

Multitude of Medical Practices with Limited Efficacy

Criticism of Cholesterol Guidelines

Cholesterol Is Not the Cause of Heart Attacks. Then What Is?

Bempedoic Acid May Shorten Life



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Multitude of Medical Practices with Limited Efficacy

Translated and revised from the Editorial in Med Check(in Japanese) Jul. 2026 ; 26 (126) : 75

In November 2025, the prescription of pregabalin (brand name: Lyrica®) for common "low back pain" unaccompanied by nerve damage was singled out as a medical practice with "limited efficacy." While the prescribing of antibiotics for the common cold had previously topped the list of practices flagged under the government's plan to optimize medical spending, pregabalin has now become the next target.

Pregabalin is approved for use to treat pain caused by nerve damage and the Japanese clinical guidelines for low back pain do not recommend its use for cases lacking such damage. In practice, however, it has been widely prescribed as a "stopgap painkiller." Another reason for the government's decision to review the practice is the need to reduce drug costs. Annual spending on pregabalin for low back pain is estimated at approximately 6 billion yen, and the government has set a goal to cut this figure in half. Moving forward, prefectural governments will lead initiatives urging a review of pregabalin prescriptions for low back pain cases where the drug is of limited effectiveness. The Japanese government has also indicated plans to tighten insurance claim reviews for such prescriptions in preparation for the fiscal 2028 revision of medical service fees.

Since pregabalin was first released, MedCheck has pointed out more fundamental issues: Even for the approved nerve-damage-related pain, the efficacy is low. Conversely, it is associated with numerous harms—such as severe drowsiness, dependence, abuse, and oedema—meaning it should not be used casually. We have repeatedly sounded the alarm about how the expansion of approved indications has led to unnecessary prescriptions, subsequently turning these adverse reactions into a major problem.

In this instance, the government took issue with usage that falls outside guideline recommendations. However, as we have noted in our critiques of clinical guidelines, there remain countless drugs that are problematic even when used strictly according to the rules—often because the guidelines themselves are flawed. "Cholesterol-lowering drugs," the subject of this issue, are a case in point. Flawed guidelines have led to the widespread practice of inappropriate treatments; this not only drives up wasteful medication costs but also entails enormous expenses for addressing health issues caused by adverse reactions. Rather than focusing solely on deviations from these guidelines, the government should rigorously re-examine the evidence based on the principles of evidence-based medicine (EBM) and take steps to rectify all such medical practices characterised by limited efficacy and significant harm.

New Anti-Cholesterol Bempedoic Acid (Nexletol®) A Dangerous Substance That May Shorten Life

Translated and revised from MedCheck (in Japanese) Jul.2026; 26(126):83-33.86

MedCheck Editorial Team

Abstract

- Bempedoic acid inhibits ATP-citrate lyase, a key enzyme in cellular energy metabolism. Although it lowers plasma cholesterol concentrations, the same dose also impairs the function of multiple organs and systems, including the kidneys, liver, hematopoietic system, and coagulation system.
- In patients with a history of cardiovascular disease, bempedoic acid has been shown not to reduce mortality; rather, it significantly increases the risk of total-mortality, making it a highly dangerous drug.
- It is indicated as an add-on therapy to statins when LDL cholesterol concentrations are not sufficiently reduced. However, lowering cholesterol with drug therapy is unnecessary in the first place.
- Bempedoic acid consistently impairs renal function and is associated with high incidences of hyperuricemia, hepatic dysfunction, and cholelithiasis. Its adverse effects are systemic rather than confined to a single organ. Although carcinogenicity has not yet been demonstrated in humans, animal studies have shown a high incidence of liver cancer at doses lower than those used clinically in humans. Since its first approval outside Japan in 2020, only six years have elapsed. Continued surveillance for carcinogenicity is therefore warranted.

Conclusion: Bempedoic acid is unnecessary and should not be used.

Keywords:

ATP-citrate lyase, acetyl-CoA; statins, renal impairment, hepatic dysfunction, hyperuricemia, carcinogenicity

The History of Cholesterol-Lowering Substances Is a History of Drug-Induced Harm

Bempedoic acid (Nexletol®) had been approved in 41 countries and regions, including the United States and the European Union (EU), as of April 2026 [1]. In Japan, it received marketing approval in September 2025. Because the view that lowering cholesterol concentrations helps prevent cardiovascular diseases such as heart disease and stroke has become dominant throughout the medical community [2], use of this substance is expected to increase in Japan as well.

Historically, the development of cholesterol-lowering agents has been marked by repeated failures

[3]. In one case, blocking an intermediate step in the body's cholesterol synthesis pathway with a drug (MER-29 or triparanol) led to the accumulation of upstream substances (desmosterol), causing harmful

Rating: Not Needed — Should Not Be Used

Generic Name: Bempedoic Acid

Brand Name: Nexletol® Tablets

Indications: Hypercholesterolemia,
Familial Hypercholesterolemia

Dosage and Administration: 180 mg/day

Manufacturer: Otsuka Pharmaceutical Co., Ltd.

Drug Price: 371.5 yen per tablet

effects (cataract and alopecia) that forced the product to be withdrawn only two years after its launch. Other substances were also tested, including those with excessive thyroid hormone effects (d-thyroxine). In addition, randomized controlled trials of the conjugated estrogen resulted in an increased incidence of cancer.

Statins are not free from harm either. Rather than causing damage confined to a single organ, these substances produce adverse effects throughout the body, making any one particular toxicity less conspicuous. Furthermore, lowering cholesterol concentrations weakens immune function. As a result, the risks of infectious diseases and cancer may increase, while impaired nervous system function may also contribute to a higher incidence of dementia. Nevertheless, although these substances may reduce the incidence of myocardial infarction to a limited extent, they have been largely unable to reduce overall mortality from cardiovascular disease [4–6].

Where does bempedoic acid act to lower cholesterol?

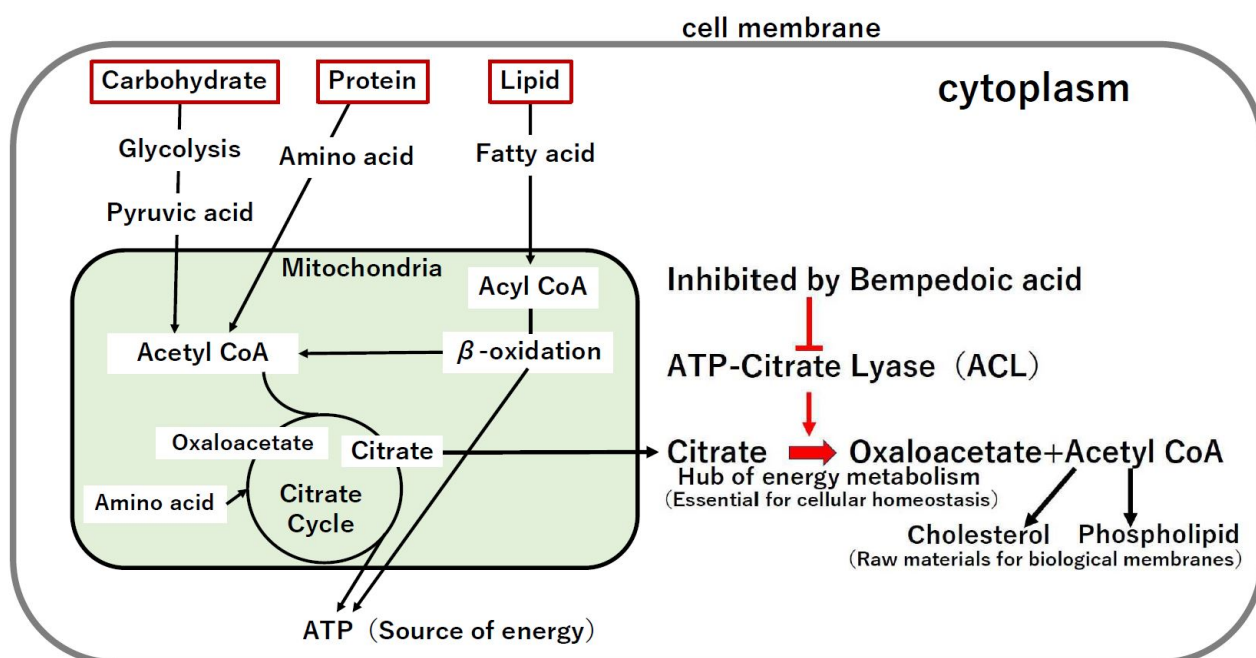
More importantly, can it prolong life span as a consequence? And what adverse effects does it have?

What Is Bempedoic Acid ?

