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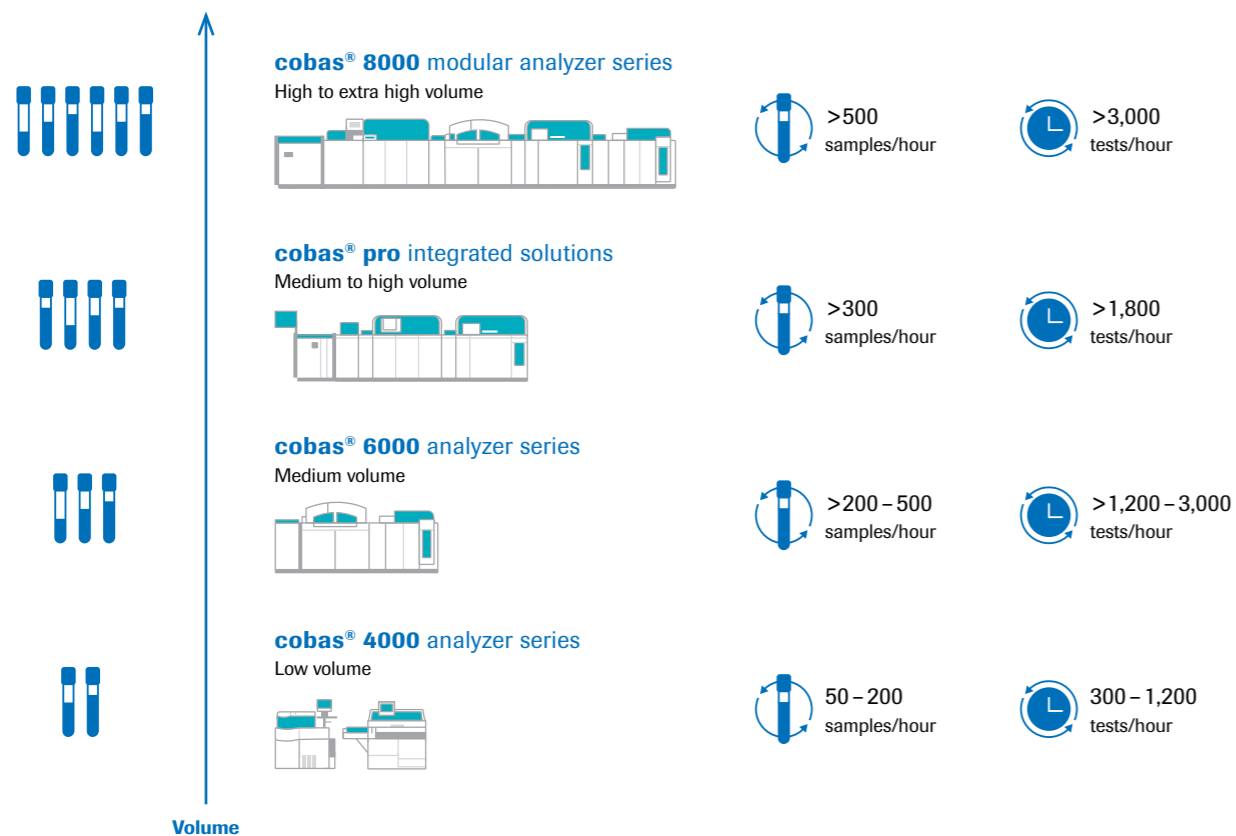
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Cardiovascular disease

Cardiovascular disease (CVD) is a major worldwide health concern that continues to grow. CVD is responsible for more deaths globally than any other disease and the huge burden it places upon healthcare systems and society is predicted to become even greater. For example, CVD was estimated to be responsible for 17.9 million deaths in 2016, which represents 31 % of global mortality.[1] This figure is predicted to reach almost 24 million by 2030, with coronary heart disease (CHD) and stroke remaining the leading causes of CVD death (Figure 1).[1,2] Furthermore, the projected economic cost to the USA alone in 2010 was $444.2 billion, which takes into account the cost of health services, medication, and lost productivity, and this is predicted to exceed $1 trillion in 2030.[3]

