

Lipids and Cardiovascular Disease

Cholesterol and Glucose Metabolism and Recurrent Cardiovascular Events Among the Elderly

A Prospective Study

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OBJECTIVES	The aim of this research was to evaluate the prognostic value of cholesterol absorption assessed with the serum cholestanol-to-cholesterol concentration ratio (lower level reflects decreased cholesterol absorption) among elderly cardiovascular patients (DEBATE [Drugs and Evidence-Based Medicine in the Elderly] study).
BACKGROUND	The components of the metabolic syndrome have been unexpectedly associated with better prognosis among elderly cardiovascular patients. On the other hand, a metabolic syndrome-type state is characterized by high synthesis and decreased absorption of cholesterol.
METHODS	This was a prospective cohort study of home-dwelling individuals age 75 years and older with cardiovascular diseases (247 women, 129 men) recruited from the community. Main outcome measure was multivariate-adjusted time to 3.4-year mortality and recurrent major cardiovascular events.
RESULTS	Serum total and low-density lipoprotein cholesterol levels did not predict outcome. Instead, the mortality risk (64 deaths) increased with increasing levels of cholestanol-to-cholesterol ratio. Patients in the 2nd, 3rd, and 4th quartiles had a relative hazard ratio (HR) for death of 2.54 (95% confidence interval [CI] 1.05 to 6.12), 2.48 (95% CI 1.03 to 6.00), and 3.53 (95% CI 1.52 to 8.19) compared with the lowest quartile, even though 50% of individuals in the lowest cholestanol quartile had metabolic syndrome or diabetes. In multivariate models, the lowest cholestanol ratio quartile was independently associated with lower mortality (relative HR, 0.37, 95% CI 0.17 to 0.81), and with fewer major cardiovascular events (115 events, relative HR, 0.59, 95% CI 0.35 to 0.98).
CONCLUSIONS	Low cholesterol absorption was associated with fewer recurrent cardiovascular events, and with better survival in elderly patients despite frequent abnormalities of glucose metabolism. (J Am Coll Cardiol 2006;48:708–14) © 2006 by the American College of Cardiology Foundation

The aging of the population and postponement of cardiovascular diseases to older ages lead to an increasing number of cardiovascular patients age 75 years and older. Prevention would be important also in old age (1), but a number of studies have suggested that established cardiovascular risk factors of mid-life—such as cholesterol, blood pressure, and overweight—may paradoxically indicate better or neutral prognosis, especially in the oldest patients (2–5). Underlying mechanisms are complex, and because predictors of vascular events in the elderly are poorly understood, new approaches are needed. The metabolic syndrome is the object of intensive research as a “combined” risk factor. It is characterized by a constellation of risk factors, including abdominal obesity, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, small dense low-density

lipoprotein (LDL) particles, elevated blood pressure, pro-inflammatory and prothrombotic states, as well as high plasma insulin (insulin resistance). Metabolic syndrome has been shown to increase cardiovascular and mortality risk in middle-aged populations (6,7). However, data on the metabolic syndrome are controversial in the elderly. In our previous population-based study of individuals age 75 years or older, the components of the metabolic syndrome, including plasma insulin, were unexpectedly associated with better prognosis especially in those with cardiovascular diseases (3,8). Interestingly, we have earlier shown that glucose metabolism and the insulin resistance syndrome are also connected to cholesterol metabolism (9–13). Specifically, a metabolic syndrome-type state is characterized by high synthesis and decreased absorption of cholesterol (9,10,13). In these studies we have used the serum measurement of some noncholesterol sterols to reflect cholesterol synthesis and absorption (14–16). Of these sterols, plant sterols (campesterol and sitosterol) as well as cholestanol are sensitively connected to cholesterol absorption (higher serum levels reflect higher absorption), and lathosterol to cholesterol synthesis (higher serum levels reflect higher synthesis).

