European Heart Journal (1997) **18**, 52–59

Low total cholesterol is associated with high total mortality in patients with coronary heart disease

S. Behar, E. Graff*, H. Reicher-Reiss, V. Boyko, M. Benderly, A. Shotan and D. Brunner for the Bezafibrate Infarction Prevention (BIP) Study Group*

*Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer, and *Institute of Physiological Hygiene, Edith Wolfson Medical Center, Holon, Israel*

The present non-intervention screening study was undertaken to explore the relationships between pre-existing low total cholesterol and all-cause mortality. Eleven thousand, five hundred and sixty-three patients with coronary heart disease who attended a screening visit but were not included in the Bezafibrate Infarction Prevention study were followed-up for a mean of 3·3 years after determination of baseline total cholesterol. Five hundred and ninety-five (5%) of this largely unselected population who had total cholesterol levels ≤ 160 mg . dl^{-1} formed the study population. The remaining 10 968 patients acted as controls. The relative risk of all-cause mortality among patients with low cholesterol compared to others was 1·49 (95% CI: 1·16–1·91). The relative risk of non-cardiac death was 2·27 times higher in the low cholesterol group than in the controls (95% CI: 1·49–3·45), whereas the risk of cardiac death was the same in both groups (relative risk 1·09; 95% CI: 0·76–1·56). The most frequent cause of non-cardiac death associated with low total cholesterol was cancer. These results in patients with coronary heart disease add weight to previous studies associating low total cholesterol with an increased risk of non-cardiac death. However, a longer follow-up of this cohort of patients is necessary in order to clarify this association.
(Eur Heart J 1997; 18: 52–59)

Key Words: Total cholesterol, coronary heart disease, cardiac mortality, non-cardiac mortality.

Introduction

The link between high total serum cholesterol levels and the risk of cardiac mortality has been well established[1–3]. A meta-analysis of 19 primary and secondary intervention studies has estimated that for every 1% reduction in total cholesterol there is a 2·5% decrease in the incidence of coronary heart disease[2]. The same study found that, on average, an 8 to 9% reduction in total cholesterol was required to lower mortality from coronary heart disease. More recently two major studies have clearly shown that lowering total cholesterol with statins in patients with proven coronary heart disease (secondary prevention) or among men at high risk but free from coronary heart disease (primary prevention) resulted in highly significant reductions of total and cardiac mortality with no effect on the non-cardiac death rates[4,5].

Although the benefits of lowering blood cholesterol in order to protect patients from premature death caused by myocardial infarction or stroke are undisputed, national campaigns to identify high cholesterol in the community need to give serious consideration to the increasing body of evidence from epidemiological studies linking low total cholesterol to an increased risk of non-cardiac mortality[1,6–9]. Lung cancer is the most consistent cause of non-cardiac death to be associated with low serum cholesterol levels[10–12]. The incidence of cancer of the colon is also strongly correlated but no association has been found for gastric, rectal[3] or brain cancer[13].

The general consensus is that the risk of non-cardiac death increases when total cholesterol falls to ≤ 160 mg . dl^{-1}. It is therefore important that the theoretical possibility of lowering cholesterol too far does not have a negative impact on health care objectives of reducing the incidence of fatal cardiac events in high risk patients. The recommended policy (especially in primary prevention) is to use drug intervention conservatively, especially in young and elderly patients and only after dietary and life style changes have been shown to have failed[8].

Most of the studies linking low total cholesterol to non-cardiac death have been conducted in general population cohorts and seldom specifically among patients with coronary heart disease. The aim of the present study was to investigate whether a relationship

Manuscript submitted 28 February 1996, and accepted 3 April 1996.

Correspondence: S. Behar, BIP Coordinating Centre, Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer 52621, Israel.

