Hypertriglyceridemia and Ischemic Stroke

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Key Words

Hypertriglyceridemia · Ischemic stroke · Triglycerides, stroke risk · Atherosclerosis

Abstract

There are no conclusive data regarding the association between dyslipidemia and the risk of ischemic stroke (IS). Clinical investigations have primarily focused on the association between elevated levels of low-density lipoprotein cholesterol and low levels of high-density lipoprotein cholesterol as stroke risk factors. Much less scientific attention has been aimed at elevated levels of triglycerides. Consequently the potential role of hypertriglyceridemia as an independent risk factor for IS remains controversial. However, accumulating evidence has shown that hypertriglyceridemia is associated with pathophysiological processes such as endothelial dysfunction, atherosclerosis and the production of a prothrombotic state, which could contribute to IS risk. The aim of this review is to critically analyze the contribution of hypertriglyceridemia to the occurrence of IS.

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Introduction

Due to the tremendous burden that stroke places on our society, there have been major efforts to identify modifiable risk factors that could reduce the incidence of ischemic stroke (IS). Multiple independent risk factors for IS have been identified. The most prevalent of these in-

clude hypertension, diabetes mellitus, smoking, atrial fibrillation, coronary artery disease, congestive heart failure and disorders of lipid metabolism. Epidemiologic studies suggest that elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C), as well as low levels of high-density lipoprotein cholesterol (HDL-C) are possible risk factors for IS [1, 2]. Cholesterol and triglycerides are the 2 main lipids found in the body. Triglycerides (triacylglycerols) are the main storage form of fatty acids. They are esters of fatty acids and trihydric alcohol glycerol [3]. Their chemical structure is: $\text{CH}_2\text{COOR}-\text{CHCOOR}'-\text{CH}_2-\text{COOR}''$ [4]. Triglycerides play an important role in transferring the energy from food into cells. Triglycerides and cholesterol are insoluble in plasma and are carried in lipoproteins (fig. 1). The metabolic pathways of triglycerides and HDL-C are related, and an increase in one will usually be accompanied by a decrease in the other (a rise in the HDL-C level will be accompanied by a drop in the triglyceride level, and vice versa). Lipoprotein lipase plays an important role in the formation of precursors of HDL-C particles and degradation of the triglycerides contained in chylomicrons, and lipoprotein lipase mutations were found to contribute to the 'atherogenic lipoprotein profile' [5, 6].

The definition of hypertriglyceridemia is based on a classification in the Third report of the National Cholesterol Educational Program and the Adult Treatment Panel (NCEP-ATP III; table 1) [7]. This report, which was published in 2002 by a panel of experts from multiple national organizations, discussed the detection, evaluation and treatment of high blood cholesterol in adults.

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Fig. 1. Triglyceride metabolism. Lipoproteins are particles that consist of a mixture of varying amounts of cholesterol, protein and triglyceride. They have an outer layer of cholesterol, phospholipids and apoproteins. Their inner core contains varying amounts of triglyceride and cholesterol ester. Triglycerides ingested as fats are broken down in the intestine into glycerol and fatty acids (lipolysis). They are then reconstituted and combined with cholesterol, phospholipids and apolipoproteins in the intestinal wall, and the resulting mixture is then transported in the plasma as lipoproteins.

Table 1. Classification of serum triglyceride levels, according to the NCEP-ATP III

Normal	<150 mg/dl (1.7 mmol/l)
Borderline high	150–199 mg/dl (1.7–2.2 mmol/l)
High	200–499 mg/dl (2.2–5.6 mmol/l)
Very high	≥500 mg/dl (≥5.6 mmol/l)

The prevalence of hypertriglyceridemia (as defined by a triglyceride level >200 mg/dl) is 10% in males >30 years and females >55 years [8]. Recent evidence suggests that hypertriglyceridemia may correlate with an increased risk of cardiovascular disease, especially in the presence of low HDL-C levels, elevated LDL-C levels, or both [9]. However, there has not been a consensus regarding the significance of hypertriglyceridemia as an independent risk factor for IS. This issue was not addressed in the most recent guidelines of the American Heart Association/American Stroke Association for stroke prevention, which were published in 2006 [2]. In this review article, we will address hypertriglyceridemia as a putative risk factor for IS. Results of epidemiologic studies that have evaluated the potential relationship between triglyceride levels and IS will be reviewed. In addition, potential mechanisms by which hypertriglyceridemia may contribute to IS will be discussed.