Figure 1 illustrates the general outline of energy metabolism and the mechanisms by which the energy metabolism hub targeted by bempedoic acid is inhibited. Bempedoic acid is an inhibitor of ATP-citrate lyase (ACL). ACL is the enzyme responsible for cleaving citrate into oxaloacetate and acetyl-CoA in the cytoplasm, thereby producing acetyl-CoA. Bempedoic acid interferes with the action of ACL and consequently inhibits the production of acetyl-CoA.

Acetyl-CoA serves as the precursor for the synthesis of cholesterol and phospholipids (Note 1). As the metabolic pathway shown in Figure 1 is the only source of cytoplasmic acetyl-CoA, inhibition of ACL by bempedoic acid impairs not only the synthesis of the cholesterol required by the body but also that of phospholipids, which are major structural components of biological membranes, such as cell membranes.

Figure 1: Target of action of bempedoic acid and the mechanism by which energy metabolism hub is inhibited



ATP-citrate lyase (ACL) is a key enzyme that catalyses the conversion of citrate into acetyl-CoA and plays a central role (hub) in energy metabolism essential for life. By inhibiting ACL, bempedoic acid reduces the production of acetyl-CoA, thereby impairing the synthesis of cholesterol and phospholipids, both of which are required for the formation and maintenance of healthy biological membranes, such as cell membranes.

In addition, citrate accumulates in the cytoplasm, which is likely to affect the tricarboxylic acid (TCA) cycle (or citrate cycle) within mitochondria, thereby reducing ATP production required for cellular energy metabolism. Because this pathway is fundamental to cellular metabolism, disruption of acetyl-CoA production is expected to impair cellular homeostasis throughout the body, particularly in tissues with high energy demands and rapid cell turnover, such as the liver, kidneys, bone marrow, thymus, and lymphoid tissues. This is likely to be followed by overt tissue injury. The findings from animal toxicity studies disclosed in the summary technical documentation (STED) and clinical trials are consistent with this proposed mechanism.

Note1 : Two molecules of acetyl-CoA are converted into mevalonate through several intermediate steps. Statins inhibit the enzyme responsible for converting HMG-CoA into mevalonate. Bempedoic acid therefore inhibits cholesterol synthesis at an earlier (upstream) stage than statins.

Cholesterol Concentrations Fall, but...

The Phase III trial that formed the basis for approval in Japan was an extremely small and short-term study, involving only 48 participants in each of the bempedoic acid and placebo groups, followed for just 12 weeks [7]. The primary endpoint was the percentage change in LDL cholesterol from baseline. Mean baseline LDL cholesterol concentrations (mg/dL) were 137.7 in the placebo group and 134.5 in the bempedoic acid group, falling to 130.9 and 99.9 mg/dL, respectively. Thus, LDL cholesterol was reduced by approximately 21% more with bempedoic acid than with placebo, and the difference was statistically significant (Note 2).

Note2 : A simple calculation gives a reduction of 4.9% in the placebo group and 25.7% in the bempedoic acid group, corresponding to a difference of approximately 21%. However, the regulatory review report calculated the percentage change using the least-squares mean, yielding reductions of 3.5% and 25.3%, respectively, and therefore reported a between-group difference of 21.8%.

Pooled Analysis of Three Trials Shows a Significant Increase in All-Cause Mortality

The two Phase III randomised controlled trials (RCTs) that supported approval in Europe and the United States each enrolled patients with a history of cardiovascular disease (heart disease, stroke, or peripheral vascular disease) or familial hypercholesterolaemia, and followed them for one year [8,9]. Following marketing approval in Europe and the United States, the results of a further study involving approximately 14,000 participants (around 7000 in each of the bempedoic acid and placebo groups), treated for a median of 42 months (3.5 years), were published in 2023 [10].

Table 1 compares all-cause mortality between the bempedoic acid and placebo groups in studies involving participants with a history of cardiovascular disease, and presents the corresponding odds ratios and p values.

In the two pre-marketing RCTs, mortality tended to be higher in the bempedoic acid groups than in the placebo groups (2.1% vs 1.6%, and 0.9% vs 0.3%). In the post-marketing study, the difference also favoured placebo and approached statistical significance (7.3% vs 6.4%, $p = 0.062$).

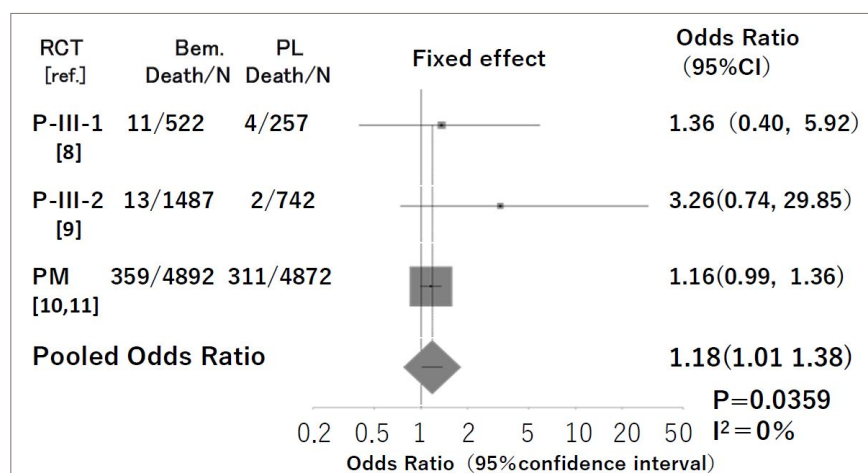
Table 1 : Rates of Major Cardiovascular Events, Cardiovascular Mortality, and All-Cause Mortality in Phase III and Post-Marketing Studies (Summary)

RCT (duration) [ref.]	Phase III-1 (1 y) [8]				Phase III-2 (1 y) [9]				Post marketing (3.5 y) [10,11]*a			
Assignment	Bem	PL	Odds	p	Bem	PL	Odds	p	Bem	PL	Odds	p
No. of Participants	522	257	Ratio	value	2,229	742	Ratio	value	4,892	4,872	Ratio	value
Outcomes												
MACE (%) *b	-	-	-	-	4.60	5.70	0.91	0.08	14.5	15.7	0.91	0.092
Death												
All cause (%)	2.1	1.6	1.36	0.599	0.90	0.30	3.26	0.100	7.3	6.4	1.16	0.062
Cardiovascular (%)	0.8	0.8	0.98	0.986	0.40	0.13	3.00	0.29	4.7	3.9	1.21	0.052

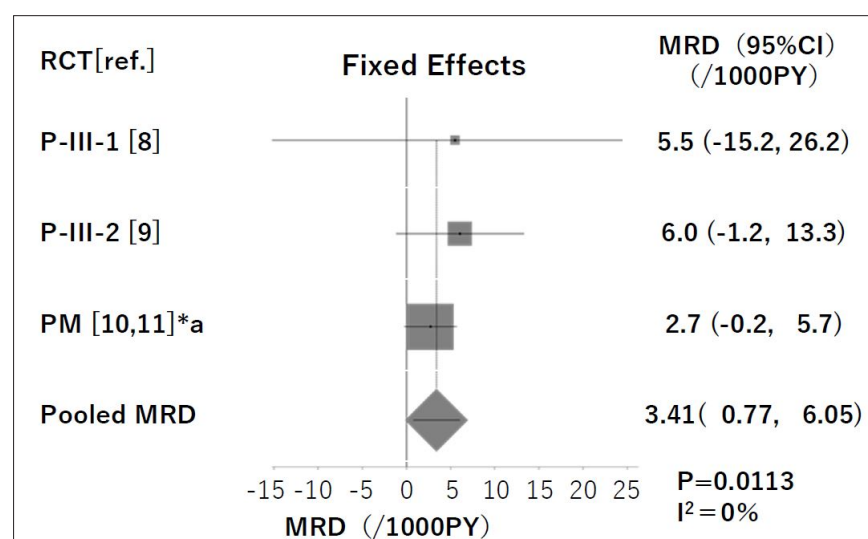
Bem: Bempedoic acid, PL: Placebo

*a : Secondary prevention data from the post-marketing RCT were derived from references 10 and 11 and analysed by the MedCheck Editorial Team.

*b : MACE (major adverse cardiovascular events): usually defined as a composite endpoint consisting of cardiovascular death plus myocardial infarction, coronary revascularisation, and stroke—Not reported in the Phase III-1 trial.

Figure 2: Meta-analysis of All-cause Mortality Odds Ratio: From the Two Phase III and Post-marketing RCTs

*a : Secondary prevention data from the post-marketing RCT were derived from the references 10 and 11 and analysed by the MedCheck Editorial Team.

