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Biomarkers and functional outcomes from ischemic cerebral events in women: a prospective cohort study

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Abstract

Introduction—Several biomarkers have been associated with increased risk of ischemic stroke. However, the association between these biomarkers and functional outcome from cerebral ischemic events is unclear. We aimed to assess the patterns of association between cardiovascular disease biomarkers and functional outcomes after incident ischemic cerebral events in women.

Methods—Prospective cohort study among 27,728 women enrolled in the Women's Health Study who provided information blood samples and were free of stroke or transient ischemic attack (TIA) at baseline. Multinomial logistic regression was used to determine the association between elevated biomarker levels and functional outcomes from ischemic cerebral events. Possible functional outcomes included TIA and ischemic stroke with mRS (modified Rankin scale) score of 0–1, 2–3 or 4–6.

Results—After a mean follow-up of 15.1 years, 461 TIAs and 380 ischemic strokes occurred. Elevated levels of total cholesterol were associated with the highest risk of poor functional outcome (mRS 4–6) after incident cerebral ischemic events (relative risk=2.02 95%CI=1.18–3.46). We observed significant associations between elevated levels of total cholesterol, Lp(a), C-reactive protein, and triglycerides and mild or moderate functional outcomes after ischemic

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Competing Interests:

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cerebral events. Elevations in all other biomarkers were not significantly associated with functional outcomes.

Conclusions—While total cholesterol was associated with highest risks of poor functional outcome after stroke, we overall observed an inconsistent pattern of association between biomarkers linked with increased risk of vascular events and more impaired functional outcomes from stroke.

Keywords

stroke; epidemiology; biomarkers

Introduction

Since stroke is one of the leading causes of morbidity and mortality worldwide, finding factors that reduce the consequences of stroke has become an important public health target. This importance is particularly great among women who tend to have worse outcomes after stroke than men.[1, 2] One set of factors that may impact stroke morbidity and mortality are levels of cholesterol and other inflammatory biomarkers. Some studies have shown an association between higher serum cholesterol levels and improved ischemic stroke outcomes [3–10] while others have found no association.[11, 12] In contrast, higher levels of C-reactive protein (CRP) have been linked to worse prognosis after ischemic stroke.[13–22]

However, many previous studies were only able to assess cholesterol and CRP levels after a stroke event. This is particularly problematic for CRP, an acute-phase reactant whose levels increase following a stroke.[22] Moreover, information on the relationship between other biomarkers and functional outcomes from stroke is limited.

To address these issues, we studied the patterns of association between a large panel of cholesterol and inflammatory biomarkers and functional outcomes after first ischemic cerebral events in a large cohort of initially healthy women. Based on previous research on the association between elevated levels of total cholesterol, Apo A-1, LDL-C, Apo-B₁₀₀, non-HDL-C and CRP and the risk of cardiovascular events [23], we expected to observe a higher risk of poor outcomes after ischemic cerebral events with elevated levels of these biomarkers.

Methods

Study Population

All participants were enrolled in the Women's Health Study (WHS), a completed randomized trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. The methodology and results have been described previously.[24–26] Briefly, the WHS enrolled 39,876 US female health professionals 45 years without a history of cardiovascular disease (CVD), cancer or other major illnesses. After the end of the trial, women continued to be followed on an observational basis. All participants provided written informed consent and the institutional review board of Brigham and Women's Hospital approved the WHS. Twice in the first year and yearly thereafter, women were asked to complete questionnaires regarding personal characteristics, medical history, health habits and study outcomes (including stroke).

