

Triglycerides

*A risk factor
for*

*cardiovascular
disease*

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FOREWORD

By Professor Peter Schwandt, Chairman, Foundation for the Prevention of Arteriosclerosis

During the last decades, triglycerides and triglyceride-rich lipoprotein fractions and their degradative fractions have come under increasing suspicion – Zilversmit suspected it as early as 1970 – of aiding the development of arteriosclerosis. Already in 1923, Joslin, a leading pioneer in the field of diabetologie, originated the idea that diabetic persons are in danger from too much fat, whether in food, the blood, or the arteries.

This is, however, difficult to demonstrate, since on the one hand the dangerous triglyceride-rich lipoprotein fractions in the blood are, in practice, hard to measure, and on the other hand, raised concentrations of triglycerides rise and fall with low HDL cholesterol levels, which, for their part, present an isolated risk factor for arteriosclerosis.

Triglycerides appear in food fats in saturated, monounsaturated, and polyunsaturated forms. Next to the absolute supplied amount, the degree of saturation plays an important role in cardiovascular disease. In addition, the metabolism and concentration of the triglycerides may not only be inherited, but may also be negatively influenced through physical inactivity, overweight, alcohol, illness, e.g. a poorly-regulated diabetes mellitus, and medication, e.g. betablockers.

The brochure you hold in your hand grew out of an international workshop with top-notch participants which was sponsored by the Foundation for the Prevention of Arteriosclerosis and planned by persons experienced in preventive cardiology. The purpose of this booklet is to make those working in medical professions - in doctors' offices and hospitals, in nutritional counseling and preventive health care - aware, in the simplest way possible, of triglycerides, and thereby assist them in their endeavors to alleviate the risks of arteriosclerosis. Moreover, the booklet seeks to encourage the citizens of this country to take an active role in helping prevent cardiovascular diseases.

We should no longer accept cardiovascular diseases continuing to be the most frequent cause of illness and death, nor the fact that most women over 65 years of age die of a heart attack.

1.0 CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) – such as coronary heart disease (CHD), stroke and peripheral vascular disease – is a major cause of morbidity and mortality in industrialised countries, and one of the most important public health problems globally.

CVD involves both a long-term pathological disease process and an acute disease event. The long-term process is atherosclerosis – the formation of fatty fibrous plaques in the blood vessels supplying the heart and brain. As these plaques enlarge, the lumen of the artery may narrow and the composition of the artery walls may change, toughen and lose their elasticity, preparing the way for coronary disease. The atherosclerotic process is a complex dysfunction of a dynamic balance of many components, some of which can not be currently explained. However, recent evidence suggests that inflammation is a key element in this process.

The acute disease event is thought to result from the rapid formation of a thrombus at the site of a plaque, often as a result of the rupture of an unstable plaque. If blood flow is completely blocked by the formation of a thrombus in an artery, the heart muscle is starved of oxygen and nutrients and myocardial infarct results.

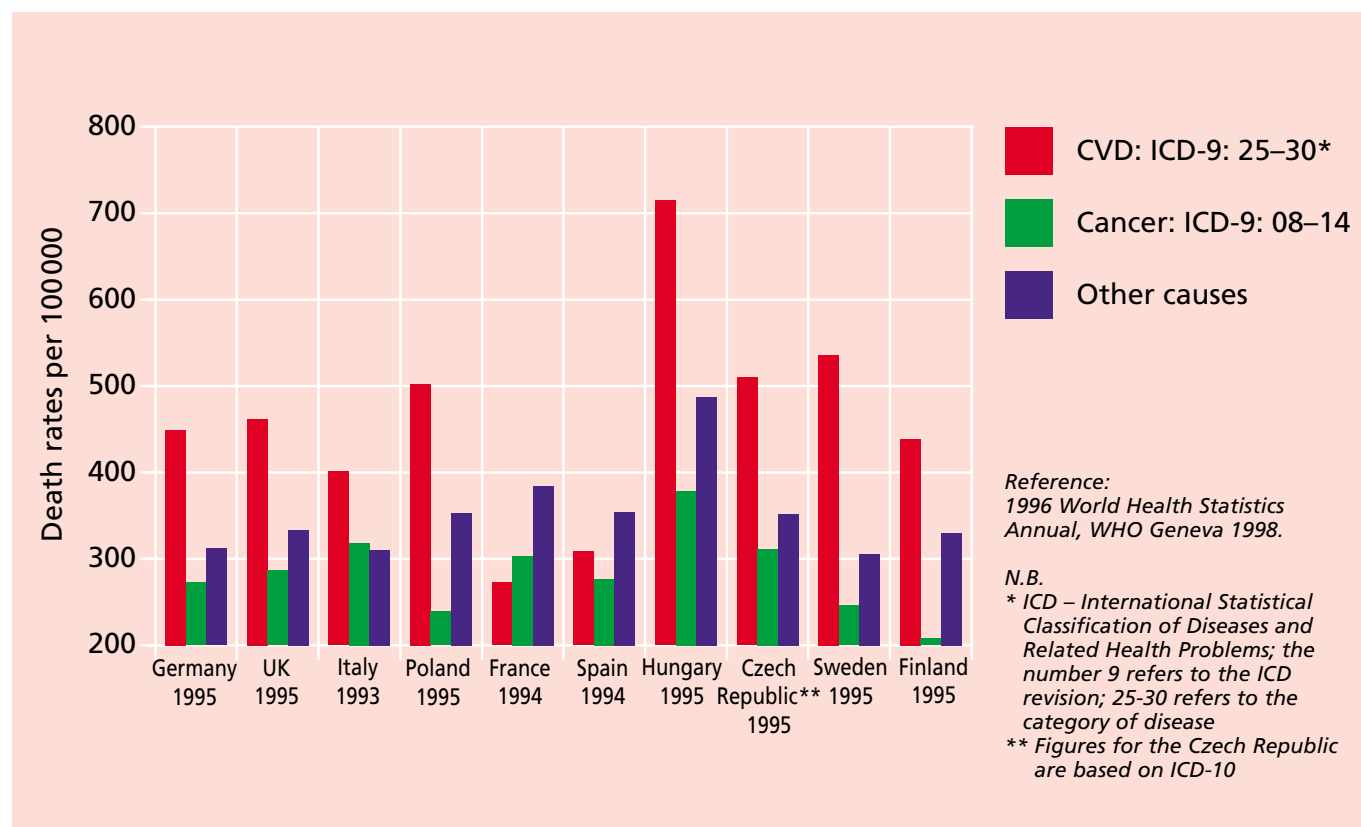
1.1 The demographics of cardiovascular disease

The cardiovascular disease epidemic began in North America, Europe and Australia in the 20th century. In many industrialised countries, deaths peaked in the 1960s and early 1970s and have since declined – by over 50% in some countries. Nevertheless, overall, CVD remains the leading cause of mortality in men over 45 years and women over 65 years in Europe accounting for 1.6 million deaths each year [Pyörälä K 1999]. The graph on page 5 shows how the number of deaths from CVD compares with other causes in men across Europe.

