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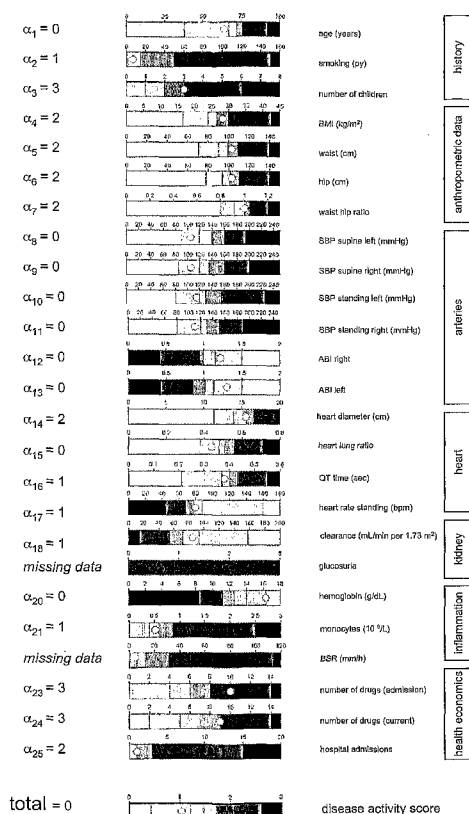
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(54) Title: INDIVIDUAL ASSESSMENT AND CLASSIFICATION OF COMPLEX DISEASES BY A DATA-BASED CLINICAL DISEASE PROFILE



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(57) Abstract: An tool and method is disclosed to assess disease activity and to classify complex diseases using basic clinical data. The tools and methods allow identifying and consulting affected individuals based on comprehensive bedside examinations and thus provide a basis for the personalized management of complex diseases.



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INDIVIDUAL ASSESSMENT AND CLASSIFICATION OF COMPLEX DISEASES BY A DATA-BASED CLINICAL DISEASE PROFILE

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. provisional application 60/744,460, filed April 7, 2006, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

The invention relates to assessment tools, including a systems and/or computer programs and methods for identifying, calculating and indicating a score associated with a disease for an individual or a population based on clinical data such as selected sets of measurable indicator variables and/or parameters obtained by physicians. The tools and methods may be employed to assess the state of one or more diseases in an individual or in a population, in the present and/or in the future,

BACKGROUND OF THE INVENTION

Chronic complex diseases are wide spread and their occurrence has been surging worldwide with an aging and an increasingly sedentary population. One of these complex diseases, namely arteriosclerosis, is a common cause of severe diseases such coronary heart disease (1). To prevent deaths and disabilities, it is important to identify individuals at risk, e .g, in the case of arteriosclerosis, at risk to develop cardiovascular events (2, 3). Several risk factor scoring systems have been developed for this purpose (4, 5). These scoring systems have several limitations (6). First, they contain a temporal and spatial bias: the baseline data from which the score formulas are derived were usually collected in the past, sometimes decades ago, and the individuals participating in the study cohort live in certain regions of the world. Thus, general lifestyle changes within a population which can occur over a short period of time and may have a strong impact on the risk factors for arteriosclerosis (7), are not being considered. Many diseases, including arteriosclerosis, are also affected by the

genetic background which varies in populations from different continents (8). Second, most risk score calculations for diseases such as arteriosclerosis end at an age of 65 to 70 years because, e.g., cardiovascular events are highly prevalent in this age group. For this age group, the probability to develop cardiovascular events within the next 10 years is 50%, but drugs used to prevent such events have to be taken infinitely and their side effects are particularly common in the elderly (9, 10). Evidence-based guidelines to treat common disorders such as cardiovascular disease, osteoporosis or diabetes with a multitude of drugs have recently been discussed in the light of the increasing number of patients with more than one of these conditions (11). In order to avoid unnecessary or even harmful multidrug regimens, it is of great importance to allocate treatment precisely to the patients who need it and not to the general population above 70. Third, patients with cardiovascular risk factors (e.g. arterial hypertension, hyperlipidemia or diabetes), e.g., for arteriosclerosis are treated for them: they take antihypertensive, cholesterol or glucose lowering drugs, which all potentially affect the variables entering the prediction algorithm and therefore may influence the estimation of the current risk. Since some of these regimens (e.g. statins or angiotensin converting enzyme inhibitors (12, 13)) have beneficial effects on important pathogenic steps of symptomatic arteriosclerosis and may even revert arteriosclerotic lesions, the question arises whether and particularly when these treatments could be discontinued.