Figure 3: Meta-analysis of All-cause Mortality Rate Difference (Excess Mortality): From the Two Phase III and Post-marketing RCTs

*a : Secondary prevention data from the post-marketing RCT were derived from the references 10 and 11 and analysed by the MedCheck Editorial Team. The NNTH for all-cause mortality is $1000/3.4 = 293$ (95%CI: 165 to 1297). Therefore, one additional death occurs annually for every 293 people treated with Nexetol; with three years of use, one additional death occurs for every 100 people.

When the results of all three trials were pooled, bempedoic acid was associated with a statistically significant 18.4% increase in all-cause mortality (odds ratio 1.18; 95% confidence interval 1.01–1.38; $p = 0.0359$) (Figure 2).

Figure 3 shows the meta-analysis results of all-cause mortality rate difference (MRD or excess mortality rate), from the two phase III and post-marketing RCTs. Pooled MRD was 3.41 /1000 person-years (95%CI: 0.77-6.05), $P=0.0113$, $I^2=0\%$. Number needed to treat for one additional harm (NNTH) for death was 293 (95%CI: 165-1297),

This means that one additional death would occur for every 293 patients treated with bempedoic acid for one year, or approximately one additional death for every 100 patients treated for three years.

Furthermore, a pooled analysis of the same three trials showed a 23% increase in cardiovascular mortality (odds ratio 1.23; 95% confidence interval 1.02–1.49; $p = 0.038$).

Adverse Effects on the Liver, Kidneys, and the Whole Body

The most serious adverse effects are an increase in all-cause mortality and cardiovascular mortality. Why does this occur? The answer becomes apparent when the following adverse reactions are examined.

First, consistent deterioration of renal function.

In all three randomised controlled trials (RCTs), proportions of increased serum creatinine concentration were significantly higher in the bempedoic acid group

Table 2 : Renal Function and Uric Acid compared with baseline in the Phase III RCTs [8,9]

RCT [ref.]	laboratory test	Bempedoic acid	Placebo	p value
Phase III-1 [8]	Creatinine (mg/dL)	0.05(0.16)	0.01(0.12)	<0.0001
	e-GFR (mL/min/1.73m ³)	-3.8(10.2)	-1.1(10.8)	<0.0001
	Uric Acid (mg/dL)	0.6(1.2)	0.1(1.1)	<0.0001
Phase III-2 [9]	Creatinine (mg/dL)	0.02(0.13)	-0.01(0.12)	<0.0001
	Uric Acid (mg/dL)	0.73(1.11)	-0.06(0.87)	<0.0001

Data are presented as averages (standard deviation). P values were calculated from the data on the number of subjects, averages and standard deviations in references 8 and 9 by the MedCheck Editorial Team.

Table 3 : Major Adverse Events in the Post-marketing Large-scale RCT [10]

Adverse Events (AEs)	Proportion (%)		Odds Ratio	95%CI		P value
	Bempedoic N=7001	Placebo N=6964		LL	UL	
Any adverse events (AEs)	86.3	85.0	1.11	1.01	1.22	0.0312
Serious adverse events	25.2	24.9	1.02	0.94	1.10	0.6292
AEs leading to discontinuation	10.8	10.4	1.05	0.94	1.17	0.3633
Renal impairment	11.5	8.6	1.37	1.23	1.54	<0.00001
Hyperuricemia	10.9	5.6	2.05	1.80	2.32	<0.00001
Gout	3.1	2.1	1.51	1.22	1.87	0.0001
Cholelithiasis	2.2	1.2	1.89	1.44	2.47	<0.00001
Elevated hepatic-enzyme level	4.5	3.0	1.53	1.28	1.83	<0.00001
AST level >3x ULN	1.1	0.6	1.86	1.28	2.70	0.0009

Subjects are all participants including both primary and secondary prevention.

95 % CI: 95% confidence interval, LL: lower limit, UL: upper limit, AEs: adverse events, AST: aspartate aminotransferase, ULN: upper limit of the normal range.

than in the placebo group ($p < 0.0001$). The results of the two phase III studies are shown in **Table 2** and the results of the post-marketing study are shown in **Table 3**.

In toxicity studies in monkeys, serum creatinine concentrations increased significantly at doses that also produced a significant reduction in cholesterol concentrations. Furthermore, in monkeys that died during a two-week toxicity study, renal tubular necrosis was observed as one of the pathological findings affecting multiple organs[12]. Therefore, the increase in serum creatinine observed in humans is highly likely to reflect renal injury.

Second, hepatic dysfunction. Compared with placebo, abnormalities in liver function occurred 1.9 times more frequently, and gallstones were likewise 1.9 times more frequent, with both differences being highly statistically significant ($p < 0.0001$) (**Table 3**). In mice and monkeys, hepatic toxicity included hepatocellular vacuolation and hepatocellular necrosis [12].

Third, increased serum uric acid concentrations.

In every trial, serum uric acid concentrations were significantly higher in the bempedoic acid group ($p < 0.0001$) (**Table 3**).

Fourth, systemic toxicity. Monkeys that died during the two-week toxicity study exhibited vomiting, reduced food intake, decreased activity, a hunched posture, and reduced or absent faecal output [12].

In the most severely affected animals, tremor, dyspnoea, collapse, pale gums, mydriasis, cold body surface, and reduced urination were also observed. These findings suggest that the toxicity is systemic rather than confined to a single organ.

Pathological examination revealed not only tissue damage to the liver and kidneys, including hepatocellular necrosis and renal tubular necrosis, but also increased serum lactate dehydrogenase (LDH) and creatine kinase (CK), enzymes released following cellular injury. In addition, sodium, potassium, and chloride concentrations were reduced; red blood cell counts and haemoglobin concentrations decreased in all groups; lymphocyte depletion was observed in the thymus, spleen, and lymph nodes; and all haematopoietic cell lineages were depleted in the bone marrow [12].

The clinical manifestations and pathological findings described above are likely to be closely related to the ability of bempedoic acid to reduce cytoplasmic acetyl-CoA concentrations. Essential substances such as cholesterol and phospholipids are synthesised from acetyl-CoA. In addition, unused citrate accumulates, indirectly affecting glycolysis, the citric acid cycle, and fatty acid β -oxidation, all of which are essential for energy production. Consequently, reduced acetyl-CoA availability may disrupt cellular homeostasis throughout the body—

including in the liver, kidneys, bone marrow, thymus, and lymphoid tissues—and may subsequently lead to tissue injury (Figure 1).

Carcinogenicity

Carcinogenicity is also a major concern. Two-year carcinogenicity studies have been conducted in mice and rats [12]. In mice, hepatocellular tumours increased significantly even at the lowest dose (equivalent to approximately 44 mg in a 50-kg human, around one-quarter of the standard clinical dose), and the incidence increased in a dose-dependent manner. Furthermore, mortality in mice also showed a significant dose–response relationship ($p = 0.0011$).

In rats, although the lowest dose was only one-hundredth of the human dose and the highest dose only 1.5 times the human dose (both in males), a clear dose–response relationship was nevertheless observed for the combined incidence of benign and malignant liver tumours ($p = 0.0003$).

When the same toxic effect is observed consistently in two different animal species, it is generally considered highly likely to be reproducible in humans. Moreover, the dose-dependent increase in all-cause mortality observed in otherwise healthy mice is consistent with the increased all-cause mortality reported in the three clinical trials in humans. Because newly induced cancers would be expected to appear only after several years of treatment, the absence of an increased cancer incidence during clinical trials provides no reassurance regarding long-term carcinogenic risk.

Other Points Requiring Attention

Bempedoic acid is used in combination with statins, except in patients who cannot tolerate statins. However, it has been shown to delay the metabolism and excretion of several statins, increasing their plasma concentrations to approximately twice their original levels [1,13].

In addition, plasma concentrations of bempedoic acid tend to be higher in Japanese individuals. Because renal impairment delays its elimination, plasma concentrations may become even higher. Consequently, toxicity may occur earlier in Japanese patients than in non-Japanese populations, and

toxicity may be even more likely to occur in elderly patients, whose renal function is relatively reduced.

In Clinical Practice

Bempedoic acid is entirely unnecessary. It increases the risk of a wide range of diseases, particularly gout, renal impairment, hepatic dysfunction, and gallstones, and shortens life expectancy. It should not be used.

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Criticism of Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases

Cholesterol Is Not the Cause of Heart Attacks. Then What Is?

Translated and revised from Med Check (in Japanese) Jul 2026: 26 (126): p76-82.