The world's highest rates of CVD are now found in eastern and central Europe. In 1990-92, there were six-fold differences in age-adjusted CVD among men aged 45 and over, ranging from 907 per 100,000 in Latvia to 142 per 100,000 in France. Differences in mortality rates vary by as much as nine-fold in women [Sans *et al*, 1997].

Although France has long been known for its low CVD mortality rates despite high fat intake – the French paradox – recent data has shed some light on this. The research suggests that this may be due to the time lag between the increase in consumption of animal fats and serum cholesterol concentration and the resulting increase in mortality from CVD. Consumption of animal fats has only recently increased in France, but did so decades ago in countries like the UK where death rates are four times as high [Law & Wald, 1999].

Major causes of death in men: Europe



1.2 Risk factors for cardiovascular disease

CVD is a disease for which many risk factors have been identified. Some such as family history, age and gender are non-modifiable. However, extensive research has shown conclusively that a number of determinants associated with a Western lifestyle and operating from childhood onwards contribute to CVD.

Western lifestyles cause adverse changes in biochemical and physiological characteristics (risk factors) that enhance the development of atherosclerosis and associated thrombotic complications. There has long been evidence that risk factor modification is effective in reducing CVD risk in asymptomatic high risk subjects (primary prevention) and reducing risk of recurrent CVD events in patients with clinically manifested CVD (secondary prevention).

However, it is increasingly recognised that risk factors should not be considered in isolation. Most recently recommendations on CVD prevention have emphasised the total burden of risk to which an individual is exposed rather than considering them as 'hypertensive', 'hyperlipidaemic', 'diabetic' and so on. This approach acknowledges that CVD has a multi-factorial aetiology and that risk factors have combined effects. A number of current guidelines have reflected this multi-factorial approach in the form of risk assessment charts.^a

The most impactful lifestyle changes are undoubtedly smoking cessation and increased physical activity. In addition, treatment of hypertension, maintenance of an appropriate body weight and avoidance of body fat distributed centred around the waist are also recognised as important preventative strategies.

Dietary factors known to be linked with an increased risk of CVD include a high intake of saturated fatty acids, which has been shown to increase cholesterol levels in the blood. The importance of elevated serum cholesterol, and specifically elevated low density lipoprotein (LDL) cholesterol, as risk factors for CVD is today indisputable. Cholesterol that is associated with high density lipoprotein (HDL) is linked to decreased coronary risk.

a. Examples of coronary risk assessment charts include:

- The International Task Force for Prevention of Coronary Heart Disease risk algorithm which also takes triglyceride levels into account, *Nutr Metab Cardiovasc Dis* 1998;8:205-271.
- Plaza I *et al*, Control de la Colesterolemia en España, 2000. Un instrumento para la prevención cardiovascular. *Rev Esp Cardiol* 2000;53:815-837.

However, it is clear from many clinical trials aimed at lowering LDL cholesterol that 25-60% of treated subjects show evidence of disease progression despite administration of the most aggressive cholesterol-lowering regimen [Hodis *et al*, 1994]. These findings imply the reduction of LDL cholesterol can slow but not completely inhibit the development of atherosclerotic lesions and that other factors are important. Analysis of the results from recent trials strongly support the belief that triglycerides as well as HDL may be such factors.

Although the role of these lipids has been controversial in the past, recently, a large body of data has revived interest in them. This data suggests that triglycerides may provide valuable information about the atherogenic potential of the lipoprotein profile, particularly when considered in the context of HDL cholesterol levels.

Hypertriglyceridemia and low HDL-cholesterol are closely linked to hyperinsulinaemia and hyperglycaemia. In many patients who eventually will develop metabolic syndrome or type 2 diabetes an elevation of triglycerides and a decrease in HDL-cholesterol are the first metabolic abnormalities. Thus, isolated hypertriglyceridemia and low HDL-cholesterol may be markers of impending insulin resistance, which represents a strong risk factor for atherosclerosis.

The following tables summarise the lifestyles and characteristics associated with increased risk of future cardiovascular disease:

Lifestyle
Habitual diet high in saturated fat, cholesterol and calories
Tobacco smoking
Excess alcohol consumption
Physical inactivity

Biochemical or physiological characteristics (modifiable)

Elevated blood pressure

Elevated serum cholesterol (LDL cholesterol)^b

Low serum HDL cholesterol^b

Elevated serum triglycerides^b

Hyperglycaemia/diabetes

Central (abdominal) obesity

Elevated thrombogenic factors (e.g. fibrinogen)

Hyperhomocysteinaemia

Elevated Lp (a)

Presence of inflammation markers

Personal characteristics (non-modifiable)

Age

Sex

Family history of CVD or other atherosclerotic disease at early age (in men < 55 years, in women < 65 years)

Genetic polymorphisms

Personal history of CVD or other atherosclerotic disease

b. In many laboratories plasma is used instead of serum to determine lipid concentrations.

2.0 TRIGLYCERIDES

2.1 What are triglycerides?

Lipids come in various forms including free fatty acids, cholesterol, and triglycerides. Fatty acids are the building blocks from which other fats in the body are made. In food, fat is usually in the form of triglycerides. These are also the main storage form of fat in the body, and usually consist of three different fatty acids attached to a backbone of glycerol. After the ingestion of fat, triglycerides are split in the intestinal tract into mono- or diglycerides and fatty acids, all of which will normally be absorbed to the enterocytes where it will be reesterified to triglycerides. These triglycerides will be incorporated into chylomicrons, which are metabolized to chylomicron-remnants and eventually will be taken up by the liver.