Biomarker measurements

Before randomization, women were asked if they would be willing to provide a fasting venous blood sample. Willing participants were mailed a blood collection kit containing

EDTA tubes. Blood samples were received from 27,939 women and stored in liquid nitrogen until being analyzed. A core laboratory certified by the National Heart, Lung and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization program analyzed the samples for lipids and a panel of inflammatory biomarkers as described previously.[27]

Outcome Ascertainment

If participants reported a stroke or transient ischemic attack (TIA) during follow-up, we asked for permission to review relevant medical records. An Endpoints Committee of physicians reviewed all available information to confirm events. A nonfatal stroke was defined as a focal neurological deficit of sudden or rapid onset and vascular mechanism that lasted >24 hours. A TIA was defined as a focal neurological deficit of sudden or rapid onset and vascular mechanism that resolved within 24 hours. In the event of a fatal stroke, all available sources, including death certificates and hospital records, were used to confirm the event. Strokes were classified according to major subtypes (ischemic, hemorrhagic or unknown) with excellent interobserver agreement.[28] In addition, the modified Rankin scale (mRS) was assigned based on the degree of impairment at hospital discharge. The mRS is a seven-point scale (0=no symptoms at all; 1=no significant disability despite symptoms; 2=slight disability; 3=moderate disability; 4=moderately severe disability; 5=severe disability; 6=death).[29, 30] Similar to a previous study, we decided a priori to categorize the mRS score into three levels (0–1, 2–3 and 4–6).[31] Therefore, our functional outcomes were “neither stroke nor TIA”, TIA, and ischemic stroke with the three categories of the mRS. If a woman experienced multiple TIAs and/or strokes, only the first event was used in our analysis.

Statistical Analysis

Of the 27,939 blood samples we received, 27,737 could be assessed for our complete panel of biomarkers. We also excluded the 9 women with TIAs before randomization, leaving 27,728 women for this analysis. Based on guidelines from the Department of Health and Human Services for lipid standardization [32], we defined quintile cutpoints for all biomarkers based on the women who were not on hormone therapy at baseline (N=15,883). Women were considered to have elevated levels of the biomarker if they had levels equal to or greater than the cutpoint for the highest quintile.[27] We used separate multinomial logistic regressions to calculate odds ratios and 95% confidence intervals as a measure of the relative risk of the relationship between elevated levels of each biomarker and functional outcome events. Our reference categories were women in the lowest four quintiles and who had not experienced a stroke or TIA. By using a reference group of women without an ischemic cerebral event, we will be able to determine the risk of experiencing an ischemic cerebral event with particular functional outcome compared to experiencing no event. This is in contrast to studies which only enroll stroke patients and therefore are only able to determine the risk of poor outcome compared to mild outcome. Women who experienced a hemorrhagic stroke (N=88) or a stroke of unknown type (N=1) were excluded from this analysis.

Our multinomial logistic regression models were adjusted for the following potential confounders: age (continuous), alcohol consumption (rarely/never, 1–3 drinks/month, 1–6 drinks/week, 1 drink/day), physical activity (rarely/never, <1 time/week, 1–3 times/week, 4 times/week), smoking status (never, past, current), migraine status (no history of migraine, migraine with aura, migraine without aura, past history of migraine), body mass index (continuous), history of diabetes (yes/no), currently using hormone replacement therapy (yes/no), treatment with cholesterol lowering medication (yes/no), family history of myocardial infarction prior to age 60 (yes/no), systolic blood pressure (<110, 110–119, 120–

129, 130–139, 140–149, 150–159, 160 mmHg) and baseline treatment with medication for high blood pressure (yes/no). Additionally, we adjusted for randomized treatment assignments. We did not adjust for initial stroke severity at hospital admission because initial stroke severity is an intermediate on the pathway between elevated biomarker levels and our functional outcomes.

If a woman was missing information on body mass index (N=23) or systolic blood pressure (N=291), we assigned her to the median value. In addition, we collapsed the highest three categories of blood pressure into one category (≥ 160 mmHg). Women who were missing information on family history of myocardial infarction (N=460) were assigned to having a family history of myocardial infarction. Less than 100 women were missing information on all other covariates and were assigned to the reference or past user category except for hormone use which were assigned to current use.

All analyses were performed using SAS 9.1 (Cary, NC). All p-values were two-tailed and p-value <0.05 was considered to be statistically significant.

Results

The mean age of the cohort (N=27,728) was 54.7 years (7.1 SD) and the mean body mass index was 25.9 kg/m² (5.0 SD). Most participants rarely or never consumed alcohol and were non-smokers (Table 1).

