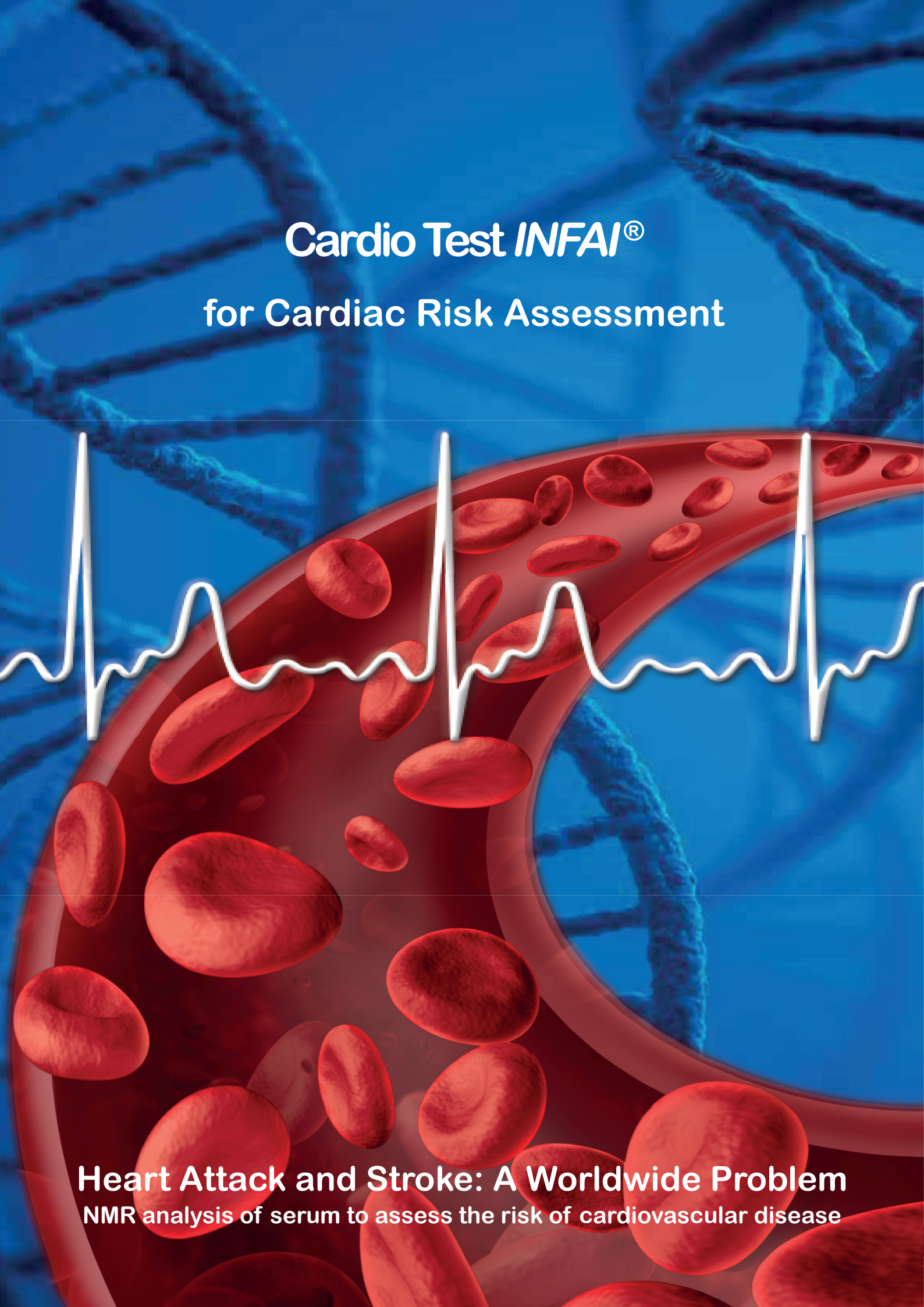
Cardio Test *INFAI*®

for Cardiac Risk Assessment



Heart Attack and Stroke: A Worldwide Problem

NMR analysis of serum to assess the risk of cardiovascular disease

INFAI is at the leading edge in the transfer of advanced analytical technology into medical diagnostics and the development of innovative pharmaceutical products. The company has pioneered the use of stable isotopes in gastroenterology, NMR in metabolic diseases and oncology. INFAI‘s laboratories in Cologne, Germany are equipped with the most advanced NMR spectrometer (Bruker 600 MHz). These facilities are used for in house research and product development and are also available for service, contract research and clinical trials.