MedCheck Editorial Team

Abstract

- The 2022 Guidelines for the Prevention of Atherosclerotic Cardiovascular Disease, published by the Japanese Atherosclerosis Society and 2026 American Guidelines also, continue to emphasise that elevated cholesterol levels should be lowered.
- However, cholesterol is an essential structural and functional component of the biological membranes such as cell membranes throughout the body and serves as the precursor for five steroid hormones synthesised in the body, among many other vital physiological functions. Numerous studies have shown that, with only a few exceptions, individuals with higher total cholesterol or LDL cholesterol levels tend to live longer, whereas those with lower cholesterol levels are more likely to develop conditions such as cancer and haemorrhagic stroke and have a higher risk of death.
- Why, then, did the "cholesterol hypothesis"—the idea that elevated cholesterol is inherently dangerous—become established? From the late nineteenth to the early twentieth century, cholesterol crystals were found within atherosclerotic lesions, leading researchers to suspect that cholesterol was the cause of atherosclerosis. This view was further reinforced by animal experiments in which rabbits developed atherosclerotic lesions after being fed cholesterol, together with observations that people who experienced myocardial infarction at a young age had markedly higher cholesterol levels than healthy individuals. These findings strengthened the belief that elevated cholesterol itself was hazardous, giving rise to what became known as the cholesterol hypothesis.
- Subsequent research, however, revealed that many individuals with extremely high total cholesterol concentrations (280 mg/dL or above) who developed myocardial infarction at a young age also had an increased tendency towards blood coagulation and inflammatory responses. This suggests that the underlying causes of myocardial infarction may lie not in cholesterol itself but rather in abnormalities of coagulation and inflammation. Nevertheless, correcting the long-established cholesterol hypothesis has proved exceptionally difficult.

Key words:

cell membrane; steroid hormones; cholesterol hypothesis; inflammation; blood coagulation; genetics; familial hypercholesterolaemia

The Current Guidelines: Main Claims

Q: MedCheck first addressed the subject of cholesterol in the second issue of Kusuri-no-Check (April 2001) [1]. Later, in our 2006 special issue

on metabolic syndrome, we discussed evidence suggesting that Mevalotin, a statin developed in Japan, was associated with reduced survival [2]. We revisited the topic in Issue 48 (2012) [3], concluding that cholesterol is indispensable for the body,

should not be lowered, and that cholesterol-lowering medication is not required.

In this issue, we once again examine and criticise the Japanese Guidelines for the Prevention of Atherosclerotic Cardiovascular Disease (hereafter referred to as J-GLs). Although we have repeatedly argued that elevated cholesterol levels are not in themselves a cause for concern, routine health examinations continue to identify cholesterol values above the reference range as problematic, and patients are frequently advised to begin lipid-lowering treatment.

Why has the belief that "high cholesterol is dangerous" become so deeply entrenched? The Guidelines were revised again in 2022 [4]. Do they contain any important new evidence or perspectives?

A: Readers of this journal may well have the same question. In 2018, MedCheck critically reviewed the Japanese Atherosclerosis Society's previous guidelines and discussed what we considered to be the six major adverse effects associated with statin therapy: muscle disorders, dementia, diabetes, infections, cancer, and neurological disorders [5]. We have continued to revisit this topic on several occasions since then [6–8].

In our view, the 2022 revision introduces little that is fundamentally new. It continues to place overwhelming emphasis on lowering blood lipids—particularly LDL cholesterol, commonly referred to as "bad cholesterol"—as the principal strategy for preventing atherosclerosis (Note 1).

However, except in very specific circumstances, higher cholesterol levels are associated with a lower incidence of disease and lower overall mortality. This is a consistent finding not only in Japan but also internationally [5,9–12]. This remains true today, nearly a decade after MedCheck published its critique of the Japanese Atherosclerosis Society Guidelines (2017 edition) in 2018. Since then, several additional studies have become available [13–19], all of which have likewise reported that, apart from a few exceptional situations, individuals with higher cholesterol levels experience fewer illnesses and lower mortality (See Supplement 1).

Note1 : This is not different from the newly revised 2026 Guidelines on the management of dyslipidemia by ACC/AHA/AACVPR/ABC/ACPM/ADA/ AGS/APhA/ASPC/NLA/PCNA(2026A-GLs)
<https://www.ahajournals.org/doi/10.1161/CIR.0000000000001423>
 2026A-GLs has stricter lowering target of LDL-cholesterol than J-GLs: less than 55 mg/dL for secondary prevention of myocardial infarction.

The Cholesterol-Culprit Theory and Public Perception

Q: Many people believe that high cholesterol makes the blood "thick" or "sludgy", that this is dangerous, and that cholesterol levels therefore need to be lowered. Even one of our readers, who had suffered from one of the drug induced sufferings "SMON" and sympathised with the views expressed in this journal, began taking a cholesterol-lowering agent after being advised by her physician that "your blood will become sludgy if you leave it like this." She added, "Don't tell Dr. Hama, or he'll tell me off."

The physician concerned was highly trusted by patients for providing compassionate, patient-centred care. Hearing this story was therefore particularly disappointing, as it illustrated just how powerful prevailing public opinion and conventional medical thinking can be.

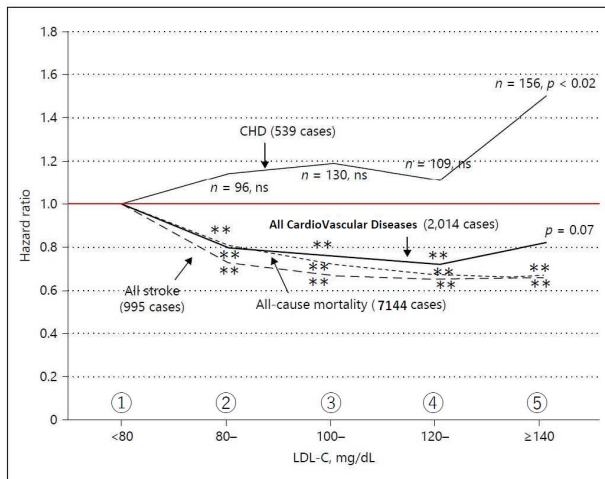
Has the belief that "bad cholesterol must be lowered" become equally widespread among healthcare professionals? More fundamentally, what exactly is the harm associated with elevated cholesterol levels?

A: Indeed, the view that "bad cholesterol must be lowered" is widespread among healthcare professionals. Even among the readership of this journal, there are physicians who regard the involvement of LDL cholesterol in atherosclerosis as "an established fact" [20].

We conducted a thorough review of all the studies cited in the J-GLs (See Supplement 2).

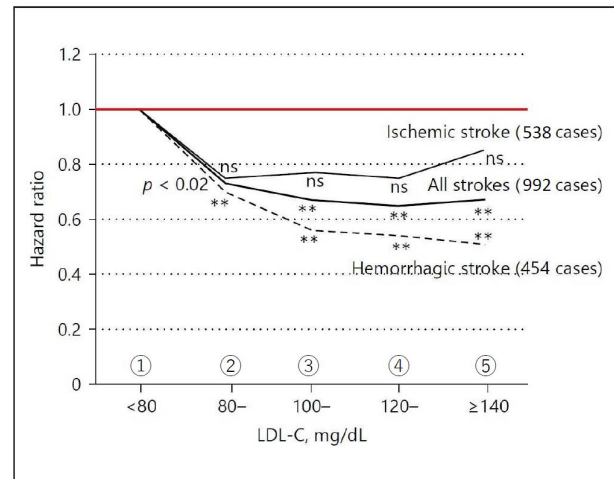
Our assessment found that, among individuals with extremely high cholesterol levels, death from coronary heart disease (CHD) such as myocardial infarction is virtually the only disease consistently reported to occur more frequently [8,10,11]. Figure 1 shows one of the typical examples [10,11]. Nevertheless, many healthcare professionals also appear to assume that stroke—another condition associated with atherosclerosis—is more likely

Figure 1: Only CHD death is positively associated with high LDL-Cholesterol



CHO: coronary heart disease Figure is from ref. 10 with some correction of data according to the original data by Noda et al.[11] Meta-analysis of Hazard ratios (HRs) of group ②, ③ and ④ of the mortality from CHD yielded 1.15(95%CI: 0.94-1.40, $p=0.176$, $I^2=0\%$). Only the group ⑤ of the mortality from CHD is significantly higher than the group ① among many causes of death.

Figure 2: Not only total stroke but also ischemic stroke is inversely associated with LDL-Cholesterol level



CHO: coronary heart disease Figure is from ref. 10 with some correction of data according to the original data by Noda et al. [11] Meta-analysis of Hazard ratios (HRs) of group ② and ③ of ischemic stroke yielded 0.76(95%CI: 0.62-0.94, $p=0.011$, $I^2=0\%$) and Group ④ and ⑤ 0.80 (0.64-0.99, $P=0.043$, $I^2=0\%$). All combined HR of group ② through ⑤ is 0.78(0.67-0.91, $p=0.0013$, $I^2=0\%$).

to occur in people with high cholesterol levels. However, the evidence indicates otherwise: mortality from not only the total stroke including both from haemorrhagic and ischaemic stroke increases clearly as cholesterol levels decrease [8,10,11]. **Figure 2** shows one of the typical examples[10,11].