The publications and other materials, including patents, used herein to illustrate the invention and, in particular, to provide additional details respecting the practice are incorporated herein by reference in their entirety. For convenience, the publications are referenced in this text by numerals corresponding to those in the appended bibliography.

Thus, there is a need for accurate assessment of current disease activity for the individual patient to replace or supplement risk prediction tools which are based on probabilities rather than facts. Particularly in view of the fact that complex disease, such as cardiovascular disease, are emerging in less developed countries (14) where accessibility to, e.g., coronary catheterization or

other modern vascular imaging facilities is limited, this assessment should preferably be based on data obtained, at least in part, from the patient in a concise, short and affordable examination.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. The Data-based clinical disease profile and the Disease activity score.

The statistical comparison of more than 70 clinical parameters between patients with proven symptomatic arteriosclerosis and patients without cardiovascular events in the past revealed 25 numerical variables that were different between the two groups. The range of the complete dataset for the symptomatic patients is shown, visually weighed and color coded: lighter gray shading (or green color) represents the quartile closest to the asymptomatic patients, light gray shading (or yellow color) the second, dark gray shading (or orange color) the third quartile and darker gray shading (or red color) the quartile most distant to the asymptomatic patients. This quartile distribution is the basis for the assignment of the individual data-based clinical disease profile and for the calculation of the disease activity score for the individual patient according, in this case, to the following formula: disease activity score = $\sum [\alpha_1 + \alpha_2 + \alpha_3 + \dots + \alpha_{25}] / (25 - [\text{missing variables}])$.

Figure 2. Reproducibility of the clinical assessment and of the disease activity score.

A. The numerical variables which were collected by different investigators during two different time periods were compared and show an ideal linear correlation. B. The quartile distribution of the disease activity score is nearly identical for the two study periods confirming the consistency and reliability of the method to establish a data-based clinical disease profile.

Figure 3. Alignment of the data-based clinical disease profiles into an array format.

The clinical data arrays are grouped in four quadrants according to the absence or presence of cardiovascular events in the past (left and right panel,

respectively) and according to the gender (upper and lower panel, respectively). M = patients with metabolic syndrome. BMI = body mass index. SBP = systolic blood pressure. ABI = ankle brachial index. BSR = blood sedimentation rate.

Figure 4. The disease activity score correlates with prognosis and severity of arteriosclerosis.

A. The 10 year risk to develop cardiovascular events was calculated using the Framingham algorithm (18) and could be shown to be correlated with the disease activity score. B. The disease activity score (median and interquartile range are represented as columns with error bars; maximum and minimum values as circles) are shown for three patients groups: the first including patients without cardiovascular events (n=110), the second including patients with a cardiovascular event at a single site (n=72) and the third including patients with cardiovascular events affecting more than one organ (n=28).

Figure 5. The disease activity score correlates with age.

Figures 6-1 and 6-2. The phenotypical correlation plot of asymptomatic and symptomatic arteriosclerosis.

The 61 clinical datasets for which more than 75% of the data were available were correlated and the linear regression coefficient R calculated. 6-1. Patients without cardiovascular events. 6-2. Patients with symptomatic arteriosclerosis. R-values are shown. If gray scale coded, the figure legend assigns R-values to certain gray scales.

Figure 7. Symptomatic arteriosclerosis is linked with osteoporosis.

In patients with symptomatic arteriosclerosis but not in patients without cardiovascular events, the body size decreases with age (A) and is negatively correlated with systolic blood pressure (B).