0195-668X/97/010052+08 S18.00/0

exists between a pre-existing low total cholesterol (≤ 160 mg . dl^{-1}) at screening and subsequent mortality resulting from both cardiac and non-cardiac events in patients with coronary artery disease. The population was selected from the total cohort of 14 685 patients who were screened for the Bezafibrate Infarction Prevention (BIP) study[14,15]. This population of cardiac patients is probably one of the largest ever studied. The BIP study is an intervention trial designed to assess the efficacy of long-term bezafibrate administration on reduction of fatal and non-fatal coronary events in patients with coronary heart disease, a low HDL cholesterol, and moderately elevated total cholesterol[14].

Methods

Patient selection

The patients were recruited from 18 cardiac departments in Israel. It was our intention to conduct this investigation in a largely unselected group of patients of either gender, aged between 45 and 74 years, who had a history of myocardial infarction or coronary insufficiency. The diagnosis of coronary insufficiency included typical angina documented by a positive exercise test, radionuclear studies or coronary angiography.

Out of the 14 685 patients screened for the BIP study, 3122 patients with moderately elevated total cholesterol (>180 mg . dl^{-1} and <250 mg . dl^{-1}) and relatively low HDL-cholesterol (≤ 45 mg . dl^{-1}) were randomized to be treated with placebo or bezafibrate (Bezalip Retard) and therefore excluded from the present analysis. Eleven thousand, five hundred and sixty-three patients who failed to fulfil the BIP entry criteria form the cohort of the present study.

Clinical assessments

Age-eligible patients with documented coronary heart disease were invited to a screening examination during which medical and historical data were recorded and blood was drawn for the assessment of the lipid profile. Baseline blood cholesterol, HDL-cholesterol and triglycerides were measured at a central laboratory (Edith Wolfson Medical Center, Holon) from samples taken at the screening visit after the patients had fasted for 14 h. The samples were drawn into vacuum tubes containing a separation gel. After 30 min at room temperature, the tubes were centrifuged at 4 °C for 15 min at 3000 rpm and the serum was separated from the plasma.

All assays were performed on a Boehringer–Hitachi 704 random access analyser using Boehringer–Mannheim diagnostic kits. Free glycerol was determined separately with an enzymatic kit (Sigma Chemical, St Louis, MO, U.S.A.) and was subtracted from the triglyceride level. HDL-cholesterol was determined by precipitation of LDL- and VLDL-cholesterol with phosphotungstate. The total cholesterol concentration was determined in the supernatant.

The low cholesterol group included patients with spontaneous total cholesterol of ≤ 160 mg . dl^{-1}. Per protocol none of these patients were included in the intervention study (BIP). All others screened with a total cholesterol of >160 mg . dl^{-1}, but not randomized to BIP, formed the control group.

Mortality data were obtained from the Israeli population registry a mean 3·3 years (range 31–55 months) after the screening visit.

Statistical assessments

The objective of the analysis was to compare mortality in patients with low baseline cholesterol (≤ 160 mg . dl^{-1}) with those in a control group who had baseline cholesterol >160 mg . dl^{-1}. Cause of death was classified using the DHHS ICD-9 system[16]. Cardiac deaths included codes 410–414 (coronary) and 415–429 (other cardiac). SAS software was used for statistical analysis. Multivariate analysis of long-term mortality was performed using the Mantel–Haenszel pooled relative risk model (procedure FREQ with CMH option). Actuarial survival curves were produced using the LIFETEST procedure[17].

Results

Demographic data

Only patients who were excluded from the BIP study and who had complete mortality data were included in the present analysis (n=11 563). Low total cholesterol (≤ 160 mg . dl^{-1}) was prevalent in approximately 5% of this large unselected study cohort (n=595). The baseline characteristics of these 11 563 patients are summarized in Table 1. There was a slightly higher proportion of male patients in the low cholesterol group (89%) than in the control group (78%), but in terms of age, previous cardiovascular disease, co-existing illness and smoking habit the two groups were directly comparable. The majority of patients were in NYHA Class 1; 68% of the study group and 71% of the control group had previously suffered myocardial infarction. All other patients had proven coronary insufficiency. Approximately 28% of patients in both groups presented with symptoms of angina and approximately 33% were hypertensive. Patients with known cancer were excluded from the screening programme. However, four patients with low total cholesterol (0·7%) and 42 in the control group (0·3%) were diagnosed as having cancer during the screening period.