Table 2. Mechanisms by which hypertriglyceridemia may contribute to IS

Promotion of atherosclerosis
Endothelial dysfunction
Oxidative stress due to lipid-derived free radicals
Impairment of endothelial-dependent vasodilatation
Association with elevation of the markers of atherosclerosis (C-reactive protein, fibrinogen levels and circulating adhesion molecules)
Promotion of thrombogenicity
Elevated plasma viscosity
Elevated plasma fibrinogen levels
Lowered fibrinolytic activity
Elevated levels of clotting factor Xc compared to normolipidemic controls
Elevated fibrinogen levels

Mechanisms by Which Hypertriglyceridemia May Contribute to IS

Hypertriglyceridemia may lead to IS through its contribution to atherosclerosis and/or thrombogenicity. Studies suggest that hypertriglyceridemia fosters the development of atherosclerosis via several mechanisms (table 2). Postprandial hypertriglyceridemia in diabetic patients was found to produce endothelial dysfunction, oxidative stress

due to lipid-derived free radicals, and impairment of endothelium-dependent vasodilatation [10]. Triglyceride-rich lipoproteins, including very-low-density lipoprotein and intermediate-density lipoprotein, in addition to LDL-C particles, become trapped in blood vessel walls and have been demonstrated in human atherosclerotic plaques [11]. Transient hypertriglyceridemia, induced by intravenous infusion of a triglyceride emulsion, was associated with decreased vascular reactivity in young healthy men who had no risk factors for coronary heart disease (CHD) [12]. Chronic hypertriglyceridemia was independently associated with endothelial dysfunction in an observational study of patients with normal LDL-C [13]. Increased expression of adhesion cell molecules is considered to be a marker of endothelial cell dysfunction [14]. An increase in cell adhesion molecules has been noted in patients with hypertriglyceridemia [14, 15].

Another potential mechanism by which hypertriglyceridemia may contribute to atherosclerosis is through its association with elevated C-reactive protein (CRP). CRP is an inflammatory marker that has been associated with systemic inflammation and an increased risk of coronary artery disease (CAD). Elevated CRP levels have been associated with elevated triglyceride levels as well as LDL triglyceride levels [16]. In a study of 83 obese women (mean body mass index 33.8) treated with a calorie- and fat-restricted diet, baseline CRP correlated with body mass index ($p = 0.01$) [17]. After 12 weeks of dieting, CRP levels correlated with triglyceride levels ($p = 0.009$), but not with other lipids or the glucose level. In patients treated with statins, elevated triglycerides >150 mg/dl were found to be associated with elevated CRP levels ($p = 0.0001$) [17]. Although elevated LDL-C and CRP levels are each predictive of a first cardiovascular event, very little correlation between the 2 measurements was found [18]. Thus, the increased risk of CAD found with elevated CRP levels does not appear to be due to an associated elevation of LDL-C levels. In contrast, LDL triglycerides (triglycerides are a small component of the LDL particle) do appear to be associated with elevated CRP and an increased risk for CAD. In a study of 739 subjects with CAD and 570 matched controls, a significant correlation was found between LDL triglycerides and CRP levels, adhesion molecules, interleukin 6 and fibrinogen. LDL triglycerides were found to be a stronger predictor of CAD than LDL-C (odds ratio 1.3 vs. 1.1; $p < 0.001$) [19]. In humans, carotid intima-media thickness measures are considered reliable markers for early atherosclerosis. Increased carotid intima-media thickness has been found to be associated with an elevation of inflammatory markers, fibrin-