Figure 8. Receiver operating characteristic (ROC) curve for the disease activity score (A) and the number of risk factors (B). Area under the curve is shown within the graph.

Figure 9. ROC curve for the Framingham score.

Figure 10. Comparison of the disease activity score over time for a group of individuals without the disease (left) and a group of individuals with the disease (right).

SUMMARY OF THE INVENTION

The present invention is directed towards an assessment tool for a disease comprising:

- (a) a first set of data recorder said first set of data comprising data of measurable indicator parameters and/or variables collected from a first group of individuals having said disease;
- (b) a second set of data recorder, said second set of data comprising data of said measurable indicator parameters and/or variables in (a), but collected from a second group of individuals without said disease;
- (c) a comparing unit/function which compares said first set of data with said second set of data; and
- (d) a selecting unit/function which selects a profiling set from said measurable indicator parameters and/or variables, wherein a coding, such as color, shade or value coding, attributed to each of said measurable parameters and/or variables of said profiling set reflects a disease activity measured by said measurable parameters and/or variables.

Said coding may contribute to a data-based clinical disease profile and/or an activity score of said disease. Said selecting unit/function or a further selecting unit/function may select a correlation set, wherein said coding may correlate at least two different of said measurable indicator parameters and/or variables of the correlation set.

An attribution unit/function may calculate the percentile distribution of each measurable indicator parameter and/or variable of said profiling set of said first and/or second group, wherein said coding reflects this percentile distribution.

The coding may be based on percentile ranges such as, but not limited to, tertile, quartile, quintile, sextile, septile, octile or nonile ranges of said percentile distribution.

The selecting unit/function may select said profiling set from parameters and/or variables having a P-value of less than 0.5, preferably less than 0.4, more preferably less than 0.3, even more preferably less than 0.2, even more preferably less than 0.1, 0.05, 0.025, 0.01, 0.005, 0.0025 or 0.001 in a statistical test comparing two groups such as, but not limited to, the Mann Whitney U test, the student t-test, or the χ^2 test when compared in (c).

The invention is also directed towards a method for determining measurable parameters and/or variables correlated to a condition and/or disease comprising:

- (a) compiling measurable indicator parameters and/or variables;
- (b) collecting and/or storing a first set of data for each of said measurable parameters and/or variables collected from a first group of individuals having said disease;

(c) collecting and/or storing a second set of data for each of said measurable parameters and/or variables collected from a second group of individuals without said disease,

wherein said individuals of (b) and (c) are selected from the same population and, optionally, the first and second set of data were collected approximately within the last 5 years, 4 years, 3 years, 2 years, 1 year, 9 months, 6 months, 3 months, 2 months, 1 months, 2 weeks, 1 week, 5 days, 2 days or 24 hours;

(d) selecting a profiling set from said measurable parameters and/or variables;
and

(e) optionally, selecting a correlating set from said measurable parameters and/or variables.

The method may further comprise assigning said measurable indicator parameters and/or variables a coding, such as a color, shade or value coding, wherein said coding may reflect a disease activity measured by the measurable parameters and/or variables to the disease and/or condition. The method may also comprise calculating a percentile distribution of each measurable indicator parameter and/or variable of said profiling set and/or correlation set, wherein said coding may reflect this percentile distribution for said first and/or second group. The coding may be based on certain percentile ranges such as, but not limited to, tertile, quartile, quintile sextile, septile, octile or nonile ranges of said percentile distribution.

The invention is also directed towards determining an activity score for at least one condition and/or disease in an individual and/or in a population comprising
measuring the measurable indicator parameters and/or variables of the profiling set in said individual; and
determining the activity score of said disease in said individual or a population from an average of the sum of said coding.

The invention is also directed to uses of any embodiment of the invention.

DETAILED DESCRIPTION OF VARIOUS AND PREFERRED EMBODIMENTS OF THE INVENTION

The article “a” in the context of the present invention means one or more unless otherwise specified.