In the last years we have developed a range of non-invasive and highly effective stable isotope breath tests. One of these tests is already licensed and available for the routine diagnosis of Helicobacter pylori infection. Other tests to determine gastric emptying rate and pancreatic insufficiency will be available soon.

NMR spectroscopy are used at INFAI to investigate a range of metabolic disorders and malignant conditions. The non-invasive characteristics of these techniques make them particularly suitable for pediatric use. INFAI conducted a clinical trial for newborn screening with 12 clinical centers Turkey in cooperation with Bruker. The Metabo Test was developed and validated for inborn errors of metabolism. More than 1000 pathological metabolites are already tested and validated.

Additionally, Cardio Test *INFAI* ® will be performed from INFAI in cooperation with Numares. This is a new test, based on NMR-spectroscopic investigation of serum samples, to asses the risk of cardiovascular disease, using lipid concentrations of several main- and subclasses from different lipoprotein fractions and average sizes of the main lipoprotein fractions.

INFAI is affiliated with a range of companies throughout Europe.

COMPREHENSIVE ANALYSIS OF BLOOD SERUM LIPOPROTEINS USING NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Recently, nuclear magnetic resonance (NMR) spectroscopy are used to detect inborn metabolic diseases. Cardio Test *INFAI* ® is new a test, based on blood serum sample investigation using NMR spectroscopy, which evaluates the risk of cardiovascular diseases. It determines several main groups and subgroups of concentrations of lipids of various lipoprotein fractions and examines average sizes of the main lipoprotein fractions. This process is routinely used in the USA where over 16 million samples have been analysed. Cardio Test *INFAI* ® is operated by INFAI in co-operation with Numares.