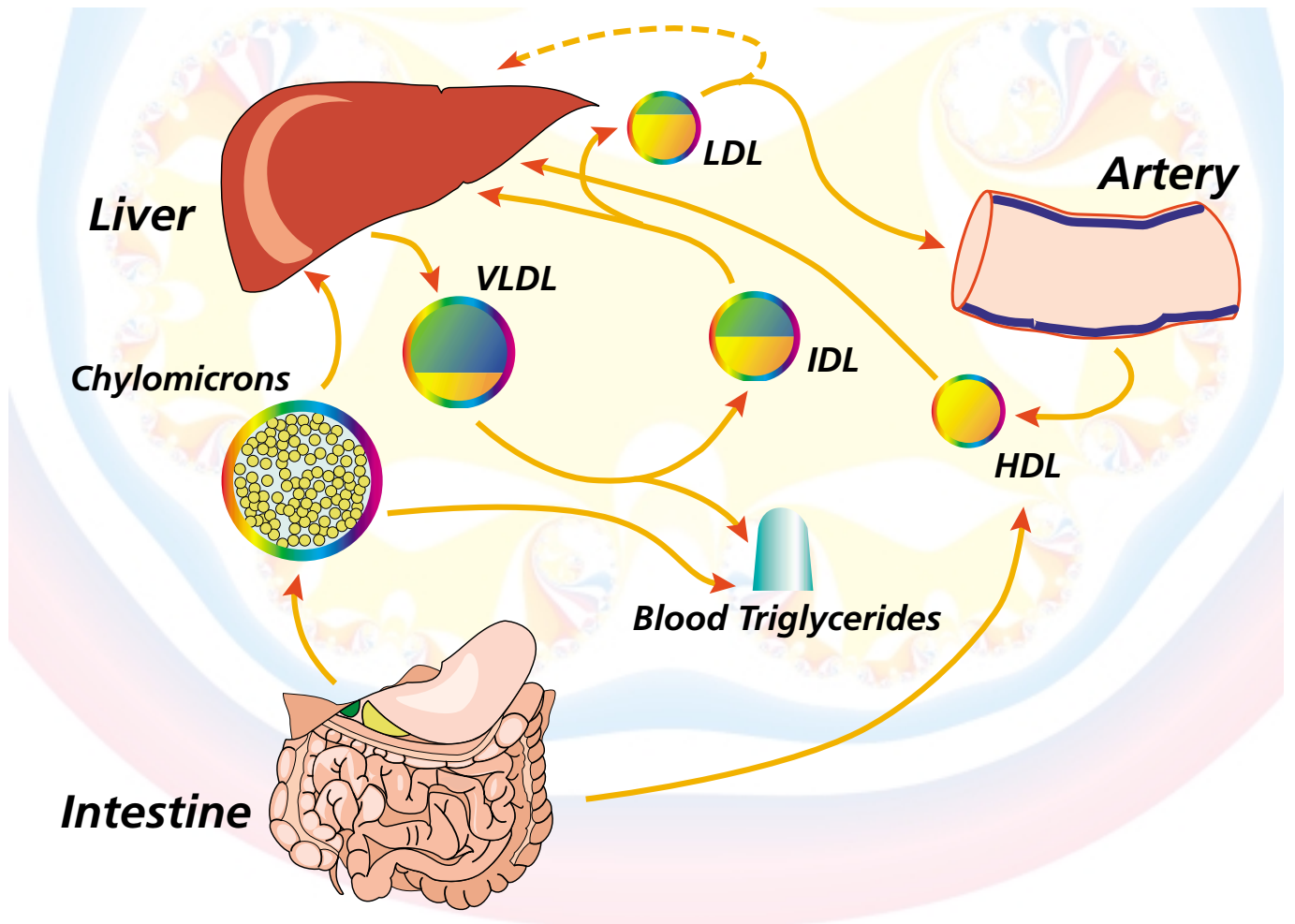
Serum triglycerides are transported as triglyceride-rich lipoproteins made up of a core lipid in very low density lipoproteins (VLDL) in the fasting state, and in both VLDL and chylomicrons in the fed state. If triglycerides are limited in the liver, apoprotein B – the structural protein necessary for the assembly of VLDL – is degraded rapidly; if triglycerides are abundant, apoprotein B is assembled with them and VLDL are secreted.

VLDL are hydrolysed gradually via the VLDL catabolic cascade into small particles by the concerted action of lipoprotein lipase to produce remnants – intermediate density lipoproteins (IDL). These are subsequently converted to LDL, rich in cholesterol esters, which are cleared from the plasma by the LDL receptor. However, 30 – 50% of VLDL particles, after a partial delipidation, are taken up again by the liver, particularly in the postprandial state.

Triglyceride levels are elevated in the setting of decreased lipoprotein lipase activity, leading to higher chylomicron remnant and VLDL levels. In addition, lower lipoprotein lipase activity could prolong circulation time of VLDL, and may result in increased density of VLDL particles. Furthermore, an increased secretion rate of VLDL may lead to hypertriglyceridemia.

However, the metabolism of triglyceride rich particles (chylomicrons, VLDL and their remnants) is intimately linked to the metabolism of other lipoproteins such as LDL and HDL. Triglyceride molecules from triglyceride-rich lipoproteins are exchanged for cholesteryl ester molecules which come from both HDL and LDL. As a result, these latter particles become triglyceride-enriched and in hypertriglyceridaemic conditions are more exposed to the hydrolytic activity of hepatic lipase.

Diagram shows the transportation of lipids in normotriglyceridemic subjects



HDL and LDL subsequently become smaller and denser than their precursors. This makes HDL more prone to catabolism and results in small, dense LDL, which are known to be particularly atherogenic.

Thus, high triglycerides, low HDL-cholesterol and the predominance of small, dense LDL are very often in combination. This factor cannot be ignored when assessing the value of elevated triglycerides as a relevant risk factor for CVD.

Lifestyle factors that significantly aggravate hypertriglyceridaemia are obesity, smoking, inactive lifestyle and alcohol.

