CARDIO TEST INFAI®

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

USES BLOOD SERUM ANALYSIS TO DETERMINE THE RISK OF CARDIOVASCULAR DISEASES

BECAUSE MYOCARDIAL INFARCTION AND STROKE ARE GLOBAL ISSUES

„Everyone is only as healthy as their blood vessels“

ABOUT INFAI

INFAI is a leader in the transfer of advanced analytical technologies into medical diagnostics and the development of innovative pharmaceutical products. It was one of the first companies to use stable isotopes and nuclear magnetic resonance (NMR) spectroscopy for gastroenterology, metabolic disorders, oncology, and cardiology.

INFAI's laboratories in Cologne, Germany are equipped with state-of-the-art NMR devices and imaging technology for both research and product development, and are also available for collaboration, contracted research, and commercial purposes.

Cardio Test INFAI ®

USING NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY FOR COMPREHENSIVE ANALYSIS BLOOD SERUM LIPOPROTEINS

Nuclear magnetic resonance (NMR) spectroscopy and NMR imaging are investigating the extent of metabolic diseases and malignancies.

Cardio Test INFAI is a modern test produced by INFAI in cooperation with Numares and Allmedical that examines serum using MRI-spectroscopy to evaluate the risk of cardiovascular diseases. It determines the number of main groups and subgroups of lipid concentrations from various lipoprotein fractions and average sizes of the main lipoprotein fractions. This procedure is now commonly used in the United States, where more than 16 million samples have been tested.

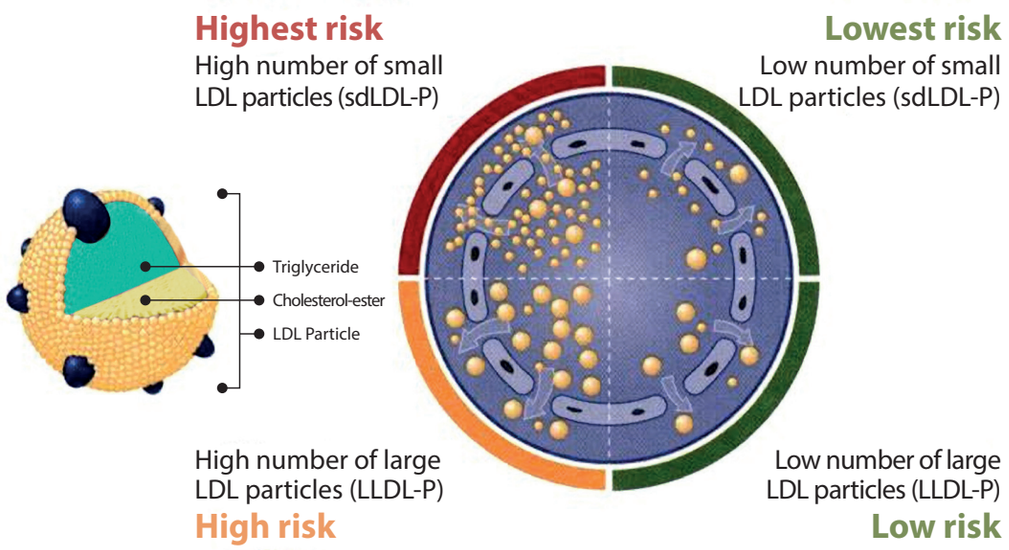


Figure 1: Cardio Test - CVD risk based on the number and size of particles (P) of lipoprotein fraction LDL. The higher the number of LDL particles (LDL-P), the higher the risk of CVD.

LIPOPROTEINS AND CARDIOVASCULAR DISEASES

Lipoproteins are not classified in standardized classes, but form a continuous mixture composed of both small, dense particles alongside large and less dense ones. After a more detailed analysis, they can be divided into categories labeled as lipoprotein subgroups (also called subclasses/subfractions). These are distinguished not only by size, density, and composition, but also by their aterogeneity.

There is no dispute about the importance of measuring LDL and HDL to determining cardiovascular risk. Both parameters are used to indicate possible treatment with statins and to monitor treatment. Enzymatic tests are used all over the world to measure cholesterol content in lipoproteins (LDL-C, HDL-C). For LDL-C, there are generally accepted benchmarks for statin treatment as well as target values for monitoring it, from which a stronger statin therapy may be recommended [1, 2].