A **disease** according to the present invention is any condition that, when manifested in an individual including non-human animals and humans such as patients, can be associated with a set of parameters and/or variables that are measurable and are indicative of said condition or disease (hereinafter “**measurable indicator parameters and/or variables**”). Variables are numerical, while parameters comprise non-numerical clinical data. (see, "Sapira's Art & Science of bedside diagnosis". Second Edition, Jane M. Orient. Lippincott Williams & Wilkins. 2000). In a preferred embodiment the disease is a common, complex condition or diseases for which a clear clinical definition exists, such as, but not limited to, a definition provided by the World Health Organization (WHO). An individual is said to **have a disease** if the individual could be diagnosed with the disease according to such a clear clinical definition. An individual I said to be **without a disease** if either his/her history or an examination does not indicate that the individual has the disease.

A **disease activity** according to the present invention is a quantifiable measurement of disease ranging from no disease activity (=0) to maximal disease activity (=m, wherein m is the maximum activity value assigned to a disease).

An **assessment tool** according to the present invention is any system, e.g., a computer system, or an array of functions, such as a computer program, which is associated with a physical structure such as, but not limited to, a server, a CD, DVD or similar. The tool may be made available to clients, such as, but not limited to, hospitals, teleconsultants or the end user, via the internet. In a

preferred embodiment, the assessment tool and methods of the invention allow for consideration of environmental changes that occur or have occurred, e.g., in a population in the assessment of a disease. This means, the assessment may be performed based on data that was collected proximate to its use and/or within the relevant population. Thus, in a preferred embodiment of the invention, the data for a **standard reference**, is collected within the time frame of less than two years, less than one year, less than six month, less than 3 month, or less than one month or even less than a fortnight from its use, e.g., as part of the assessment tool of the present invention. Accordingly, the standard reference might stem from a contemporary cohort of, e.g., individuals with or without the disease or set of diseases in question.

A **recorder** is, in the context of the present invention any collecting and/or storing unit or function. A recorder may collect and/or stores a **sets of data (a set of data recorder)**, such as **measurable indicator parameters and/or variables**, pertaining to, e.g., a particular disease or a variety of diseases. In a preferred embodiment, the recorder stores measurable indicator parameters and/or variables that have been collected from individuals. As the person skilled in the art will appreciate, a wide variety of options exists how data such as such a set of data can be collected and stored all of which form part of the present invention. In one embodiment, the recorder is a central processing unit of a PC or a server. The recorder can also take the form of a function that is associated with, including embedded in, a physical structure such as, but not limited to, a CD, DVD or other, e.g., storing device. The term **unit/function**, e.g. a selecting or comparing unit/function, similarly indicates that selecting and/or comparing can be taken over by a distinct physical entity, but can also just be a function associated with a distinct physical structure such as, but not limited to, a CD, DVD or other, e.g., storing device. The measurable indicator parameters and/or variables are preferably readily assessable ones, e.g., via bedside examination and/or a number of laboratory tests. Thus, they can be assessed in facilities lacking sophisticated equipment, such as expensive imaging equipment. For example, the indicator parameters and/or variables may be assessed in a mobile

or temporary facility. As the person skilled in the art will appreciate, the measurable indicator parameters and/or variables vary to different degrees from disease to disease. The questionnaire in **Appendix I** as well as the Table in **Appendix II** provide convenient tools to ascertain these parameters and/or variables for a wide variety of diseases. However, it is well within the skill of the artisan to modify a questionnaire and/or table of this kind. Also, it might be desirable to adjust such a questionnaire and/or table to take into consideration the specifics of, e.g., a population, location or time in which/where/when the assessment is performed.