Q: Why is that?

A: Once misinformation becomes widely accepted, it is extremely difficult to correct or revise it. People are naturally influenced by the first information they receive. Moreover, pharmaceutical companies that manufacture and market cholesterol-lowering drugs, together with cardiovascular societies, have become the dominant voices within the medical community, disseminating an overwhelming volume of information worldwide. As a result, the prevailing view appears unlikely to change.

How the Cholesterol-Culprit Theory Became Established

Q: You have suggested that the main adverse consequence associated with high cholesterol is myocardial infarction. But is cholesterol really the cause of myocardial infarction?

A: That assumption itself is open to question. However, there are historical reasons why it came to be accepted. More than a century ago, researchers

observed that atherosclerotic lesions (the formal pathological term is atheroma) contained large amounts of cholesterol. This led to the hypothesis that cholesterol might be the cause of atherosclerosis [21].

In 1913, a Russian pathologist successfully induced atherosclerotic lesions closely resembling those seen in humans by feeding cholesterol to rabbits whose normal serum cholesterol concentrations were only about 30–60 mg/dL, thereby increasing their cholesterol levels to approximately 500–1000 mg/dL [21]. At the time, this was regarded as a landmark discovery. Following this experiment, similar studies were conducted in rats, mice, dogs, and other animals by administering large quantities of cholesterol. However, these attempts were unsuccessful. Apart from rabbits, atherosclerosis could be induced only in herbivorous animals such as guinea pigs, goats, and monkeys, as well as in birds such as chickens [22]. In chickens and other avian species, cholesterol concentrations had to be raised to extremely high levels—exceeding 1000–2000 mg/dL—before atherosclerotic lesions developed [23].

In contrast, omnivorous and carnivorous mammals, including rats, mice, and dogs, possess mechanisms that efficiently metabolise excess dietary cholesterol. Consequently, their cholesterol concentrations did not increase substantially even when large amounts

of cholesterol were administered, and atherosclerosis did not develop [22]. This led to the widely held view that rabbits and chickens represented exceptional cases.

Q: If that was the case, how did the idea arise that cholesterol causes the atherosclerosis underlying myocardial infarction in humans?

A: By the 1940s, numerous clinical observations had accumulated. These included: (1) individuals who experienced myocardial infarction at a young age tended to have elevated blood cholesterol concentrations; and (2) patients with xanthomas—cholesterol deposits in the eyelids or Achilles tendons—were more likely to develop myocardial infarction and also had high blood cholesterol concentrations [22]. It also became clear that some individuals have familial hypercholesterolaemia, a hereditary condition characterised by markedly elevated cholesterol levels [22].

Against the backdrop of these observational findings and case reports, pharmaceutical companies began developing cholesterol-lowering drugs in the late 1940s [1].

Q: At that stage, had a causal relationship actually been established?

A: No. The causal relationship had not been rigorously demonstrated. Nevertheless, shortly afterwards, in 1950, evidence emerged that was widely regarded as providing strong support for the cholesterol hypothesis.

One report compared total cholesterol concentrations in 97 men under the age of 40 who had experienced myocardial infarction with those in 146 healthy men of similar age—what is termed a case-control study in epidemiology [24]. Among the healthy men, fewer than 10% had total cholesterol concentrations exceeding 280 mg/dL, whereas more than half of the patients with myocardial infarction had total cholesterol levels of 280 mg/dL or higher. Based on these findings, it was estimated that individuals with total cholesterol concentrations of at least 280 mg/dL had a twelvefold greater risk of

developing myocardial infarction before the age of 40.

Because this comparison between patients with myocardial infarction and healthy controls suggested a twelvefold increase in risk associated with markedly elevated cholesterol concentrations, many came to believe that cholesterol itself must be the cause of myocardial infarction. This, in turn, appears to have accelerated pharmaceutical companies' efforts to develop cholesterol-lowering drugs.

Subsequently, a large-scale investigation of blood lipids was conducted [25], followed by the publication of the Framingham Study ([Note 2](#)) in 1961 [26]. As this was a prospective cohort study, it confirmed that the risk of myocardial infarction increased with rising cholesterol concentrations. As a result, the cholesterol hypothesis—the concept that cholesterol is the cause of atherosclerosis—became widely accepted.

Note 2: The Framingham Study was a prospective cohort study conducted among residents of Framingham, Massachusetts, USA. A total of 5127 participants, consisting of randomly selected residents who agreed to participate together with volunteers free of cardiovascular disease, were followed for approximately six years. The first report, published in 1961, focused primarily on participants in their forties and fifties.

Later, cholesterol-lowering agents, including fibrates and statins, were developed. Backed by extensive promotional campaigns from pharmaceutical manufacturers, the readily understood terms "bad cholesterol" and "good cholesterol" were introduced. These simple labels, presenting cholesterol in terms of "good versus bad", helped to entrench the cholesterol (or "bad cholesterol") hypothesis in both medicine and the wider public [12].

Q: I see how that view became established. If so, what actually causes myocardial infarction?

A: That question goes to the heart of the limitations of the cholesterol hypothesis as an explanation for myocardial infarction. We shall therefore examine it in detail in the following section. The discussion will necessarily become somewhat more technical.

What Is the True Cause of Myocardial Infarction?

We begin by presenting the findings of an epidemiological study that provides an important clue to understanding the causes of myocardial infarction.

The **Figure 3** is based on prospective data from the National Health and Nutrition Examination Survey (NHANES) conducted by the US National Center for Health Statistics (NCHS) [15].

The analysis included members of the general population who were free from cancer and cardiovascular disease at enrolment between 1999 and 2014 and who were followed for a median of 8.2 years.

Participants were divided into six groups according to their total cholesterol concentrations. In both individuals aged 65 years or older and those younger than 65 years, the five groups with total cholesterol concentrations below 280 mg/dL showed a similar pattern: in general, the lower the cholesterol concentration, the higher the risk of death.

A Different Pattern in the Group with Total Cholesterol ≥ 280 mg/dL

The only group in which the findings differed markedly

according to age was that with total cholesterol concentrations of 280 mg/dL or higher. Among individuals aged 65 years or older, the hazard ratio for mortality was lowest in the ≥ 280 mg/dL group, regardless of the cause of death ($\square$).

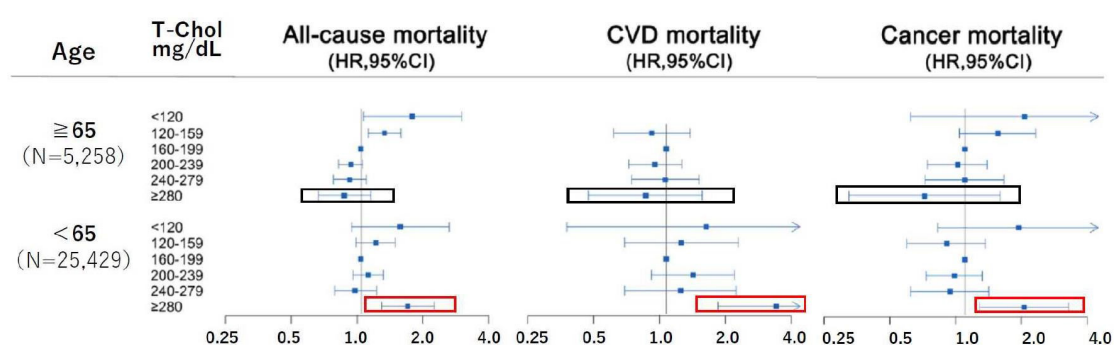
In contrast, among those younger than 65 years, the pattern differed from that observed in the groups with total cholesterol concentrations between 160 and 279 mg/dL. In the ≥ 280 mg/dL group, hazard ratios were higher for all categories of mortality ($\square$), with the greatest increase seen for deaths from cardiovascular disease. How should these findings be interpreted?

At the very least, this figure suggests that, in older adults, high cholesterol is not a risk factor for heart disease or, indeed, for any major cause of death. One might even regard it as a marker of longevity.

By contrast, among middle-aged individuals under the age of 65 years, markedly elevated cholesterol appears to be associated with an increased risk of death from cardiovascular disease, particularly coronary heart disease (CHD).

