Review

Are high density lipoprotein (HDL) and triglyceride levels relevant in stroke prevention?

Evangelos Rizos, Dimitri P. Mikhailidis*

Department of Clinical Biochemistry (Cardiovascular Disease Prevention service), Royal Free and University College Medical School, University College (University of London), Royal Free Campus, London NW3 2QG, UK

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Abstract

Although statins reduce the risk of non-haemorrhagic strokes and transient ischaemic attacks (TIA), little is known about the efficacy of fibrates. This situation has been partly remedied by the recent publication of two-fibrate based trials — The Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial (VAHIT) and the Bezafibrate Infarction Prevention Trial (BIP). In BIP, bezafibrate did not significantly reduce the risk of a cerebrovascular event (CVE). Bezafibrate increased the high density lipoprotein cholesterol (HDL) level by 18% to 40 mg/dl (1.03 mmol/l) and decreased triglyceride (TG) levels by 21% to 115 mg/dl (1.29 mmol/l). In contrast, in VAHIT, gemfibrozil significantly reduced the risk of investigators designated stroke (P<0.04) and TIA (P<0.001). Gemfibrozil increased HDL by 6% to 33 mg/dl (0.85 mmol/l) and decreased TG by 31% to 110 mg/dl (1.25 mmol/l). However, the baseline low density lipoprotein cholesterol (LDL) levels were higher in BIP than in VAHIT (148 versus 111 mg/dl; 3.82 versus 2.87 mmol/l). LDL levels were not markedly altered by treatment in either trial. Fibrates can improve several CVE predictors, like fibrinogen, lipoprotein (a), insulin sensitivity and platelet activity. Furthermore, lowered HDL and/or raised TG levels are associated with an increased risk of a CVE; fibrates are an appropriate treatment for this lipid profile. In conclusion, the evidence suggests that not only total cholesterol and LDL, but also HDL and TG levels predict the risk of a CVE. Statins, fibrates or a combination of these drugs can modify these variables. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

There is evidence [1–31] (epidemiological and trial-based) supporting an association between elevated serum total cholesterol (TC) and low density lipoprotein cholesterol (LDL) levels and the risk of thrombotic (non-haemorrhagic) stroke. Epidemiological studies have also linked low serum levels of high density lipoprotein cholesterol (HDL) with the risk of a cerebrovascular event (CVE) [1–4,9–17,19–23]. In contrast, there is relatively less evidence supporting a causative role for triglycerides (TG). All these links are both complex and weaker [4] than those seen between these lipid variables and ischaemic heart disease (IHD).

Several factors influence the strength of the lipids–stroke relationship. For example, low levels of TC represent an increased risk of haemorrhagic stroke [30,31]. This dual effect may explain why early epidemiological surveys and clinical trials did not detect a consistent association between TC and non-haemorrhagic–haemorrhagic strokes considered together [1,17]. Furthermore, stroke is a heterogeneous condition. For example, atrial fibrillation or cerebral small vessel disease may cause some strokes but dyslipidaemias do not necessarily play a causal role in these conditions. Unlike IHD, thrombotic stroke is mainly a disease of the elderly [3]. It follows that some patients with IHD will have died or benefited from lipid lowering prior to reaching old age and an increased risk of having a CVE. A further problem is that lipid variables alter with aging [1,32]; this may weaken the relationship between lipids and stroke.

*Corresponding author. Tel.: +44-20-7830-2258; fax: +44-20-7830-2235.

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As a result of these limitations, if stroke is considered as a single entity, inconsistent results may be generated regarding the predictive value of any risk factor. This disadvantage can be overcome because it is now possible to differentiate the type of stroke by using imaging techniques. However, many epidemiological studies and clinical trials did not benefit from this classification.

The link between elevated TC levels and the risk of non-haemorrhagic stroke or transient ischaemic attacks (TIA) is reinforced by the findings of several trials that assessed the effect of statins in patients with IHD [1,5–8,18,24–29]. This benefit was limited to nonfatal and non-haemorrhagic stroke (approximately a 30% decrease in risk). The primary prevention trials involving statins showed a similar trend, but this did not achieve statistical significance [33,34] possibly because of the small number of events that occurred. However, all these trials had limitations, in terms of HDL and TG entry criteria. Furthermore, statins did not exert major effects on TG levels at the doses used in these studies. This situation has changed because the findings of two fibrate-based secondary prevention trials have recently been published [35,36].