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Abbreviations and Acronyms

APOE	= apolipoprotein E
CI	= confidence interval
DEBATE	= Drugs and Evidence-Based Medicine in the Elderly study
HDL	= high-density lipoprotein
HR	= hazard ratio
HsCRP	= high-sensitivity C-reactive protein
LDL	= low-density lipoprotein
MMSE	= Mini-Mental State Examination

We hypothesized that closer analysis of the relationship between cholesterol and glucose metabolism could shed light on the controversial survival data in the elderly cardiovascular patients. Therefore we investigated—using levels of serum noncholesterol at baseline—whether the details of cholesterol metabolism would be related to mortality and cardiovascular diseases during a 3.4-year follow-up in home-dwelling elderly individuals.

METHODS

The subjects of the present study were the participants of the DEBATE (Drugs and Evidence-Based Medicine in the Elderly) study, the design of which has been described in detail previously (17–19). Briefly, in a population-based setting, we recruited 400 home-dwelling individuals (mean age 80 years, 260 of them women) age 75 to 90 years into a “real life” prevention trial. They were retrieved from a random sample of 4,821 subjects age 75 to 95 years and living in Helsinki, Finland. All subjects had a diagnosis of an atherosclerotic disease (prior myocardial infarction, coronary artery disease, previous stroke or transient ischemic attack, peripheral artery disease). During the first visit in the clinic, the participants underwent a brief clinical examination performed by the study nurse including the measurements of blood pressure, waist circumference, weight and height, peak expiratory flow, and laboratory tests. Cognitive function was assessed with a Mini-Mental State Examination (MMSE) where a score of <24 points suggests possible dementia. The history of an atherosclerotic disease and possible diabetes and hypertension was reviewed and confirmed (from hospital records where appropriate) by the investigators. The patients signed an informed consent, whereafter they were randomized to the intervention ($n = 199$) and control groups ($n = 201$) of the multifactorial prevention study. The research protocol of the DEBATE study had been approved by the Ethics Committee of the Department of Medicine, University of Helsinki. No specific exclusion criteria were set because of the real-life nature of the study.

During the mean follow-up of 3.4 years, the treatment in the intervention group was tailored according to current European guidelines (20) by a geriatrician-internist with consultations as appropriate. The procedures were every-day clinical practice; no experimental treatments were used. The

control group received the usual care by primary care physicians, and only visited the study nurse (not the study geriatrician) yearly. Because the present analyses relate baseline characteristics (signs of metabolic syndrome) to study end points, we initially planned to restrict the analyses to the control group only. Preliminary analyses (including analyses of clinical end points) showed, however, that the relationships were similar in both control and intervention groups, and, therefore, the results are presented for the total study population. Moreover, the 1-year feasibility analysis showed that while the intervention procedures improved cardiovascular medications and decreased LDL cholesterol, they failed to change significantly factors related to the metabolic syndrome (body mass index, waist circumference, blood pressure, glucose, HDL cholesterol, or triglycerides) (18).

All routine laboratory measurements (including serum lipids, glucose, and high-sensitivity C-reactive protein [hsCRP]) were performed in the fully qualified central laboratory of the Helsinki University Central Hospital. To convert glucose from mmol/l to mg/dl, multiply by 18.0; to convert cholesterol from mmol/l to mg/dl, multiply by 38.6; to convert triglycerides from mmol/l to mg/dl, multiply by 88.6.

The metabolic syndrome was defined according to the clinical criteria of the Adult Treatment Panel III of the National Cholesterol Education Program (21). A patient had metabolic syndrome if they had 3 or more of the following risk factors: waist circumference of more than 102 cm in men and 88 cm in women, a triglyceride level of 1.7 mmol/l or more, a level of HDL cholesterol of <1.04 mmol/l in men and <1.30 mmol/l in women, a blood pressure of 130/85 mm Hg or more, and a fasting glucose level of 6.1 mmol/l or more. Apolipoprotein E (APOE) alleles were determined as described earlier (22).

Noncholesterol sterols were measured as described previously (9–13), and they are expressed as a ratio to serum cholesterol to standardize for variations in cholesterol concentrations. These noncholesterol sterols include lathosterol (which reflects cholesterol synthesis) and plant sterols (campesterol and sitosterol) and cholestanol (which reflects cholesterol absorption). The level of baseline serum cholestanol-to-cholesterol ratio was used to divide the participants into quartiles of cholesterol absorption efficiency. Cholestanol was used in the analyses because it is not influenced by dietary plant sterols. However, end point data were similar whether any of the absorption markers (absolute or ratios) were used.