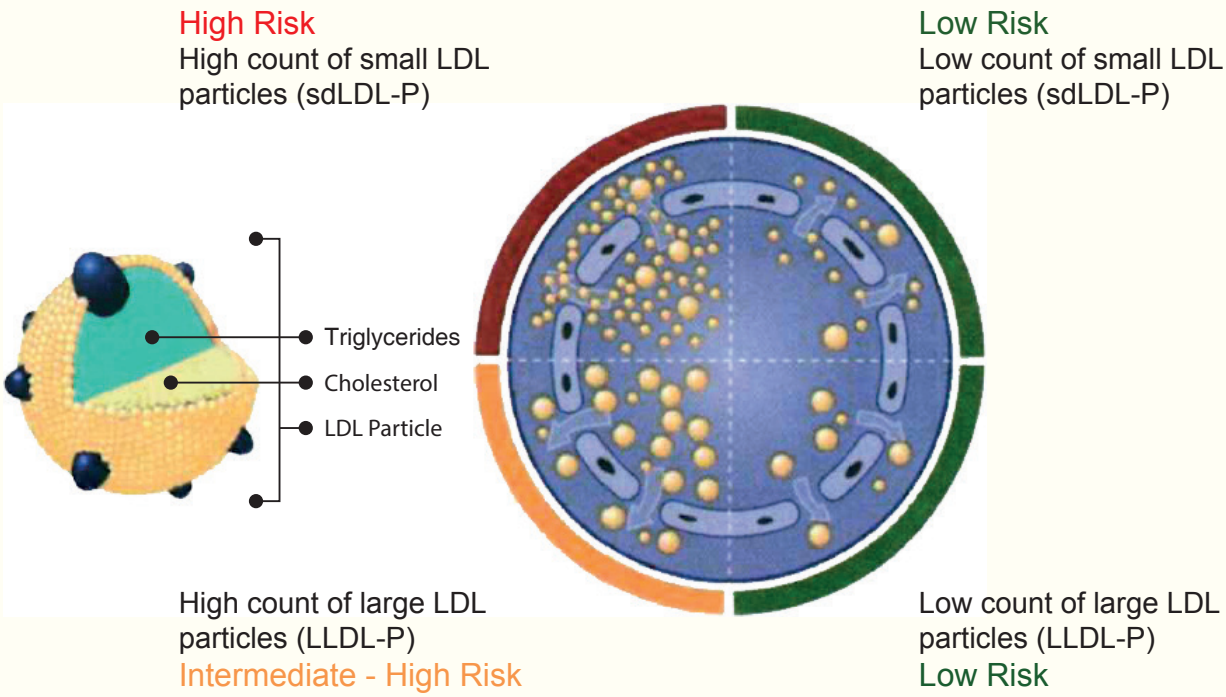


Figure 1: Cardio Test - evaluation of the risk of a cardiovascular disease based on the count and size of particles (P) of lipoprotein fraction LDL. A higher count of LDL particles (LDL-P) proves a higher risk of cardiovascular disease.

LIPOPROTEINS AND DISEASES

Lipoproteins do not represent standardized classes, but form a continuous mixture comprised of small dense particles up to large less dense ones. After a detailed analysis they can be classified into categories labeled as subgroups of lipoproteins (also called subfractions). These subclasses are signified not just by size, density and composition, but also by their atherogenicity.

The importance of measuring levels of LDL and HDL is undisputed for predetermination of a cardiovascular risk. Both parameters are used to indicate possible treatment with statins and for management of treatment. Enzyme tests that measure cholesterol content in lipoproteins (LDL-C, HDL-C) are used globally for this purpose. In case of LDL-C there are commonly recognized reference values for treatment by statins as well as target treatment monitoring values, which then warrant recommendation of a more intensive treatment by statins [1, 2].

WHY SHOULD LIPOPROTEIN SUBGROUPS BE MEASURED?

Lipoprotein subgroups are becoming an even more important risk factor to trigger cardiovascular diseases (CVD) [3–6]. The relationship between cholesterol in lipoprotein subgroups, concentration of particles, size of particles and CVD was proven in a series of studies. Especially the small LDL-P particles are significantly linked to the risk of CVD within the LDL fraction [7-28]. It has been cited for several years that enzyme tests are not an optimal predictor of cardiovascular risk [29]. This is partly due to the fact that a traditional test measures the cholesterol fraction of LDL particles. However, it cannot determine the count of small, dense particles (sdLDL-P), despite this specific subclass being specifically responsible for especially high risk of a cardiovascular disease. Predominantly for this reason the count of LDL particles (LDL-P) is a significantly more important predictor of cardiovascular risk.

The figure below illustrates the risk of a heart attack occurrence in two patients with the same values of LDL-C, but with different values of LDL-P. This increased value of LDL-P, despite the low or referential value of LDL-C, represents the heightened risk of heart attack.