ogen levels and circulating adhesion molecules, each of which has been associated with hypertriglyceridemia [16]. In the Framingham Study [20], fasting triglyceride levels (drawn according to the Lipid Research Clinics Program Protocol, in which all lipids are drawn after a ≥ 12 -hour fast) were not associated with ultrasound evidence of carotid atherosclerosis when the data were analyzed with a multivariate logistic regression model. However, triglyceride levels remain elevated for 3–6 h after each meal; therefore, exposure to elevated postprandial triglyceride levels may persist for many hours each day and may be more representative of the patient's usual state than are fasting levels [21]. In an observational study, postprandial hypertriglyceridemia was reported to be associated with increased carotid wall thickness, and remained so in a multivariate analysis; the correlation coefficient ($r = 0.52$) between peak triglyceride level and B-mode score on ultrasonography was significant ($p < 0.002$) [22]. More recently, Teno et al. [21] confirmed the association of postprandial hypertriglyceridemia with carotid intima-media thickness in a cohort of 61 patients with type 2 diabetes. The investigators found that those with the highest postprandial triglyceride levels had the greatest degree of carotid intima-media thickness, as measured by ultrasound ($p < 0.01$). Postprandial remnant particles of triglyceride-rich lipoproteins have also been found to be an independent risk factor for early atherosclerosis and may be responsible for the increased rate of carotid intima-media thickness in these subjects [21]. The difference in the results of these studies may be related to measurement of triglycerides in the fasting versus postprandial state.

Hypertriglyceridemia may also contribute to cerebrovascular disease through its effects on thrombosis. This effect is produced by thrombogenic alterations of the coagulation system as well as elevations in plasma viscosity. Simpson et al. [23] reported that 18 patients with severe hypertriglyceridemia (mean fasting plasma triglyceride level 504.4 mg/dl) had higher concentrations of plasma fibrinogen, lower fibrinolytic activity and higher levels of clotting factor Xc compared to normolipidemic controls. Elevated fibrinogen has been found to be a powerful and independent predictor of vascular events [24], and it has been associated with the progression of carotid artery disease [25]. Hyperviscosity may lead to tissue ischemia due to impaired microcirculatory flow, damage at the blood-endothelium interface by shear stress, and an increased tendency to thrombosis [26]. Hyperviscosity due to hypertriglyceridemia may contribute to endothelial dysfunction, tissue ischemia and chylomicronemia [27].

Triglyceride-rich lipoproteins such as chylomicrons and very-low-density lipoprotein have been shown to cause an exponential increase in viscosity when added to normolipidemic or lipoprotein-free plasma *in vitro*. This effect is greater than that for LDL-C, supporting the greater contribution of triglycerides to plasma viscosity [28]. Patients with type IV and type IIb hyperlipoproteinemia (characterized by markedly elevated triglyceride levels) have higher plasma viscosity than those with type IIa hyperlipoproteinemia (which is usually associated with elevated cholesterol but normal triglycerides) or normal subjects [29]. In addition, lowering the level of triglycerides using gemfibrozil in patients with type IV or V hyperlipoproteinemia decreased plasma viscosity without changing the fibrinogen level [30]. Rosenson et al. [26] studied the fasting levels of lipids and fibrinogen in 257 subjects, correlating these with plasma viscosity. Elevated levels of triglycerides (as well as fibrinogen, total protein, LDL-C and total cholesterol) correlated positively and independently with elevated plasma viscosity [26]. Therefore, hypertriglyceridemia may increase the risk of IS by inducing a prothrombotic state through its effects on coagulation and plasma viscosity.

Triglycerides and Insulin Resistance

Hypertriglyceridemia is one of the features of dyslipidemia seen in type 2 diabetes and the metabolic syndrome, which may also include insulin resistance, abdominal obesity and hypertension. Hyperinsulinemia leads to an increase in the production of very-low-density lipoprotein [31]. Hyperglycemia also impairs removal of triglyceride-rich lipoproteins from the circulation. Patients with poorly controlled diabetes have higher triglyceride levels than those who have the condition well controlled. Postprandial hyperlipidemia in diabetics appears to be prolonged, which means that the arteries are exposed to atherogenic particles for extended periods of time [31, 32]. The metabolic syndrome, with its associated dyslipidemia, is felt to be one of the most important risk factors for atherosclerosis. The dyslipidemia associated with metabolic syndrome is characterized by hypertriglyceridemia, low plasma HDL-C, a predominance of small dense LDL particles and increased plasma apolipoprotein B [33]. The metabolic syndrome is also associated with the development of a prothrombotic state. This state is a result of the direct effects of hyperinsulinemia and other associated metabolic abnormalities (including postprandial hyperglycemia, increased free fatty acids