This review focuses on the CVE-related findings of the recently published fibrate-based secondary prevention trials [35,36]. We also consider the epidemiological evidence linking stroke and HDL or TG levels.

2. Overview of recent epidemiological studies that assessed the role of HDL and TG as predictors of stroke

The association between lipid levels and the risk of stroke has been reviewed elsewhere [1,8]. Here we consider recent major prospective epidemiological studies that highlight the role of HDL and/or TG as CVE predictors.

2.1. The British regional heart study [9]

In this prospective study, 7735 men (40–59 years old) were followed up for 16.8 years. The end point was fatal or nonfatal stroke. No information on the type of stroke was available.

Multivariate analysis revealed a significant negative association between HDL levels and nonfatal stroke. The adjusted relative risk (RR) for nonfatal stroke was 0.59 (95% confidence interval, CI = 0.39–0.90; \( P = 0.03 \)) when comparing the top and the lowest HDL quintiles. For fatal stroke, there was no significant association with HDL. This lack of significance may reflect the small number (n = 60) of fatal events. The TC and non-fasting TG levels were not significantly related to fatal or nonfatal stroke. However, elevated TC levels showed a trend for an increased risk of stroke.

In hypertensives (approximately 34.5% of the subjects), HDL levels in the top quintile were associated with a significant 50% reduction in the risk of nonfatal stroke compared with men in the lowest quintile for HDL values.

As expected, the presence of IHD (24.4% of the subjects) or diabetes (1.4% of the subjects) was associated with an increased risk of a CVE. A trend for a protective effect of HDL levels was evident within the IHD group and smokers.

2.2. The Israeli ischaemic heart disease study [10]

This prospective study included 8586 men (>42 years) followed up for 21 years. The end point was fatal ischaemic stroke. Stroke type was determined on clinical grounds. Therefore, some degree of misclassification may have occurred.

Multivariate analysis revealed a significant negative association between HDL levels and ischaemic stroke mortality; the RR was 1.17 (95% CI = 1.02–1.36) per 0.26 mmol/l (10 mg/dl) decrement in HDL. For comparison, the RR for IHD-related mortality was 1.28 for the same decrement in HDL. For TC levels, the RR for 21 year ischaemic stroke mortality was 1.11 (95% CI = 0.96–1.28) per 1.03 mmol/l (40 mg/dl) increment.

The RR associated with ageing (5 year increment) was 1.72, with a 20 mmHg increment in systolic blood pressure was 1.68, with diabetes mellitus was 1.78 and with smoking 11–20 cigarettes per day (compared to never smokers) was 1.67.


In this Finnish study, 28,519 men, aged 50–69 years, were followed up for 6 years. All those included in the study were smokers and none had a previous stroke. The end point was cerebral infarction and cerebral or subarachnoid haemorrhage. Most (85%) of the cases were diagnosed using CT, MRI or angiography.

Multivariate analysis showed a significant negative association between HDL and cerebral infarction or subarachnoid haemorrhage. No relation between HDL and intracerebral haemorrhage was found. Serum TC was inversely correlated with the risk of intracerebral haemorrhage whereas the risk of cerebral infarction was increased at TC levels >7.0 mmol/l (270 mg/dl).

2.4. The Dubbo study [12]

This Australian prospective study included 2805 elderly (>60 years; mean age 69 years) men and women followed up for 98 months. The end point was ischaemic stroke and TIA. Most of the strokes (70%) were diagnosed using CT. There were few (n = 29) haemorrhagic strokes. These were not included in the analysis.

Multivariate analysis revealed a significant negative
association between HDL and all strokes (fatal, nonfatal and TIA) as well as between HDL and fatal strokes. There was a 36% reduction in risk for a 1.0 mmol/l (39 mg/dl) increment in HDL. There was no association between fasting TG and strokes. In comparison, a previous stroke conferred a 227% higher risk of a subsequent CVE. Atrial fibrillation and the highest category of blood pressure reading were associated with a 58 and a 67% higher risk of stroke, respectively.

