.[15,24] BP was collected by self-report rather than direct measurement, and that may bias results toward the null; however, these self-reported measures have shown high validity and reliability in this and similar populations of physicians.[19,33] In addition, analyses examining variation by key stroke risk factors may have been underpowered and warrant further study.

Notable strengths of this study include ≈15 years of follow-up with hsCRP concentrations collected prior to stroke events and a comprehensive collection of potential confounders in a socioeconomically homogenous population. Furthermore, in contrast to previous studies,[8] our data suggested a strong positive association between CRP and hemorrhagic stroke despite the smaller number of incident hemorrhagic events, of which the majority were intraparenchymal (n=40) rather than subarachnoid hemorrhage (n=6).

Summary

In this cohort of middle-aged and older men free of baseline cardiovascular disease, we found a positive association between hsCRP concentrations and risk of total stroke. The association was not significantly different between prehypertensive and hypertensive men compared with normotensive men. Elevated hsCRP (>3 mg/L) demonstrated a strong positive association with risk of hemorrhagic stroke; however, estimates were not statistically significant. Our data suggest that evaluating CRP concentrations among these high-risk groups may provide a useful tool to identify populations requiring more intensive risk factor reduction and stroke education.

Sources of Funding

This work is supported by HL102122-S1, CA097193, CA34944, CA40360, HL26490, and HL34595 from the National Institutes of Health (Bethesda, MD, USA). K01HL124391 from the National Heart, Lung, and Blood Institute and the Brigham and Women's Hospital Faculty Career Development Award (Dr. Jiménez).

Disclosures

Dr Ridker, a co-author, is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Seimens.

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