and hypertriglyceridemia) on platelet function, coagulation and fibrinolysis. Treatments that improve insulin sensitivity ameliorate the prothrombotic state [34]. Features of the metabolic syndrome that have been identified by ATP-III and the World Health Organization to significantly increase the risk of cardiovascular and peripheral vascular events include abdominal obesity (based on waist circumference), HDL-C level (<40 mg/dl in men and <50 mg/dl in women), hypertension (blood pressure >130/85), fasting blood glucose level >110 mg/dl and triglyceride level >150 mg/dl [35, 36].

The metabolic syndrome has been previously linked to myocardial infarction (MI) and stroke, but the role of hypertriglyceridemia in patients with the metabolic syndrome, as an independent risk factor for stroke, has been unclear. Recently, Ninomiya et al. [36] evaluated 10,357 subjects for the metabolic syndrome, based on data in the NHANES III survey (National Health and Nutrition Examination Survey), which was carried out in the USA between 1988 and 1994. They performed a logistic regression analysis to estimate the association between each of the components of the metabolic syndrome and MI or stroke. The metabolic syndrome was found to be significantly associated with both MI and stroke, and 4 of the component conditions – insulin resistance, low HDL, hypertension and hyperlipidemia – were each independently and significantly associated with both MI and stroke. The parameter most strongly correlated with the prevalence of stroke was hypertriglyceridemia. The odds ratio for stroke in those patients with hypertriglyceridemia was 1.87 [95% confidence interval (CI) 1.22–2.87; $p < 0.0052$].

Triglycerides and the Risk of IS

Several studies have not found triglycerides to be an independent risk factor for IS [37–42] (table 3). For example, Bowman et al. [37] conducted a prospective, randomized, nested case-control study among patients from the Physician Health Study, which included 296 fatal and nonfatal IS in white male physicians and an equal number of controls. No correlation between nonfasting triglycerides and IS was found, once multivariate analysis was performed. The adjusted odds ratio for the highest quartile of triglycerides, compared with the lowest quartile, was 1.07 (95% CI 0.63–1.82). In a case-control study of 204 patients with acute IS and 204 controls, Sridharan [39] did not find any significant association between fasting triglycerides (checked within 7 days of the stroke on-

Table 3. Studies addressing the association between hypertriglyceridemia and IS

	Shahar et al. [42] (ARIC)	Bowman et al. [37] (PHS)	Simons et al. [38] (Dubbo)	Sridharan [39]	Rossner et al. [40]	Aronow et al. [41]	Tanne et al. [43] (BIP registry)	Patel et al. [44] (APCSC)	Njølstad et al. [45] (Finnmark)	Lindenstrom et al. [46] (Copenhagen)
Association	+	+	+	+	+	+	–	–	–	–
Study design	P	Nested CC	P	CC	CC	P	P	MA	PB	P
Year	2003	2003	1998	1992	1978	1988	2001	2004	1996	1994
Patients, n	14,175	296	2,805	204	61	708	11,177	96,224	13,226	19,698
Controls, n	0	296	0	204	157	0	0	0	0	0
Nutritional status	F	NF	F	F	F	F	F	F (90%)	NF	NF

ARIC = Atherosclerosis Risk in Communities study; PHS = Physician Health Survey; BIP = Bezafibrate Infarction Prevention; APCSC = Asia-Pacific Cohort Studies Collaboration; P = prospective; CC = case-control; MA = meta-analysis of prospective studies; PB = population based; TG = triglyceride; F = fasting; NF = nonfasting.

set) and acute IS. The mean triglyceride level in the patients was 150.7 ± 85.3 mg/dl, and in the controls it was 158.3 ± 101.7 mg/dl ($p = 0.42$). In another case-control study by Rossner et al. [40], fasting triglyceride levels were not found to be elevated in 61 patients who had survived a cerebral ischemic event and in 157 controls. In patients with cerebral infarction, the total triglyceride levels were 1.78 ± 0.22 mmol/l in males and 1.54 ± 0.14 mmol/l in females; in controls, the levels were 1.94 ± 0.08 mmol/l in males and 1.7 ± 0.06 mmol/l in females. No p value was published for these concentrations.