The population with low cholesterol comprised 6% of all male patients and 3% of all female patients. The higher prevalence of male patients with low cholesterol was statistically significant. There was also a tendency towards low cholesterol being more prevalent in patients >60 years than in the younger age group (Table 2).

Table 1 Baseline patient characteristics

	Number (%) patients	
	Total cholesterol ≤160 mg . dl^{-1} (n=595)	Total cholesterol >160 mg . dl^{-1} (n=10 968)
Male	531 (89)	8522 (78)
Age (mean ± SD) years	60·6 ± 7·3	59·8 ± 7·1
Previous myocardial infarction	401 (68)	7760 (71)
NYHA class		
I	421 (73)	7557 (71)
II	120 (21)	2424 (23)
III–IV	37 (6)	666 (6)
Angina class (II to IV)*	159 (27)	3187 (29)
Hypertension	188 (32)	3681 (34)
Diabetes	146 (25)	2336 (21)
Cerebrovascular accident	10 (2)	206 (2)
Peripheral vascular disease	27 (5)	456 (4)
Chronic obstructive pulmonary disease	17 (3)	334 (3)
Current smoking	64 (11)	1251 (11)

NYHA=New York Heart Association.
*Symptoms reported during the screening visit.

The mean total blood cholesterol at baseline was 147 mg . dl^{-1} in the low cholesterol group and 230 mg . dl^{-1} in the control group. HDL-cholesterol and plasma triglyceride levels were also lower in the patients with total cholesterol ≤160 mg . dl^{-1} than in those with total cholesterol >160 mg . dl^{-1} (Table 3).

Treatment with beta-blockers, nitrates, calcium antagonists, digitalis and aspirin was comparable in the two groups of patients (Table 4). Fifteen patients with low total cholesterol (2·5%) and 524 in the control group (3·7%) were taking lipid lowering agents at the time of the screening visit.

Survival analysis

The patients were followed-up for a mean of 3·3 years after the screening visit. There were a total of 903 deaths (8%). Mortality from all causes was significantly higher in patients with low total cholesterol (11·8%) than in patients with total cholesterol >160 mg . dl^{-1} (7·6%). Multivariate analysis showed that the relative risk of death from all causes was 1·49-times higher (95% CI: 1·16–1·91) in patients with low total cholesterol than in the control population (Table 5).

The total incidence of cardiac death was similar in both groups (relative risk: 1·09); the most frequent cause was coronary artery disease which accounted for mortality in 4·0% of study patients and in 3·8% of the control population (Table 6). The cardiac death rate was only slightly higher in patients above 60 years of age than in the younger patients. In both age groups mortality was higher in those with low cholesterol than in the control patients (Table 5).

The relative risk of non-cardiac death was 2·27-times higher (95% CI: 1·49–3·45) in patients with low total cholesterol than in the control population (Table 5). The incidence of non-cardiac death appeared to be at least twice as high in patients >60 years of age than in younger patients. However, at least a two-fold increase in relative risk of non-cardiac death associated with low total cholesterol was preserved within each age category (Table 5). The increased risk appeared to be highest in the younger patients with lower cholesterol (relative risk=3·23) but the results in this sub-group showed wide variation (95% CI: 1·38–7·57).

Neoplasms were the most frequent single cause of non-cardiac death (Table 6). Cancer-related deaths occurred in 1·8% of patients with low total cholesterol and in 1% of the control group. Although the prevalence of cancer during the screening period was higher in the study population (0·7%) than in the control population (0·3%), the results indicate an increased incidence of newly acquired cancer in approximately 1·1% of the low cholesterol group compared with 0·7% of the control group. It is noteworthy that liver disease was the second most common cause of non-cardiac death associated with low cholesterol (0·8%) although it was not a cause of death in the control group. The likelihood of dying from other non-cardiac causes was also approximately 1·5 times higher amongst patients with low total cholesterol. Deaths caused by injury or poisoning occurred rarely (Table 6).