Mitigating the impact of increasing CVD can be achieved by combining early detection of at-risk individuals with the adoption of risk-lowering behaviors. Approximately 30 % of CVD deaths occur in individuals not displaying conventional risk factors, such as elevated serum cholesterol or blood pressure.[4] For example, more than 75 % of heart attacks occur in patients with normal serum cholesterol.[5] Therefore, there is a clinical need to expand the number of diagnostic tools available for evaluating an individual's risk of CVD.

"Furthermore, it is entirely appropriate that Lp(a), as a causal, independent risk factor, should be integrated into existing treatment algorithms."[15]

Numerous extensive studies have demonstrated that the concentration of lipoprotein (a) (Lp(a)) in an individual's plasma, but not the mass of Lp(a), can serve as a clinically useful risk factor for CVD.[6-13] The use of expanded test panels combining conventional risk factors with less well-known risk factors, such as Lp(a), homocysteine, and high-sensitivity C-reactive protein, can provide a better predictive power than results from test panels composed solely of conventional risk factors (Figure 2).[14] Therefore, the use of expanded test panels should allow optimal use of therapeutic options in high-risk individuals.[14]

Global deaths from cardiovascular disease in 2016[1]

17.9 million deaths

- 43 % Coronary heart disease
- 33 % Stroke
- 5 % Hypertensive heart disease
- 3 % Inflammatory heart disease
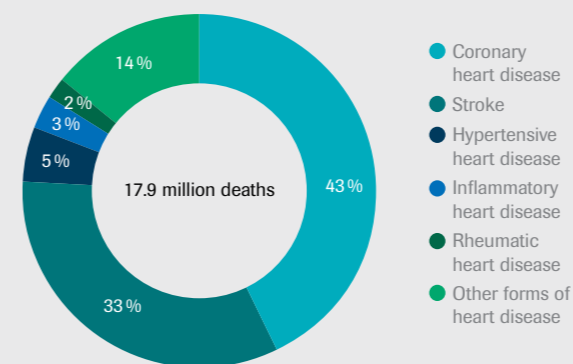- 2 % Rheumatic heart disease
- 14 % Other forms of heart disease

Figure 1: Coronary heart disease and stroke remain the leading causes of cardiovascular death.[1]

Prediction of cardiovascular disease can be improved by analyzing an expanded panel of risk factors[14]

HDL	LDL

70 % of individuals identified with conventional risk profile; 30 % not identified

HDL	LDL

+

Lp(a)	HCY	hs CRP

Incorporating Lp(a), HCY, and hsCRP, into a diagnostic test panel improves prediction of an individual's risk.
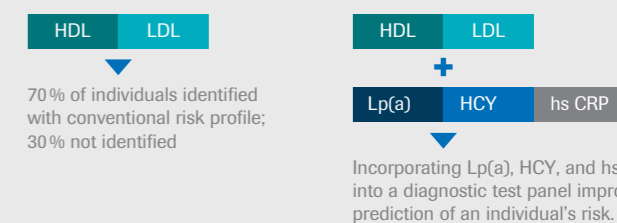
Figure 2: The use of conventional risk factors, such as serum cholesterol, blood pressure, obesity, and smoking, fails to identify a considerable proportion (30%) of individuals at risk of CVD.[4] Incorporating other risk factors, such as Lp(a), HCY, and hsCRP, into a diagnostic test panel improves prediction of an individual's risk.[14] Abbreviations: CVD, cardiovascular disease; HCY, homocysteine; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a).