2.5. The Copenhagen study [13]

In this prospective study, 19,698 men and women were followed up for 12 years. The end point was cerebral infarction, TIA and cerebral haemorrhage. The diagnosis was made using CT or brain autopsy in 40% of cases. The remaining events were classified as unspecified and were presumed to be mostly ischaemic.

A significant negative association was shown between HDL and ischaemic strokes; the decrement in RR per 1.0 mmol/l (39 mg/dl) rise in HDL was 47%. TC was positively associated with the risk of non-haemorrhagic events, but only for levels >8.0 mmol/l (310 mg/dl). Additionally, TG levels (non-fasting) were significantly associated with the risk of ischaemic strokes. The RR increment was 1.12 (95% CI = 1.07–1.16) per 1.0 mmol/l (88.5 mg/dl) increase in TG.

2.6. The Finmark study [14]

In this Norwegian study, 13,266 men and women, aged 35–52 years, were followed up for 14 years. The end point was fatal or nonfatal stroke.

There was a significant association between non-fasting TG and strokes, but only for women [RR = 1.29 per 1.0 mmol/l (88.5 mg/dl) increase in TG]. HDL was measured only at the second screening (three years after the beginning of the study) in a sub-population of 11,286 men and women. There was an inverse relationship between HDL and stroke, but this association was not significant.

3. Other epidemiological studies

In the Multiple Risk Factor Intervention Trial (MRFIT) [15,30,31], 353,340 men were followed up for 12 years. TC was positively associated with death from non-haemorrhagic stroke and inversely associated with intracranial haemorrhage. These authors did not comment on HDL levels.

In the Framingham [37] study, HDL had a non-significant effect on the overall risk of stroke in both men and women and on ischaemic stroke in men. This apparent discrepancy may be attributed to the ‘study size’. For example, the Copenhagen study [13] had more subjects (11,342 versus 2723) and cases (279 versus 99) than the Framingham study [37].

In another analysis from Framingham [16], 1116 men and women free of cardiovascular disease, aged 66–93, were studied prospectively for 12 years. TC levels (no evidence for HDL), but not TG, were positively associated with ultrasonographic evidence of carotid atherosclerosis [16].

A meta-analysis [17] of 45 prospective observational cohorts (450,000 individuals) found no association between TC and stroke. However, there was no separation of the types of stroke. Therefore, the lack of any overall relation might conceal a positive association with ischaemic stroke and a negative association with haemorrhagic stroke.

In the Atherosclerosis Risk In Communities (ARIC) [38] study, 12,205 men and women, aged 45–64 were evaluated for symptoms of stroke and TIA through a questionnaire and data were collected on HDL, LDL, and TG levels. No relation was found between these lipid values and stroke/TIA symptoms. However, it may be relevant that the evaluation of stroke was made using a questionnaire.

4. HDL and TG levels as targets for CVE prevention

The evidence described above suggests the need to increase HDL and decrease abnormal TG levels to prevent stroke/TIA. These objectives could be accomplished by using fibrates but there are no trials that specifically evaluate the protection from strokes using these drugs. However, two trials, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VAHIT) [35] and the Bezafibrate Infarction Prevention Trial (BIP) [36], assessed the contribution of low HDL levels (and TG levels at the upper limit of the reference range) on the risk of vascular events in patients with established IHD.

4.1. The VAHIT study [35]

In this double blind study conducted in the USA, 2,531 men with IHD received gemfibrozil 1200 mg or placebo. Mean follow up was 5.1 years and the primary end point was nonfatal myocardial infarction (MI) or death due to coronary causes. Gemfibrozil increased HDL levels by 6% (32–33.2 mg/dl; 0.82–0.85 mmol/l), reduced TG levels by 31% (161–110 mg/dl; 1.81–1.25 mmol/l); LDL levels remained unaltered (111 mg/dl; 2.87 mmol/l). The reduction in the risk in primary end points (22%) and in all end points combined (nonfatal MI, death due to CHD and stroke) was 24%; both these results were significant (P = 0.006 and P < 0.001, respectively).

