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Body composition assessment for the definition of cardiometabolic risk.

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Names of the Authors:

MC Amato[1], V Guarnotta[1] and C Giordano[1].

Department: [1]Section of Endocrinology, Diabetology and Metabolism; Biomedical Department of Internal and Specialist Medicine (Dibimis); University of Palermo; Palermo; Italy.

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Corresponding Author:

Carla Giordano, MD

Endocrinology

Piazza delle Cliniche 2

90127 Palermo, Italy

Email carla.giordano@unipa.it

Tel. +39 091 6552110

Fax +39 091 6552123

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Abstract

Obesity is associated with a major prevalence of cardiovascular risk factors and high risk of cardiovascular events and contributes to the increase in cardiovascular morbidity and mortality worldwide.

Beyond the fat mass per se, the pattern of fat distribution has a profound influence on cardiometabolic risk. The increase in abdominal adipose tissue confers an independent risk, while the amount of gluteofemoral body fat is thought to be protective. Changes in the capacity of different depots to store and release fatty acids and to produce adipocytokines are important determinants of fat distribution and its metabolic consequences.

Because of the complexity of the assessment of body fat with imaging techniques, great attention has been paid to other measures of adiposity, such as waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR), which provide information on body fat distribution, although BMI is the established clinical measure to estimate the cardiovascular risk disease associated with excessive body weight. Abdominal obesity is a main predictive factor of the Metabolic Syndrome, so it is certain that it represents a better marker of cardiovascular risk than BMI. Visceral adiposity index (VAI) has recently proven to be a marker of visceral adipose distribution and function, associated with insulin sensitivity in patients at metabolic risk; however, the evidence needs to be further confirmed.

In summary, BMI, WC, WHR, WHtR and VAI are all useful tools for assessing adiposity/obesity in clinical practice, and should be evaluated along with other cardiometabolic risk factors to define cardiovascular risk stratification.

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INTRODUCTION

Obesity is considered the most important predisposing factor for type 2 diabetes mellitus and cardiovascular disease (1). In particular, the increase in visceral adipose tissue (VAT) is linked to insulin resistance, dyslipidemia, low grade inflammation, diabetes, hypertension and cardiovascular disease (2-14). However, subcutaneous adipose tissue (SAT) can also contribute to insulin resistance and metabolic syndrome (MetS) (7,15). Therefore several studies which may evaluate the quantitative body distribution of VAT and SAT and the quantitative ratio between VAT and SAT are needed. Body composition and fat mass assessment involve technical-methodological issues that should be considered because adipose tissue partitioning plays an important role in metabolic and cardiovascular risk assessment.

In the assessment of body fat the first big mistake that is commonly made is failure to distinguish fat mass and adipose tissue (16). Indeed, excluding a priori poor specific and sensitive impedentiometry, the most reliable method of fat mass assessment, dual-energy x-ray absorptiometry (DEXA), which quantifies total body fat, is not able to differentiate between subcutaneous adipose tissue, visceral adipose tissue and the ectopic fat of other tissues such as liver, pancreas and muscle.

Regarding cardiometabolic risk it is now widely recognized that a key role is played by both visceral adipose tissue (omental and perimesenteric) and ectopic fat (17).

To date, several techniques have been developed to assess visceral fat, though almost all only give an indirect measurement of body fat (impedentiometric techniques). Only Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) can provide direct cross-sectional or volumetric measurements of visceral fat. By these methods it is possible to quantify visceral adipose tissue, which is distributed in the chest, abdomen and pelvis (VAT), and subcutaneous tissue, between the skin and the bands that cover muscles (SAT).

Advanced techniques like CT and MRI are not easily applicable, and in any case the quantification of visceral adipose tissue does not always give a correct idea of impaired adipose tissue function, strong lipolysis and impaired adipocytokine production, which are the basis of lean tissue lipotoxicity and cardiometabolic complications in patients with abdominal obesity.

There are functional differences between subcutaneous and visceral fat. Indeed VAT (defined as an endocrine organ, because of its ability to produce cytokines and to be the place of strong lipolytic activity in selected conditions), can play an important pathophysiological role in the onset of cardiovascular disease and diabetes. Moreover, the amount of subcutaneous adipose tissue (SAT)

can also contribute to the development of obesity-related insulin resistance and metabolic syndrome (MetS).