Lp(a) as an independent risk factor for CVD

Lp(a) has been considered a risk factor for CVD for many years. However, it is only recently that conclusive causal genetic evidence has been generated to support the earlier epidemiologic data demonstrating an association between Lp(a) level and the risk of CVD (Table 1).[11–13]

Increasing level of evidence	Type of epidemiologic study	Findings and interpretation
	Meta-analysis	
	Individual data	• Risks of CHD and ischemic stroke increase by 13 % and 10 %, respectively, with every 3.5-fold increase in plasma Lp(a) • Association between plasma Lp(a) and CVD risk is continuous and independent of other risk factors
	Literature-based	• Relative risk of CHD is 30 – 80 % higher in individuals in the top vs. bottom tertile for plasma Lp(a)
	Individual study	
	Prospective studies	• Lp(a) associated with risk of CVD, although some studies fail to demonstrate an association
	Retrospective case-control studies	• Lp(a) associated with risk of CVD, although conclusions limited by retrospective design

Table 1: Epidemiologic evidence for Lp(a) as a strong, independent risk factor for CVD.[13]
Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; Lp(a), lipoprotein (a).

"Some of the earlier studies failed to demonstrate an association between Lp(a) and CVD, possibly due to insufficient power or poor assay quality."[13]

Cardiovascular disease

Genetic evidence of a causal role for Lp(a) in CVD

Blood levels of Lp(a) can vary between individuals and between ethnic groups, although the variation between ethnic groups is typically not more than five-fold.[13] Genetic studies have revealed that a large proportion (70 – 90 %) of the natural variation observed within a population is due to polymorphisms of the *LPA* gene encoding apolipoprotein (a) (apo (a)).[13] A single apo (a) molecule is present in each Lp(a) particle, and the most important determinant of each apo (a) isoform's size is the number of kringle IV type 2 (KIV-2) repeats it contains (Figure 3).[13,15,16] At least 34 apo (a) isoforms, which display a number of KIV-2 repeats ranging from 2 to >40, have been identified.[15,17] Larger apo (a) isoforms, i.e. those with a high number of KIV-2 repeats, are associated with lower hepatic secretion rates and hence lower plasma Lp(a) concentrations and vice versa.[13,15]

The considerable influence of the *LPA* gene on plasma Lp(a) levels means that it is an ideal candidate for Mendelian randomization studies investigating whether CVD is caused by lifelong, genetically elevated levels of plasma Lp(a).[15] A large genetic study investigating plasma Lp(a) levels and the risk of myocardial infarction (MI) in more than 40,000 Danish individuals genotyped for apo (a) isoforms demonstrated increasing hazard ratios with increasing plasma Lp(a) levels.[11] Compared with individuals with a plasma Lp(a) level <22nd percentile, the hazard ratio for MI was 1.2 for those in the 22 – 66th percentile, 1.6 for those in the 67 – 89th percentile, 1.9 for those in the 90 – 95th percentile, and 2.6 for those with Lp(a) levels >95th percentile. The study also found that approximately 25 % of all variation in plasma Lp(a) levels was attributable to the number of KIV-2 repeats within individuals' apo (a) isoforms. Individuals in the fourth quartile, i.e. those having the highest total number of KIV-2 repeats, displayed the lowest mean plasma Lp(a) level, while those in the first quartile displayed both the highest mean plasma Lp(a) level and greatest hazard ratio for MI.

Another large genetic study demonstrated that the chromosomal locus of the *LPA* gene had the strongest association with the risk of CHD.[12] Two relatively common single-nucleotide polymorphism variants, which were present as a combination in approximately 17 % of individuals, explained 36 % of the variation in plasma Lp(a) levels and were associated with an odds ratio for CHD of 1.5 and 2.6 depending on whether they were present either individually or in combination, respectively.