2.2 Triglycerides as a cardiovascular disease risk factor

2.2.1 Epidemiological evidence

A high serum triglyceride level has been implicated as a risk factor for CVD since 1953 when an increase in triglyceride-rich lipoproteins among myocardial infarction cases was reported [Gofman *et al*, 1953]. A few years later the first case control study reporting that fasting triglyceride levels (where fasting refers to 12 hours after the last meal) were increased among CVD cases compared to controls appeared [Albrink and Man, 1959]. But even at that stage, the authors speculated that the triglyceride association may not be independent of other serum lipid levels.

Since then, the relationship between serum triglyceride concentrations and risk of CVD has been an issue of great controversy. Unlike analysis with LDL and HDL cholesterol for which very strong and consistent relations with CVD have been demonstrated, those with triglycerides have been more ambiguous. The issue has been confounded both by methodological difficulties such as the biological variability in fasting triglyceride concentrations and the failure of many investigators to control for HDL cholesterol. However, as a recent editorial in the *British Medical Journal* pointed out, rumours of the death of triglycerides as an indicator of cardiovascular risk are greatly exaggerated [Sattar *et al*, 1998].

In fact, recent epidemiological evidence which has taken HDL cholesterol into account, strengthens the case that there is an association between triglyceride and CVD which cannot be ignored.

- Ten-year data from the Prospective Cardiovascular Munster Study [PROCAM] found a significant and independent association between serum triglyceride concentration and the incidence of major coronary events [Assmann *et al*, 1996].¹
- In a prospective case-control study, based on a cohort from the Physician's Health Study, the researchers concluded that elevated triglyceride levels may help identify individuals at high risk of CVD [Stampfer *et al*, 1996].²
- Another more recent case-control study examined the inter-relationships of fasting triglyceride level, other lipid parameters and non-lipid risk factors with risk of MI in 340 men and women with MI and an equal number of controls. The results showed that elevated fasting triglyceride levels are strongly associated with risk of myocardial infarction [Gaziano *et al* 1997].³

A meta-analysis of 17 population-based prospective studies also presents a strong case that elevations in triglyceride levels are an important independent risk factor for CVD. Elevated triglyceride was associated with about a 30% increase in cardiovascular risk in men and a 75% increase in cardiovascular risk in women [Hokanson & Austin, 1996].⁴

- The eight year follow-up to the Copenhagen Male Study shows increased CVD risk in middle-aged and elderly men in the middle and highest thirds of triglyceride levels and a gradient of risk for triglyceride levels even when stratified for HDL. Once again fasting triglyceride was a strong predictor of CVD independent of other factors including HDL cholesterol [Jeppesen *et al*, 1998].

1. This was an observational follow-up of over 4500 middle-aged men which found that the combination of an increased ratio of LDL:HDL cholesterol with an elevated triglyceride level carried the highest risk for CVD. (Please refer to <http://www.chd-taskforce.com> for regular PROCAM result updates).

2. Results were based on 266 cases and 308 controls. Serum triglyceride concentration was found to be a strong predictor of outcome over seven years of follow up, independently of HDL cholesterol.

3. Adjustment for hypertension, diabetes mellitus, physical activity and other non-lipid risk factors did not materially affect the risk estimates. Adjustment for HDL substantially attenuated the associated risk of triglyceride, but nevertheless fasting triglyceride remained an independent predictor of myocardial infarction.

4. The studies with an average follow-up period of more than eight years included more than 46,000 men and nearly 11,000 women. Adjustment for HDL cholesterol and other risk factors attenuated these risks, but did not render them insignificant: for every 1 mmol/L increase in serum triglyceride concentration, the relative risk of CVD increased by 14% in men and 37% in women after adjusting for HDL.

- Over a mean follow-up time of 5.1 years among 9033 male and 2499 female CVD patients, a stepwise increase in mortality with increasing serum triglyceride levels was observed in patients with desirable or elevated serum total cholesterol levels and in patients with either desirable or abnormally low HDL cholesterol levels [Haim M *et al*, 1999].
- In two prospective cohort studies of 2512 men and 2348 men respectively, men with triglyceride concentrations in the top 20% of the distribution were found to have a relative odds value for ischaemic heart disease of 2.3, compared with men in the bottom 20%. In these populations triglyceride is a more important predictor than total cholesterol concentration [Bainton D *et al*, 1992].⁵
- The Baltimore Coronary Observational Long-Term Study (COLTS) determined whether triglyceride levels in patients presenting for diagnostic coronary arteriography between 1977 and 1978 were related to CVD risk. Analysis revealed significantly reduced survival from coronary artery disease in patients with baseline triglyceride levels of 100 mg/dL or more – supposedly desirable levels – compared with levels lower than this. The authors suggested the results may indicate that triglyceride levels within this range [100 to 199 mg/dL] may pose an additional risk of new coronary artery disease events in this patient group [Miller *et al*, 1998].

Triglyceride concentration appears to be a particularly efficient marker for CVD among diabetics [Fontbonne A *et al*, 1989].⁶

Thus, from the epidemiological evidence alone, it is clear that although the role of triglycerides as a risk factor for cardiovascular disease has been controversial for over three decades, accumulating evidence is now demonstrating that triglycerides are associated with increased risk, probably in combination with decreased levels of HDL cholesterol and increased levels of small dense LDL particles.

5. Adjustment for both plasma total and HDL cholesterol, and non-lipid risk factors was made. Plasma triglyceride concentration was shown to predict major ischaemic events after allowance was made for total and HDL cholesterol concentrations and other risk factors.

6. The results of the 11-year follow up of the Paris Prospective Study documented that baseline plasma triglyceride was significantly higher in men with glucose intolerance or non-insulin dependent diabetes mellitus who died of CVD. This association persisted after adjustment for other risk factors including smoking, blood pressure, body mass index and cholesterol.

2.2.2 Triglyceride-rich lipoproteins and atherogenesis

The potential strength of triglyceride to predict CVD lies in its ability to reflect the presence of potentially atherogenic serum triglyceride-rich lipoprotein remnants. Indeed, one particular explanation for the lack of clarity regarding a causal relationship between elevated triglycerides and CVD may be caused by the heterogeneity of triglyceride-rich lipoproteins. Using ultra-centrifugal techniques, it is possible to separate multiple sub-populations of chylomicrons, VLDL and IDL. Another source of heterogeneity is the existence of various combinations of apo-lipoproteins.