Kaplan–Meier survival curves for total mortality, non-cardiac mortality and cardiac mortality are shown in Figs 1 to 3, respectively. In the control group the mortality rate associated with both cardiac and non-cardiac events was linear throughout the observation period.

Discussion

The main objective in this observational study was to establish if there was a link between increased

Table 2 Prevalence of low total cholesterol (i.e. ≤160 mg . dl^{-1}) among subgroup of patients

	All patients	Patients with total cholesterol ≤160 mg . dl^{-1}	
		Number of patients	% of total population in each category
Male	9053	531	6*
Female	2510	64	3
Age			
≤60 years	5616	246	4
>60 years	5947	349	6*
Previous MI			
yes	8161	401	5
no	3359	192	6
NYHA class			
I	7978	421	5
II–IV	3247	157	5
Angina class			
I	3589	205	6
II–IV	3346	159	5
Hypertension			
yes	3869	188	5
no	7653	404	5
Diabetes			
yes	2482	146	6
no	9041	448	5
CVA			
yes	216	10	5
no	11 309	583	5
PVD			
yes	483	27	6
no	10 979	564	5
COPD			
yes	351	17	5
no	11 140	574	5
Current smoking			
yes	1315	64	5
no	10 215	530	5

COPD=chronic obstructive pulmonary disease; CVA=cerebrovascular accident; PVD=peripheral vascular disease; MI=myocardial infarction; *P<0·001 Chi-square test.
Note: details of some variables were not available for all patients.

Table 3 Baseline lipid profile

	Mean ± SD	
	Total cholesterol ≤160 mg . dl^{-1} (n=595)	Total cholesterol >160 mg . dl^{-1} (n=10 968)
Total cholesterol (mg . dl^{-1})	147 ± 12	230 ± 40
HDL-cholesterol (mg . dl^{-1})	32·5 ± 8·5	39·1 ± 10·9
Triglycerides (mg . dl^{-1})	119·1 ± 66·1	167·9 ± 103

Table 4 Medical treatment

	Number (%) patients	
	Total cholesterol ≤160 mg . dl^{-1} (n=595)	Total cholesterol >160 mg . dl^{-1} (n=10 968)
Medical treatment		
Beta-blockers	182 (31)	3773 (34)
Nitrates	303 (51)	5427 (49)
Calcium antagonists	284 (48)	5553 (51)
Digitalis	38 (6)	508 (5)
Aspirin	333 (56)	6274 (57)
Lipid lowering agents	15 (2·5)	524 (3·7)

non-cardiac mortality and low total cholesterol in a largely unselected population of patients with coronary artery disease.

Our findings clearly show that total cholesterol levels ≤160 mg . dl^{-1} were associated with an excess of non-cardiac and total mortality amongst 11 563 coronary patients of both genders aged between 45 and 74 years. The incidence of non-cardiac death was twice as high as in the control population, the most frequent single cause of non-cardiac death being cancer. It should be emphasised that these low levels of total cholesterol were pre-existing at the screening visit. They were not the consequence of pharmacological

Table 5 Relative risk of mortality after mean follow-up of 3·3 years from screening visit