At the yearly evaluations, all participants (intervention and control) visited the study nurse, and baseline clinical evaluation and laboratory examinations were repeated (17). Possible study end points and hospital admissions were reviewed, and hospital records retrieved as needed (19).

The study period ended December 31, 2003, whereafter all surviving participants, not residing in institutions, of both groups were contacted by telephone during January 2004. The aim of the interview was to check current

medications and possible hospital admissions after the latest visit at the clinic. In order to assess end points among dropouts and institutionalized patients, we also used the national hospital discharge register to find data on them. Death certificates were retrieved from hospitals or Statistics Finland, where appropriate. The assessment of vital status was 100% complete. All possible end points (fatal and nonfatal) were reviewed and adjudicated by a blinded outside review board (19). For the present analyses, major cardiovascular end points were determined and categorized as follows: nonfatal myocardial infarction, hospitalization for congestive heart failure, cerebrovascular event, or any cardiovascular death, as originally stated in trial design (17). Cause of death was classified into 4 classes: coronary, other cardiovascular disease, cancer, or other causes. A hospital-verified acute coronary event was defined according to the European Society of Cardiology/American College of Cardiology definitions (23). Hospitalization for congestive heart failure was verified when heart failure was deemed the primary cause for hospitalization, and for which additional medication was administered. Cerebrovascular event required sudden onset of a neurological deficit. Current hospital routine in Finland includes brain imaging in these cases.

Statistical analyses. We used the NCSS statistical program (2000 version, NCSS, Kaysville, Utah). Analysis of covariance was used to compare continuous variables. Kaplan-Meier curves were constructed for primary cardiovascular end points and total mortality from start of trial to event or to the end of the trial period. Cox proportional hazards models were used for multivariate analyses. For continuous variables, relative hazard ratio (HR) (with 95% confidence interval [CI]) were calculated per standard deviation (SD). Values of $p < 0.05$ were considered statistically significant.

RESULTS

In the whole group, absolute mean serum cholestanol concentration was 313.3 $\mu\text{g}/\text{dl}$ (SD 100.2, median 294.0, interquartile range 241.3 to 362.0), and the mean concentration relative to 100 mg of serum cholesterol was 156.7 μg (SD 40.5, median 149.3, interquartile range 129.7 to 177.5). Cholestanol-to-cholesterol ratio was used in all subsequent analyses. Baseline characteristics of the participants in the cholestanol-to-cholesterol quartiles are shown in Table 1. Lathosterol-to-cholesterol ratio decreased, and plant sterol (campesterol and sitosterol) to cholesterol ratios increased with increasing cholestanol-to-cholesterol quartile, demonstrating the relationships between synthesis and absorption of cholesterol also in this elderly cohort. Several features of the metabolic syndrome (waist circumference, fasting plasma glucose, triglycerides, and HDL cholesterol) were significantly different between the quartiles, the lowest cholestanol-to-cholesterol quartile showing the most metabolic syndrome-like pattern. Of note was that the lowest quartile also included the highest proportion of patients

with diabetes (30.9% vs. 14.9% in other quartiles combined, $p = 0.0006$). On the other hand, hsCRP concentrations, blood pressure, or the proportion of hypertensives were not significantly different between the quartiles. Of the major cardiovascular diseases (Table 1), there tended to be fewer individuals with a history of myocardial infarction in the lowest cholestanol quartile (36.2%) as compared with other quartiles combined (43.6%), but the difference was not statistically significant ($p = 0.2$). No consistent pattern in the New York Heart Association functional classification or the history of cancer was observed between the quartiles (data not shown). Age was slightly and significantly different between the quarters, whereas there were no differences in cognitive function assessed with MMSE or the proportion of the APOE 4 genotype between the quartiles.