RADIODIAGNOSTIC METHODS FOR VISCERAL AND SUBCUTANEOUS ADIPOSE TISSUE QUANTIFICATION.

In the last few years there has been a major increase in the use of both CT and MRI, which are direct techniques based on the unique adipose tissue properties and can differentiate SAT and VAT through multidimensional images. MRI does not use ionizing radiations, allowing its repeatability in prospective studies and its use in infantile adolescent age groups, making it an important tool for the quantification of fat (18).

However, to date, difficult and in some cases expensive procedures are needed to extract a moderate volume of adipose tissue and a fraction of lean tissue fat (ectopic fat) from MRI data (there are free packages such as ImageJ and Osirix and commercial programs such as SliceOmatic, Analyze and Matlab) are commonly used for segmentation (19). Moreover in some cases, the post-processing phase of the analysis is limited to expert consultants. This procedure provides for image transfer to a workstation offline, followed by the use of dedicated software for data segmentation and for obtaining a 3-D abdominal adipose volume. However, in cases of manual segmentation, on average an operator needs about 45-60 min to achieve this type of analysis (19). However, recently an algorithm has been developed permitting the reliable and completely automatic creation of adipose tissue distribution profiles, reducing the total examination and analysis time to less than half an hour (20).

Because of these limits, even today most imaging studies designed to investigate the role of fat distribution in cardiometabolic risk are based on a single MRI or CT image of the abdomen, generally at the L4-L5 intervertebral space. However, this technique is not considered as a gold standard in the assessment of VAT and SAT by the scientific community. Indeed, there are studies using different protocols with multiple images, suggesting that the L4-L5 image, compared to L2-L3 upper abdomen images, is a significantly worse predictor than both total VAT volume and cardiovascular risk and MetS (21-23). In addition, individual variation in the spatial distribution of VAT storage in both the upper and lower abdomen has not been significantly considered. In 2005 (24) some authors already showed the variations in adipose tissue “topography”, but most epidemiological studies still did not consider the pattern of VAT spatial distribution as an independent predictor of health risk.

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ANTHROPOMETRIC METHODS FOR EVALUATION OF TOTAL FAT MASS.

PLICOMETRY

Plicometry has been widely used for body mass fat determination both in clinical practice and in several epidemiological studies. It is based on the measurement of subcutaneous adipose tissue thickness in selected body areas. Plicometry provides an indirect measurement of total fat mass from evaluation of the thickness of skin folds using regression formulas that include three to seven measurements. The Durnin-Womersley formula is the most widely used (25). It involves the use of four subcutaneous folds (biceps, subscapular, suprailiac e triceps). However, the use of skin fold thickness originates from a main assumption which is the presence of a constant relationship between superficial and deep subcutaneous fat. In actual fact there are sex and age related differences between superficial and deep subcutaneous adipose tissue (26), as well as specific sex and age differences in the relationship between plicometry and body fat. Moreover, this method has major methodological limits related to individual subcutaneous tissue thickness in different body areas, poor intra- and interindividual reproducibility of the method, and increasing difficulty in the use of this method with increasing body weight leading to an increase in fold size.

This method has not been further considered in the main guidelines for the evaluation of overweight patient, due to its limitations. To date there are no convincing scientific data to show any correlation between plicometry determination of body fat and cardiometabolic risk.

BODY MASS INDEX (BMI)

About 150 years ago the Belgian Adolphe Quételet realized that the height/weight ratio was a more faithful indicator of the weight state than just weight. Then, for statistical reasons, the height was squared to determine the body mass index (BMI). The BMI is universally considered a satisfactory predictor of the percentage of body fat, and it is known that it shows a curvilinear and not a linear association with the body fat percentage in both men and women (27).

However, many factors affect the relationship between BMI and body fat percentage, such as gender, race, high muscle mass (for example, subjects who practice body building), changes in hydration status (in particular subjects having retention of extracellular fluids may lead to significant mistakes in interpretation about BMI). In older people, significant changes also occur on both BMI numerator and denominator.