The correlation between elevated Lp(a) levels, although not Lp(a) mass, and the risk of CVD observed in these genetic studies clearly demonstrates that Lp(a) is an independent and causal risk factor for CVD. These findings also highlight the need for diagnostic assays that are standardized to measure the molarity of Lp(a) particles within a sample, rather than the particles' combined mass. This need is addressed by the Tina-quant® Lipoprotein (a) Gen. 2 assay.
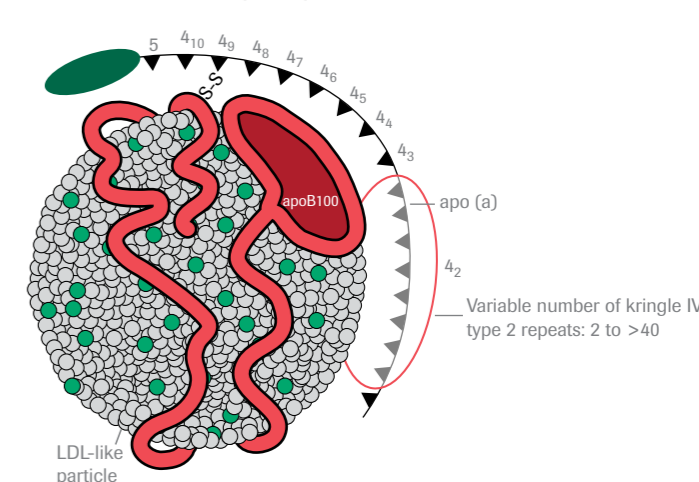
Structure of an Lp(a) particle

Figure 3: Each Lp(a) particle is composed of a cholesterol-rich, LDL-like core associated with a single molecule of apoB100, which is in turn joined to a single molecule of apo (a) via a disulfide bond. Genetic variation in the number of kringle IV type 2 repeats is present in the different isoforms of apo (a) and strongly influences phenotypic variation in the size of Lp(a) particles and their concentration in plasma.[13,15,16] Hepatic secretion of larger Lp(a) particles is slower than smaller Lp(a) particles and there is an inverse correlation between the size of the apo (a) isoform and the plasma concentration of Lp(a).[13,15] The apo (a) isoform with the smallest number of repeats is predominant in heterozygous individuals.[15]
Abbreviations: apo (a), apolipoprotein (a); apoB100, apolipoprotein B100; LDL, low-density lipoprotein; Lp(a), lipoprotein (a).

Diagnostic measurement of Lp(a)

Diagnostic methods have previously been standardized to measure Lp(a) levels in terms of mass per unit volume (i.e. mg/dL). However, mass assays fail to take into consideration the size heterogeneity of Lp(a) particles between individuals. This is important and can result in patient misclassification.[16] It is the molarity of Lp(a) particles rather than their combined mass that is correlated with CVD risk, and so measurements based on mass do not provide physicians with the correct values by which to assess an individual's risk of CVD.[16] For example, the evidence described in the previous section demonstrates that an individual producing a small number of very large Lp(a) particles is likely to have a lower risk of CVD than someone who produces a large number of small Lp(a) particles. However, using mass assays to determine Lp(a) levels in these two individuals would be likely to provide similar results. In contrast, diagnostic assays based on Lp(a) molarity would provide a low Lp(a) concentration for the individual with the large particles and a high Lp(a) concentration for the individual with the small particles, thus providing a more accurate assessment of each individual's risk of CVD (Figure 4).

Using immunoassays to measure Lp(a) levels in terms of mass rather than molarity can also lead to size-related bias **if the detection reagents are sensitive to the size heterogeneity of Lp(a) particles.[16,18]** Immunoassays rely on an assay calibrator of a fixed size, with the choice of which Lp(a) particle size to use being arbitrary. The size of calibrator particle chosen cannot be representative of all the Lp(a) particle sizes present within a specific population. Therefore, differences between the size of the calibrator particle and the size of an individual's own Lp(a) particles can lead to an underestimation or overestimation of Lp(a) concentration by assays that are sensitive to the size heterogeneity of Lp(a) particles (Figure 5).