The atherogenic potential of triglycerides is likely to be a function of a number of factors including: the type of lipoprotein particle responsible for carrying the triglyceride, associated changes in other lipoprotein classes, including LDL and HDL, and the metabolic processes involved in triglyceride transport and metabolism.

Triglyceride-rich lipoproteins have been discovered in atherosclerotic plaques [Rapp *et al*, 1994]. In addition recent trials involving the HMG-CoA reductase inhibitors or statins have provided interesting insights into the atherogenicity of triglyceride-rich lipoprotein, suggesting that they can predict the extent of coronary artery disease.

Subjects of the Monitored Atherosclerosis Regression Study (MARS), who showed angiographic evidence of atherosclerotic progression in the placebo group, had significantly higher levels of serum triglyceride than non-progressors. Similarly in the treatment group, progressors had levels of serum triglyceride that were double those seen in non-progressors [Alaupovic *et al*, 1997].⁷

Triglyceride and cholesterol-rich lipoprotein appeared to affect the progression of atherosclerotic lesions differently: triglyceride-rich lipoproteins were related to progression of mild to moderate atherosclerotic lesions; whereas cholesterol-rich lipoproteins to progression of severe lesions. Mild to moderate lesions are most susceptible to plaque fissuring and rupture. The authors suggested that this result indicated that triglycerides have a role in atherogenesis that is distinct from cholesterol [Alaupovic *et al*, 1997].

7. MARS was set up to determine the effect of two-year lovastatin therapy on angiographic findings in subjects with documented coronary artery disease and moderate hypercholesterolaemia.

These results mirrored earlier findings from the Cholesterol Lowering Atherosclerosis Study (CLAS). It found that markers of triglyceride-rich lipoproteins such as VLDL and IDL were positively related to disease progression in drug-treated subjects, strongly supporting the role of triglyceride-rich lipoproteins in the progression of human atherosclerosis [Blankenhorn *et al*, 1987].⁸

These findings suggest that alterations in the metabolism of triglyceride-rich lipoproteins are of importance in the pathogenesis of atherosclerosis and its clinical consequences.

2.2.3 Postprandial triglycerides

Although most studies have focused on fasting triglyceride concentrations, Zilversmit (1979) was the first to point out that the magnitude of the postprandial lipaemia – the characteristic rise in blood triglycerides following a fat-containing meal – is a significant risk factor for CVD. Research has suggested that serum triglycerides at two hours, LDL cholesterol and basal proinsulin are consistently and independently related to carotid artery intima-media thickness (IMT) when cumulative tobacco consumption, alcohol intake, waist-to-hip circumference ratio and systolic blood pressure are included as confounders [Boquist 1999].

Patsch *et al* [1992] showed that postprandial triglyceride levels six and eight hours after a standardised fat load were independently predictive of the presence of severe coronary artery disease. Postprandial triglyceride levels increased at all time points following the meal in men with CVD relative to controls, and peak concentrations were also delayed. Similarly, observations from the Atherosclerosis Risk In Community (ARIC) trial showed that the triglyceride area under the curve after a fat load is related to carotid arterial initial medial thickness [Sharrett *et al*, 1995]. This association of postprandial triglyceride concentrations with CVD can in part be explained by changes of thrombogenic factors.

These studies support a relationship between postprandial lipaemia and atherosclerosis, and suggest that the degree of postprandial lipaemia may be a better indicator of atherogenicity than fasting serum levels. This suggests that efforts to reduce the extent of postprandial lipaemia may be particularly effective in reducing the risk of atherosclerosis in relation to triglyceride levels.

8. This was a placebo-controlled trial of colestipol and niacin therapy in men with moderate hypercholesterolaemia and previous coronary bypass surgery.

2.2.4 Specific role of triglycerides in CVD

Although the pathogenic basis for the apparent relationship between elevated triglyceride-rich lipoproteins and atherosclerosis is still uncertain, evidence is accumulating that endothelial dysfunction may be involved.

Research suggests that triglyceride-rich particles may be directly damaging to the endothelium: this may be principally via oxidative mechanisms. Triglyceride-rich particles can cross the endothelial barrier and enter the arterial wall thus placing them in a position to promote direct endothelial damage. [Sattar *et al*, 1998].

Recent evidence has also linked triglyceride levels with alterations of the coagulation system leading to suggestions that some of the deleterious effects of elevated triglyceride may be mediated through its effects on clotting and fibrinolytic mechanisms [Kohler 2000, Deloughery 1999]. In this context the observation that factor VII gets activated on the surface of triglyceride-rich particles may be of interest.

2.2.5 Does lowering triglycerides make any difference?

While the case for a causal role for serum triglycerides in the pathogenesis of coronary heart disease seems increasingly convincing, the main clinical issue is whether there is any evidence that patients benefit from interventions to lower serum triglyceride concentrations [Rubins *et al*, 1999]. Some studies are based on angiographic measures of atheroma progression.

- BECAIT (The Bezafibrate Coronary Atherosclerosis Intervention Trial) established whether bezafibrate could retard or prevent the progression of atherosclerotic lesions in dyslipidaemic male survivors of myocardial infarction. Mean serum triglyceride levels fell by 31% and HDL cholesterol increased by nine per cent in the treatment group, but drug treatment did not affect serum LDL cholesterol. Nevertheless, patients randomised to bezafibrate had a slower rate of progression of focal coronary atherosclerosis and fewer coronary events after five years. The authors suggested that a reduction in triglycerides may have been responsible for the drug effect [Ericsson *et al*, 1996].⁹

9. This was a double-blind, placebo-controlled intervention trial. Subjects had a serum cholesterol of at least 5.2 and a serum triglyceride of at least 1.6 mmol/L. They received bezafibrate or placebo for five years. The primary endpoint was change in mean minimum lumen diameter as measured by angiography.