After a mean of 15.1 years of follow-up, a total of 461 TIAs and 380 ischemic strokes occurred. The average length of time from randomization to TIA or stroke event was 8.4 years. The association between elevated levels of each biomarker and ischemic cerebral events can be seen in Table 2. While most of the elevated biomarkers were not significantly associated with any of our functional outcomes, some statistical associations are apparent. Elevated levels of lipoprotein (a) and CRP are associated with mild outcomes from cerebral ischemic events (TIA or mRS 0–1) while elevated levels of triglycerides were associated with an increased risk of moderate stroke (mRS 2–3). For total cholesterol, the associations with mild versus moderate or severe outcomes were not as clear. Compared with women who did not have elevated levels of total cholesterol and who did not experience a stroke or TIA, women with elevated levels of total cholesterol had multivariable-adjusted relative risks (95% CI) of 1.24 (1.01–1.53) for TIA, 1.43 (1.04–1.97) for mRS 0–1, 1.04 (0.71–1.54) for mRS 2–3, and 2.02 (1.18–3.46) for mRS 4–6. This means that those with elevated levels of total cholesterol have 1.24 times the risk of experiencing an ischemic cerebral event with mild functional outcome compared to experiencing no event. Despite evidence of some statistically significant results, the overall patterns of associations between elevated levels of the biomarkers were not clear and consistent across our outcome categories.

Since not all women were fasting at the time of blood draw, we performed a separate analysis for triglycerides among fasting women only. Results for fasting versus non-fasting triglyceride levels and risk of functional outcomes were similar, although we did not see a significant increase in risk of mRS=2–3 among those with fasting triglycerides (RR=1.51, 95% CI=0.97–2.34).

Adjusting for systolic blood pressure and baseline treatment with medication for high blood pressure did not significantly change our results (results not shown).

Discussion

While total cholesterol showed the strongest association with poor functional outcome after ischemic cerebrovascular disease events, we did not find an association pattern indicating

that elevated levels of biomarkers that lead to increased risk of ischemic stroke result with more adverse functional outcomes in this cohort of middle-aged, primary white, female health professionals. Given the increased risk of cardiovascular events seen among women with elevated levels of total cholesterol, Apo A-1, LDL-C, Apo-B₁₀₀, non-HDL-C and CRP [23], we would expect to see a similar pattern of association for all of these biomarkers and our functional outcomes. However, no consistent pattern emerges and some of these biomarkers are even associated with less severe stroke outcomes.

While a few studies have shown no association between cholesterol levels and functional outcomes after stroke [11, 12], most previous studies have shown an association between elevated levels of cholesterol and improved functional outcomes.[3–10] Unlike previous studies, we found an increase in the risk of poor functional outcomes for elevated levels of total cholesterol. One potential reason for the different results may be the different cohorts studied. Most previous studies only enrolled stroke patients and collected blood measurements after the stroke event. As a result, these studies were not able to enroll participants who experienced a fatal stroke or even perhaps a very severe stroke. If higher levels of cholesterol are truly associated with severe stroke, the design of these studies would prevent this association from being observed.

Previous research has shown that higher CRP levels at hospital admission are related to poor functional outcomes after stroke.[15] In contrast, our study only found a statistically significant increase in the risk of mild strokes among those with elevated levels of CRP. One reason for the difference in results between our studies and previous studies may be due to the time when CRP is measured in relation to the stroke event. Since CRP is an acute phase reactant whose levels increase over time, the CRP levels in stroke patients may be affected by their stroke. Therefore, it is difficult to determine if the association seen between CRP and severe stroke in previous studies is due to CRP elevation causing a severe stroke or a severe stroke causing an elevation in CRP. By measuring CRP at baseline, our study avoids this uncertainty.

Information on the association between other biomarkers and functional outcomes is more limited, but a few studies do exist. High levels of fibrinogen have been associated with increased risk of a poor outcome after stroke [16, 21], while evidence on the association between triglycerides and functional outcomes is mixed.[5, 11] Additionally, one study found that a panel of lipids and inflammatory markers were not related to functional outcome six-months after stroke.[12] Our study did not find any significant associations between fibrinogen and functional outcomes after cerebral ischemic events, but we did see a significant association between elevated levels of lipoprotein (a) and mild functional outcomes.