"Based upon a large amount of scientific and clinical findings, the next decade is expected to be an exciting time for Lp(a) research."[23]

Measuring Lp(a) levels in terms of concentration rather than mass provides results that are independent of the size of individual particles
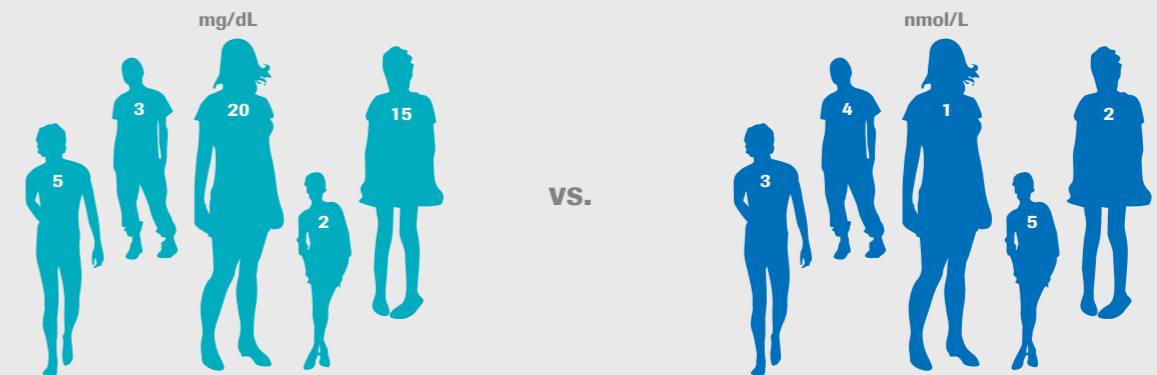

Figure 4: The risk of CVD correlates with the molarity of Lp(a) particles and not the combined mass of Lp(a) particles. Classifying patients based on the results from mass assays may lead to an incorrect assessment of CVD risk. For example, individuals with low numbers of large Lp(a) particles can display similar Lp(a) levels to individuals with high numbers of small Lp(a) particles when analyzed using mass assays, but have a lower risk of CVD.
Abbreviations: CVD, cardiovascular disease; Lp(a), lipoprotein (a).

Size-related bias in immunoassays sensitive to the size heterogeneity of Lp(a) particles

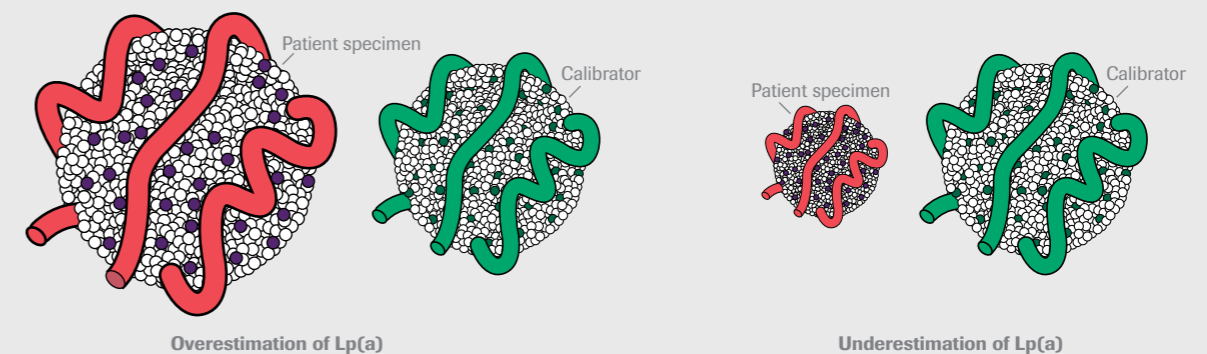**Overestimation of Lp(a)**   **Underestimation of Lp(a)**

Figure 5: Lp(a) concentrations will tend to be overestimated in samples containing particles larger than the assay calibrator and will tend to be underestimated in samples containing particles smaller than the assay calibrator.
Abbreviations: Lp(a), lipoprotein (a).