- A second angiography trial LOCAT (the Lipid Coronary Angiography Trial) included 372 men with a history of coronary bypass surgery who were randomised to treatment with gemfibrozil or placebo and followed for 2.5 years. Gemfibrozil was associated with a triglyceride reduction of 40%, a 14% increase in HDL and only modest decreases in LDL. Nevertheless, once again drug treatment was associated with significant decline in disease progression. Subsequent analysis revealed that the level of triglyceride-rich lipoprotein, intermediate lipoprotein and low density lipoprotein achieved with therapy were strong predictors of progression [Frick *et al*, 1997].

Large primary prevention studies with fibrates are now in progress in dyslipidaemia patients with type 2 diabetes which may extend these promising findings. Preliminary data of one of these studies indicate that type 2 diabetic patients benefit from primary/secondary prevention with fenofibrate [Dais 2000].

- Data from the Helsinki Heart Study also provides further information on the potential benefits of lowering triglyceride. Gemfibrozil resulted in an 11% reduction in LDL cholesterol, an 11% increase in HDL cholesterol and a 35% decrease in fasting triglycerides. Those patients who benefited most from treatment, namely a 70% reduction in clinical events, had what is described as the lipid triad – an LDL/HDL ratio greater than five along with a triglyceride level over 2.3 mmol/L. This suggested that triglyceride is a synergistic risk factor when considered alongside other lipid risk factors [Manninen *et al*, 1992].¹⁰
- The Veterans Affairs High density lipoprotein Intervention Trial (VA-HIT) investigated whether gemfibrozil would reduce the incidence of non-fatal MI and CVD deaths in 2531 men with established CVD, low HDL and low LDL cholesterol. Gemfibrozil resulted in no change in LDL cholesterol, modest increases in HDL cholesterol and a large reduction in triglycerides (31% decrease) [Rubins *et al*, 1999].¹¹

10. This study was a primary prevention study designed to investigate whether gemfibrozil reduced the risk of major cardiac events in men with high levels of non-HDL cholesterol. Treatment resulted in a 34% reduction in non-fatal MI and coronary death. Only modest differences were seen in the first two years suggesting that perseverance over time in the management of hyperlipidaemia pays off.

11. Results showed a 22% reduction in primary endpoints. In addition, this population had a high prevalence of features of the metabolic syndrome – central obesity, hypertension, low HDL and diabetes.

There is evidence that lowering triglycerides can reduce cardiovascular disease progression. A new clinical trial which specifically addresses the value of triglyceride-lowering interventions also suggests that the rate of coronary events is reduced by raising HDL cholesterol levels and lowering levels of triglycerides.

2.3 Management implications

Clearly, many factors should be taken into consideration when assessing an individual's risk of CVD. The current evidence makes a compelling argument for including triglyceride in the lipoprotein profile in evaluating patient risk for coronary disease. At the current time a measurement of fasting triglyceride and its assessment in conjunction with LDL and HDL cholesterol and other risk factors would seem to be the most practical way of assessing risk posed by hypertriglyceridaemia [Gotto 1998].

A National Institutes of Health consensus panel recommended assays of both HDL cholesterol and triglyceride in the following circumstances:

- to assess risk for disease progression and development of additional cardiovascular complications in persons with known CVD
- to refine CVD risk assessment in patients with total cholesterol above the desired range
- to refine CVD risk assessment in patients with desirable total cholesterol levels but two or more CVD risk factors or other disorders that may be associated with increased triglyceride levels
- where familial hyperlipidaemia disorders are suspected

This panel recommended that at least two and preferably three samples should be taken in the fasting state at least one week apart [NIH Consensus Conference, 1993].

A number of existing guidelines around the world already offer recommendations with regard to triglyceride levels [e.g. Study Group of the European Atherosclerosis Society 1988, National Cholesterol Education Program 1993, International Task Force for the Prevention of Coronary Heart Disease]. Non-pharmacological therapy such as weight reduction, nutritional changes, and an increase in physical activity is usually recommended if triglyceride concentrations exceed 200 mg/dL. This lifestyle modification is particularly effective in hypertriglyceridemia.

Lower thresholds (150 mg/dL) are recommended in patients with specific forms of hypertriglyceridemia, such as familial dysbetalipoproteinemia (type III hyperlipoproteinemia) or in those with diabetes mellitus. Drug therapy may be indicated for individuals with persistent hypertriglyceridaemia and other 'atherogenic dyslipidaemias' such as high total cholesterol or low HDL cholesterol level.

Current evidence strongly supports the use of triglyceride assessment in evaluating patient risk for CVD. In the event of hypertriglyceridaemia, recommendations favour the use of non-pharmacological therapy initially, but add that drug treatment can be considered if such strategies fail.

2.4 Strategies to lower triglyceride level

Obesity and sedentary lifestyle significantly aggravate hypertriglyceridaemia and low HDL suggesting that diet and weight control, exercise and smoking cessation must be the primary emphasis of treatment for elevated triglyceride and low HDL cholesterol. Frequently weight loss alone can normalise serum triglyceride levels. Alcohol also increases serum triglyceride in some patients and in those with very high levels should be eliminated.

2.4.1 Nutritional approaches

Nutritional therapy includes avoidance of alcohol, a reduction in non-complex carbohydrates and a reduction in fat intake. Ideally no more than 30% of total calories should be derived from fat of which less than 10% are saturated fats.

However, it is clear that some fats have beneficial effects when it comes to CVD. The Omega-3 (or n-3) family of fatty acids has attracted significant scientific interest since the late 1970s when studies in Greenland Eskimos suggested they had potential anti-atherogenic effects. These fatty acids are provided in abundance in fish oils and are present in the flesh of oil-rich fish such as mackerel, salmon, kipper, herring, trout and sardines. The smallest amount of Omega-3 fatty acids to significantly lower serum triglycerides appears to be approximately 1 g/day, as provided by a fish diet [Agren *et al*, 1996; Pauletto *et al*, 1996]. Alternatively, a fish oil supplement providing as little as 0.21g EPA and 0.11g DHA per day has been found to considerably lower serum triglycerides in hyperlipidemics [Schindler 1996], though further clinical studies are being carried out to investigate the optimal minimum amount required. Other foods such as walnuts, sweet potato and soybean oil, to name but a few, all contribute Omega-3 fatty acids and indeed often together provide the bulk of the Omega-3 in the diet (due to the relatively low intake of oily fish these days). Alternatively, supplements and foods fortified with Omega-3 fatty acids can also help to increase intake.