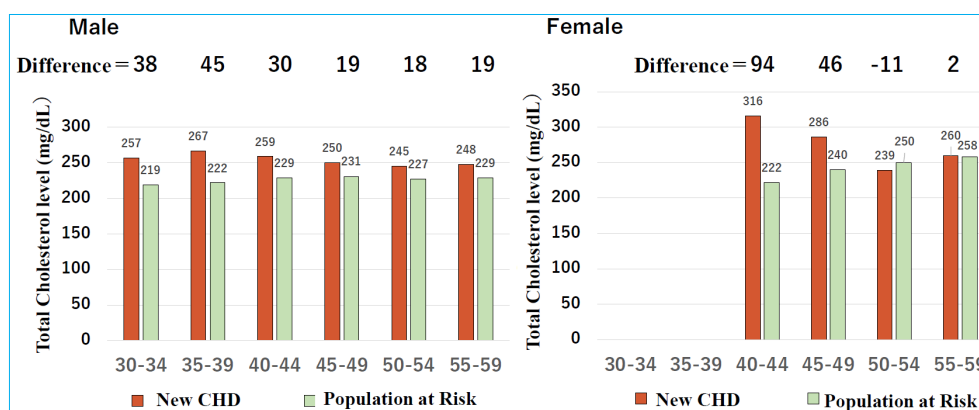
This age-related pattern was already appeared in the first report from the Framingham Study published in 1961

Figure 3: Association of Total Cholesterol with All-cause and Cardiovascular Mortality by age

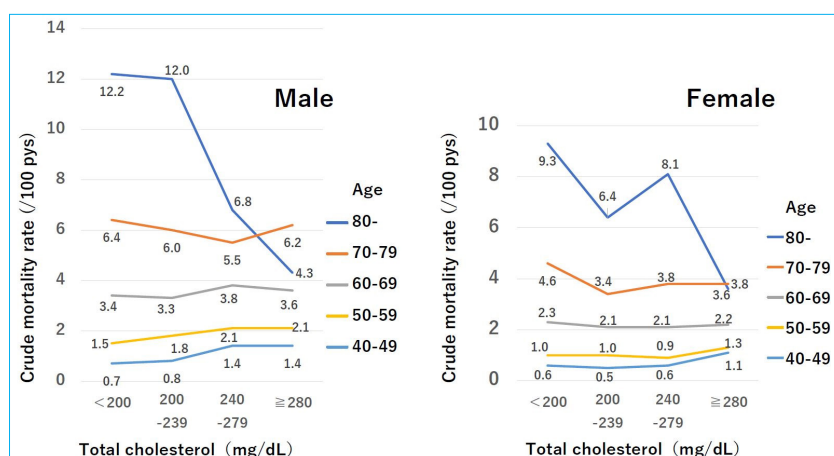


Adapted from Reference [15]. Forest plots of subgroups analyses by age (age, gender, race, education level, married, smoking, body mass index, systolic blood pressure, estimated glomerular filtration rate, high density lipoprotein cholesterol, energy intake, hypertension, diabetes, antihypertensive drugs, hypoglycemic agents, and lipid-lowering drugs were all adjusted except the variable itself)

The most notable difference between the age groups of 65 and older and those less than 65 is observed in the group with levels of 280 mg/dL or higher. Among those aged 65 and older, the hazard ratio for death from any disease is lowest in the ≥ 280 mg/dL group; in contrast, among those under 65, the hazard ratios for all disease categories are high in this range—particularly for cardiovascular disease (CVD) mortality, which is markedly elevated. This is likely because individuals with familial hypercholesterolemia (FH)—who face a high risk of fatal myocardial infarction at a young age due to coagulation abnormalities and elevated TNF- α levels—experience high mortality before age 65, resulting in a drastically lower prevalence of the condition in the population aged 65 and older.

Figure 4: Mean Serum Cholesterol at Initial Examination: Comparison New CHD and Population at Risk

Based on the data in the Table 5 in the Framingham Study published in 1961 [26]). Among women, there are no coronary disease events in the 30s, whereas total cholesterol levels are markedly high in those who experience new coronary heart disease (CHD) in their early 40s. However, at age 50 and older, cholesterol levels can no longer be considered a risk factor for CHD. Similarly, among men, the difference in cholesterol levels between those who experience a new CHD and the general population exceeds 30 mg/dL up to age 44, but narrows to less than 20 mg/dL at age 45 and older.

Figure 5: Crude mortality within age categories by sex and total cholesterol

Based on data in the Table 2 in the Framingham Study published in 1993 [28]

In both men and women up to their 50s, an increase in total cholesterol levels is associated with a slight rise in all-cause mortality. In the 60s, there is no correlation between total cholesterol levels and all-cause mortality. Among those aged 70 and older—and particularly in the 80s—an inverse correlation is evident.

[26] (Figure 4), and in its 1987 report [27]. It became even more evident in the 1993 Framingham report [28] (Figure 5).

(Supplement 3)

A Japanese study published in 1995 also demonstrated a similar trend [29] (Supplement 4).

Furthermore, the 1987 Framingham report [27] found that total cholesterol concentrations declined over time in 14% of men and 20% of women. Among participants who were initially free from cardiovascular disease and cancer, a decrease in total cholesterol of 14 mg/dL over 14 years (approximately 1 mg/dL per year) was associated with an 11% increase in all-cause mortality and a 14% increase in

cardiovascular mortality over the subsequent 18 years (Supplement 5).

These observations raise an important question. If lower cholesterol concentrations are associated with increased mortality, and if higher cholesterol concentrations are clearly associated with longevity in older adults, is it plausible that elevated cholesterol itself becomes a risk factor in younger people? Viewed from another perspective, might factors other than cholesterol be the true underlying cause of myocardial infarction in younger individuals? If so, what might those factors be?

The Association Between Hypercholesterolaemia, Coagulation, and Inflammation

Familial Hypercholesterolaemia: More Than High LDL Cholesterol

In addition to diet, genetic factors play a major role in determining cholesterol concentrations. The most

striking example is familial hypercholesterolaemia (FH), an inherited disorder caused by mutations affecting LDL-receptor function and characterised by markedly elevated cholesterol concentrations. FH is estimated to

affect approximately 0.3–0.4% of the general population [30]. Individuals with FH may develop total cholesterol concentrations exceeding 280 mg/dL from a young age, with concentrations of 300–1000 mg/dL having been reported [22]. LDL cholesterol concentrations may exceed 190 mg/dL and, in some cases, reach 300 or even 500 mg/dL [31].

Furthermore, individuals with LDL cholesterol concentrations of 190 mg/dL or higher who carry an FH-associated genetic variant have been reported to have a 22-fold greater risk of developing myocardial infarction or other forms of coronary artery disease at a young age than individuals with LDL cholesterol concentrations below 130 mg/dL who do not carry such variants [31].

Taken at face value, these findings might appear to support the view that elevated cholesterol itself is responsible for the increased cardiovascular risk. However, susceptibility to myocardial infarction is influenced by numerous inherited factors other than cholesterol concentrations, including increased blood coagulability, impaired fibrinolysis, enhanced inflammatory responses, platelet hyperreactivity, vascular endothelial dysfunction, and elevated blood pressure.

By 2000, numerous studies had reported the involvement of such factors, and by 2010 several reviews had evaluated this evidence collectively [32,33]. More recently, a 2022 review examined in detail the possible contribution of coagulation abnormalities and thrombogenicity to premature cardiovascular disease in FH [34].

Enhanced Coagulation, Platelet Reactivity, and Impaired Fibrinolysis in FH

Several studies have demonstrated haemostatic abnormalities in FH. Ekholm et al. found that 16 otherwise healthy adults with FH, with a mean age of 43 years, had significantly higher plasma fibrinogen concentrations than 16 age- and sex-matched controls (270 vs. 210 mg/dL), together with increased peak thrombin concentration and endogenous thrombin generation potential [35].

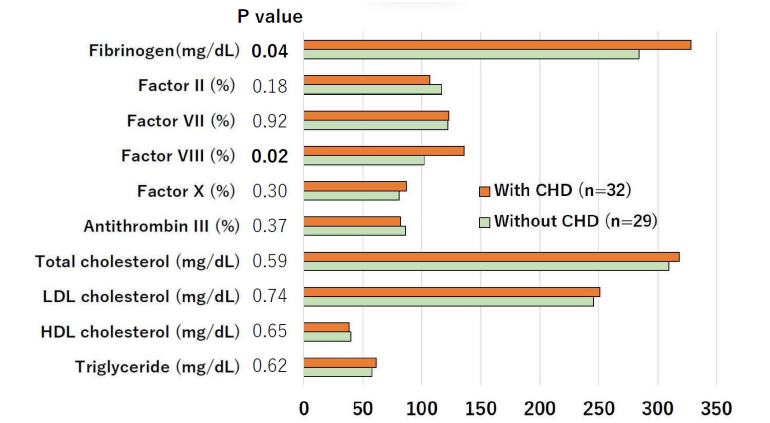
Lowe et al. also reported significantly increased plasma fibrinogen concentrations in patients with FH [36,34]. Increased fibrinogen and increased numbers of circulating platelet aggregates were already evident from the age of 15 to 29 years. Importantly, the haemostatic abnormalities did not correlate with serum cholesterol concentrations and were not corrected by cholesterol reduction by cholestyramin [36].Lowe et al also showed that the plasma viscosity is corelated with the level of fibrinogen ($r=0.67$, $p<0.001$) within 21 subjects with type II hyper lipoproteinemia (HLP) who had 6.09 mmol/L of LDL-cholesterol in average [37].