A profiling set is a collection of measurable indicator parameters and/or variables from a relevant number of individuals that forms the basis to profile a certain disease, e.g., arteriosclerosis. A profiling set will comprise at least a majority (more than 50%) of measurable indicator parameters and/or variables that can be clearly linked to a particular disease, e.g. by establishing statistically significant differences between individuals having a disease and individuals without the disease and selecting those that showed such differences between the two groups. Thus, in a preferred embodiment of the invention, the profiling set comprises, consists of or essentially consists of a set of parameters and/or variables having a P-value of less than 0.5, preferably less than 0.4, more preferably less than 0.3, even more preferably less than 0.2, even more preferably less than 0.1, 0.05, 0.025, 0.01, 0.005, 0.0025 or 0.001 in a statistical test comparing two groups such as, but not limited to, the Mann Whitney U test, the student t-test, or the χ^2 test, wherein this set is a subset of parameters/variables selected after comparing parameters/variables of a first group of individuals having the disease and a second group not having the disease.

A data-based clinical disease profile according to the present invention profiles a disease in an individual employing a profiling set. It comprises, consists of or essentially consists of measurable indicator parameters and/or variables that have been attributed a coding which relates the value measured

for this parameters and/or variables to a **reference value**, such as the average value measured for this parameter and/or variable in a relevant number of individuals having the disease or, alternatively, in a relevant number of individuals not having the disease. These groups of individuals are also referred to herein as **reference** or **standard reference**. In one embodiment the reference consists of or consists essentially of individuals having the disease.

A **disease activity score** according to the present invention is an average of the measurable indicator parameters and/or variables of a **data-based clinical disease profile**. It can thus provide a single measurement for an individual's **disease activity**. In certain embodiment, the disease activity score obtained from individuals of a population is averaged to obtain a disease activity score for such a population or for specific segments thereof. For example, the population may be individuals treated in a particular clinic and the specific segments may be male or female patients or patients above or below a certain age. In certain embodiment of the invention, the disease activity may also be assessed via a simple summation of the measurable parameters and/or variables.

A **correlation set** is a collection of measurable indicator parameters and/or variables from a relevant number of individuals that forms the basis to **correlate** members of said collection to each other and/or to a certain disease, e.g., arteriosclerosis, e.g., via a phenotypical correlation plot. "**Correlating**" or "**to correlate**" in this context means establishing a link between, e.g., two variables, irrespective of whether or not statistically significant. The data set of the correlation set is broader of a profiling set and thus allows correlating, that is making a connection between of measurable indicator parameters and/or variables between a connection has previously not or not clearly been determined.

A **population** according to the present invention is a group of individuals that stem from the same geographical area, which may be a continent, a country, a state, a city, a town, a district or a building such as a hospital or a clinic. In a

preferred embodiment of the present invention, the profiling set and/or correlation set is drawn from individuals from one population. The tools and or methods of the present invention are, in a preferred embodiment, tied to such a population or a subset thereof. This allows personalized and targeted treatment of patients with complex diseases or with a risk to develop them. The invention also allows to determine trends of a disease within a population.

The invention is, in a preferred embodiment, directed at a comprehensive clinical data array that describes a common, complex human disease such as symptomatic arteriosclerosis. In one embodiment, the invention is directed at accurately determining the individual patient's disease activity using a set of non-invasive, affordable and accessible clinical tests. In a particularly preferred embodiment of the invention, the patient's data is compared with a contemporary cohort of patients suffering from the disease (i.e. symptomatic arteriosclerosis), a feature classical cardiovascular risk calculation tools generally do not have. The patients who serve as an internal reference group, are, e.g., living in the same area and they are treated at the same institution. Thus, they are drawn from the same population. This circumstance avoids the temporal and spatial bias that may affect the accurate disease prediction by most known risk algorithms (6).

Facing the diagnostic break-through of modern imaging technologies in the late 20th century, clinical examination is becoming an orphan science among clinicians and particularly among young physicians. In the following, data-based clinical disease profiles, will be discussed using symptomatic arteriosclerosis as a non-limiting example. The data-based clinical disease profile, is, in this embodiment, entirely based on simple clinical findings such as patient's history, bedside procedures and a few lab tests. Its strength lies in the detection of the individual disease activity both for asymptomatic patients without treatment but also for patients with fully established secondary prevention. This individualized assessment forms the basis for the personalized treatment of arteriosclerosis. It facilitates focused treatment of the system which is most involved in (such as

body shape or general inflammation) or most affected by (such as arteries, the heart or the kidney) the disease.