Two prospective studies, the Dubbo study [38] and one by Aronow et al. [41], did not show fasting hypertriglyceridemia to be an independent risk factor for IS. A third prospective study, the Atherosclerosis Risk in Communities (ARIC) study [42], showed only a weak and inconsistent association between fasting triglyceride levels and IS. The Dubbo study was an Australian prospective community study of the elderly (2,805 men and women aged 60 years and older) which did not find the fasting triglyceride level to be a significant risk factor for IS or transient ischemic attack (TIA); the relative risk (RR) was 1.06 (95% CI 0.97–1.16) [38]. The study by Aronow et al. did not show an association between fasting hypertriglyceridemia and IS in 708 elderly patients. During a 3-year follow-up, the incidence of new cerebral infarcts was 17 and 16% among men and women, respectively, who had serum triglycerides ≥ 190 mg/dl, and it was 12 and 11% for men and women, respectively, who had serum triglycerides < 190 mg/dl [41]. The ARIC study included a cohort of 14,175 men and women who were free of prior clinical cardiovascular disease and who were followed prospectively for a mean of 10 years. In that study, there was no significant association between IS and fasting lipid levels (LDL-C, HDL-C, apolipoprotein B, apolipoprotein A1

and triglycerides) reported in either gender. However, there was a nonsignificant trend towards an increased risk, based on quartile analysis in women only. The hazard ratio (HR) for the second quartile was 1.13 (95% CI 0.59–2.15), for the third quartile it was 1.43 (95% CI 0.78–2.62) and for the fourth quartile it was 1.48 (95% CI 0.8–2.73). The authors also conducted a subanalysis based on octiles and found that the HR for the highest octile of triglyceride levels was 1.97 (95% CI 1.01–3.84) [42].

In contrast to the findings of the above studies, other trials have reported a positive association between hypertriglyceridemia and IS [43–46] (table 3). In the Blood Lipids and First-Ever Ischemic Stroke/Transient Ischemic Attack in the Bezafibrate Infarction Prevention (BIP) registry [43], a large prospective trial of 11,177 patients with known underlying CHD, fasting hypertriglyceridemia was found to be an independent risk factor for the development of first-ever IS or TIA. In a multivariable analysis, after adjusting for traditional risk factors, the odds ratio for IS or TIA for triglyceride levels > 200 mg/dl was 1.47 (95% CI 1.19–1.8) in comparison with lower triglyceride levels. No subanalysis of IS patients alone was conducted. The meta-analysis of prospective studies by the Asia-Pacific Cohort Studies Collaboration (APCSC) included 96,224 individuals, with 796,671 person-years of follow-up [44]. In 90% of the participants the triglyceride levels were measured after fasting. Patients with triglyceride levels in the highest fifth had a HR of 1.97 (95% CI 1.52–2.55) for the risk of fatal or nonfatal IS, compared with those in the lowest fifth. The results indicated a significant association between elevated serum triglycerides and IS (fatal and nonfatal combined) that was independent of other major measured risk factors. The Finnmark Study [45], a population-based study of 13,266 men and women, mean ages 35–52, with a follow-up of 14 years,

reported a significant association between nonfasting triglyceride levels and stroke for women only. For every 88.57 mg/dl (1 mmol/l) increment in triglycerides, the adjusted RR of stroke was 1.01 (95% CI 0.88–1.15) for men and 1.29 (95% CI 1.05–1.57) for women [45]. The Copenhagen City Heart Study [46], a prospective observational study of 19,698 men and women, found a strong linear association between nonfasting triglyceride levels and cerebral ischemic events (IS or TIA). For every 1 mmol/l increment in nonfasting triglycerides, the RR increment for ischemic events was 1.12 (95% CI 1.07–1.16).