Strengths to our study include its prospective nature, the large number of participants and outcome events, confirmation of TIAs and strokes by medical record review, and the homogenous structure of the cohort.

Some limitations to our study should be noted. While there are limitations to using the mRS, it widely accepted for use in clinical trials, can be assessed retrospectively from medical records, has strong test-retest reliability, inter-rater reliability, and validity [33, 34], accounts for pre-stroke disability [30], and does not exhibit a “ceiling effect” like the Barthel Index. [35] Biomarker levels were measured at baseline and may not accurately reflect biomarker levels over the course of the study. This intra-individual variation in biomarkers levels would lead to non-differential misclassification and could cause us to underestimate the true association between elevated biomarker levels and the risk of functional outcomes from

ischemic cerebral events. Additionally, as our cohort was composed of mostly white female health professionals, our results may not be generalizable to other populations.

Given the inconsistent patterns and unexpected results seen, it is possible that some of our findings could be due to chance. Alternatively, we may not have enough events in our study to detect true biological effects, especially if these effects are weak or unclear.

In conclusion, while total cholesterol was associated with the highest risk of poor functional outcome after ischemic cerebral events, we could not verify that the set of biomarkers leading to increased risk of ischemic vascular events also leads to more adverse functional outcomes in this cohort of middle-aged, primary white, female health professionals.

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References

1. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke*. 2009 Apr; 40(4):1032–7. [PubMed: 19211484]
2. Kapral MK, Fang J, Hill MD, et al. Sex differences in stroke care and outcomes: results from the Registry of the Canadian Stroke Network. *Stroke*. 2005 Apr; 36(4):809–14. [PubMed: 15731476]
3. Dyker AG, Weir CJ, Lees KR. Influence of cholesterol on survival after stroke: retrospective study. *Bmj*. 1997 May 31; 314(7094):1584–8. [PubMed: 9169402]
4. Lee YS, Chen DY, Chen YM, et al. First-ever ischemic stroke in Taiwanese elderly patients: predicting functional independence after a 6-month follow-up. *Arch Gerontol Geriatr*. 2009 Dec; 49(Suppl 2):S26–31. [PubMed: 20005422]
5. Li W, Liu M, Wu B, Liu H, Wang LC, Tan S. Serum lipid levels and 3-month prognosis in Chinese patients with acute stroke. *Adv Ther*. 2008 Apr; 25(4):329–41. [PubMed: 18414815]
6. Olsen TS, Christensen RH, Kammergaard LP, Andersen KK. Higher total serum cholesterol levels are associated with less severe strokes and lower all-cause mortality: ten-year follow-up of ischemic strokes in the Copenhagen Stroke Study. *Stroke*. 2007 Oct; 38(10):2646–51. [PubMed: 17761907]
7. Pan SL, Lien IN, Chen TH. Is higher serum total cholesterol level associated with better long-term functional outcomes after noncardioembolic ischemic stroke? *Arch Phys Med Rehabil*. 2010 Jun; 91(6):913–8. [PubMed: 20510983]
8. Tanne D, Yaari S, Goldbourt U. High-density lipoprotein cholesterol and risk of ischemic stroke mortality. A 21-year follow-up of 8586 men from the Israeli Ischemic Heart Disease Study. *Stroke*. 1997 Jan; 28(1):83–7. [PubMed: 8996494]
9. Vauthey C, de Freitas GR, van Melle G, Devuyst G, Bogousslavsky J. Better outcome after stroke with higher serum cholesterol levels. *Neurology*. 2000 May 23; 54(10):1944–9. [PubMed: 10822434]
10. Zuliani G, Cherubini A, Atti AR, et al. Low cholesterol levels are associated with short-term mortality in older patients with ischemic stroke. *J Gerontol A Biol Sci Med Sci*. 2004 Mar; 59(3): 293–7. [PubMed: 15031316]
11. Cuadrado-Godia E, Jimenez-Conde J, Ois A, Rodriguez-Campello A, Garcia-Ramallo E, Roquer J. Sex differences in the prognostic value of the lipid profile after the first ischemic stroke. *J Neurol*. 2009 Jun; 256(6):989–95. [PubMed: 19252778]