WHY SHOULD SUBCLASSES OF LIPOPROTEINS BE MEASURED?

Lipoprotein subclasses are increasingly becoming important risk factors for cardiovascular diseases (CVD) [3 – 6], with the relationship between cholesterol in lipoprotein subclasses and the concentration of particles, particle size and CVD having been proved in a series of studies. In LDL fractions, especially small LDL-P particles are significantly associated with CVD risk [7 – 28]. For several years it has been thought that enzyme tests are not an optimal predictor of cardiovascular risk [29], partly due to the traditional test measuring the cholesterol fraction of LDL particles.
However, the number of small, dense particles (sdLDL-P) cannot be determined, although this specific subclass is responsible for a particularly high risk of cardiovascular diseases. For this reason, the number of LDL particles (LDL-P) is a significantly more important predictor of cardiovascular risk.

The picture below shows the risk of a heart attack in two patients with the same LDL-C values, but their LDL-P values are different. Despite the low LDL-C reference values, the higher LDL-P value represents the increased risk of heart attack.

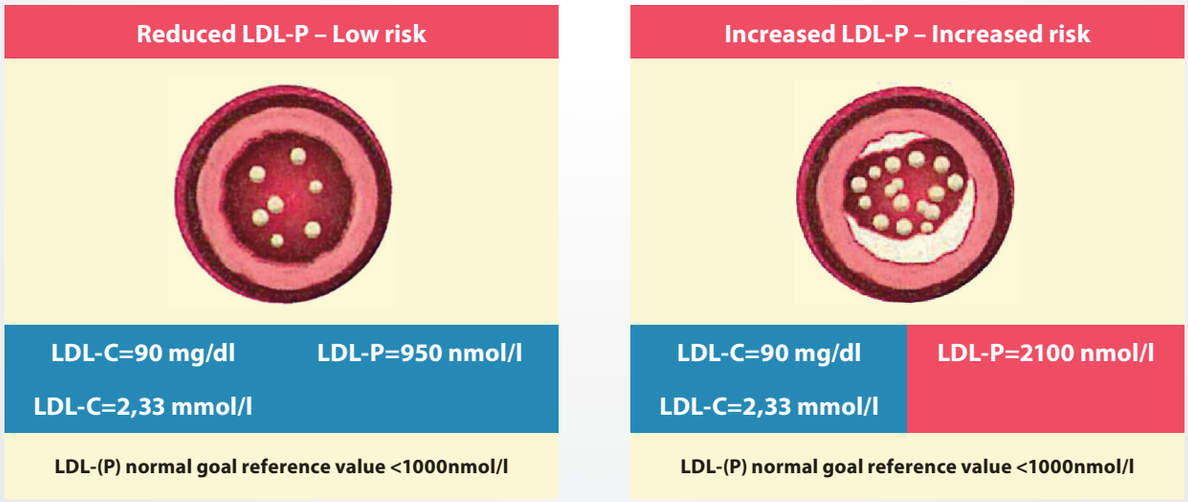


Figure 2: Two patients with the same values of LDL-C and different values of LDL-P.

A BREAKTHROUGH IN CLINICAL RESEARCH

Lipoprotein particles have been analyzed with NMR spectroscopy in more than 1,000 clinical studies involving more than one million samples of blood serum. Data from studies such as JUPITER, MESA, DPP, PLAC-1, Gramingham, Heart Protection Study, VA-HIT, Cardiovascular Health Study, Women's Health Study, Women's Health Initiative, EPIC Norfolk, ANCHOR, HEALTHY, IRAS FIELD and MARINE have been included in more than 350 publications. These studies focused on cardiovascular and metabolic diseases, rheumatoid arthritis, Alzheimer's disease, obesity, thyroid diseases, immunodeficiency disorders, hypertension and diseases of the eye, kidneys, and liver. A number of studies have shown high values of LDL-P to constitute a higher risk of heart attack, even if LDL-C levels are normal or low.

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

Using NMR to determine LDL-P is clinically more reliable than just measuring LDL

The MESA and Framingham studies found the risk of cardiovascular diseases to be even higher because of increased LDL-P, even though LDL-C was low. When LDL-P and LDL-C differ, then LDL-P becomes the more reliable predictor of CVD risk. The significance of LDL-C can be incorrectly assessed (by either over- or underestimating the risk of cardiovascular events).