	Number (%) patients		Relative risk* (95% CI)
	Total cholesterol ≤160 mg . dl^{-1}	Total cholesterol >160 mg . dl^{-1}	
All patients (n=11 563)	(n=595)	(n=10 968)	
Cardiac†	33 (5·6)	502 (4·6)	1·09 (0·76; 1·56)
Non-cardiac	27 (4·5)	248 (2·3)	2·27 (1·49; 3·45)
Unknown	10 (1·7)	83 (0·8)	—
Total	70 (11·8)	833 (7·6)	1·49 (1·16; 1·91)
Age ≤60 years (n=5616)	(n=246)	(n=5370)	
Cardiac†	11 (4·5)	197 (3·7)	1·17 (0·65; 2·11)
Non-cardiac	6 (2·4)	62 (1·2)	3·23 (1·38; 7·57)
Unknown	3 (1·2)	39 (0·7)	—
Total	20 (8·1)	298 (5·6)	1·54 (0·98; 2·43)
Age >60 years (n=5947)	(n=349)	(n=5598)	
Cardiac†	22 (6·3)	305 (5·4)	1·05 (0·67; 1·64)
Non-cardiac	21 (6·0)	186 (3·3)	2·08 (1·24; 3·36)
Unknown	7 (2 0)	44 (0·8)	—
Total	50 (14·3)	535 (9·6)	1·47 (1·09; 1·98)

CI=confidence interval.
*Pooled relative risk; adjustment for age, gender, HDL <35 mg . dl^{-1}; glucose >120 mg . dl^{-1}, NYHA, previous MI, diabetes, COPD, hypertension, PVD, angina, current smoking.
†ICD-9 codes 410–429.

Table 6 Causes of cardiac and non-cardiac mortality — all patients

ICD-9 code	Number (%) patients	
	Total cholesterol ≤160 mg . dl^{-1} (n=595)	Total cholesterol >160 mg . dl^{-1} (n=10 968)
Cardiac		
410–429 all	33 (5·6)	502 (4·6)
410–414 coronary	24 (4·0)	421 (3·8)
415–429 other cardiac	9 (1·5)	81 (0·7)
Non-cardiac		
Total	27 (4·5)	248 (2·3)
neoplasms	11 (1·8)	111 (1·0)
liver disease	5 (0·8)	—
injury and poison	2 (0·3)	18 (0·2)
CVA	2 (0·3)	36 (0·3)
other	7 (1·2)	83 (0·8)
Unknown	10 (1·7)	83 (0·8)

intervention. Indeed only 2·5% of the low cholesterol group had previously been treated with lipid lowering drugs.

Studies linking low total cholesterol to non-coronary mortality often fail to demonstrate cause and effect relationships[8]. A study in over 360 000 men aged between 35 and 57 years, found a statistically significant excess of cancer during the early years of follow-up in patients who were in the lowest 10% of the serum cholesterol distribution[9]. Low levels of serum cholesterol were more marked in the 150 patients who died from cancer than in the survivors. It was concluded that the relationship between low serum cholesterol and cancer is, at least in part, due to an effect of preclinical cancer on serum cholesterol levels. There may also be an association between the low total cholesterol and the wasting component of the disease[12].

A second study in over 11 000 healthy men showed that the risk of lung cancer over a 15-year period was highest when total cholesterol was below 170 mg . dl^{-1}[10]. Deaths from lung cancer were not related to age, blood pressure, smoking habits or body weight. Other investigators have linked serum cholesterol levels <160 mg . dl^{-1} with a twofold increase in the risk of intracranial haemorrhage, a significantly increased risk of death from cancer of the liver, pancreas and haematopoietic system, and an increased incidence of death from respiratory, hepatic and digestive disease[11]. There is general agreement, however, that low total cholesterol is not involved in the incidence or mortality associated with brain cancer[13,18,19].

A recent study in 5941 men without a history of cardiovascular, gastrointestinal or liver disease showed that declining total cholesterol was associated with an increased risk of death due to cancer (particularly haematopoetic, oesophageal and prostatic) and non-cardiovascular death (especially liver disease)[20]. In our study liver disease was the second most common cause of non-cardiac death and was only observed amongst patients with total cholesterol ≤160 mg . dl^{-1} (Table 6). However, the mortality rates were too low to enable the statistical significance of the findings to be tested. There was a low incidence of mortality caused by injury and poisoning in both groups (0·2 to 0·3%). We are, therefore, unable to confirm previous reports linking traumatic death, depression and suicide to low serum cholesterol[21].