Sugrue et al. provided further evidence by comparing adult FH patients with coronary heart disease (CHD; $n=32$) with those without CHD ($n=29$). Plasma fibrinogen and factor VIII activity were significantly higher in FH patients with CHD, whereas LDL cholesterol and other serum lipid concentrations did not differ significantly between the two groups [38] (Figure 6)(Supplement 6).

Moreover, substantial cholesterol lowering with pre-statin lipid-lowering agents was not accompanied by reductions in fibrinogen or factor VIII activity. Antithrombin III was instead significantly reduced after treatment [37].

The findings of Holven et al. are particularly relevant. In FH subjects who had received long-term statin treatment and whose total and LDL cholesterol concentrations had been reduced to levels similar to those of age- and sex-matched healthy controls, fibrinogen remained significantly elevated ($P=0.04$). Both von Willebrand factor (vWF)

Figure 6: Hemostatic variables in patients with familial hypercholesterolemia with and without CHD.



Data based on Sugrue et al. [16]. CHD: coronary heart disease. CHD was associated with significantly increased levels of fibrinogen and coagulation factor VIII but not with increased levels of classical risk factors such as total cholesterol, LDL-C, HDL-C, and TG.

activity ($P=0.002$) and vWF antigen ($P=0.014$) were also significantly increased [39]. vWF plays a central role in primary haemostasis by tethering platelets to sites of vascular injury through interactions with platelet GPIIb and exposed subendothelial collagen, and also serves as a carrier protein that stabilises circulating factor VIII [40]. Thus, these haemostatic abnormalities cannot readily be explained simply as a consequence of elevated LDL cholesterol.

Platelet function itself is also abnormal in FH. In a study comparing 17 FH subjects with 26 non-FH subjects, platelet aggregability was significantly increased in FH [41,34]. In another experiment, washed platelets from non-FH subjects became almost as sensitive to aggregation when incubated with plasma from FH subjects, suggesting that circulating factors in FH contribute to platelet hyperreactivity [42,34]. Platelets from FH patients have also been shown to bind more fibrinogen in response to ADP, collagen, and thrombin [43].

Lipoprotein(a) [Lp(a)], which is frequently elevated in FH, provides another potential link between lipid measurements and thrombosis. Lp(a) is both prothrombotic and antifibrinolytic. It may enhance platelet aggregation and interfere with plasmin generation and fibrinolysis, thereby favouring persistence of coronary thrombi once formed [34]. Thus, enhanced coagulation, platelet hyperreactivity, and impaired fibrinolysis may act together to increase susceptibility to premature coronary thrombosis in a subset of individuals with FH.

FH Is Also Characterised by an Enhanced Inflammatory Phenotype

Evidence from genetic studies points in the same general direction. Since 2010, genome-wide association studies (GWAS) (Note 3) have demonstrated substantial genetic overlap between traits associated with blood lipid concentrations and those associated with inflammatory responses and immune-mediated diseases [44,45]. Although GWAS have not directly established that genetic variants causing elevated cholesterol concentrations also cause increased coagulability, studies of coronary artery disease have identified associations with genomic regions related to coagulation, inflammation, vascular endothelial

function, and arterial-wall biology [46]. These findings indirectly support the contribution of coagulation, inflammation, and vascular-wall pathology to inherited susceptibility to coronary artery disease.

The study by Holven et al. provides particularly striking evidence that this inflammatory phenotype persists even after substantial LDL-cholesterol reduction. Their FH patients had received statin treatment for a median of 17 years and had LDL-cholesterol concentrations similar to those of healthy controls. Nevertheless, several tumour necrosis factor (TNF)-related genes were expressed at higher levels in peripheral blood mononuclear cells (PBMCs) from FH patients; expression of TNF receptor 1 (TNFR1) was particularly increased ($P<0.001$). Furthermore, following stimulation with lipopolysaccharide (LPS), TNF- α release from PBMCs of FH patients was more than twice that from controls ($P=0.004$) [39].

Taken together, these findings indicate that FH should not be regarded simply as a disorder characterised by elevated LDL cholesterol. When interpreting the increased risk of myocardial infarction and premature cardiac death in FH, the contributions of enhanced coagulation, platelet hyperreactivity, impaired fibrinolysis, inflammation, and endothelial abnormalities should also be taken into account.

Note 3: In this article, the term genome refers to the complete DNA of an organism, including not only genes but also regulatory and non-coding regions. Genome-wide association studies (GWAS) are analytical methods used to identify associations between genetic variants across the genome and disease, as well as associations among genomic variants themselves.

An Evolutionary Link Between Cholesterol, Coagulation, and Inflammation?

There is evidence suggesting that traits associated with cholesterol concentrations, coagulation and inflammatory responses, as well as the ABO blood-group system—particularly non-O blood groups—may have become associated with one another during human evolution [47].

Today, relatively few people in industrialised countries die from infectious diseases or trauma compared with the past. Historically, however, infection and injury were major threats to survival. Under such conditions, the ability to

mount a vigorous inflammatory response capable of eliminating pathogens and repairing damaged tissue would have conferred an important survival advantage. Enhanced coagulation would likewise have been beneficial by rapidly limiting blood loss after injury and helping to prevent pathogens from penetrating more deeply through wounds.

Higher cholesterol concentrations may also have conferred advantages. Cholesterol is an essential component of biological membranes such as cell membranes and is required for tissue repair and for the synthesis of steroid hormones. Higher cholesterol availability may therefore have supported tissue repair, host responses to invading pathogens and other foreign substances, and physiological responses to severe stress. These characteristics, acting together, may have improved survival under conditions dominated by infection, injury, and other acute stresses.

As infectious diseases became less common and life expectancy increased, however, exceptionally strong inflammatory and coagulation responses became less important for survival. Consequently, in a subset of individuals in whom high cholesterol concentrations coexist with inherited tendencies towards enhanced inflammation, coagulation, platelet activation, or impaired fibrinolysis, a different consequence may become apparent: increased susceptibility to coronary thrombosis and myocardial infarction.

The Relationship Between Inflammation and Myocardial Infarction

We may now ask why inflammation increases the likelihood of myocardial infarction. A familiar example is the healing of a skin wound, which depends on the inflammatory response. As healing progresses, a scab forms and the repaired tissue becomes uneven. A similar process may occur within the arterial wall. When injury to the inner surface of a blood vessel heals, the resulting irregularity may disrupt normal blood flow, creating turbulence and areas of stagnation that favour blood clot formation and increase the likelihood of arterial occlusion. For this reason, individuals who are genetically predisposed to stronger inflammatory responses may also be more prone to developing atherosclerosis

and, consequently, myocardial infarction. When individuals who possess both elevated cholesterol concentrations and enhanced inflammatory and coagulation activity develop myocardial infarction, cholesterol concentrations are also high, and cholesterol crystals are often found deposited within the atherosclerotic lesions. Observing these deposits, early pathologists concluded that cholesterol itself was the cause of atherosclerosis. From the outset, however, there were also researchers who argued that cholesterol accumulation was merely a consequence of the disease process rather than its cause. Nevertheless, this interpretation was largely overshadowed by the overwhelmingly influential cholesterol hypothesis.

In other words, the true cause of myocardial infarction may not be elevated cholesterol itself. Rather, among individuals with markedly elevated cholesterol concentrations, those who also have a genetic predisposition to enhanced inflammation and blood coagulation are more likely to develop myocardial infarction because of these underlying characteristics. Around 1950, however, these mechanisms were not yet understood, and elevated cholesterol itself came to be regarded as the principal cause.

What About Individuals Without a Predisposition to Inflammation or Increased Coagulation?

Let us next consider how common markedly elevated cholesterol concentrations actually are.

In a US survey conducted in 1950 [24], fewer than 10% of healthy men under the age of 40 had total cholesterol concentrations exceeding 280 mg/dL. More recently, analysis of US adults with a mean age of 46 years during the 2000s showed that only 3.6% of participants—and only 3% of men—had total cholesterol concentrations of 280 mg/dL or higher [15]. In Japan, only 2.7% of men aged 30–60 years have total cholesterol concentrations of 260 mg/dL or above [29]. The proportion with concentrations exceeding 280 mg/dL is therefore likely to be even smaller.

Individuals with familial hypercholesterolaemia (FH) account for only 0.3–0.4% of the general population. They therefore represent roughly one-

tenth of those whose total cholesterol concentrations exceed 280 mg/dL. What, then, characterises the remaining individuals with markedly elevated cholesterol concentrations?