Screening for elevated Lp(a)

Screening of specific groups at intermediate or high risk of CVD/CHD has been recommended in clinical guidelines recently published by the European Atherosclerosis Society (EAS) Consensus Panel (Figure 6).[15] The guidelines suggest that screening only needs to be performed once, except in cases where Lp(a)-lowering therapy is initiated and repeat screening is necessary in order to monitor response.

The recommendations of the European guidelines have subsequently been endorsed by the International Atherosclerosis Society, with the caveat that much of the data used in the development of the guidelines was derived from European populations, or those with European ancestry, and therefore alternative medical decision limits may be more relevant for non-European populations.[19] Furthermore, Lp(a) was one of several biomarkers of CVD risk evaluated by an expert panel convened by the United States National Lipid Association, whose recommendations were similar to the European guidelines.[20] The expert panel recommended that Lp(a) measurement be considered in selected patients with, or at intermediate risk of, CHD or equivalent conditions. They also recommended that Lp(a) measurement be considered reasonable in patients with a family history of CHD or those experiencing recurrent CVD-related events despite receiving therapy. The expert panel also recommended that Lp(a) measurements should be considered for on-treatment patients with CHD or equivalent conditions, those with a family history of CHD, and those with a history of recurrent CVD-related events, but measurement was not recommended for on-treatment patients not in these groups and considered to be at low or intermediate risk of CHD.

The acceptance of elevated Lp(a) as an independent risk factor for CVD has been delayed in the past due to the prior absence of causal genetic evidence (described previously). Furthermore, the comparison of Lp(a) results obtained with different testing methods has been challenged by a lack of standardization between diagnostic methods and by the use of different calibrators in the various assays (described in more detail on opposite page).[15] These uncertainties have meant that Lp(a) screening and Lp(a)-lowering therapy has previously only been used by lipid specialists.

To aid Lp(a) screening and clinical decision making, the European guidelines also highlight the need for the introduction of diagnostic assays whose performance is insensitive to the size heterogeneity of the various apo (a) isoforms, thus being highly accurate, reliable, and reproducible. The guidelines also recommend that Lp(a) assays should be approved by and traceable to the reference materials of organizations such as the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).[15]

Finally, the guidelines also suggest it is critical that diagnostic assays for Lp(a) should be standardized to measure and express Lp(a) concentrations in terms of Lp(a) molarity (nmol/L) rather than Lp(a) mass (mg/dL), as done in the past, because it is the concentration and not the mass that is correlated with CVD risk. The importance of measuring the concentration of Lp(a) particles rather than mass of Lp(a) has been further highlighted by a recent meta-analysis showing that individuals with small apo (a) isoforms have a two-fold increase in the risk of CHD and ischemic stroke.[21] Furthermore, a prospective study revealed a significant association between small apo (a) isoforms and advanced atherosclerotic disease involving a component of plaque thrombosis.[22]

Lp(a) screening of groups at intermediate or high risk of CVD/CHD is recommended

01 Premature CVD*
02 Familial hypercholesterolemia
03 Family history of premature CVD and/or elevated Lp(a)
04 Recurrent CVD despite statin treatment
05 ≥3 % 10-year risk of fatal CVD according to the European guidelines
06 ≥10 % 10-year risk of fatal and/or non-fatal CHD according to the US guidelines

Figure 6: Indications for Lp(a) screening in intermediate- and high-risk groups according to the European Atherosclerosis Society Consensus Panel.[15]
Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; Lp(a), lipoprotein (a).
*Previous heart attack or stroke.

Tina-quant® Lipoprotein (a) Gen. 2

The Tina-quant® Lipoprotein (a) Gen. 2 assay from Roche is the first diagnostic method in the world capable of accurately and reliably measuring Lp(a) on a consolidated testing platform. The assay is also one of the first methods on a consolidated platform to follow the recommendations made in the recent clinical guidelines published by the EAS Consensus Panel, being insensitive to natural variations in Lp(a) particle size and standardized to measure Lp(a) molarity rather than Lp(a) mass.[15]

A pioneering assay based on established technology
In addition to its outstanding diagnostic performance, the Tina-quant® Lipoprotein (a) Gen. 2 assay also exhibits a range of other features common to **cobas®** assays, which aim to ensure reliability, ease of use, and efficient laboratory workflows (Table 2). The assay is compatible with all automated chemistry analyzers from Roche, including the **cobas c** analyzers and COBAS INTEGRA® analyzers.