Potential Explanations for Negative Studies

There are several potential reasons for the lack of association between hypertriglyceridemia and IS in the negative studies, including the study designs, the relatively small number of cases studied and the methodologies employed. Three of the negative studies (Rossner et al. [40], Sridharan [39] and Bowman et al. [37]) were case controlled. This type of study can potentially be affected by selection bias. This form of bias can contribute to type II error (an erroneous conclusion that there is a negative association between the risk factor and the condition being studied). Among the positive studies, the Finnmark and Copenhagen studies were both prospective, the APCSC was a meta-analysis and the BIP was a registry. The Finnmark study, the only prospective, population-based study found in our review, was a positive study.

The negative studies included fewer cases than the positive studies. Each of the 3 negative case-control studies (table 3) included fewer than 300 cases of IS. The 3 negative prospective studies included more patients (2,805, 708 and 14,175), but the combined number of cases in these studies is much less than those in the positive studies (table 3). There were 11,177 patients in the BIP registry, 96,224 in APCSC, 13,266 in Finnmark and 19,698 in the Copenhagen study.

Measuring triglyceride levels in the fasting, and not the postprandial, state may have contributed to a lack of association between IS and triglyceride levels. Ryu et al. [22] found that in 47 asymptomatic, moderately hypercholesterolemic volunteers who were fed a standard high-fat meal, the peak adjusted postprandial triglyceride response (highest postprandial triglyceride level – baseline triglyceride level) was a mean of 264.34 mg/dl. The mean peak triglyceride level was 436.85 mg/dl and the mean baseline triglyceride level was 172.51 mg/dl; this correlates with an increase in the mean postprandial triglyceride level of

253% compared to baseline. Since the postprandial lipemia state is present for many hours each day, it may be more representative of overall triglyceride levels than the fasting state. Measuring only fasting levels can, therefore, greatly underestimate the patient's state of hypertriglyceridemia. With the exception of the Physician Health Study, all the negative studies included fasting, rather than postprandial triglyceride levels [38–42]. Among the positive studies, triglyceride levels were measured in the postprandial state in the Copenhagen and Finnmark studies. Although the BIP registry and the APCSC meta-analysis both included patients whose triglyceride levels were drawn in the fasting state (90% of those in the APCSC), case ascertainment was superior in these studies compared to the negative studies (see below).

Case ascertainment may have contributed to negative results in some studies in the following ways. The diagnosis of IS in the study by Aronow et al. [41] depended heavily on clinical criteria, and there was no mention of whether or not magnetic resonance imaging (MRI) or computed tomography of the brain was done. The study by Rossner et al. [40] depended on a clinical diagnosis and computed tomography scan, but MRI was not done. The lack of MRI confirmation of IS could have led to inclusion of some patients without IS in this study. If some of the patients with hypertriglyceridemia had only MRI evidence of infarction, they would not have been counted, which could have contributed to the negative result of these studies. In the Physician Health Study the diagnosis of stroke or TIA was made based on periodic questionnaires mailed to patients every 6 months for the first year and every year thereafter. Although the diagnosis of stroke was confirmed by a committee reviewing the patient's records and reports of brain imaging, the use of questionnaires could have resulted in recall bias. Similarly, the ARIC and Dubbo studies relied on patients' self-reports. In the ARIC study, participants were asked by phone about their hospitalizations during the previous year, if the patient was not available his/her next of kin was interviewed by phone. Although lists of hospital discharges from community hospitals were also reviewed, these lists may not have been complete if the patients were not admitted or were admitted to a hospital not on the list. Some of the negative studies included record reviews which used the International Classification of Diseases, ninth revision (ICD-9), codes in their diagnosis of stroke. Codes 433–433.9 are specific for IS. The ARIC and Dubbo studies accepted a greater range of codes than these selective IS codes. In the ARIC study the ICD-9 codes 430–438 were used, and in the Dubbo study 433–437

Table 4. Studies demonstrating evidence for benefits from lowering elevated triglyceride levels in IS

Study name	Study design	Author	Year	Drug	Patients, n	Fasting vs. nonfasting	Results	
							RRR	p, 95% CI
GREACE	R	Athyros et al. [50]	2002	Atorvastatin	800 patients, 9 developed stroke 800 controls, 17 developed stroke ¹	Fasting	Atorvastatin decreased triglyceride levels by 31% compared with 3% in the usual care group RRR: 47%	p < 0.0001 p = 0.034
VAHIT	DBR	Rubins et al. [52]	1999	Gemfibrozil	Gemfibrozil: 1,264 patients, 58 developed stroke Controls: 1,267, 76 developed stroke ¹	Fasting	For stroke: 25% For TIA: 59%	p = 0.1 95% CI: 6–47% p < 0.001 95% CI: 33–75%

R = Randomized; DBR = double-blind randomized.