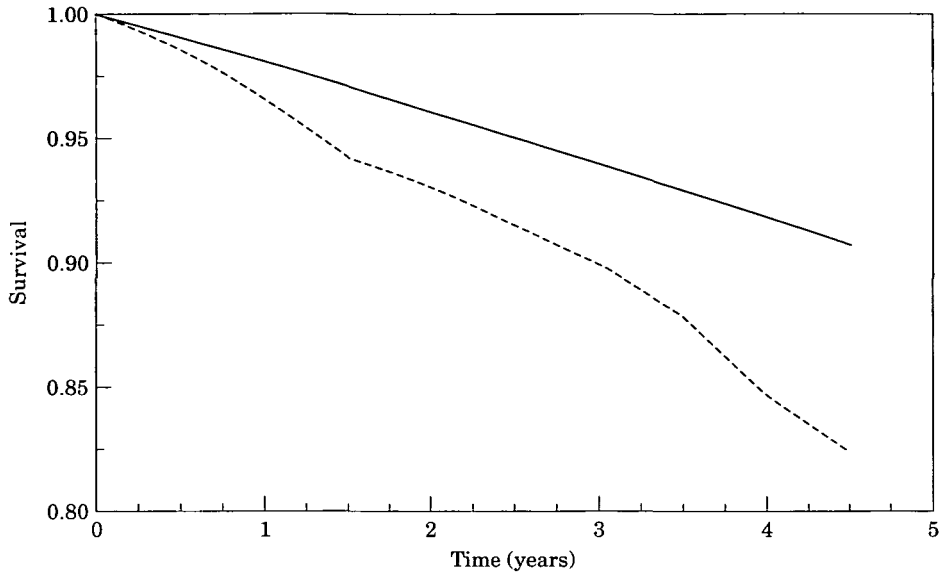

Figure 1 **Kaplan–Meier survival curve for all causes of death in patients with total cholesterol ≤ 160 mg . dl^{-1} (– –) and >160 mg . dl^{-1} (———).**

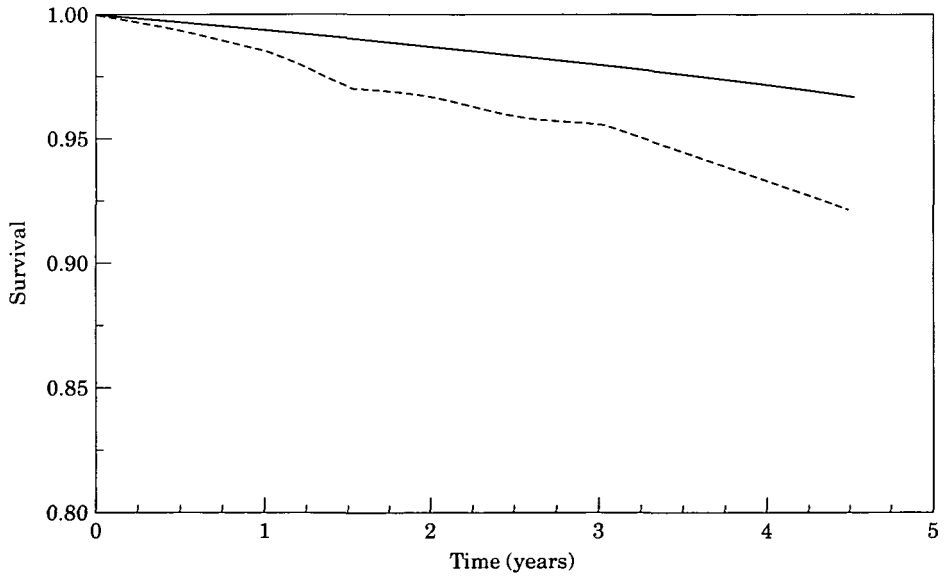

Figure 2 **Kaplan–Meier survival curve for non-cardiac deaths in patients with total cholesterol ≤ 160 mg . dl^{-1} (– –) and >160 mg . dl^{-1} (———).**