Assay feature	Findings and interpretation
Compliant with clinical guidelines	• First method to be standardized and report Lp(a) results in nmol/L according to the recommendations of the EAS Consensus Panel on a fully consolidated platform • Fully traceable to the IFCC reference material • Excellent correlation with the reference ELISA method developed by Prof. Marcovina, Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, USA
Highly accurate	• The first method in the world capable of accurately and reliably measuring Lp(a) on a consolidated platform • Standardization to nmol/L provides the correct values for patient samples; highly accurate results due to apo (a) size-independent determination of Lp(a) levels • Excellent total and within-run precision around the medical decision point of 75 nmol/L
Efficient and cost-effective	• More than 115 clinical chemistry markers are available for the consolidated platform so that several tests can be performed from a single tube/sample, thus improving turnaround time and minimizing loss of sample • No need for time-consuming reconstitution steps that can introduce variability into results • High on-board stability with calibration only required at change of reagent lot

Table 2: Features and benefits of the Tina-quant® Lipoprotein (a) Gen. 2 assay.
Abbreviations: apo (a), apolipoprotein (a); EAS, European Atherosclerosis Society; ELISA, enzyme-linked immunosorbent assay; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; Lp(a), lipoprotein (a).

Summary

CVD is the biggest cause of morbidity and mortality in terms of global disease, and its impact is predicted to grow due to the ageing populations of many countries. Approximately 30 % of all cases of CVD death fail to correlate with conventional risk factors, such as serum cholesterol and blood pressure. The molarity of Lp(a), but not the mass of Lp(a), is an independent, causal risk factor for CVD and clinical guidelines recently published by the EAS Consensus Panel recommend Lp(a) screening of individuals at intermediate or high risk of CVD.

There is considerable natural variation in Lp(a) levels within a population, and the size of Lp(a) particles produced by different individuals also varies. These variables in Lp(a) phenotype are largely determined by polymorphisms in the *LPA* gene, which encodes the protein apo (a). The differing isoforms of apo (a) contain a variable number of KIV-2 repeats – higher numbers of KIV-2 repeats produce larger Lp(a) particles, which are produced in smaller quantities and are less atherogenic compared with small Lp(a) particles.

The size heterogeneity of Lp(a) particles has previously presented technical challenges to the diagnostic measurement of Lp(a) levels. Previous Lp(a) assays have been configured to provide results in terms of mass (mg/dL) rather than molarity (nmol/L). However, it is the molarity and not the mass of Lp(a) that correlates with CVD risk and, therefore, results from mass assays are not able to classify patients based on risk of CVD.

Individuals with a high number of small Lp(a) particles can display similar Lp(a) mass results to individuals with a low number of large Lp(a) particles and yet be at a higher risk of CVD and vice versa. Immunoassays sensitive to the size heterogeneity of Lp(a) particles tend to overestimate or underestimate results depending on the size of Lp(a) particle used as a calibrator for the specific assay. The recent EAS guidelines clearly state the importance of assays insensitive to Lp(a) particle size variation and standardized to report plasma Lp(a) values in terms of molarity and not mass.