¹ In these studies, the term 'stroke' is not defined.

were used. This could have led to the inclusion of other causes of stroke, such as hemorrhagic stroke, in these 2 studies. Although the BIP registry was similar to the ARIC and Dubbo studies in that it included ICD-9 codes 430–438, it differed by using a stroke neurologist, in addition to another investigator, to review all the stroke classifications. This adjudication method likely helped to minimize the inclusion of patients who had nonischemic strokes in the BIP study. The APCSC study included only ICD-9 codes 433–433.9. Use of these IS-specific codes probably minimized type II errors.

Hypertriglyceridemia and IS Subtypes

The relationship between hypertriglyceridemia and IS subtype is unknown. Few studies have evaluated the plasma lipid profile and its relationship to IS subtypes. In a case-control study of 240 consecutive cases with IS (n = 182) or TIA (n = 58), the ischemic event was felt to be due to large-artery disease in 61 (25%) cases, small-vessel disease in 65 (27%), and cardioembolism in 114 (48%) [47]. All 3 stroke subtypes showed higher triglyceride levels than controls (large-artery disease, p = 0.014; small-vessel event, p < 0.001; cardioembolic event, p = 0.37), but there was no significant difference in triglyceride levels between the stroke subtypes [47]. In a recent study of 71 patients with IS (30 with large-artery atherosclerosis, 41 with a small vessel event) the investigators found significantly higher triglyceride levels in cases with IS due to large-artery disease, but not in cases caused by small-vessel disease, compared to controls (large-artery disease group vs. controls, p < 0.005) [48]. However, in that study the ratios

of LDL-C to HDL-C and total cholesterol to HDL-C were also significantly higher in patients with large-vessel disease compared to controls, which could have confounded the results. We cannot conclude from these studies that hypertriglyceridemia is not definitely associated with a specific stroke subtype, although it may possibly be associated more with large-vessel than small-vessel IS.

Evidence for Benefit of Lowering Elevated Triglyceride Levels

The Helsinki Heart Study was a primary prevention study which demonstrated that the use of gemfibrozil reduced triglyceride levels by 43% and CHD events by 34%. The greatest benefit in reducing CHD events was seen in those patients who had baseline triglyceride levels >200 mg/dl [49]. Lowering triglycerides may also be beneficial in reducing the risk of IS, although it is not as clear that lowering triglycerides is independently associated with relative risk reduction (RRR) for IS, as it is for CHD [50, 51] (table 4).

The Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study was a randomized trial of 800 CHD patients and 800 controls with a mean baseline fasting triglyceride level of 184 mg/dl. Atorvastatin decreased triglyceride levels by 31%, compared with 3% in the usual care group (p < 0.0001), and it also decreased LDL-C levels by 46% compared to 5% in the usual care group (p < 0.0001). There were significant reductions in mortality as well as in stroke [50]. The RRR for IS in the atorvastatin group was 47% compared with the group that received usual care (p = 0.034). Although the reduc-

tions in stroke were dramatic, multivariate analysis was not carried out, and it cannot be determined if the results were due to the reduction in triglycerides or to another factor, such as the lowering of LDL-C or the effect of atorvastatin as a neuroprotectant.