For many years there have been some doubts about the real efficacy of BMI in predicting cardiovascular risk. In 2005 Katherine Flegal published in JAMA one of the first studies (28) to analyze in detail, on a large series, the correlation between BMI and all causes of mortality

(including the quantitatively most relevant significant component, the cardiovascular one). This study, based on National Health and Nutrition Examination Survey (NHANES) data, showed that BMI is not a good predictor of mortality risk: up to 69 years of age, only a very high BMI (> 35 Kg/m^2) is associated with a significant increase in death risk (approximately doubled). Beyond this age, only underweight is associated with an increased risk, while obesity, though it may be severe, does not significantly affect it (Fig. 1).

A subsequent meta-analysis published in *Lancet* in 2006 (29), evaluating the data of over 250,000 subjects (40 epidemiological studies for a mean follow-up of 3.8 years) confirmed Flegal's data. According to the results of this study, all-cause mortality is low among those patients classified as overweight according to BMI; it is significantly higher than those with normal weight only among subjects that are underweight according to the BMI. Cardiovascular mortality, evaluated separately in the meta-analysis, has a trend which is at least partly different: there is no significant difference for cardiovascular mortality among subjects with normal weight and ones that are overweight or obese (according in relation to the BMI), while both severely obese subjects and (again) underweight ones show a significant increase for cardiovascular mortality.

These data led in 2006 to an editorial (30) published in Lancet signed by the Italian researcher Maria Grazia Franzosi, provocatively titled, "Should we continue to use BMI as a cardiovascular risk factor?", which states that "the BMI may now be withdrawn permanently as a clinical or epidemiological tool for evaluation of cardiovascular risk in both primary and secondary prevention."

This is a condition which after all does not appear desecrating to those who are concerned with prevention of cardiovascular disease: the BMI does not appear in any of the versions of the algorithm of Framingham, one of the strongest tools for defining coronary and cardiovascular risk. Indeed, in the Framingham study it was assumed that there could be "metabolically healthy obese subjects."

An important contribution to evaluation of the influence of obesity on cardiovascular risk is the Interheart study (31), a large case-control study performed in 52 countries of the world on about 15,000 patients with myocardial infarction and a similar number of control subjects, published by Salim Yusuf in Lancet in 2004.

This study shows inconvertible evidence that abdominal obesity makes a higher contribution than BMI to the probability of these events. The following year, focusing attention on the relation between obesity and heart attack risk, Yusuf published a study (32) defining the results more accurately, showing that the association between abdominal adiposity and coronary heart disease

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risk is highly significant in all geographical areas in which Interheart Study dates were collected. With the increase in abdominal adiposity, in particular, the heart attack risk increases in a linear way: the relative risk increases from 1 to over 2.5 moving from the 1st to the 5th quintile of the distribution. The increase in risk does not change even after adjustment for the BMI, while the small increase in the risk of heart attack that is associated with BMI increase disappears after adjustment for abdominal adiposity, showing that this – not the BMI – is the factor responsible for this observed association.

METHODS FOR EVALUATION OF REGIONAL DISTRIBUTION OF ADIPOSE TISSUE

WAIST CIRCUMFERENCE

Waist circumference measurement has been considered the most valid index of regional distribution of adipose tissue. Measurement of body circumferences, although it is a valid method, requires an accurate performance method in order to provide reproducible information. Several studies have shown that waist circumference is strongly related to visceral fat and abdominal adiposity, more than the BMI and waist/hip ratio.

In the literature there are many methods for measuring the waist circumference (33) using different reference points such as:

- the space immediately below the last rib;
- the midpoint between the last rib and the iliac crest;
- the point immediately above the iliac crest;
- the determination of the minimal abdominal circumference between the last rib and the iliac crest.

The technical error of the measurement of waist circumference, when performed properly, is about 2-4% with similar results at other reference points (33).