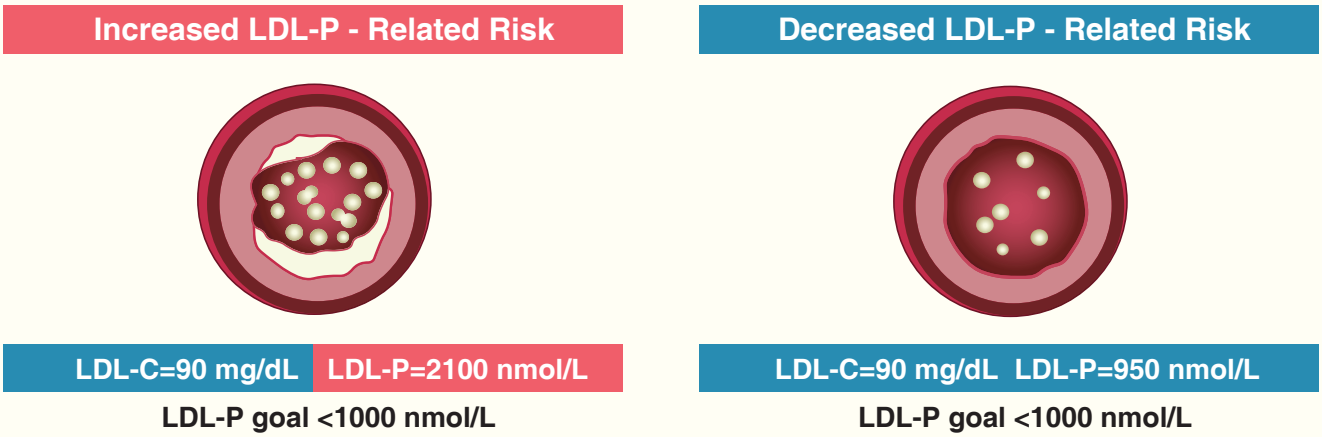


Figure 2: Two patients with same LDL-C and different LDL-P values.

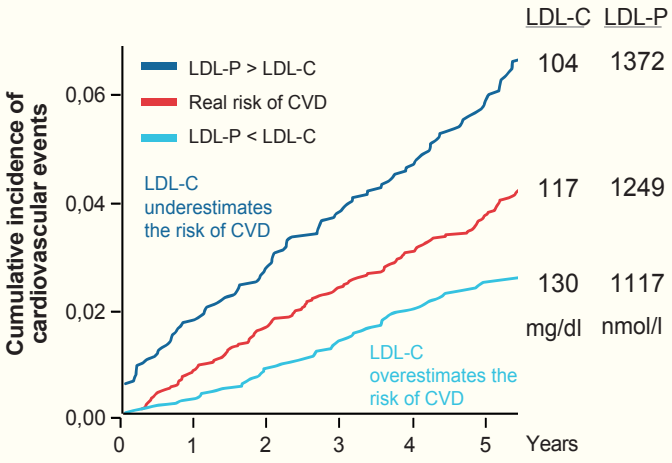
A CLINICAL RESEARCH BREAKTHROUGH

Analysis of lipoprotein particles using NMR spectroscopy is verified by more than 1000 clinical studies which contained over 1 million of blood serum samples. Data from some studies, for example JUPITER, MESA, DPP, PLAC-1, Gramingham, Heart Protection Study, Women's Health Study, Women's Health Initiative, EPIC Norfolk, ANCHOR, HEALTHY, IRAS FIELD, MARINE, were included in over 350 publications. The studies were focused on cardiovascular and metabolic diseases, as well as rheumatoid arthritis, Alzheimer's disease, obesity, thyroid diseases, states of immunodeficiency, hypertension, and diseases of the eye, kidneys and liver. Several studies show, that high values of LDL-P represent a higher risk of heart attack, despite normal or low levels of LDL-C.

CLINICAL RESULTS OF MEASURING LDL-P USING NMR (SPECTROSCOPY)

Determination of LDL-P using NMR is clinically more reliable than simply measuring LDL

As found by the studies MESA and Framingham the risk of cardiovascular diseases increased, despite low LDL-C, because of the increased LDL-P count. If LDL-P and LDL-C differ then LDL-P is a more reliable indicator of the CVD risk. Importance of LDL-C might thus be judged incorrectly (overestimates or underestimates the risk of occurrence of a cardiovascular event).