The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VAHIT) was a randomized, double-blind trial of 2,531 men with CHD in which gemfibrozil at a dosage of 1,200 mg daily was compared with placebo [51]. In this study, gemfibrozil was associated with a significant RRR for TIA of 59% (95% CI 33–75%; $p < 0.001$) and a significant RRR for carotid endarterectomy of 65% (95% CI 37–80%; $p < 0.001$). The RRR for IS, of 25%, was not significant (95% CI –6 to 47%; $p = 0.10$). Gemfibrozil decreased the mean fasting triglyceride level by 31%, decreased mean fasting total cholesterol level by 4%, and it increased mean fasting HDL-C by 6% ($p < 0.001$ for all 3 lipid levels). LDL-C levels, however, did not significantly change with gemfibrozil treatment when compared with placebo and, therefore, did not account for the benefits seen [51]. In a later publication analyzing the results of the VAHIT, the RRR of IS was calculated after adjusting for age, race, smoking, diabetes, hypertension, prior MI, aspirin use, β -blocker use and baseline lipids (LDL-C, HDL-C, and triglycerides); gemfibrozil was associated with an adjusted RRR of 31% (95% CI 2–52%; $p = 0.036$) [52]. RRR of IS was greatest for those with HDL-C levels < 31.5 mg/dl but, statistically, it was not significantly different between subjects with triglyceride ≥ 151 mg/dl and those with triglyceride < 151 mg/dl. In individuals with HDL-C < 31.5 mg/dl, the RRR for IS was 48% (95% CI 13–69%), and in subjects with HDL-C ≥ 31.5 mg/dl the RRR for IS was –4% (95% CI –67 to 35%); for heterogeneity, $p = 0.05$. The RRR for IS in subjects with triglyceride levels < 151 mg/dl was 28% (95% CI –18 to 57%), and the RRR for IS in subjects with triglyceride levels ≥ 151 mg/dl was 21% (95% CI –26 to 51%); for heterogeneity, $p = 0.77$. The results of the VAHIT and the subsequent analysis would suggest that gemfibrozil can reduce the incidence of TIA in men with CHD and IS in men with CHD and low HDL-C levels. The results also suggest that reduction of triglyceride levels, independent of reductions in LDL-C, are probably responsible for this [52]. However, the contribution of mild HDL-C elevation to the RRR of TIA and IS cannot be excluded. Also there are other mechanisms by which gemfibrozil itself can potentially lower the risk of TIA or IS, including stabilization of atherosclerotic plaques due to anti-inflammatory effects, improvement of endothelial function, and reductions of factor VII, thrombin and platelet reactivity [52].

Table 5. Recommendations of the NCEP-ATP III

<i>Management of factors contributing to hypertriglyceridemia</i>	
Obesity and overweight	
Physical inactivity	
Cigarette smoking	
Excess alcohol intake	
High carbohydrate diets (>60% of energy intake)	
Metabolic syndrome or type 2 diabetes	
Chronic renal failure	
Nephrotic syndrome	
Medications (corticosteroids, estrogens, retinoids and high-dose β -blockers)	
Genetic disorders (familial combined hyperlipidemia, familial hypertriglyceridemia and familial dysbetalipoproteinemia)	
<i>Drug therapy</i>	
3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins): 7–30% reduction	
	Lovastatin 20–80 mg daily
	Pravastatin 20–80 mg daily
	Simvastatin 20–80 mg daily
	Fluvastatin 20–80 mg daily
	Atorvastatin 10–80 mg daily
Nicotinic acid: 20–50% reduction	
	Immediate-release (crystalline) nicotinic acid 1.5–4.5 g daily
	Extended-release nicotinic acid 1–2 g daily
	Sustained-release nicotinic acid 1–2 g daily
Fibric acids: 20–50% reduction	
	Gemfibrozil 600 mg twice daily
	Fenofibrate 200 mg daily
	Clofibrate 1,000 mg twice daily

Although it seems likely that reduction of triglyceride levels in both the GREACE study and the VAHIT contributed to the reduction of risk of IS, it is not entirely certain to what extent other factors contributed.

Conclusion

Based on our review of the existing evidence, we conclude that there is biological plausibility and epidemiological evidence to suggest that hypertriglyceridemia potentially contributes to an increased risk for IS. To definitively determine if hypertriglyceridemia is an independent risk factor for IS, additional well-planned epidemiologic research is necessary. Future studies should, ideally, be large, prospective population-based studies that measure nonfasting triglyceride levels. If epidemiologic studies confirm an association between hypertriglyceridemia and IS, then prospective, randomized, con-

trolled trials should be conducted to assess the benefit of pharmacologic and dietary triglyceride reduction with respect to primary and secondary prevention of IS. In the meantime, health care providers can follow the recommendations of the NCEP-ATP III [7] (table 5) regarding the treatment of hypertriglyceridemia.

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