The Tina-quant® Lipoprotein (a) Gen. 2 assay is the first method in the world capable of accurately and reliably measuring Lp(a) on a fully consolidated testing platform. The assay is also one of the first to follow the recommendations of the EAS Consensus Panel by being insensitive to natural variations in apo (a) size and standardized according to units of molarity (nmol/L). In addition to being fully compliant with the recent clinical guidelines, the Tina-quant® Lipoprotein (a) Gen. 2 assay also displays other features and benefits common to **cobas®** assays, such as excellent and reliable diagnostic performance, and high stability and speed for efficient laboratory workflows.
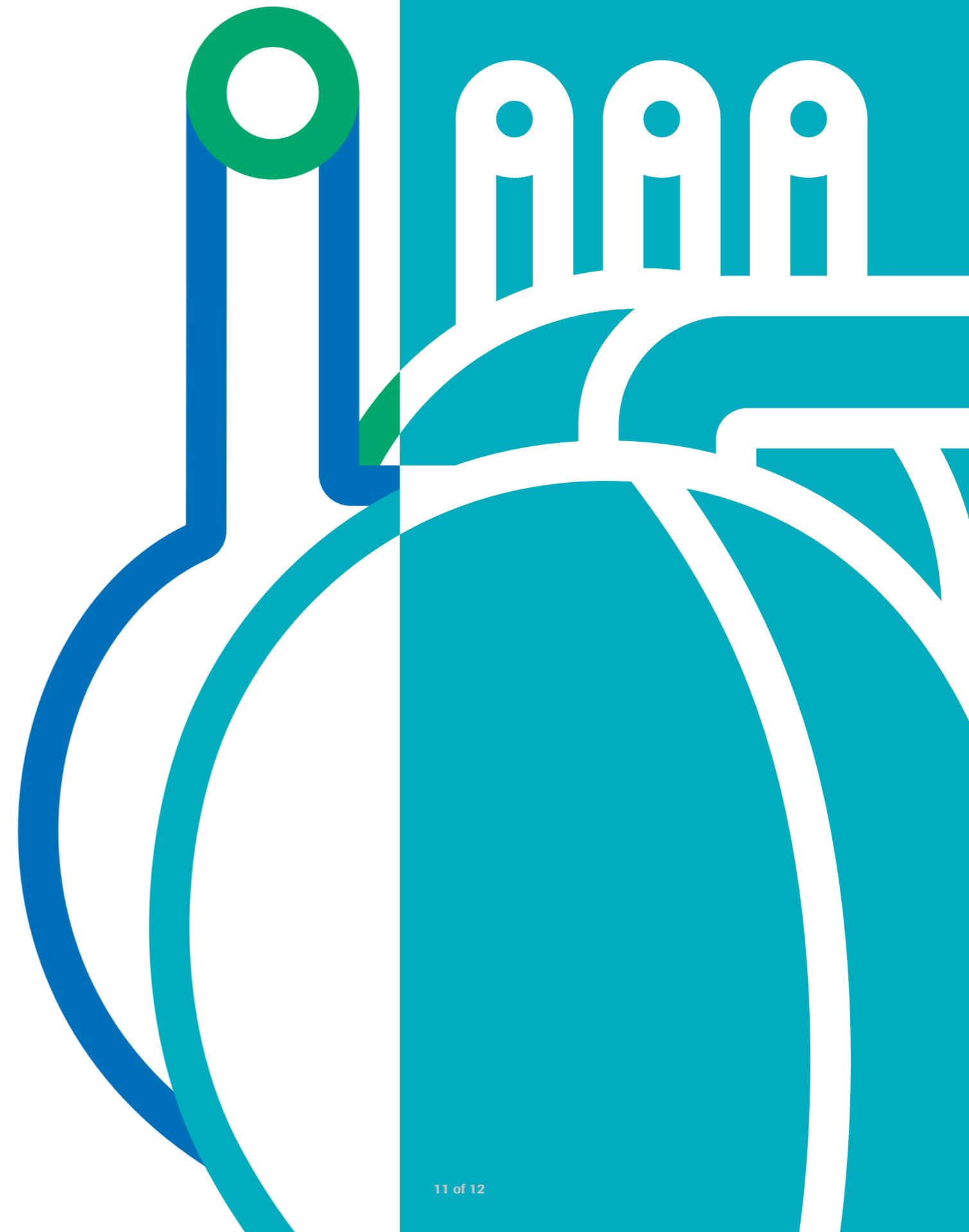
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