Regarding stroke/TIA, the outcome was also favorable (Table 1).
Table 1
Cerebrovascular events in VAHIT (follow up=5.1 years)

<table>
<thead>
<tr>
<th></th>
<th>Gemfibrozil (n=1264)</th>
<th>Placebo (n=1,267)</th>
<th>RR (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed by committee*</td>
<td>58 (4.6%)</td>
<td>76 (6%)</td>
<td>25</td>
<td>0.1</td>
</tr>
<tr>
<td>Investigators designated</td>
<td>64 (5.1%)</td>
<td>88 (6.9%)</td>
<td>29</td>
<td>0.04</td>
</tr>
<tr>
<td>TIA</td>
<td>22 (1.7%)</td>
<td>53 (4.2%)</td>
<td>59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid endarterectomy**</td>
<td>16 (1.3%)</td>
<td>44 (3.5%)</td>
<td>65</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

RR=Relative Risk Reduction, expressed as a percentage.
* Confirmed stroke was judged by a blinded adjudication panel of three neurologists.
** There is no information about the criteria that determined the need for carotid endarterectomy.

4.2. The BIP study [36]

In this double blind study conducted in Israel, 3090 men (90%) and women (10%) with known CHD received bezafibrate 400 mg once daily or placebo. Mean follow up was for 6.2 years and the primary end point was fatal or nonfatal MI or sudden death. Bezafibrate increased HDL by 18% (34–40 mg/dl; 0.89–1.03 mmol/l), reduced TG by 21% (145–115 mg/dl; 1.63–1.29 mmol/l) and LDL by 6.5% (148–139 mg/dl; 3.82–3.6 mmol/l). The reduction in the risk for the primary end point was not significant. However, in a subgroup of patients (bezafibrate: 184 from 1548 patients; placebo: 162 from 1542 patients) with TG>200 mg/dl (2.25 mmol/l) and HDL<35 mg/dl (0.9 mmol/l), bezafibrate was associated with a significant (P=0.02) reduction in primary end point outcome.

Regarding stroke, the results were not significant, although the trend was favorable (Table 2).

5. Differences between the BIP and VAHIT studies

Although the findings of VAHIT [35] support the concept that fibrates lower the risk of a CVE by modifying HDL and TG values, BIP [36] did not confirm this assumption. However, BIP [36] and VAHIT [35] differ in several ways. These differences could account for the apparent discrepancy in outcome regarding stroke and IHD-related events.

The incidence of the primary end point was greater in VAHIT [35] (22%) than in BIP [36] (15%). There are several reasons for this difference. In VAHIT [35], more patients were: men (100 versus 91%), older (mean age 64 versus 60 years), smokers (22 versus 11%), hypertensive (57 versus 31%), diabetics (24 versus 10%) and the BMI was greater (29 versus 26.7). Furthermore, 12% of the placebo and 22% of the active group in BIP received other lipid modifying therapy, whereas only 2% of the active and placebo groups in VAHIT [35] took other lipid-lowering drugs.

On the other hand, more patients in VAHIT [35] used aspirin (81 versus 70%) and fewer patients had a prior MI (61 versus 78%).

BIP had higher TC and LDL values and VAHIT [35] had higher TG and lower HDL levels. In VAHIT [35], gemfibrozil decreased TG by 31% (161 to 110 mg/dl; 1.81 to 1.25 mmol/l) and increased HDL by 6% (32 to 33.2 mg/dl; 0.82 to 0.85 mmol/l). In BIP, bezafibrate decreased TG by 21% (145 to 115 mg/dl; 1.63 to 1.29 mmol/l) and increased HDL by 18% (34 to 40 mg/dl; 0.89 to 1.03 mmol/l). The LDL values were higher in BIP than in VAHIT (148 versus 111 mg/dl; 3.82 versus 2.87 mmol/l). The final value of HDL in VAHIT (33.2 mg/dl; 0.85 mmol/l) is close to the starting value in BIP (34 mg/dl; 0.89 mmol/l). The final TG values are not markedly different in both studies (110 mg/dl; 2.6 mmol/l in VAHIT and 115 mg/dl; 3.0 mmol/l in BIP).