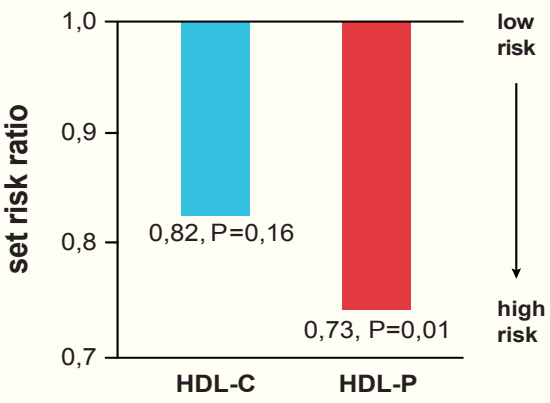


Graph 1: Interpretation of the occurrence of risk of CV events on the basis of measuring LDL-C and LDL-P [30].

CLINICAL RESULTS OF MEASURING HDL-P USING NMR (SPECTROSCOPY)

HDL particle count (HDL-p) is a better predictor of risk of a CVD event

Distribution of subfractions (labeled as phenotype of LDL) and the count of HDL particles are also important factors. Lipoprotein particle concentrations as well as particle sizes were measured using NMR spectroscopy as part of a broad prospect study of 20,000 healthy women. This way the occurrence of cardiovascular diseases was predicted regardless of the classic risk factors [21]. The JUPITER study had proven that the HDL-P particle count is a better predictor of a CVD occurrence and also ensures a more accurate and reliable selection of new therapeutic options aimed at HDL than at HDL-C. The level of risk of a CVD event was determined by age, gender, race, smoking, systolic BP, BMI, glucose level when fasting, LDL-C, triglycerides, and by positive family history of CVD occurrence.



Graph 2: Prediction of risk of a CVD event occurrence on the basis of HDL-C and HDL-P in participants of the JUPITER study which were treated with rosuvastatin [31].

METHODS OF LIPOPROTEIN SUBGROUP ANALYSIS

There are various methods to analyse lipoprotein subclasses. NMR spectroscopy is based on mathematical deconvolution of NMR signals of methyl groups of lipids (CH_3). Each lipoprotein particle of certain size generates a characteristic signal. The area under this signal is directly proportional to the number of particles in different subclasses. Lipoproteins are divided according to their density through the process of ultracentrifugation. Lipoproteins are separated according to their size and charge during gel electrophoresis. Following densitometric analysis of separate bands results in percentage distribution of lipids in different subclasses. The enzymatic procedure to quantify sdLDL cholesterol is based on selective surface active substances and enzymes. Further procedures, such as chromatography, ion mobility, coagulation method, and others, are less common. Large studies have shown that cardiovascular risk can be predicted significantly better by measuring LDL-P using Cardio Test than with a traditional test. Most importantly, they shown that if the findings were inconsistent (LDL-P vs. LDL-C) then LDL-P was the only determinant of risk [32] (Table 1).

	Nuclear magnetic resonance spectroscopy (NMR)	Density-gradient ultracentrifugation (UC)	Polyarylamide gel electrophoresis (GE)	Direct method - enzymatic reaction
Main classes	+	+	+	-
VLDL subclasses	+	+	-	-
LDL subclasses	+	+	+	Only sdLDL
HDL subclasses	+	+	+	-
Particle size	+	-	-	-
Particle concentration	+	-	-	-
Cholesterol subclasses	+	+	+	Only sdLDL
Reproducibility	(Very) high	Moderate	Moderate	Very high
Throughput	High	Moderate	Moderate	Very high
Hands-on time	(Very) low	Moderate	Low	Very low
Automation	High	Moderate	Moderate	Very high

Table 1: Methods of lipoprotein subgroup analysis.

LDL-P vs. LDL-C

Inconsistent findings (LDL-P vs. LDL-C) affect a significant portion of the patient population. 10 - 30 % of patients are assigned to a different risk category, depending on set reference values which determine the indication of their treatment. The new measurement method thus offers even a bigger advantage to the patients that are already undergoing treatment.