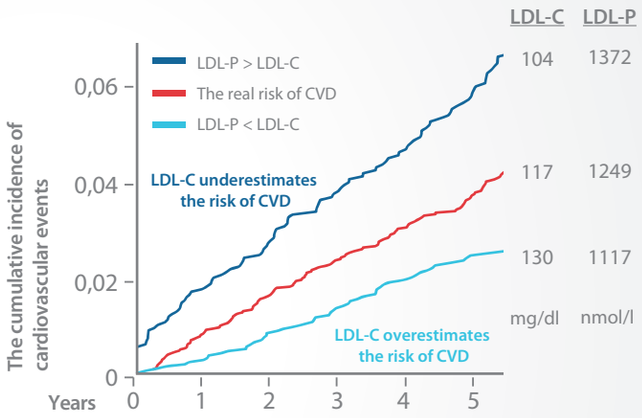
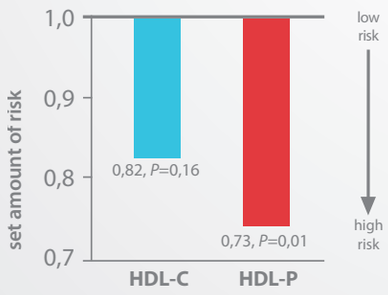


Chart 1: Interpretation of the risk of CV events on the basis of LDL-C and LDL-P measurements [40].

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

THE NUMBER OF PARTICLES (HDL-P) IS A BETTER PREDICTOR OF THE RISK OF CVD

How subfractions are laid out (known as LDL phenotype) and the number of HDL particles are also important factors. NMR spectroscopy was used in an extensive, prospective study of more than 20,000 healthy women to measure the concentration of lipoprotein particles and particle size, predicting the incidence of cardiovascular diseases regardless of the classic risk factors [21].



The JUPITER study showed the number of HDL-P particles to better predict CVD risk, while also providing a more accurate and reliable selection of new therapeutic options targeted at HDL rather than HDL-C. The risk of CV events was determined by age, sex, race, whether the patient smoked, systolic blood pressure, BMI, glucose levels on an empty stomach, LDL-C, triglycerides and a positive family history of CVD.

Chart 2: CV event risk predicted from HDL-C and HDL-P in JUPITER study participants who were treated with rosuvastatin [38].

METHODS FOR ANALYZING LIPOPROTEIN SUBGROUPS

There are various methods used to analyze lipoprotein subclasses. NMR spectroscopy is based on a mathematical deconvolution of NMR signals of methyl groups (-CH3) of lipids. Each lipoprotein particle of a certain size generates a characteristic signal. The area under the signal is directly proportional to the number of particles in different subclasses.

Ultracentrifugation fractions lipoproteins according to their density. Lipoproteins are separated by their size and charge during gel electrophoresis. The densitometry analysis shown below of various bands provides a percentage distribution of lipids in different subclasses. The enzymatic method for quantifying sdLDL cholesterol is based on selective surfactants and enzymes. Other methods such as chromatography, ion mobility, precipitation are less advanced. Many studies have shown a significantly better prediction of cardiovascular risk from measuring LDL-P with the Cardio Test than in traditional testing. In particular, indicating, when findings were inconsistent (LDL-P vs. LDL-C), that the number of LDL-P particles was the only determinant of risk [30] (Table 1).

	Nuclear magnetic resonance spectroscopy (NMR)	Density gradient ultracentrifugation (UC)	Polyacrylamide 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 of the method	(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 for analysis of lipoprotein subgroups.

LDL-P vs. LDL-C

A significant percentage of patients can be affected by inconsistent findings (LDL-P vs. LDL-C). Depending on the set reference values for the treatment indication, up to 30% of patients would be classified in a different risk group. The advantage of the new measurement method is even greater in treated patients.