12. Protopsaltis J, Kokkoris S, Korantzopoulos P, et al. Prediction of long-term functional outcome in patients with acute ischemic non-embolic stroke. *Atherosclerosis*. 2009 Mar; 203(1):228–35. [PubMed: 18602106]
13. Christensen H, Boysen G. C-reactive protein and white blood cell count increases in the first 24 hours after acute stroke. *Cerebrovasc Dis*. 2004; 18(3):214–9. [PubMed: 15273437]
14. Di Napoli M, Papa F, Bocola V. C-reactive protein in ischemic stroke: an independent prognostic factor. *Stroke*. 2001 Apr; 32(4):917–24. [PubMed: 11283392]
15. Idicula TT, Brogger J, Naess H, Waje-Andreassen U, Thomassen L. Admission C-reactive protein after acute ischemic stroke is associated with stroke severity and mortality: the 'Bergen stroke study'. *BMC Neurol*. 2009; 9:18. [PubMed: 19400931]
16. Iyigun I, Bakirci Y. Plasma concentrations of C-reactive protein and fibrinogen in ischaemic stroke. *J Int Med Res*. 2002 Nov-Dec; 30(6):591–6. [PubMed: 12526286]
17. Masotti L, Ceccarelli E, Forconi S, Cappelli R. Prognostic role of C-reactive protein in very old patients with acute ischaemic stroke. *J Intern Med*. 2005 Aug; 258(2):145–52. [PubMed: 16018791]
18. Muir KW, Weir CJ, Alwan W, Squire IB, Lees KR. C-reactive protein and outcome after ischemic stroke. *Stroke*. 1999 May; 30(5):981–5. [PubMed: 10229731]
19. Rallidis LS, Vikelis M, Panagiotakos DB, et al. Inflammatory markers and in-hospital mortality in acute ischaemic stroke. *Atherosclerosis*. 2006 Nov; 189(1):193–7. [PubMed: 16388807]
20. Song IU, Kim JS, Kim YI, Lee KS, Jeong DS, Chung SW. Relationship between high-sensitivity C-reactive protein and clinical functional outcome after acute ischemic stroke in a Korean population. *Cerebrovasc Dis*. 2009; 28(6):545–50. [PubMed: 19844093]
21. Whiteley W, Jackson C, Lewis S, et al. Inflammatory markers and poor outcome after stroke: a prospective cohort study and systematic review of interleukin-6. *PLoS Med*. 2009 Sep. 6(9):e1000145. [PubMed: 19901973]
22. Winbeck K, Poppert H, Etgen T, Conrad B, Sander D. Prognostic relevance of early serial C-reactive protein measurements after first ischemic stroke. *Stroke*. 2002 Oct; 33(10):2459–64. [PubMed: 12364738]
23. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *Jama*. 2005 Jul 20; 294(3):326–33. [PubMed: 16030277]
24. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA*. 2005 Jul 6; 294(1):56–65. [PubMed: 15998891]
25. Rexrode KM, Lee IM, Cook NR, Hennekens CH, Buring JE. Baseline characteristics of participants in the Women's Health Study. *J Womens Health Gend Based Med*. 2000 Jan-Feb; 9(1):19–27. [PubMed: 10718501]
26. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005 Mar 31; 352(13):1293–304. [PubMed: 15753114]
27. Kurth T, Ridker PM, Buring JE. Migraine and biomarkers of cardiovascular disease in women. *Cephalalgia*. 2008 Jan; 28(1):49–56. [PubMed: 17986270]
28. Atiya M, Kurth T, Berger K, Buring JE, Kase CS. Interobserver agreement in the classification of stroke in the Women's Health Study. *Stroke*. 2003 Feb; 34(2):565–7. [PubMed: 12574576]
29. Uyttenboogaart M, Stewart RE, Vroomen PC, De Keyser J, Luijckx GJ. Optimizing cutoff scores for the Barthel index and the modified Rankin scale for defining outcome in acute stroke trials. *Stroke*. 2005 Sep; 36(9):1984–7. [PubMed: 16081854]
30. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988 May; 19(5):604–7. [PubMed: 3363593]
31. Rist PM, Buring JE, Kase CS, Schurks M, Kurth T. Migraine and functional outcome from ischemic cerebral events in women. *Circulation*. 2010 Dec 14; 122(24):2551–7. [PubMed: 21126968]