Several studies have currently been published with the aim to confirm the positive effect of measuring LDL-P on the survival rate of patients [33]. Recent publication [34] suggested that use of the new method on 80 - 90 patients at risk could prevent one cardiovascular event (myocardial infarction, brain stroke, or death) in the period of 10 years (for comparison: during treatment with inhibitors of blood platelets aggregation about 200 at risk patients need to be treated for 10 years to prevent one event). This study recognised the new method of measuring lipoprotein subgroups as a principally cost effective step.

WHICH PATIENTS SHOULD BE EXAMINED?

This new method of measurement of count is a benefit for all patients. Depending on the criteria set for treatment is generally expected that 10 - 30 % of patients could be reclassified into a different risk group which could potentially lead to a better choice of treatment option. Probable benefit for patients increases with higher risk of arteriosclerosis.

Examination Cardio Test *INFAI*® is especially beneficial for younger patients with positive family history, and for those who are considering an early treatment. The examination is also recommended for patients with higher risk of arteriosclerosis, for example with a known cardiovascular disease, or diabetes mellitus and a disease of kidneys and liver. Treatment monitoring using this new test should also be considered for selected patients as a consequence of shift in LDL subfractions. Target reference values of risk parameters, displayed in Table 2.

LDL-p		SLDL-p	
■ Entity of all LDL particles ■ Important parameter for the estimation of the CHD risk ■ More significant than LDL-c [10, 35]		■ Entity of all small LDL particles ■ Increased SLDL particle concentrations are associated with an increased CHD risk [21]	
Normal range:	< 1000 nmol/l	**Normal range:**	< 500 nmol/l
Possible risk:	1000 - 1300 nmol/l	**Possible risk:**	500 -1000 nmol/l
Increased risk:	> 1300 nmol/l	**Increased risk:**	> 1000 nmol/l
LDL.C-c (= sdLDL-c)		**LDL-s**	
■ Cholesterol in small, dense LDL ■ This subclass carries a higher CHD risk than big LDL particle [36]		■ Averaged diameter of all LDL particles ■ A low value correlates with an increased CHD risk [21]	
Normal range:	< 10 mg/dl	**Normal range:**	> 20.5 nm
Possible risk:	10-30 mg/dl	**Increased risk:**	≤ 20.5 nm
Increased risk:	> 30 mg/dl		
HDL-s		**HDL-p**	
■ Averaged diameter of all HDL particles ■ A low value correlates with an increased CHD risk [21, 37]		■ Entity of all HDL particles ■ More predictive parameter than HDL-C ■ A low HDL-p value is associated with an increased CHD risk [38]	
Normal range:	> 9.0 nm	**Normal range:**	> 38 µmol/l
Increased risk:	≤ 9.0 nm	**Increased risk:**	≤ 38 µmol/l

Table 2: Risk parameter reference values.

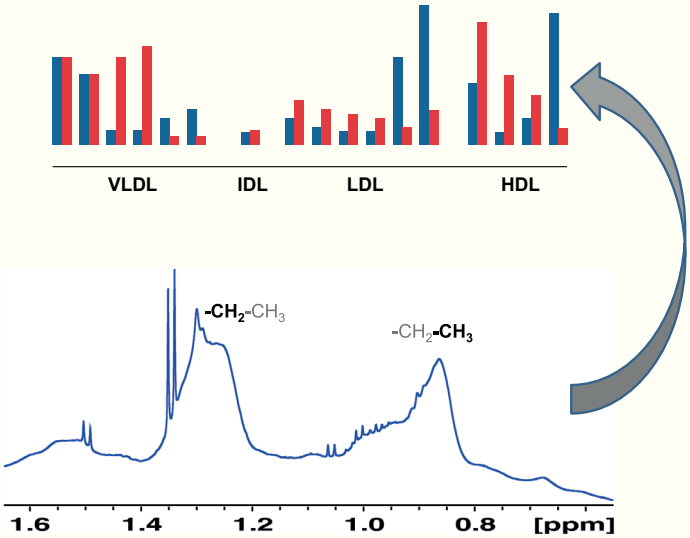
HOW DOES THE NEW TEST WORK AND WHY IS IT MORE ACCURATE?