It is not possible on the basis of the present observational study to determine whether low total cholesterol is a marker or a precursor of the diseases which cause higher non-cardiac mortality among patients with coronary heart disease. Although our findings generally support those of other epidemiological studies, a recent systematic review of the 10 largest cohort studies examining relationships between serum cholesterol and non-cardiac mortality found that the only cause of death attributable to low serum cholesterol was haemorrhagic stroke[22]. The general population studies, which included subjects with chronic disease, demonstrated clear associations between low total cholesterol and lung cancer, liver disease, chronic bronchitis, suicide and bowel disease. However, these associations were not found in studies confined to healthy working men. The authors, therefore, concluded that the low total cholesterol concentrations were caused by the same factors that precipitated these ultimately fatal diseases[21]. The hypothesis that catabolic diseases such as cancers and liver disease may decrease total cholesterol has been supported by results from a recent study in which total cholesterol levels were determined in a population over 10 years[20]. The study included patients with a 'naturally' low cholesterol and those with low total cholesterol due to cholesterol-lowering treatments.

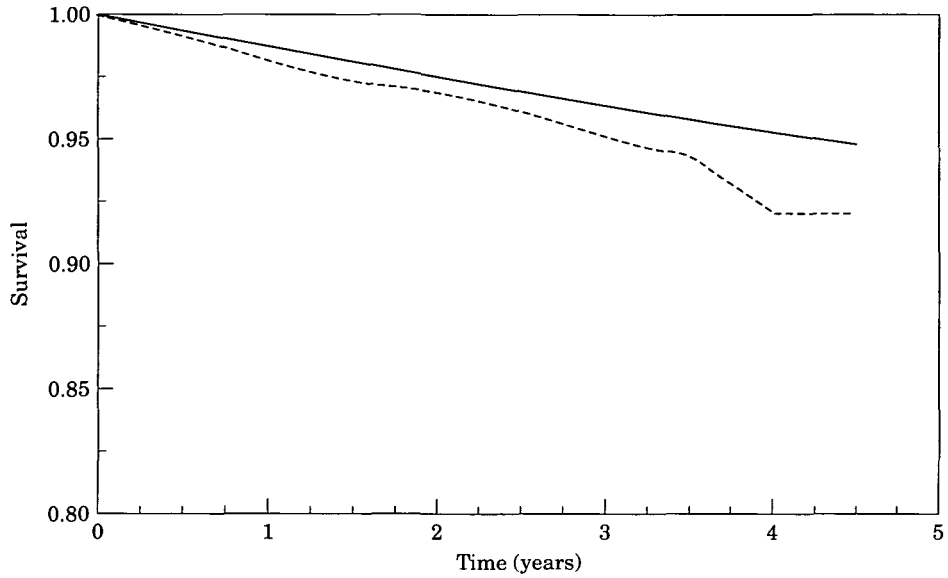

Figure 3 **Kaplan–Meier survival curve for cardiac deaths in patients with total cholesterol ≤ 160 mg . dl^{-1} (– –) and >160 mg . dl^{-1} (———).**

In a meta-analysis of 35 trials which evaluated the effect of cholesterol lowering therapy on coronary and non-coronary mortality, cholesterol lowering was shown to be beneficial[23]. Recently two major publications[4,5] have clearly shown that lowering total cholesterol was strongly associated with decreased total and cardiovascular mortality without any increase of the non-cardiac cause of death. It is therefore important to emphasize that in the present study, increased non-cardiac cause of death was observed among patients with spontaneously low total cholesterol and that low levels of total cholesterol resulting from diet or medical treatment, were not incriminated with excess mortality[4,5]. It seems, therefore, that spontaneous low total cholesterol should be considered as a marker rather than a precursor of subsequent non-cardiac death among patients with coronary artery disease.