Therefore, the profile of the patients in VAHIT was more appropriate for the use of a fibrate. The mean LDL value in VAHIT (111 mg/dl; 2.87 mmol/l) was near the guideline target values for patients with IHD [35] (100 mg/dl; 2.6 mmol/l for the USA and 115 mg/dl; 3.0 mmol/l for the UK). In contrast, the mean LDL in BIP (148 mg/dl; 3.82 mmol/l) was above these target values. This suggests that a statin could have been a more appropriate choice in BIP.

Some of the reasons mentioned above may explain why there are more investigator designated strokes ( χ² test+ Yates’ correction: P=0.035) in the VAHIT placebo group when compared with the corresponding group in BIP (Tables 1 and 2). This difference is present despite the fact that VAHIT was of a shorter duration (Tables 1 and 2). In the placebo groups there were 13.6 strokes/1000 patients/year in VAHIT, in contrast to 8.0 strokes/1000 patients/year in BIP (a 41% relative increase in strokes). There were 9.9 strokes/1000 patients/year in the treatment group.
in VAHIT, compared to 7.5 strokes/1000 patients/year in BIP (a 24% relative increase in strokes). However, comparisons are limited by the design differences in both trials (see above). For example, the mean age of patients was greater in VAHIT than in BIP (64 and 60 years, at baseline and 69.1 versus 66.2 years at the end of the trials). Accordingly, age confers a greater CVE risk in VAHIT. Furthermore, there was no distinction between haemorrhagic and ischaemic stroke in both trials. In addition, the incidence of TIA, which are strongly linked with ischaemic events, were significantly \((P<0.001)\) reduced in VAHIT but are not documented in BIP.

One possible conclusion based on the findings of both VAHIT and BIP is that when serum LDL levels reach a satisfactory value, altering HDL (and possibly TG) levels results in a significant reduction in the risk of vascular events. This interpretation is compatible with the findings of early trials involving lipid lowering drugs (or dietary intervention) \([1,17,24±29]\) since LDL levels were not markedly reduced in these trials. This may be the reason why they did not show any benefit in terms of stroke prevention. These early (pre-statin) trials had several additional limitations. For example, there was no differentiation between haemorrhagic and non-haemorrhagic strokes. Furthermore, overviews of these early trials pooled results from studies that involved patients with and without IHD \([1]\).

6. Are the additional actions of fibrates relevant?

Fibrinogen \([19,20,39±41]\) is a powerful and independent predictor of vascular events in healthy individuals and patients with vascular disease. Elevated levels of this coagulation factor are also associated with the progression of carotid artery disease \([42]\). Furthermore, when low levels of HDL are combined with high fibrinogen levels, ultrasound examination shows that the association with carotid artery disease is strengthened \([42]\). There are no drugs that selectively lower plasma fibrinogen levels \([39,40]\). Therefore, it may never be possible to prove that lowering the circulating levels of fibrinogen is beneficial \([39,40]\). The best available trial-based evidence comes from BIP \([43]\) where elevated fibrinogen levels were associated with a greater risk of vascular events. Of greater interest were the results within the group of patients who initially had the highest plasma fibrinogen levels \([43]\). There were significantly fewer events in those who then showed a fall in the levels of fibrinogen when compared with those patients that did not show such a fall \([43]\). Another potentially relevant factor when considering fibrinogen is that gemfibrozil, unlike the other fibrates (e.g. bezafibrate, ciprofibrate and fenofibrate), may not consistently lower plasma fibrinogen levels \([44±48]\). Therefore, it is possible to speculate that the VAHIT results would have been even more impressive had another fibrate been used. These differences in potentially clinically relevant properties raise the question ‘are all fibrates equally effective?’

Platelet inhibitors prevent strokes and TIA \([49,50]\). In this context, there is evidence that fibrates and statins reduce platelet activity \([49]\). This may be an additional beneficial action of these drugs.