People with FH carry a single-gene mutation, most commonly affecting the LDL receptor (LDLR), which is responsible for the markedly elevated LDL cholesterol concentrations characteristic of the disorder. However, several other genes also influence cholesterol concentrations. Some individuals carry multiple genetic variants that each contribute modestly to elevated cholesterol, although not to the extent seen in FH. This condition is referred to as “polygenic hypercholesterolaemia”.

Many postmenopausal women have total cholesterol concentrations exceeding 280 mg/dL, while among men with concentrations above this threshold, a large proportion are thought to have polygenic hypercholesterolaemia. Studies have shown that many of these individuals also possess inherited traits that predispose them to stronger inflammatory responses and increased blood coagulability [33,34,44].

Furthermore, individuals with polygenic hypercholesterolaemia are also more likely to experience myocardial infarction or die from myocardial infarction at a relatively young age.

The Risk Associated with Markedly Elevated Cholesterol Differs Between Middle-Aged and Older Adults

Not everyone with markedly elevated cholesterol concentrations has an inherited tendency towards enhanced inflammation or increased blood coagulation. Individuals whose cholesterol concentrations are high from an early age but who do not possess these additional predispositions may avoid myocardial infarction altogether and enjoy a long lifespan. Consequently, among people aged 65 years or older, those whose total cholesterol concentrations remain 280 mg/dL or higher have remarkably low mortality rates and, on average, live considerably longer than individuals with lower cholesterol concentrations.

The **Figure 3** presented earlier (p.32) illustrates this point clearly.

Individuals with total cholesterol concentrations of 280 mg/dL or higher are more likely to die from myocardial infarction at a relatively young age. This is likely to reflect the fact that some of these individuals have familial hypercholesterolaemia (FH) or polygenic hypercholesterolaemia, conditions that are collectively classified as primary hypercholesterolaemia. Among people born with markedly elevated total cholesterol concentrations, those who also possess inherited predispositions to enhanced coagulation or inflammatory responses are likely to have experienced myocardial infarction and premature death. By contrast, there are also individuals with total cholesterol concentrations of 280 mg/dL or higher who do not have such predispositions. These individuals appear to be less susceptible to a wide range of diseases than those with lower cholesterol concentrations and therefore tend to live longer.

It is also noteworthy that these data [15] were obtained not from Japan but from the United States, where mortality from myocardial infarction is substantially higher. In Japan, the mortality rate from myocardial infarction is only about one-third to one-fifth of that observed in the United States. Nevertheless, Japanese cohort studies that included younger adults have likewise shown that only the group with total cholesterol concentrations of 260 mg/dL or higher had higher all-cause mortality than those with concentrations around 200 mg/dL [29].

The Framingham Investigators Themselves Warned About Low Cholesterol Concentrations

It should also be noted that the first report from the Framingham Study, published in 1961 [26], emphasised that the incidence of myocardial infarction increased with rising total cholesterol concentrations. However, the analysis was restricted to middle-aged adults in their forties and fifties, and among women the increased risk of myocardial infarction was observed only up to the age of 49 years. As follow-up continued and outcomes expanded beyond the incidence of myocardial infarction to include deaths from myocardial infarction, cardiovascular mortality, and all-cause mortality, the apparent impact of elevated total

cholesterol concentrations became progressively less pronounced [26–28].

Furthermore, another report Gotman's Livemore Cohort, based on a cohort enrolled in 1954 to 1956 and followed for 53 years, was published in 2012 [48]. In the study population as a whole, the hazard ratio for all-cause mortality associated with total cholesterol concentration was 1.01 ($p = 0.09$), indicating no statistically and no practically significant association.

Because the cohort consisted primarily of company employees and community residents, it is likely that it included a proportion of individuals with markedly elevated cholesterol concentrations due to familial hypercholesterolaemia or polygenic hypercholesterolaemia. If the influence of these individuals were excluded, the findings might well resemble the more recent pattern illustrated in the figure presented earlier. Indeed, signs of this age-dependent pattern were already evident among women in the original 1961 Framingham report [26] (Figure 4), which has long been regarded as one of the principal foundations of the cholesterol hypothesis. In the 1993 report [28], the pattern had become much clearer: among men and women younger than 60 years there was a positive association between cholesterol concentration and mortality; in participants in their sixties there was essentially no association; and among those aged 70 years or older—particularly those over 80 years—there was a marked inverse association (Figure 5), closely resembling the pattern shown in the Figure 3.

Studies Cited in the Guidelines Also Reported an Inverse Association with All-Cause Mortality

Finally, we summarise the findings of our review of all the studies cited by the Japanese Atherosclerosis Society [4] as evidence supporting its recommendation that cholesterol concentrations should be lowered (Supplement 2 and 7 for details).

We identified six Japanese studies [49–54] examining the relationship between LDL cholesterol concentrations and coronary heart disease outcomes including incidence and mortality.

Four of these reported only that elevated cholesterol concentrations were risk factors for the incidence of, or

mortality from, myocardial infarction, without providing any data on all-cause mortality. The remaining two studies reported an inverse association between cholesterol concentration and all-cause mortality; in other words, the lower the cholesterol concentration, the higher the all-cause mortality rate, whereas individuals with higher cholesterol concentrations had lower overall mortality. However, in the Japan Atherosclerosis Society's evaluation [4], only the positive association with myocardial infarction was discussed (Supplement 2).

In addition, the Guidelines [4] cited 12 Japanese studies examining the relationship between total cholesterol and all-cause mortality[55–66] (Supplement 7-A). Of these, 11 were cited solely as evidence that total cholesterol is a risk factor for the incidence of, or death from, myocardial infarction, whereas only one addressed its association with all-cause mortality [57] (Supplement 7-B).

This study, reported by Okamura et al. [57], was based on the same cohort as Reference 29, which was the initial report after 14 years of follow-up; Reference 57 presented the 17-year follow-up results. In the 14-year report [29], when individuals with total cholesterol concentrations of 240 mg/dL or higher were analysed together, all-cause mortality showed an inverse association with total cholesterol. In contrast, in their 17-year follow-up analysis, Okamura et al. adjusted mortality risk for plasma albumin concentration and excluded deaths from all liver diseases as well as all deaths occurring within the first five years of follow-up. Under these conditions, the previously significant excess risk observed in the lowest total cholesterol group (<160 mg/dL) disappeared, while the group with total cholesterol concentrations of 260 mg/dL or higher showed a significantly increased risk.

If it is appropriate to adjust plasma albumin level and to exclude death from liver diseases and all deaths occurring within the first five years of follow-up, they should adjust for various relevant factors of thrombogenesis, coagulation and inflammation. But they ignored these important factors which independently associated with coronary heart disease and all-cause mortality.

In fact, the original 14-year data [29] demonstrated a pattern similar to that shown in the Figure 3. Among men aged 60 years or younger, individuals with total cholesterol concentrations of 260 mg/dL or higher showed a trend towards increased all-cause mortality (hazard ratio 2.04)

compared with those whose concentrations were 160–179 mg/dL. By contrast, among individuals aged 61 years or older, those with total cholesterol concentrations of 260 mg/dL or higher had the lowest risk of all-cause mortality (hazard ratio 0.67). Thus, the age-dependent pattern shown in the **Figure 3** appears to be reproducible in the Japanese population as well (**Supplement 4**).

Furthermore, another Japanese study (Nago et al., 2011) [18] reported that, even after excluding deaths from liver disease (including hepatocellular carcinoma and liver failure) and deaths occurring within the first five years of follow-up, the group with the lowest total cholesterol concentrations (<160 mg/dL) still had a significantly higher risk of all-cause mortality (**Supplement 7-C**). However, this study was not cited in the Japan Atherosclerosis Society Guidelines [4].

Conclusions

Current academic guidelines for the prevention of atherosclerotic cardiovascular disease continue to emphasise lowering elevated cholesterol levels. However, cholesterol is an essential structural and functional component of biological membranes and a precursor of steroid hormones, with numerous other vital physiological roles. A substantial body of evidence indicates that, with few exceptions, higher total or LDL cholesterol levels are associated with longer survival, whereas lower levels are associated with increased risks of cancer, haemorrhagic stroke, and all-cause death. Furthermore, many individuals with extremely high cholesterol levels who develop myocardial infarction at a young age exhibit abnormalities of coagulation and inflammation consistent with a prothrombotic and pro-inflammatory state. These findings suggest that the increased risk of myocardial infarction traditionally attributed to high cholesterol may arise not from cholesterol itself, but from associated abnormalities in coagulation and inflammation. Thus, the conventional cholesterol hypothesis and current recommendations for cholesterol lowering warrant critical re-evaluation.

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