The waist circumference cut-offs suggested for cardiovascular risk stratification are based on measurements performed above the ridge (34). It should be clear that these cut-offs, per se, cannot also be used for determinations of waist circumference at other reference points, because using the same cut-off would lead to a significant underestimation of cardiovascular risk in overweight and obese patients. Finally, it should be pointed out that for waist circumference many different cut-offs have been proposed, based on race. Regarding these differences on the proper procedure for the determination of waist circumference, in 2008 an authoritative systematic review of 120 studies (35) was published. This review showed that the different protocols of determination of waist circumference do not substantially influence the association between waist circumference, cardiovascular mortality, ischemic heart disease and diabetes. The only limitation of waist

circumference is inaccurate distinction between visceral and subcutaneous adipose tissue in the abdominal region.

WAIST/HIP RATIO (WHR)

The waist/hip ratio (WHR) was a method widely used in the past for the evaluation of adipose tissue distribution in epidemiological studies. Its predictive power in visceral fat is less than that of waist circumference.

This assumption led people to prefer only the measurement of waist circumference in the guidelines for the study of obesity and the quantification of visceral fat, both for clinical and research purposes (34).

Recent epidemiological and clinical observations appear to assign particular importance to the determination of hip circumference. This arises from the results published in 2005 by the Interheart Study. This study demonstrated that the waist/hip ratio is a stronger predictor of myocardial infarction than BMI and waist circumference (32). In particular, a protective effect against myocardial infarction mortality, independently of hip circumference, was observed.

It is likely that the hip circumference, as an indicator of district peripheral adipose tissue and possibly also as a surrogate, although indirect, of muscle mass, may provide additional information for cardiovascular risk stratification of obese subjects.

WAIST-TO-HEIGHT RATIO

The waist-to-height ratio (WHtR) is defined as the person's waist circumference, divided by the person's height. In the 1990s the use of the waist-to-height ratio was first proposed for detecting abdominal obesity and the associated health risk (36-38). Interest in the effectiveness of this measurement is still rising for both adults and children in many different ethnic groups (39-44). Although the mechanisms that explain the health risk predicted by the WHtR are not firmly established, it is often suggested that the risk is explained by its association with elevations in abdominal obesity (45). Several authors have demonstrated that WHtR is the most practical and convenient index of regional adipose tissue distribution and has been widely used to investigate the relations between regional adipose tissue distribution and metabolic profile (43, 46, 47). However, the WHtR value does not account for the large variations in the level of abdominal visceral adipose tissues (48). The WHtR has been considered a strong screening tool for cardiometabolic risk in adults. A meta-analysis looking at several risk factors, but only including 10 papers published up to the end of 2006 (42), concluded that statistical evidence supported the superiority of measurements

of centralized adiposity, especially WHtR, over BMI, for detecting cardiovascular risk factors in men and women. A recent systematic review showed that WHtR is a better predictor than WC for diabetes, dyslipidemia, hypertension and cardiovascular risk factors in both sexes and in different ethnic groups (50).

A NEW METHOD FOR EVALUATION OF ADIPOSE DISTRIBUTION AND FUNCTION (VISCERAL ADIPOSITY INDEX)

The Visceral Adiposity Index (VAI) is a mathematical model, gender-specific, based on simple parameters such as BMI, CV, Triglycerides and HDL Cholesterol, indicative of fat distribution and function (51). It is an empirical mathematical model that does not originate from theoretical assumptions but from observation in a healthy normal/overweight population of a linear relationship between BMI and CV, from which a linear equation has been extrapolated (Fig. 2).

A Model of Adipose Distribution was created based on this linear equation (which shows a strong correlation with visceral fat mass determined by MRI) and then subsequently was corrected for triglycerides and HDL cholesterol levels, determining the VAI. The VAI has shown a strong positive correlation with peripheral glucose utilization during Euglycemic Hyperinsulinemic Clamp and seems to be independently associated with cardio- and cerebrovascular events (51) (Fig 3). Then VAI was studied in a selected patient population, proving to be a good indicator of impaired visceral function (though there are some contrasting data in patients with NAFLD), in particular in all borderline conditions in which a frank metabolic syndrome has not yet been established (52-62).