Several studies have now been published with the intention of substantiating the positive effect that using LDL-P measurement has on patient survival [31]. A recent paper [32] proposed that using the newer test on 80–90 at-risk patients would prevent one cardiovascular event (myocardial infarction, stroke or death) in 10 years (for comparison: with treatment using platelet aggregation inhibitors, approx. 200 at-risk patients must be treated for 10 years to prevent one event). This study considered a fundamental shift from lipoprotein measurement to the new procedure to be cost-effective.

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

Nuclear magnetic resonance spectroscopy was developed by Felix Bloch and Edward Purcell and in 1952 both men received the Nobel Prize for Physics for their work in this area. NMR spectroscopy analyzes samples in a high-frequency magnetic field (600 MHz, 14.1 Tesla, compared with 1-3 Tesla in MRI tomography, Figure 3).

In principle, NMR spectroscopy takes advantage of atoms having a different resonance frequency, based on their molecular bond. The NMR spectrum shows most of the proton-containing compounds, providing an overall view of metabolism. This non-invasive procedure can be carried out quickly and easily.

With modern technology, up to 200 serum samples can be measured fully automatically within 24 hours, with high throughput. Integrated cooling of the sample to 2 – 8 °C minimizes the normal aging process to increase the quality and reliability of the results obtained from analysis.

Fully automated processing and evaluation of samples provides up to 29 parameters for an optimal assessment of the potential risk of myocardial infarction.

Figure 3: 600 MHz NMR spectrometer with SampleJet autosampler.

Analysis of different resonant frequencies in the 1H spectrum can provide conclusions about the molecules and supramolecular particles (such as lipoproteins) examined (Fig. 4), allowing for a highly detailed analysis of different lipoproteins. It is possible not only to determine the proportion of HDL, LDL, VLDL and IDL, but also to further divide the fractions into large and small particles.