Nuclear magnetic resonance spectroscopy was developed by Felix Bloch and Edward Purcell, who were awarded the Nobel Prize for this work in 1952. In NMR spectroscopy samples are analysed in a strong high-frequency magnetic field (600 MHz, 14.1 Tesla, in comparison to 1-3 Tesla in NMR tomography, Figure 3).

In principle, NMR spectrometry utilises the fact that atoms have different resonance frequency corresponding to their molecular binding. NMR spectrum shows the majority of compounds that contain proton and that provides an overview of the metabolism. This is a non-invasive process which can be completed easily and quickly.

With the modern automated technology of SampleJet it is possible to measure up to 200 samples of sera within 24 hours at full automation when using high throughput. Integrated cooling of sample to 2 - 8°C minimizes the usual ageing processes and thus increases the quality and reliability of results obtained by analysis.

Figure 3: 600 MHz NMR spectrometer with auto sampler. Fully automated processing and evaluation of samples offers up to 29 parameters for optimal judgement of a potential risk of myocardinal infarction.



Analysis of various resonance frequencies in the ^{1}H spectrum can lead to conclusions about the examined molecules and supramolecular particles (such as lipoproteins) (Fig.4).

This allows for a highly detailed analysis of various proteins. It is possible not just to determine the ratio of HDL, LDL, VLDL and IDL, but also further divide the fractions into large and small particles.

Figure 4: ^{1}H spectrum of CH_2 and CH_3 lipoprotein groups in serum.

HIGHER ATHEROGENIC POTENTIAL OF SMALL PARTICLES

In any case a detailed examination of lipoproteins is medically relevant [39]. Especially small LDL particles (small, dense LDL-P, sdLDL) have a higher atherogenicity potential. Larger LDL particles (known as LDL phenotype A) are prevalent among majority of people. However, for 10 - 30 % of people the ratio of sdLDL (immune phenotype B) is higher. In a traditional enzyme test the concentration of small dense particles (sdLDL) is underestimated because it has a low cholesterol content. Therefore the risk of CVD can be for some patients potentially judged incorrectly. This is generally a bigger problem during a statin treatment, because this treatment also leads to a shift within the LDL subfractions.

Recent findings confirm the recommendation to treat patients with the aim to reach the target concentrations of LDL-P levels. Therapeutic changes of lifestyle, or several groups of medication such as statins, fibrates, niacin, and some glitazones, as well as a combination of therapies with positive effect on the lipid subgroups distribution can be used to reach the treatment target of LDL-P.

Decreasing cholesterol content in LDL particles	Increasing cholesterol content in LDL particles
Statins	Fibrates
Statins + ezetimibe or bile acid sequestrants	Niacin
Estrogen substitution therapy	Pioglitazone
Anti-retrovirus therapy	Omega-3 fatty acids
Low-fat diet	Exercise
Diet high in saccharides	Diet low in saccharides
This treatment ↓LDL-C more than LDL-P	This treatment ↓LDL-P more than LDL-C

Table 3: Treatment that changes cholesterol content in lipoprotein particles might alter the levels of LDL-C and LDL-P differently [40].

LIPOPROTEIN SUBGROUPS PUBLISHED IN GUIDELINES OF PROFESSIONAL ASSOCIATIONS

As the NMR technology to examine lipoproteins is predominantly accessible in the United States, it is assumed that the new test protocol will be first established in international or American guidelines.

Current guidelines of the American College of Cardiology and the American Heart Association (ACC / AHA) for 2013 (source) recommend to use enzymatic test to measure LDL. However, a following directive especially closely examines the benefit of measuring LDL particles to aid the treatment decision.