Lipoprotein (a) \([\text{Lp(a)}]\) is thought to contribute to atherogenesis (by transporting LDL molecules and influencing vascular smooth muscle proliferation), to inhibit fibrinolysis (because of a structural analogy with plasminogen) and possibly to influence platelet function \([2,51]\). Epidemiological studies suggest that elevated serum Lp(a) levels are associated with an increased risk of stroke and carotid disease \([2,51±53]\). The link between Lp(a) and vascular risk appears to be magnified when other cardiovascular risk factors are present \([52]\). In addition, some but not all, studies have shown a correlation between the circulating levels of Lp(a) and fibrinogen \([46]\). Lp(a) levels were not reported in VAHIT, BIP or for that matter in most of the major statin-based prevention trials \([5±7,33±36]\). This is unfortunate because there is some evidence showing that fibrates can lower raised Lp(a) levels \([45,46]\). In contrast, there is evidence that some statins may slightly raise the serum levels of this lipoprotein \([45,46,54]\).

Diabetes and impaired insulin sensitivity represent a considerable increment in vascular risk (including stroke and TIA) \([55]\). For example, in the Helsinki Policemen study \([56]\), the age-adjusted hazard ratio (22 year follow up) for ‘insulin resistance’ was 1.64 (95% CI=1.29–2.08) with regard to stroke risk. ‘Insulin resistance’ was a less powerful risk factor for IHD \([1,28\ (95\%\ CI=1.1–1.5)]\). The ARIC study also showed that glucose levels in non-diabetics predicted stroke \([21]\). This finding probably represents a causative role for insulin resistance \([21,22]\). There are no intervention trials specifically assessing the effect of fibrates or statins in patients with diabetes or insulin resistance. We need to await the outcome of ongoing trials. However, the results from patient subgroups included in secondary prevention trials using pravastatin, simvastatin or gemfibrozil are encouraging in terms of reducing the risk of vascular events in diabetics and patients with insulin resistance \([57,58]\). Fibrates may be ideally suited for patients with non-insulin dependent (Type 2) diabetes because the main lipid abnormality is low HDL and raised TG levels \([57,59]\). Furthermore, fibrates increase insulin sensitivity, although this is a relatively minor effect \([44±48,57]\).

Fibrates can exert unwanted effects. For example, fibrates can raise the plasma levels of homocysteine (Hcy) probably by interfering with the renal excretion of Hcy \([60]\). Such an effect may be relevant because elevated plasma Hcy levels have been associated with an increased risk of stroke (and other vascular events) \([52,61]\). This effect may be especially relevant in patients who tend to have elevated plasma Hcy levels and a high risk of a CVE.
(e.g. those with peripheral vascular disease) [60]. Statins do not appear to adversely affect Hcy levels [60].

The additional actions of fibrates described above are scientifically credible but a definitive judgement on their clinical relevance must await trial-based evidence.

7. Interactions between lipids and other factors that are associated with an increased risk of a CVE

Cardiovascular risk factors may be considered in isolation. This is unacceptable because these factors act synergistically and tend to cluster [62]. Furthermore, one risk factor may adversely affect another. For example, dyslipidaemias adversely affect platelet activity and this effect may be reversed by lipid lowering agents [49]. Smoking, obesity and insulin resistance raise fibrinogen levels [39,40,55]. Although serum Lp(a) levels are largely genetically determined, the circulating levels of this lipoprotein rise after the menopause [63]. It is at this time that the cardiovascular risk of women becomes similar to that of men [63]. It is therefore of interest that the menopause is also associated with a rise in plasma fibrinogen levels and adverse changes in the lipid profile [32,39,40,55]. Smoking is associated with several adverse effects. These include a fall in HDL and a rise in TG and fibrinogen levels as well as an increase in insulin resistance [55]. Diabetics have a higher incidence of hypertension and dyslipidaemia [57]. Hypertension, a major CVE risk factor, usually occurs in conjunction with other risk factors; only in 20% of patients does it occur in isolation [62]. Thus, in hypertensives, clusters of three or more additional risk factors (e.g. raised TG and reduced HDL levels) occur at four times the rate expected by chance [62]. This clustering is attributed to insulin resistance [62]. Based on the Framingham study, the prevalence of insulin resistance in the general population could be as high as 22% in men and 27% in women [62].

The presence of vascular disease (e.g. IHD) itself increases the probability of strokes [1]. Therefore, it is worth noting that some models [64] for IHD and CVE risk estimation include TG and HDL levels. Furthermore, prediction equations for several vascular end points demonstrated the potential importance of controlling multiple risk factors [65], as opposed to focusing on a single risk factor.