During the 3.4-year follow-up, 64 individuals died and 115 either died or had a major recurrent cardiovascular event. Comparison of the cholestanol-to-cholesterol quartiles revealed that the lowest quartile had the lowest incidence and the highest quartile the highest incidence of end points; the incidences in the 2nd and 3rd quartiles were between the lowest and highest quartiles, and not different from each other (data not shown). The lowest cholestanol-to-cholesterol quartile had systematically the lowest incidence. Patients in the 2nd, 3rd, and 4th quartiles had a relative HR for death of 2.53 (95% CI 1.05 to 6.1), 2.48 (95% CI 1.03 to 6.0), and 3.53 (95% CI 1.5 to 8.2) compared with the lowest quartile. Thereafter, we compared the lowest quartile versus other quartiles combined. Unadjusted curves for total mortality and primary end point or death combined are shown in Figures 1A and 1B. We also performed the survival analyses separately in the intervention and control groups, and they were essentially similar (data not shown). We further compared noncholesterol sterol values at baseline in survivors and those with cardiovascular event or death (Table 2). The results showed that both cholestanol-to-cholesterol and sitosterol-to-cholesterol ratios were significantly lower and lathosterol-to-cholesterol ratio tended to be higher in survivors.

Multivariate analyses with the use of the Cox proportional hazards model were performed comparing the lowest cholestanol quartile with the other quartiles combined. The results with the use of various covariates are shown in Table 3. Also in these analyses, the lowest cholestanol quartile systematically has the best prognosis, both for total mortality (62% lower) and mortality and cardiovascular disease end points combined (41% lower). If the presence of the metabolic syndrome or diabetes was added to the fully adjusted model, it was an independent predictor of death or nonfatal cardiovascular events ($p = 0.03$), but also the lowest cholestanol quartile remained statistically significant ($p = 0.02$), and its point estimate did not change much (0.55).

Finally, we tested the impact of various noncholesterol sterol-to-cholesterol ratios as continuous variables on the risk of mortality and cardiovascular disease end points. With

Table 1. Characteristics of the DEBATE Study Population According to the Cholestanol-to-Cholesterol Quartiles*

	Lowest (n = 94)	2nd (n = 94)	3rd (n = 94)	Highest (n = 94)	p Value
	Cholestanol-to-Cholesterol Quartile				
Noncholesterol sterols, $\mu\text{g}/100$ mg cholesterol					
Cholestanol	115.5 (2.2)	139.3 (2.1)	162.1 (2.2)	210.2 (2.2)	
Lathosterol	177.9 (6.0)	133.1 (6.0)	126.6 (6.1)	119.7 (6.1)	<0.0001
Sitosterol	76.2 (5.2)	102.3 (5.2)	132.7 (5.3)	156.1 (5.2)	<0.0001
Campesterol	159.8 (10.6)	201.7 (10.6)	265.8 (10.8)	294.6 (10.7)	<0.0001
Age, yrs	79.0 (0.5)	79.9 (0.5)	80.6 (0.5)	80.9 (0.5)	0.042
Women/men	58/36	58/36	60/34	71/23	0.14
PEF1	357.4 (9.9)	345.9 (9.9)	340.8 (10.1)	319.2 (10.0)	0.054
APOE 4 genotype, n (%)	25 (26.6)	28 (29.8)	24 (25.5)	32 (34.1)	0.74
History of hypertension, n (%)	33	38	35	37	
Diabetes, n (%)	29 (30.9)	16 (17.0)	15 (16.0)	11 (11.7)	0.005
Metabolic syndrome, n (%)†	18 (27.7)	8 (10.3)	11 (13.9)	15 (18.1)	0.039
Metabolic syndrome or diabetes, n (%)	47 (50.0)	24 (25.5)	26 (27.7)	26 (28.0)	0.0007
History of myocardial infarction, n (%)	34 (36.2)	45 (47.9)	37 (39.4)	41 (43.6)	0.39
History of cerebrovascular disease, n (%)	33 (35.1)	35 (37.2)	36 (38.3)	36 (38.3)	0.97
History of congestive heart failure, n (%)	37 (39.4)	32 (34.0)	34 (36.2)	42 (44.7)	0.47
History of peripheral vascular disease, n (%)	12 (12.8)	13 (13.8)	18 (19.4)	14 (14.9)	0.61
Statin treatment at baseline, n (%)	14 (14.9)	17 (18.1)	26 (27.7)	20 (21.3)	0.16
	Adjusted for Age, Gender, PEF1, and Baseline Statin Use				
MMSE points	26.0 (0.3)	26.5 (0.3)	26.4 (0.3)	26.5 (0.3)	0.47
Body mass index, kg/m^2	27.5 (0.4)	26.9 (0.4)	26.2 (0.4)	26.0 (0.4)	0.09
Waist circumference, cm	94.9 (1.0)	92.7 (1.0)	91.2 (1.0)	91.2 (1.0)	0.041
Blood pressure, mm Hg					
Systolic	152 (3)	150 (3)	150 (3)	150 (3)	0.92
Diastolic	74 (1)	74 (1)	75 (1)	73 (1)	0.60
Pulse rate, per min	70.2 (1.2)	68.4 (1.2)	68.9 (1.2)	66.4 (1.2)	0.19
High-sensitivity C-reactive protein, mg/l	2.9 (0.6)	2.3 (0.6)	3.6 (0.6)	3.4 (0.6)	0.22‡
Fasting glucose, mmol/l	5.94 (0.15)	5.24 (0.15)	5.32 (0.16)	5.07 (0.15)	0.0008‡
Fasting lipids, mmol/l					
Cholesterol	5.5 (0.1)	5.4 (0.1)	5.6 (0.1)	5.4 (0.1)	0.39
HDL cholesterol	1.37 (0.04)	1.51 (0.04)	1.56 (0.04)	1.55 (0.04)	0.008
Triglycerides	1.67 (0.07)	1.31 (0.07)	1.43 (0.07)	1.24 (0.07)	0.0002‡
LDL cholesterol	3.3 (0.08)	3.3 (0.08)	3.4 (0.09)	3.2 (0.08)	0.59