Cited studies about the advantages of measuring LDL particles were mostly published on the basis of the current ACC / AHA guidelines. There are many professional associations which emphasise the basic benefit of particle measurement (see selection in Table 4):

2009	**Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices**
America Association of Analytical Chemists (AACC) states that LDL-P are “ever more predictive of the occurrence of a cardiovascular disease than LDL-C”, and “offers a better evaluation of residual risk during treatment than the measurement of LDL-C”. They suggested a treatment target of LDL-P < 1000 nmol/l similarly to LDL-C from the point of view of percentage of the population [41].	
2011	**Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists**
National Lipid Association (NLA) recommends to evaluate LDL-P at the time of the initial clinical evaluation and decision on treatment management for medium to high risk patients [42].	
2013	**AACE comprehensive diabetes management algorithm 2013**
AACE included LDL-P measurement into the diabetes treatment algorithm. Treatment intensity should focus at reaching LDL-P < 1200 nmol/l in medium risk patients and <1000 nmol/l in high risk patients [43].	
2013	**Association of apolipoprotein B and nuclear magnetic resonance spectroscopy-derived LDL particle number with outcomes in 25 clinical studies: assessment by the AACC Lipoprotein and Vascular Disease Division Working Group on Best Practices**
AACC reached a conclusion that “Apo B and LDL-P are consistently shown as the more important risk factors than LDL-C”. AACC recommends that “…particle count measurement […] be included into binding CVD risk evaluation directives” [44].	

Table 4: Conclusions and recommendations of professional associations.

Recent findings confirm the recommendation that patients should be treated so as to achieve target values in LDL-P concentration. Therapeutic lifestyle changes or several classes of medications, such as statins, fibrates, niacin, and some glitazones as well as combination therapies can be used to achieve the treatment objectives for LDL-P with a positive effect on the lipoprotein subclass distribution.

NMR PARAMETERS OF CARDIO TEST *INFAI* ®

Metabolite	Unit	Description
Lipoprotein fractions		
LVLDL-p	nmol/l	Concentration of large VLDL particles
LDL-p	nmol/l	Concentration of LDL particles
LLDL-p	nmol/l	Concentration of large LDL particles
SLDL-p	nmol/l	Concentration of small LDL particles
HDL-p	nmol/l	Concentration of HDL particles
LHDL-p	nmol/l	Concentration of large HDL particles
SHDL-p	nmol/l	Concentration of small HDL particles
Particle size		
VLDL-s	nm	Average size of VLDL particles
LDL-s	nm	Average size of LDL particles
HDL-s	nm	Average size of hDL particles
Cholesterol concentration		
VLDL-c	mg/dl	Cholesterol concentration in VLDL group
IDL-c	mg/dl	Cholesterol concentration in IDL group
LDL-c	mg/dl	Cholesterol concentration in LDL group
LDL.A-c	mg/dl	Cholesterol concentration in LDL subgroup A (large particles)
LDL.B-c	mg/dl	Cholesterol concentration in LDL subgroup B (medium particles)
LDL.C-c	mg/dl	Cholesterol concentration in LDL subgroup C (small particles)
HDL.A-c	mg/dl	Cholesterol concentration in HDL subgroup A (large particles)
HDL.B-c	mg/dl	Cholesterol concentration in HDL subgroup B (medium particles)
HDL.C-c	mg/dl	Cholesterol concentration in HDL subgroup C (small particles)
Standard parameters		
Total cholesterol	mg/dl	Total concentration of cholesterol in serum
LDL cholesterol	mg/dl	Concentration of LDL-cholesterol in serum
HDL cholesterol	mg/dl	Concentration of HDL-cholesterol in serum
Triglycerides	mg/dl	Concentration of all triglycerides in serum
Lactate	mg/dl	Concentration of lactate in serum
Glucose	mg/dl	Concentration of glucose in serum

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QUALITY MANAGEMENT

INFAI has established an integrated quality management system based on ISO 9001: 2015, in compliance with national and international regulations. The high quality standards defined within this framework ensure the production of reliable and high-quality pharmaceutical products. Customer satisfaction is at the centre of all our activities. The permanent improvement of our quality management system enables us to act quickly upon changing market conditions.

Cardio Test *INFAI* ® is conducted in co-operation with Numares.

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