In one preferred embodiment of the invention, the positive predictive value of the disease activity score is assessed. For asymptomatic patients this score correlates with the 10-year risk to develop cardiovascular events as calculated by the Framingham algorithm (18), thus suggesting its prognostic significance. Accordingly, in a preferred embodiment of the present invention the disease activity score of an individual without the respective disease, is used prognostically forecasting a disease development and/or onset for about 15 years, about 10 years, about 5, years, about 4 years, about 3, years or about 2 years. The data-based clinical disease profile and the disease activity score is, in a preferred embodiment, defined by the same cohort of patients for which it sets the reference, that is, its data is drawn from the same population as, e.g., the assessed individual. Notably, both single numerical variables and the disease activity score have been shown reproducible when collected by different investigators during different time periods. The fact that the disease activity score increases with the severity of arteriosclerosis as assessed by the number of organ beds affected by the disease reflects a biologically relevant assessment. Third, age is an important risk factor for cardiovascular events (26) and, not surprisingly, age also affects the disease activity score. Patients with symptomatic arteriosclerosis show an accelerated progression of arteriosclerosis as measured with the disease activity score that is revealed after age forty. Although the disease activity score is significantly higher for symptomatic patients, there is significant overlap with asymptomatic individuals. Additional, comprehensive diagnostic tools such as genomic or transcriptomic tests can, in certain embodiment, be employed to separate the two patient groups, but also to identify presymptomatic individuals accurately. Finally, the conditions that precipitate the development of symptomatic arteriosclerosis are evolving with time. They may be different in various regions of the world and are subject to the medical management, be it primary or secondary prevention strategies or access to revascularization procedures. Therefore, this data-based clinical disease profile may look different 10 or 20 years from now, it may look different in the

setting of a private practice or in a tertiary care referral center of a university hospital.

As the person skilled in the art will appreciate, the present approach of assessing a complex disease with bedside, accessible and affordable clinical tests can be adopted for other common conditions such as chronic obstructive pulmonary disease, osteoporosis, even cancer or other conditions as those described elsewhere herein. The comprehensive, unbiased collection of clinical datasets together with an unambiguous assignment of the diagnostic vignette allows to confirm or discover linked conditions such as osteoporosis which seems to accompany symptomatic, but not asymptomatic arteriosclerosis.

The invention will be explained in the following using symptomatic arteriosclerosis as a non-limiting example.

In the context of this example, it was tested whether non-invasive, bedside diagnostic procedures and a set of additional, simple tests that are usually part of the initial evaluation of a patient are able to identify individuals with symptomatic arteriosclerosis. In a prospective observational clinical cohort study data was collected that were obtained by a physician in a standardized clinical exam. A set of more than 70 numerical variables were systematically compared between patients who suffered from symptomatic arteriosclerosis and patients who had no cardiovascular events in the past. 25 of these datasets were clearly different between the two patient groups. The quartile distribution of these data was the basis of a quantitative scoring system which formed the basis for a color coded, data-based clinical disease profile of arteriosclerosis. This comprehensive clinical approach to describe a complex disease such as symptomatic arteriosclerosis may be the first step to evaluate personalized, targeted treatment strategies for individual patients.

Methods

Patient recruitment

718 in-patients who were treated for any reason at one single ward of a department of a Hospital, were screened for exclusion criteria to participate in the study. Exclusion criteria that were fulfilled by 40% of the patients were either the