To convert glucose from mmol/l to mg/dl , multiply by 18.0; to convert cholesterol from mmol/l to mg/dl , multiply by 38.6; to convert triglycerides from mmol/l to mg/dl , multiply by 88.6. *Continuous variables indicate mean (SE); †individuals with diabetes excluded; ‡logarithmic transformed values used for analysis.

APOE = apolipoprotein E; DEBATE = Drugs and Evidence-Based Medicine in the Elderly; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MMSE = Mini-Mental State Examination, points <24 indicate possible dementia; PEF1 = peak expiratory flow.

the fully adjusted model (Model C in Table 3), the relative HR (per SD) were as follows: cholestanol ratio 1.25 (95% CI 1.07 to 1.46), sitosterol ratio 1.21 (95% CI 1.03 to 1.41), campesterol ratio 1.14 (95% CI 0.96 to 1.35), and lathosterol ratio 0.82 (95% CI 0.65 to 1.04).

DISCUSSION

Our results show that low cholesterol absorption, as assessed with serum cholestanol-to-cholesterol ratio, was associated with fewer recurrent cardiovascular events, and especially with better survival in cardiovascular patients age 75 years or older. The results also suggest a novel interaction on survival between glucose and cholesterol metabolism. Despite more metabolic syndrome and diabetes, those elderly subjects with low cholesterol absorption had better prognoses. Because cholesterol absorption is a partly inherited phenomenon (24,25), an intriguing explanation would be a lower

arterial cholesterol burden during lifetime in these elderly individuals.

Our population was selected from elderly individuals with a history of various cardiovascular diseases. However, they were all home-dwelling at baseline. With the selection, it is quite possible that many individuals with the metabolic syndrome or diabetes and low cholesterol absorption (and high synthesis) have died earlier in life. Our elderly population would thus represent survivors who are resistant to the deleterious effects of diabetes. Only long-term follow-up studies starting from mid-life or earlier would settle this issue. One-half of the population also participated in an intervention study whereupon their medications and risk factors were treated with usual clinical methods. This improved blood pressure and serum LDL cholesterol level in the intervention group and made the cardiovascular drug treatments more evidence-based (18). However, the intervention did not affect clinical end points (19), and, in