32. Hanline, A.; Karon, J.; Lippel, K. Lipid research clinics program and lipid and lipoprotein analysis. 2. Bethesda, MD: US Department of Health and Human Services; 1982. Manual of laboratory operations.
33. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke*. 2007 Mar; 38(3): 1091–6. [PubMed: 17272767]
34. New PW, Buchbinder R. Critical appraisal and review of the Rankin scale and its derivatives. *Neuroepidemiology*. 2006; 26(1):4–15. [PubMed: 16272826]
35. Weimar C, Kurth T, Kraywinkel K, et al. Assessment of functioning and disability after ischemic stroke. *Stroke*. 2002 Aug; 33(8):2053–9. [PubMed: 12154262]

Table 1

Baseline characteristics of participants in the Women's Health Study (n=27,728).

Characteristic	Data
Age, mean (SD), years	54.7 (7.1)
Body mass index, mean (SD), kg/m ²	25.9 (5.0)
Alcohol use	
Rarely/never, %	44.2
1–3 drinks/month, %	13.3
1–6 drinks/week, %	32.3
1 drinks/day, %	10.3
Exercise	
Rarely/never, %	37.3
<1 time/week, %	19.5
1–3 times/week, %	31.9
4 times/week, %	11.4
Smoking status	
Never, %	51.8
Past, %	36.8
Current, %	11.5
Current hormones use, %	42.6
History of diabetes, %	2.5
Parental history of myocardial infarction, %	14.4
Migraine status	
Migraine with aura, %	5.1
Migraine without aura, %	7.8
Past history of migraine, %	5.4
Randomized to aspirin, %	50.0
Randomized to vitamin E, %	50.0
Cholesterol lowering medication use, %	3.2
Treatment for high blood pressure, %	13.3
History of hypertension, %	25.1
Biomarker values, median (IQR)	
Total cholesterol, mg/dl	208.0 (184.0, 236.0)
LDL-C, mg/dl	121.4 (100.6, 144.4)
HDL-C, mg/dl	51.9 (43.1, 62.3)
Non-HDL cholesterol, mg/dl	154.4 (129.2, 182.0)
CRP, mg/l	2.0 (0.8, 4.4)
Apo A-1, mg/dl	148.9 (132.3, 167.8)
Apo B ₁₀₀ , mg/dl	100.2 (84.0, 121.3)
Lipoprotein (a), mg/dl	10.6 (4.4, 32.8)
Fibrinogen, mg/l	350.9 (307.6, 403.0)
Homocysteine, μmol/l	10.5 (8.7, 12.9)

Characteristic	Data
Creatinine, mg/dl	0.7 (0.6, 0.8)
Triglycerides, mg/dl	119.0 (84.0, 175.0)

Table 2

Multivariable-adjusted^a relative risks for the association between elevated biomarker levels^b and functional outcomes after ischemic cerebral events in the Women's Health Study (N=27,639).