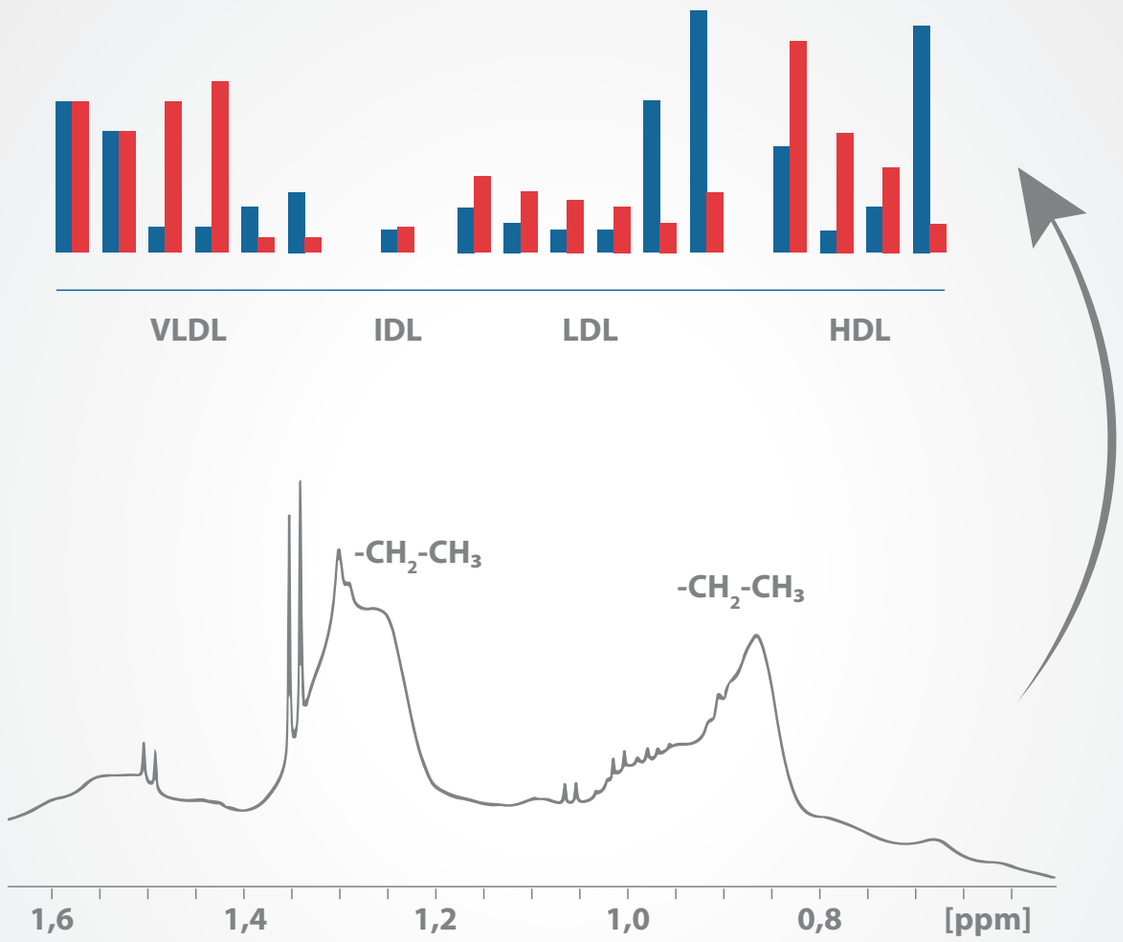


Figure 4: [1]H spectrum of CH2 and CH3 groups of lipoproteins in serum.

HIGHER ATEROGENIC POTENTIAL OF SMALL PARTICLES

In any case, a detailed examination of lipoproteins is medically relevant [33]. In particular, small LDL particles (small dense LDL, sdLDL) have a higher aterogenic potential. Large LDL particles (known as LDL phenotype A) prevail in most people, although the proportion of sdLDL is higher in 10 – 30 % (immune phenotype B). The traditional enzymatic test underestimates the concentration of small dense particles (sdLDL) because of low cholesterol content. Therefore, some patient's CVD risk may be incorrectly assessed. This problem is generally encountered more often during statin treatment because of a shift in LDL subfractions.

WHICH PATIENTS SHOULD BE EXAMINED?

This new method for measuring LDL particles benefits all patients. Depending on the treatment criteria, it is widely expected that 10 – 30 % of patients could be transferred to a different risk group, potentially leading to the selection of an effective treatment option. The probable benefit for patients increases as risk of atherosclerosis grows.

The Cardio Test INFAI® examination particularly helps younger patients with a positive family history and anybody considering early treatment. In addition, the examination is recommended for patients at higher risk of atherosclerosis, such as those with a known cardiovascular disease or diabetes mellitus, as well as kidney or liver disease. Monitoring of treatment should also be considered for selected patients due to the new test's transfer of LDL subfractions.

The target LDL-P reference values listed in Table 2 have been recommended by the NLA (National Lipid Association), based on conclusions drawn from a panel discussion of experts and specialists [35].

LDL-P	1,473	below 1,000	1,000 – 1,299	1,300 – 1,599	1,600 – 2,000	above 2,000
Number of LDL particles	nmol/l	normal	low risk	moderate – increased risk	high risk	very high risk

Table 2: Reference LDL-P values

Recent findings confirm the recommendation to treat patients in order to achieve target LDL-P concentration levels that correspond to the standard. Therapeutic lifestyle changes and several groups of medications, such as statins, fibrates, niacin and some glitazones can be used to reach the LDL-P treatment target, as well as a combination therapy with a positive interactive effect on the distribution of lipoprotein subgroups.

Cholesterol content in LDL particles decreases	Cholesterol content in LDL particles rises
Statins	Fibrates
Statins + ezetimibe or bile acid sequestrants	Niacin (vitamin P, B3)
Estrogen replacement therapy	Pioglitazone
Antiretroviral therapy	Omega 3 fatty acids
Low fat diet	Exercise
High carbohydrate diet	Low carbohydrate diet
Treats ↓ LDL-C more than LDL-P	**Treats ↓ LDL-P more than LDL-C**

Table 3: Treatment altering lipoprotein particle cholesterol content can vary LDL-C and LDL-P levels [39].

LIPOPROTEIN SUBCLASSES PUBLISHED IN CURRENT GUIDELINES OF PROFESSIONAL ASSOCIATIONS

Because NMR for examining lipoproteins is primarily available in the United States, it is likely that the new test procedure will be initially established under either international or or United States guidelines.

The current guidelines used by the American College of Cardiology and the American Heart Association (ACC/AHA) for 2013 (source) recommend the enzyme test for measuring LDL. However, the upcoming guideline will examine, in particular, the benefit of measuring LDL particles when deciding on treatment.