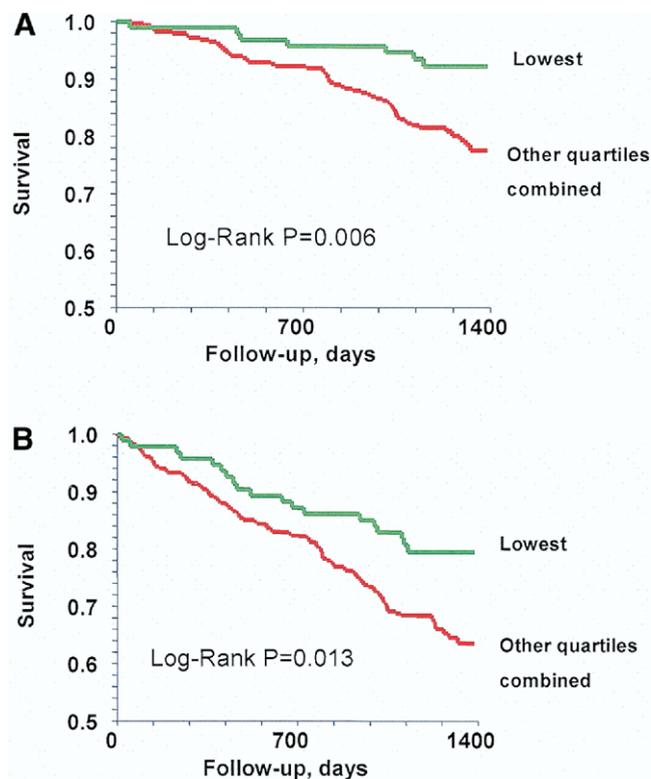


Figure 1. (A) Unadjusted Kaplan-Meier curve for total mortality in the lowest quartile of serum cholestanol-to-cholesterol ratio versus other quartiles combined. (B) Unadjusted Kaplan-Meier curve for primary end point or death in the lowest quartile of serum cholestanol-to-cholesterol ratio versus other quartiles combined.

accordance with this separate analyses of the intervention and control groups, did not change the present conclusions. All primary clinical end points and deaths were reliably collected and adjudicated. Cholesterol metabolism was assessed indirectly using plasma markers (noncholesterol sterols), but this approach has been assessed suitable for epidemiologic studies (15).

As compared with triglyceride and HDL metabolism, cholesterol metabolism has received much less attention in the context of diabetes and metabolic syndrome. However, it is now well established that glucose metabolism interacts with cholesterol absorption and synthesis. In nondiabetic men, high normal plasma glucose was associated with lower cholesterol absorption and higher synthesis (9). The same association has been demonstrated also in patients with diabetes and overweight (10–12). In this context, it would be interesting to study the glucose metabolism in Tarahumara Indians who have inherently low cholesterol absorption (26).

There are no previous studies of the relationship between details of cholesterol metabolism and survival, and thus it is an intriguing finding that elderly cardiovascular patients with the metabolic syndrome and diabetes have a better prognosis if they have a concomitantly low cholesterol absorption. The most probable explanation would be that outcome is related to cholesterol absorption. A population-

based study in Finland showed that—at least in men—LDL cholesterol level is dependent on cholesterol absorption (14). Because cholesterol absorption efficiency is genetically determined, it probably tracks well through the lifespan. Thus, elderly individuals with low cholesterol absorption could represent a subgroup with lower lifetime cholesterol burden on their arteries, with better prognosis as the result. Fasting serum LDL cholesterol levels were similar in the quartiles of cholesterol absorption (Table 1), but we did not measure postprandial lipids. Compensating mechanisms could also contribute to the similarities in the LDL cholesterol levels. A classic example is the man who, despite a massive egg consumption, did not have hypercholesterolemia probably due to low absorption and efficient conversion of cholesterol to bile acids (27). Bile acid production could not be studied in the present study. A more speculative explanation for the survival findings would be that low cholesterol absorption represents lower burden of serum plant sterols, which have been suspected to be a cardiovascular risk factor (28). There is no consensus on this, however (29). Finally, an alternative explanation is that better prognosis is related primarily to the presence of the metabolic syndrome, and diabetes and low cholesterol would be secondary phenomenon. The metabolic syndrome could thus reflect a better nutritional state in these oldest survivors with low cholesterol absorption. This is unlikely, however, and overall the presence of the metabolic syndrome or diabetes did predict recurrent cardiovascular events also in the present cohort (HR of primary end point 1.61, 95% CI 1.09 to 2.39) (30). This is not controversial with the finding that lowest cholestanol quartile (with more diabetes and metabolic syndrome) had less cardiovascular disease, because our analyses showed that lower cholesterol absorption was associated with reduced events among individuals with or without the metabolic syndrome or diabetes.