	Neither Stroke nor TIA (n=26,798)			TIA (n=461)			MRS 0-1 (n=184)			MRS 2-3 (n=139)			MRS 4-6 (n=57)		
	N	%		N	%	RR 95% CI	N	%	RR 95% CI	N	%	RR 95% CI	N	%	RR 95% CI
Total cholesterol	5281	95.6		128	2.3	1.24 (1.01, 1.53)	56	1.0	1.43 (1.04, 1.97)	35	0.6	1.04 (0.71, 1.54)	24	0.4	2.02 (1.18, 3.46)
LDL-C	4670	95.7		114	2.3	1.25 (1.00, 1.56)	45	0.9	1.27 (0.90, 1.80)	30	0.6	0.99 (0.66, 1.50)	19	0.4	1.53 (0.87, 2.70)
HDL-C	7098	97.3		101	1.4	0.82 (0.64, 1.03)	54	0.7	1.31 (0.93, 1.85)	26	0.4	0.72 (0.46, 1.14)	15	0.2	1.36 (0.71, 2.59)
Non-HDL	4993	95.6		118	2.3	1.16 (0.93, 1.44)	51	1.0	1.28 (0.92, 1.78)	41	0.8	1.31 (0.90, 1.91)	19	0.4	1.34 (0.76, 2.36)
Apo A-1	9191	96.8		167	1.8	1.03 (0.83, 1.27)	77	0.8	1.36 (0.98, 1.90)	37	0.4	0.68 (0.45, 1.03)	22	0.2	1.73 (0.94, 3.18)
Apo B ₁₀₀	5301	95.4		129	2.3	1.13 (0.91, 1.40)	59	1.1	1.35 (0.98, 1.87)	47	0.9	1.37 (0.95, 1.98)	22	0.4	1.42 (0.80, 2.47)
Lipoprotein(a)	5163	96.2		106	2.0	1.21 (0.97, 1.51)	51	1.0	1.57 (1.13, 2.17)	32	0.6	1.23 (0.83, 1.84)	13	0.2	1.20 (0.64, 2.24)
CRP	6943	95.8		156	2.2	1.13 (0.91, 1.41)	76	1.1	1.56 (1.12, 2.17)	53	0.7	1.29 (0.88, 1.89)	20	0.3	1.21 (0.66, 2.23)
Fibrinogen	4409	95.6		101	2.2	1.00 (0.78, 1.26)	48	1.0	1.26 (0.88, 1.79)	37	0.8	1.10 (0.73, 1.66)	15	0.3	0.85 (0.45, 1.60)
Homocysteine	4719	96.2		90	1.8	0.96 (0.76, 1.22)	41	0.8	1.12 (0.79, 1.61)	38	0.8	1.33 (0.90, 1.95)	16	0.3	1.19 (0.65, 2.16)
Creatinine	5285	96.6		101	1.9	1.02 (0.81, 1.28)	44	0.8	1.13 (0.80, 1.60)	24	0.4	0.76 (0.49, 1.18)	15	0.3	1.25 (0.69, 2.28)
Triglycerides	5993	95.8		131	2.1	1.08 (0.87, 1.34)	58	0.9	1.13 (0.81, 1.58)	58	0.9	1.92 (1.34, 2.74)	18	0.3	1.05 (0.58, 1.91)

TIA=transient ischemic attack; mRS=modified Rankin scale; RR=relative risk; CI=confidence interval; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; Apo A-1=Apolipoprotein A-1; Apo B₁₀₀=apolipoprotein B₁₀₀; CRP=C-reactive protein. This table excludes the 88 women who experienced a hemorrhagic stroke and the 1 woman who experienced a stroke of unknown type.

^a Adjusted for age, alcohol consumption, physical activity, smoking status, migraine status, body mass index, history of diabetes, currently using hormone therapy, baseline treatment with cholesterol lowering medication, randomized treatment assignment to aspirin and vitamin E, family history of myocardial infarction prior to age 60, systolic blood pressure and baseline treatment with medication for high blood pressure.

^b Elevated biomarker level was defined as the highest quintile of that biomarker in women not taking postmenopausal hormones, with values as follows: total cholesterol=242.0 mg/dl, LDL-C=153.9 mg/dl, HDL-C=61.5 mg/dl, non-HDL cholesterol=191.1 mg/dl, apo A-1=159.8 mg/dl, apo B₁₀₀=126.2 mg/dl, lipoprotein (a)=45.3 mg/dl, CRP=4.19 mg/l, fibrinogen=427.5 mg/l, homocysteine=14.0 μmol/l, creatinine=0.83mg/dl, triglycerides=182 mg/dl.

To convert cholesterol values to millimoles per liter, multiply by 0.02586.