ROLE OF LEAN BODY MASS EVALUATION

As already mentioned in the previous paragraphs, a linear relationship does not always exist between BMI and clinical cardiometabolic outcomes; indeed, obesity is not necessarily an expression of cardiometabolic risk, given that there exists “Metabolically Healthy Obesity” (MHO) in which the particular gynoid distribution of fat does not confer a cardiometabolic risk (63, 64). Conversely, there are subjects that are “Metabolically Obese but Normal Weight” (MONW) (65), who despite having a normal BMI, have insulin-resistance, higher visceral adiposity and a high cardiometabolic risk (65, 66). The underlying mechanisms by which the MHO subjects present lower cardiovascular complications are unknown. It has been hypothesized that the age-related decrease in lean body mass (sarcopenia) associated with an increase in visceral fat mass may increase the cardiometabolic risk, even in the absence of an increase in BMI (67, 68).

Furthermore, age-linked sarcopenia is characterized by a decrease in the total number of skeletal muscle fibres, and an increase in Intramyocellular lipid content (69),with a consequent reduction in

insulin sensitivity. In a recent study (70), the computed tomography assessment of lean body mass, in midthigh (cross-sectional area), showed a lower risk of low muscle mass MHO compared to "Metabolically Abnormal Obese" (MAO) subjects. In the future lean body mass evaluation could explain the different metabolic consequences related to body size phenotype.

CONCLUSIONS

Anthropometric measurements show good reliability in epidemiological studies and clinical practice and can be considered a valid surrogate for the essential methods for body composition imaging studies (CT and MRI). However, it should be noted that they have a large degree of collinearity. For example, in the Quebec Family Study and Heritage Family Study, the relationship between BMI, fat mass, waist circumference and abdominal visceral fat, evaluated by CT, showed strong collinearity. Therefore waist circumference is not a better predictor of abdominal visceral fat than BMI or fat mass (61). In particular, anthropometric indicators overlap and the classical distinction between regional adiposity indicators is widely discretionary. However, it should be noted that in clinical practice it is difficult to classify a patient using a single indicator, and it is often necessary to associate several indicators. Also, in clinical practice using the more sophisticated VAI should not lead one to exclude BMI and CV from weight evaluation, in the phenotypic definition of patients. In this respect, the National Institute of Health guidelines recommend the measurement of waist circumference in all subjects with BMI between 30 and 35 kg/m2, as well as in those with BMI between 25 and 30 kg/m2 in order better to define the cardiovascular risk profile, but not in those with BMI > 35 Kg/m2.

This view was shared by George Bray, who a few years ago, in a brief editorial on the use of anthropometric indicators in the definition of obesity and cardiometabolic risk linked to it, entitled his article: "Don't throw the baby out with the bath water" (71). The measurement of waist circumference or VAI could be very useful in cardiovascular risk stratification of those subjects with BMI between 20 and 30 kg/m2, who are not old and do not have a frank metabolic syndrome, among whom there could be a subgroup of "metabolically obese normal-weight subjects" with high cardiometabolic risk.

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Figure Legends

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Figure 1. Relative Risks of mortality by BMI category, survey and age (combined NHANES I, II and III). Modified by Flegal KM et al. JAMA 2005; 293: 1861-7

Figure 2. Linear relationship observed between BMI and CV in 315 Primary Care Patients, with BMI between 20 and 30 Kg/m2 and aged 43.46 ± 14.30 years (range 19-83), selected from the absence of diabetes mellitus or FPG ≥ 5.6 mmol/l, high blood pressure, dyslipidemia, MetS and cardiovascular disease (CVD). A Model of Adipose Distribution (MOAD) was created based on this gender specific linear equation. Taken from Amato MC et al. Diabetes Care 2010; 33:920-2

Figure 3. Comparison of ROC Curves (VAI, BMI, WC and Tg/HDL ratio) for Coronary Heart Disease (CHD) and/or Myocardial Infarction (MI) (A) and Transient ischemic attack (TIA) and/or Ischemic Stroke (IS) (B). Taken from Amato MC et al. Diabetes Care 2010; 33:920-2