Later trials, specifically the Diet and Reinfarction Trial and the Indian Experiment of Infarct Survival, have demonstrated a reduction in cardiac death rates and in the incidence of cardiac symptoms in patients receiving fish oil [Harris 1999].

Many studies investigating the effects of Omega-3 fatty acids from fish oils have been conducted. Both crossover and parallel group design studies, providing less than 7g/day of marine Omega-3 fatty acids and with treatment periods of greater than two weeks duration, have found consistent results. Namely, total cholesterol is not materially affected, LDL is minimally affected in the long-term and HDL cholesterol is largely unaffected compared to placebo. However, serum triglycerides concentrations consistently decrease by 25 to 30% – an effect which is greatest in patients with hypertriglyceridaemia [Harris 1997].

Furthermore there is evidence of a dose response relationship [de Deckere *et al*, 1998].

Omega-3 fatty acids also seem to have a particularly beneficial effect on the rise in blood triglycerides after a meal. In one study, encapsulated fish oil supplements (2.7 g/day) resulted in a significant reduction in postprandial triglyceride response [Williams *et al*, 1992].

There is a large body of evidence which shows that Omega-3 fatty acids reduce serum triglyceride concentration through reduced endogenous production of VLDL. This in turn may account for the reduced postprandial lipaemic response following n-3 supplementation and may partly explain why intake is inversely related to CVD mortality [Roche & Gibney, 1999].

The GISSI trial has investigated the effects of long-term supplementation with foods rich in n-3 long-chain polyunsaturated fatty acids in patients who have had myocardial infarction. Results showed that n-3 supplements can reduce the risk of death, non-fatal myocardial infarction and non-fatal stroke after a heart attack [Valagussa F *et al*, 1999].

Until recently, it was commonly believed that diabetics should not receive fish oils because of concerns that they cause a deterioration in diabetic control. However, current evidence suggests that diabetic control does not worsen if the calorific burden of the diet is not increased [Toft 1995, Ha 1998, American Diabetes Association 2000].

Knowledge on the beneficial effect of n-3 fatty acids has also resulted in the recommendation of the American Heart Association to eat sea fish twice a week [AHA 2000].

2.4.2 Mechanisms of the triglyceride-lowering effect of Omega-3 fatty acids

Many studies have investigated the mechanism by which Omega-3 fatty acids reduce triglyceride levels, although a comprehensive single mechanism of action has yet to be advanced. The hypotriglyceridemic action of Omega-3 fatty acids is believed to be primarily due to a reduction in hepatic triglyceride synthesis and hence a diminished secretion of triglyceride-rich lipoproteins from the liver into the circulation, rather than an increased clearance of VLDL [Nenseter MS *et al*, 1992].

The main Omega-3 long chain polyunsaturated fatty acids found in fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), induce peroxisomal β -oxidation [Gronn M *et al*, 1992; Willumsen N *et al*, 1993] and recent studies suggest that these effects are mediated by activation of the peroxisomal proliferator-activated receptors (PPARs). Polyunsaturated fatty acids are natural ligands for PPARs and they regulate the peroxisomal oxidation of fatty acids by induction of the acyl-coA oxidase gene that encodes the rate-limiting enzyme of the pathway [Forman BM *et al*, 1997; Kliewer SA *et al*, 1997].

Omega-3 long-chain polyunsaturated fatty acids are potent activators of PPARs and hence of the degradation of fatty acids via peroxisomal beta-oxidation [Issemann I *et al*, 1993; Keller H *et al*, 1993; Göttlicher *et al*, 1992].

Evidence suggests that increasing consumption of foods rich in n-3 fatty acids can both maintain a low fasting triglyceride level and a low postprandial triglyceride response. A weekly dietary intake of 200 to 300g of fish rich in n-3 fatty acids – mackerel, herring and salmon – which equates to 1-2 servings per week is believed to reduce the risk of cardiovascular disease.

2.4.3 Pharmacological approaches

Pharmacological therapies should be considered when non-pharmacological approaches fail or a strong coronary risk profile is present.

Fibric-acid derivatives decrease triglycerides and increase HDL cholesterol. As has been reviewed, gemfibrozil has been associated with reduced risk of CVD in patients with mixed hyperlipidaemia and low HDL cholesterol. Statins have also been found to have variable effects on higher triglyceride levels.

Nicotinic acid decreases triglyceride levels in proportion to their elevation and is very effective in increasing low HDL cholesterol. Before the introduction of statins this drug was the only lipid-lowering agent with proven effect on overall mortality [Canner PL *et al*, 1986; Carlson and Rosenhamer, 1988]. However, it is important to note that it is contraindicated in patients with non-insulin dependent diabetes mellitus. Furthermore, nicotinic acid is characterized by a high rate of side-effects, and must be used with caution.

3 SUMMARY

- **Cardiovascular disease remains one of the most important public health problems globally. Despite recent declines in CVD mortality, the total number of patients with clinically manifest CVD has increased adding to the existing burden on health services.**
- **Although the role of triglycerides as a risk factor for CVD has been controversial for over three decades, accumulating epidemiological evidence is now demonstrating that blood triglycerides are associated with increased risk, probably in combination with decreased levels of HDL cholesterol and prevalence of small, dense LDL.**
- **Research suggests that alterations in metabolism of triglyceride-rich lipoproteins are of importance in the pathogenesis of atherosclerosis and its clinical consequences, and can predict the extent of coronary artery disease. There appears to be a close relationship between postprandial lipaemia and atherosclerosis.**
- **There is evidence that triglyceride-rich lipoproteins have a pathological role in the development of atherosclerosis perhaps by damaging the endothelium, by activating thrombogenic factors and by inducing increased formation of small, dense LDL.**
- **According to current evidence, lowering triglycerides can reduce coronary disease progression. A new clinical trial which specifically addresses the value of blood triglyceride-lowering interventions also suggests that the rate of coronary events is reduced by raising HDL cholesterol levels and lowering levels of triglycerides.**
- **Current evidence strongly supports the use of triglyceride assessment in evaluating patient risk for CVD. In the event of hypertriglyceridaemia, recommendations favour the use of non-pharmacological therapy initially, but add that drug treatment can be considered if such strategies fail.**
- **In future, to ward against cardiovascular disease, greater emphasis may be placed on dietary changes. These include reductions in total calories and in total fat consumption and greater consumption of foods rich in omega-3 fatty acids which appear to maintain a low fasting triglycerides level and a low postprandial triglyceride response, including a favourable anti-thrombotic/anti-arrhythmic action.**

GLOSSARY OF USEFUL TERMS

- **Atherosclerosis**

Atherosclerosis is a complex disorder of the arteries characterised by the development of plaques of cholesterol, lipids and cellular debris in the inner layers of the walls of large and medium-sized arteries. The process of atherosclerosis starts in childhood with the development of fatty streaks lining the arteries. During adulthood these changes progress by scarring and calcifying, which may lead to irregular narrowings within the arteries eventually resulting in thrombus formation and in vessel blockage.