There are scarce studies of possible subgroups of risk within diabetes and the metabolic syndrome. However, the present findings suggesting varying cardiovascular risk is indirectly supported by some earlier data. In a population-based study, high insulin predicted better survival in elderly individuals with cardiovascular disease (8). It could be considered that this is due to “senile devitalization” or

Table 2. Baseline Values of Noncholesterol Sterols-to-Cholesterol Ratios in Survivors and Those With Primary End Point or Death*

Lipid	Group		p Value
	Alive (n = 261)	Primary End Point or Death (n = 115)	
Noncholesterol sterols, $\mu\text{g}/100 \text{ mg cholesterol}$			
Lathosterol	142.2 (4.1)	130.9 (6.2)	0.14
Sitosterol	111.2 (3.7)	128.3 (5.5)	0.01
Campesterol	223.0 (7.3)	245.5 (11.0)	0.10
Cholestanol	152.9 (2.5)	165.4 (3.7)	0.006

*Values are mean (SE) adjusted for age and gender.

Table 3. Multivariate Relative Hazard of End Points During the 3.4-Year Follow-Up According to Baseline Cholestanol-to-Cholesterol Quartile

	Relative Hazard With 95% CI*		
	Model A†	Model B‡	Model C§
Total mortality (n = 64)			
Higher cholestanol-to-cholesterol quartiles combined	1.0 (referent)	1.0	1.0
Lowest cholestanol-to-cholesterol quartile	0.38 (0.17–0.84), p = 0.016	0.38 (0.17–0.83), p = 0.016	0.37 (0.17–0.81), p = 0.013
Death or nonfatal cardiovascular event (n = 115)			
Higher cholestanol-to-cholesterol quartiles combined	1.0 (referent)	1.0	1.0
Lowest cholestanol-to-cholesterol quartile	0.58 (0.35–0.97), p = 0.036	0.58 (0.35–0.96), p = 0.036	0.59 (0.35–0.98), p = 0.040

*Relative hazard was calculated using the Cox proportional hazards model; †Model A: adjusted for age and gender; ‡Model B: adjusted as in Model A plus treatment group during follow-up; §Model C: adjusted as in Model A plus apolipoprotein E 4 genotype and statin treatment at baseline.
CI = confidence interval.

frailty, but lower cholesterol absorption associated with high insulin would be an alternative explanation. Although diabetes has been associated with dementia in longitudinal studies, an interesting recent autopsy analysis of patients with Alzheimer's disease unexpectedly reported less Alzheimer-associated neuropathology in old survivors with diabetes (31).

What are possible clinical implications of our findings? If elderly cardiovascular patients with high cholesterol absorption have worse prognosis, they might logically benefit from agents lowering cholesterol absorption such as ezetimibe or plant stanol esters probably combined with a statin. To prove the benefits for clinical end points would require a clinical trial. The current problem is, however, that clinicians do not have easy methods to assess individual cholesterol metabolism because the measurement of noncholesterol sterols requires sophisticated equipment. Such a method would also be useful, irrespective of therapeutic implications, because our study demonstrates the clear prognostic value of cholestanol level in elderly cardiovascular patients (Fig. 1).

In conclusion, even with frequent metabolic syndrome and diabetes, a low cholesterol absorption was associated with fewer recurrent cardiovascular events, and especially with better survival in elderly cardiovascular patients. This may be due to selective survival in these elderly individuals. On the other hand, because cholesterol absorption is partly genetically determined, the mechanism may be a lower cholesterol burden during lifetime. Cholesterol absorption may thus modulate the risk associated with diabetes and the metabolic syndrome.

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