Limitations

The present study is based on only a single measure of cholesterol and therefore we could not examine the risk according to whether the low cholesterol level was stable over years or whether low cholesterol resulted from failing blood cholesterol levels. In addition, the mean time of follow-up was relatively short. It has been suggested that at least 10 years of follow-up is required to analyse fully any association between cholesterol and all cause mortality[7]. For this reason our follow-up of this large cohort of subjects is continuing.

We are most grateful to Ms Dalia Ben-David for coordinating the keying and verification of input data, to Mr Mark Goldberg for programming the data base, to Ms Lynn Goodman for typing the manuscript, and to Ms Lori Mandelzweig for editorial assistance.

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Appendix

BIP study group

Participating centres and committee membership

Scientific committee: Jacob Agmon, MD; Solomon Behar, MD; Daniel Brunner, MD (Chairman); Avraham Caspi, MD; Uri Goldbourt, PhD; Eran Graff, PhD; Elieser Kaplinsky, MD; Yehezkiel Kishon, MD; Henrietta Reicher-Reiss, MD; and Joshua Waysbort, MD.

Participating centres, principal investigators and physicians:

Assaf Harofe Hospital, Zrifin: Zwi Schlesinger, MD, and Aharon Fridensohn, MD.

Barzilai Medical Center, Ashkelon: Leonardo Reisin, MD, and Jamal Jafari, MD.

Beilinson Medical Center, Petach-Tikva: Samuel Sclarovsky, MD, Yaakov Friedman, MD, and Bruno Ostfeld, MD.

Bnei-Zion Hospital, Haifa: Edward Abinader, MD, and Shmuel Rochfleish, MD.

Carmel Hospital, Haifa: Abraham Palant, MD, and Hanan Schneider, MD.

Central HaEmek Hospital, Afula: Tiberio Rosenfeld, MD, and Suleiman Khalid, MD.

Edith Wolfson Medical Center, Holon: Yehezkiel Kishon, MD and Rene Rotzak, MD.

Hasharon Hospital, Petach-Tikva: Izhar Zahavi, MD, and Janash Vitrai, MD.

Hillel Yaffe Hospital, Hadera: Benyamin Pelled, MD, and Joseph Pardu, MD.

Ichilov Hospital, Sorasky Medical Center, Tel-Aviv: Shlomo Laniado, MD, Libi Sherf, MD, Shimon Braun, MD, and Yemima Eschar, MD.

Kaplan Hospital, Rehovot: Avraham Caspi, MD, Alexander Arditi, MD, and Shulamit Botwin, MD.

Meir Hospital, Sapir Medical Center, Kfar Saba: Daniel David, MD, and Daniel Weisnenberg, MD.

Naharia Hospital, Naharia: Nathan Roguin, MD, and Alicia Glusman, MD.

Rambam Medical Center, Haifa: Walter Markiewicz, MD, and Diav Motlak, MD.

Rivka Ziv Hospital, Tzfad: Alon Marmour, MD, and Michael Flich, MD.

Shaare Zedek Medical Center, Jerusalem: Monty Zion, MD, and Jonathan Balkin, MD.

Sheba Medical Center Heart Institute, Tel Hashomer: Babeth Rabinowitz, MD, and Eddy Barasch, MD.

Soroka Medical Center, Be'er Sheba: Natalio Kristal, MD, and Noa Liel, MD.

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Critical events and end-point committee: Chaim Almog, MD, Alexander Battler, MD, and Monty Zion, MD.

Coordinating center: Jacob Agmon, MD, Yisrael Bar-Yehuda, Solomon Behar, MD (medical director), Daniel Brunner, MD, Uri Goldbourt, PhD, Elieser Kaplinsky, MD, Lori Mandelzweig, MPH, and Henrietta Reicher-Reiss, MD.

Central laboratory: Daniel Brunner, MD, Eran Graff, PhD (director), Sara Schwartz, MS, and Joshua Waysbort, MD.

Safety evaluation: Siegfried Heimstra, MD, and Eugene Heyman, PhD.