It is also relevant that the treatment of cardiovascular risk factors may influence more than one variable. For example, thiazides and beta-blockers can adversely affect HDL and TG levels [66]. Antihypertensives [66] and lipid lowering agents may exert variable effects on HDL and haemostatic factors [43,49,54,59,67,68].

The role of carotid endarterectomy in stroke prevention has not been fully defined [69]. However, when comparing surgery with medical treatment it is important to always provide the best preventive measures. This may not have occurred in the past, especially concerning lipid lowering, because the association between dyslipidaemia and risk of stroke or TIA was not widely appreciated [1]. Such an intervention may be useful since the need for carotid endarterectomy was significantly \( P<0.001 \) decreased in the treatment group in VAHIT [35]. Regarding carotid surgery, it is also relevant to consider that some risk factors for carotid artery disease progression [e.g. lipids, fibrinogen and Lp(a)] [1,2,42,51,53,71,73] are also associated with an increased risk of restenosis in coronary and peripheral arterial grafts [70].

Despite these well-documented interactions, many epidemiological surveys and drug trials did not include the measurement of several risk factors.

8. Mechanisms that may be responsible for the decrease in CVE risk provided by lipid lowering agents

Lipid lowering drugs improve atherosclerosis as assessed by carotid angiography, duplex scanning [71] and intima-media thickness (IMT) measurements [60]. The IMT is a predictor of stroke, TIA and IHD [72]. Preliminary results suggest that the effect of statins on the IMT may be very rapid (within 8 weeks) [60]. This may represent an anti-inflammatory action [60].

Improving the lipid profile is associated with plaque stabilisation within the carotids and the aortic arch [71]. These sites are the source of emboli that may cause a CVE. It is also relevant that carotid atherosclerosis is not only associated with elevated LDL levels but also with diminished HDL levels and hypertriglyceridaemia [16,73,74].

Low levels of HDL and high TG levels are risk factors for peripheral arterial disease and IHD [75]. In turn, these patients are more likely to have a CVE [75]. This increased risk may relate to the extent of vascular damage and any concomitant inflammatory response. These changes are associated with platelet activation, as well as elevated fibrinogen and C-reactive protein (CRP) levels [76]. All these variables may be influenced by lipid lowering therapy [49].

Fibrates are peroxisome proliferator-activated receptors (PPAR)-alpha activators [77]. PPAR-alpha is present in endothelial and smooth muscle cells as well as other cell types [77]. These cells in turn can affect various processes that are involved in atherogenesis [77]. In contrast, statins may not influence PPAR-alpha [77].

Smoking reduces the overall benefit derived from statins but the effect on the risk of stroke was not analyzed separately [78]. Thus, in the major statin trials, treatment was associated with a significant reduction in events in smokers but the best outcome was observed in treated non-smokers [78]. However, the effect of smoking on
treatment with fibrates is less clear because of the small numbers of smokers and events in VAHIT [78].

9. Concluding comments

TC, LDL, HDL and TG levels can influence the risk of stroke. The intervention trials also suggest that correcting these variables results in a reduced risk of stroke, at least in patients with established IHD. Nevertheless, there is a need for trials specifically aimed at stroke prevention, especially in high-risk groups (e.g. the elderly, diabetics or those with a previous CVE).

If we accept that all lipid variables need correction, then some patients will benefit from treatment with statins or fibrates. However, those patients with a mixed dyslipidaemia not corrected by monotherapy, may benefit from combination treatment (statin+fibrate) [47,79]. There is growing evidence showing that this treatment is safe and in widespread use [47,79]. Combination therapy is also currently being evaluated in a trial involving the use of fenofibrate and cerivastatin, alone and in combination, in diabetics. The clinical usefulness of fenofibrate is supported by the recently published findings of the Diabetes Atherosclerosis Intervention Study (DAIS) [80]. In this placebo controlled study there was a significant (P=0.02) coronary angiographic improvement after treatment with fenofibrate for at least three years [80].

There was also a reduction (23%) in combined cardiac events but this did not achieve statistical significance possibly because of the size of the study (n=418) [80].

More attention should be paid to correcting all lipid variables in patients at risk of a CVE.

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