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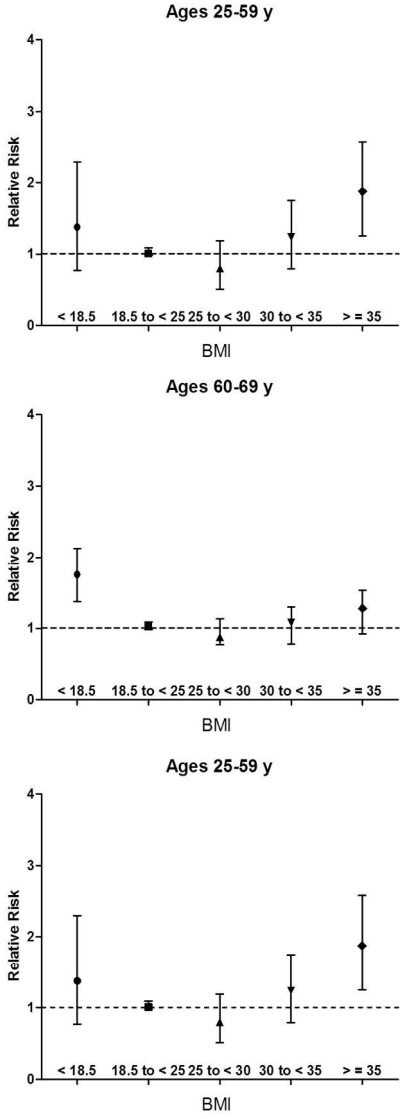

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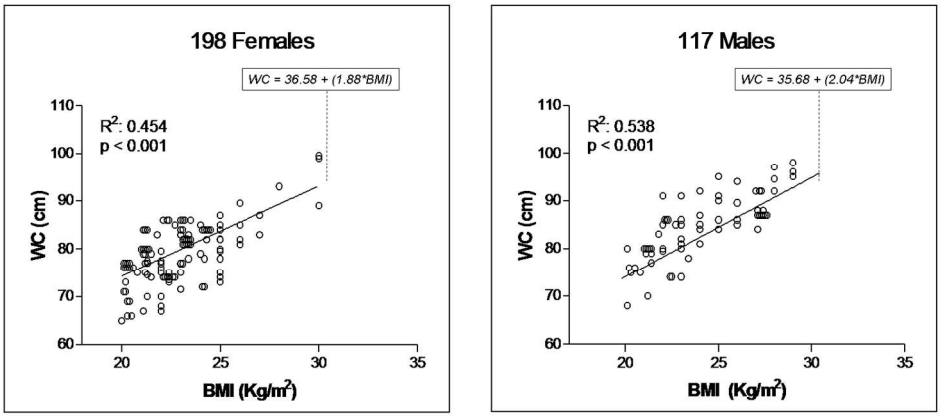

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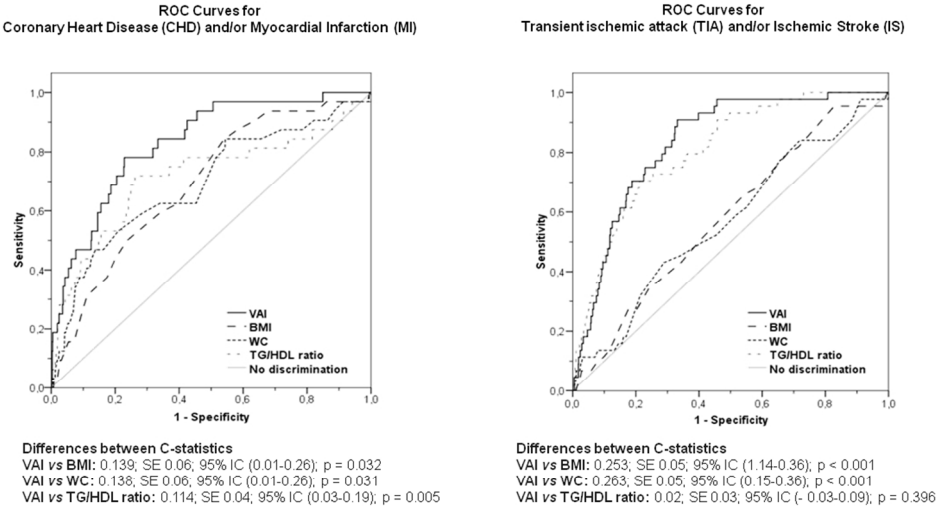

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