The previously mentioned studies on the benefits of LDL particle measurements were mostly published from current ACA/AHA guidelines. There are also many professional associations that emphasize the basic benefits of particle measurement (with selected associations shown on Table 4):

2009	**Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices**
The American Association of Clinical Chemists (AACC) states that LDL-P is „consistently more predictive of cardiovascular disease than is LDL-C" and appears to „provide a better assesment of on-treatment residual risk than LDL-C measurement". It suggested a treatment target of LDL-P of <1100 nmol/L, similar to LDL-C in terms of population percentiles. [34]	
2011	**Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists**
The National Lipid Association (NLA) recommends the evaluation of LDL-P at the time of initial clinical assessment and on-treatment management decisions for intermediate and high-risk patients [35]	
2013	**AACE comprehensive diabetes management algorithm 2013**
The AACE incorporated LDL-P measures into a diabetes managemant algorithm. Treatment should be intesified to reach treatment targets for LDL-P of < 1200 nmol/L for patients with moderate risk and < 1000 nmol/L for patients with high risk. [36]	
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**
The AACC concludes that "Apo B and LDL-P have consistently been shown to be stronger risk factors than LDL-C". They recommend that "the measurement of particle number […] should be incorporated into the guidelines for the assessment of CVD risk [37].	

Table 4: Conclusions and recommendations from professional associations.

CARDIO TEST INFAI® EXAMINING 29 PARAMETERS USING NMR

Metabolite	Unit	Description
Lipoprotein fractions		
LVLDL-p	nmol/l	Concentration of large LDL 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 (meduim-sized 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-sized 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 the serum
LDL-Cholesterol	mg/dl	Concentration of cholesterol in the serum
HDL-Cholesterol	mg/dl	Concentration of HDL-cholesterol int the serum
Triglycerides	mg/dl	Total concentration of triglycerides in the serum
Lactate	mg/dl	Lactate concentration in the serum
Glucose	mg/dl	Glucose concentration in the serum
Alanine	mg/dl	Alanine concentration in the serum
Valine	mg/dl	Valine concentration in the serum
Leucine	mg/dl	Leucine concentration in the serum
Isoleucine	mg/dl	Isoleucine concentration in the serum

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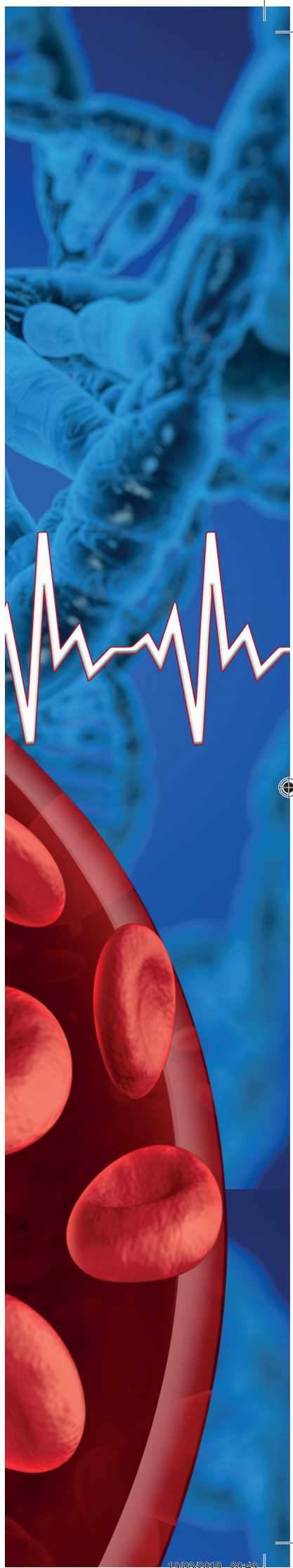
QUALITY MANAGEMENT SYSTEM

NFAI QUALITY MANAGEMENT has introduced an integrated quality management system based on ISO 9001: 2008 in accordance with national and international regulations. High quality standards defined in this framework ensure the production of reliable, high-quality pharmaceutical products. Customer satisfaction is at the heart of all our activities. Continuous improvement of our quality management system enables us to act quickly according to the changing market conditions.

Cardio Test INFAI® is carried out in collaboration with Numares and Allmedical.



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