- **Cholesterol**

Cholesterol is a fat-soluble crystalline steroid alcohol found in animal fats, which is widely distributed in the body. It is a precursor for the synthesis of steroid hormones and bile acids in the liver, vitamin D in the skin and is of vital importance in biological membranes.

- **Chylomicrons**

Chylomicrons are the largest of the lipoproteins. They are formed after a meal from fat and cholesterol in the diet. Chylomicrons are the main form in which triglycerides are carried from the intestine to the body's tissues where they are then used for energy.

- **High density lipoproteins (HDL)**

High density lipoprotein transports excess cholesterol from the cells and surface of other lipoproteins back to the liver for removal from the body. This is important for the disposal of cholesterol, as the peripheral tissues are incapable of breaking down cholesterol. HDL is commonly known as 'good' cholesterol, due to its role in transporting cholesterol away from the arteries to the liver for excretion. Increased levels of HDL are associated with a decrease in the level of coronary heart disease.

- **Hyperlipidaemia**

Hyperlipidaemia is an excess of fat in the blood characterising a group of metabolic disorders. The two most important fats circulating in the blood are cholesterol and triglycerides. Raised blood levels of cholesterol and triglycerides predispose to atheroma and coronary heart disease whereas dramatically raised triglycerides may result in acute pancreatitis.

- **Intermediate density lipoproteins (IDL)**

Intermediate density lipoproteins are the remnants produced when very low density lipoproteins are hydrolysed gradually by the concerted action of lipoprotein lipase.

- **Lipids**

Lipids refer to a heterogeneous group of fats and similar substances which are generally insoluble in water, but soluble in fat solvents such as alcohol and ether. The main lipid groups are the triglycerides, phospholipids, and cholesterol.

- **Lipoproteins**

As lipids are insoluble in water, they are transported in particles where protein is bound to lipids. These lipoproteins transport lipids like cholesterol and triglycerides throughout the body.

- **Lipoprotein (a) or Lp (a)**

Lipoprotein (a) is similar in structure to low density lipoprotein, but also contains a potential clotting factor. A high concentration of Lp (a) is often inherited, and high levels are associated with an increased risk of CVD (particularly in combination with elevated LDL-cholesterol concentrations).

- **Lipoprotein lipase**

This is an enzyme that catalyzes the breakdown of lipids through the hydrolysis of the linkages between fatty acids and glycerol in triglycerides and phospholipids.

- **Low density lipoproteins (LDL)**

Low density lipoproteins (LDL) are lipoproteins, which transport mainly cholesterol. More than 70% of cholesterol in the bloodstream is in this form. Low density lipoprotein cholesterol is commonly referred to as 'bad' cholesterol, as it may be deposited in the arteries. An increase in LDL is associated with an increase in the risk of coronary heart disease.

- **Omega-3 (n-3) fatty acids**

Omega-3 (n-3) fatty acids are long chain polyunsaturated fatty acids which differ from each other in terms of their length and in the number and position of 'rigid links'. Omega-3 long chain fatty acids are so called as they have the first rigid link at the third position on the chain. Certain fatty acids (such as the Omega-3 fatty acid, alpha-linolenic acid) cannot be produced in the body and so have to be obtained in the diet (essential fatty acid).

- **Triglycerides**

Triglycerides make up most animal and vegetable fats. Triglyceride rich particles include VLDL, secreted continuously from the liver and chylomicrons, secreted from the gut after a meal. However, other lipoproteins also contain small amounts of triglycerides.

- **Very low density lipoproteins (VLDL)**

VLDL are triglyceride-rich particles which are produced in the liver. They are converted to intermediate dense lipoproteins and eventually to low density lipoproteins by the removal of triglycerides.

CONCLUSION

High levels of blood triglyceride-rich lipoproteins can lead to an increased risk for atherosclerotic events such as myocardial infarction, stroke or peripheral vascular disease through multiple mechanisms.

There is increasing evidence that reducing the concentration of triglyceride-rich lipoproteins in the blood can decrease this risk. Non-pharmacological approaches, including weight reduction, physical activity, smoking cessation and n-3 fatty acids supplementation are efficacious in reducing triglyceride-rich lipoproteins and thus atherosclerosis risk. These should always be considered first-line intervention.

We hope that this booklet will help you to understand the role of triglycerides in atherosclerosis and offer you an insight into treating patients that present with high triglycerides.

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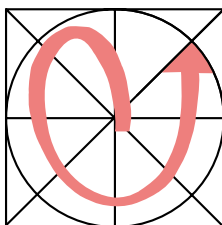
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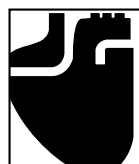
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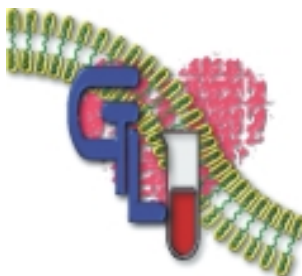
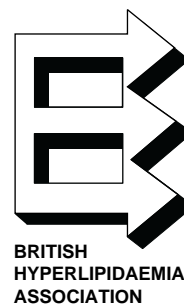


STIFTUNG ZUR PRÄVENTION DER ARTERIOSKLEROSE

POLSKIE TOWARZYSTWO BADAŃ NAD MIAŻDŻYCĄ CZŁONEK IAS
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**TÜRK
KARDİYOLOJİ
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Lipid Workgroup of the Spanish Cardiology Society