inability to give informed consent or terminal illness. Two physicians (C.S., M.M.) were sequentially involved in the data collection that covered two study periods: period 1: 11 months (C.S.), and period 2: 8 months (M.M.). Overall, 431 patients without exclusion criteria were personally confronted with the study protocol. 269 patients consented to participate. The patients were grouped in three categories based on the clinical history: group 1 – no cardiovascular events in the past; group 2 – cardiovascular events in the past which define symptomatic arteriosclerosis; group 3 – symptoms were compatible with symptomatic arteriosclerosis, but clinical evidence to prove it was lacking. For the data-based clinical disease profile, patients without cardiovascular events (group 1) and patients with proven, symptomatic arteriosclerosis (group 2) were compared (Table 1). Cardiovascular events which defined symptomatic arteriosclerosis in this patient cohort were a) *for coronary heart disease*: myocardial infarction, significant stenosis of coronary arteries as assessed by angiography, angina pectoris with signs of myocardial ischemia, history of coronary bypass surgery or other revascularization procedures, b) *for cerebrovascular disease*: ischemic stroke, history of carotid surgery, c) *for peripheral arterial occlusive disease*: ankle brachial index < 0.9 (15) and symptoms of claudicatio intermittens, significant stenosis of arteries and symptoms of claudicatio, history of peripheral bypass surgery or other revascularization procedure, d) *for aortic arteriosclerosis*: symptomatic aortic aneurysm, infrarenal diameter > 3cm (16) and e) *for arteriosclerosis of the kidney*: renal artery stenosis, impaired renal function (17) with normal urine analysis, history of renal artery revascularization procedures. Male sex, arterial hypertension, diabetes mellitus, dyslipidemia, smoking and a positive family history for cardiovascular disease were the six conventional cardiovascular risk factors which were assessed based on the clinical history (18).

Comprehensive clinical assessment

All participants were subject to a standardized interview (H, history) and examined in a standardized clinical examination (C) (**see Appendix I for questionnaire**). The clinical examination started with the patient in the standing

position. Body weight and size, waist and hip circumference, blood pressure and heart rate were measured on both arms in the standing position first. Thereafter, the examination was continued in the supine position. Blood pressure and heart rate measured in supine position were usually obtained at the end of the examination, together with the determination of the ankle brachial index (ABI). It was assessed using bedside doppler ultrasound (Dopplex 5 MHz, HNE Healthcare GmbH, Hilden, Germany). Patients with incompressible leg arteries had a formal ABI of more than 1.5 and these excessively high indexes were excluded from the dataset. The patient's record served as a source for additional information such as laboratory tests (L), X-rays (X), electrocardiogram (E), stress test or echocardiogram. For this aspect, it was a purely observational study. No additional laboratory testing were performed except what was requested by the treating physicians. From the full clinical assessment which was collected in an electronic data base, 76 numeric variables were selected (see Supplemental Table 1) for further statistical analysis. 15 (20%) were obtained from the interview, 19 (25%) from the clinical examination, 33 (43%) from the laboratory tests and 9 (12%) from x-ray, electrocardiogram, stress test or echocardiogram. For 15 of these 76 parameters, the dataset was incomplete, i.e. information from less than 75% of the patients were collected (**Appendix II**).

Data-based clinical disease profile and disease activity score

For 61 of the 76 numeric variables, data were available for more than 75% of the patients. These datasets were compared between patients without cardiovascular events in the past (group 1) and patients with proven symptomatic arteriosclerosis (group 2) using the Mann Whitney U test (**Appendix II**). For 25 variables (41%), the P-value was below 0.1 and these parameters were selected to be part of the data-based clinical disease profile (Table 2). For both groups, the percentile distribution of the data was calculated and the quartile ranges are shown (Table 2). The group of patients with the disease, i.e. with proven symptomatic arteriosclerosis (group 2, n=100 patients) was defining the standard reference for the data-based clinical disease profile. The calculated quartile ranges served for color coding the patient's individual data (Table 2 and Figure

1). For most of the numerical variables, patients with symptomatic arteriosclerosis had higher median values than the patients without cardiovascular events. Therefore, lighter gray shading (or green color) was assigned to the lowest quartile closest to the asymptomatic patients, light gray shading (or yellow color) to the second, dark gray shading (or orange color) to the third quartile and darker gray shading (or red color) to the quartile most distant to the asymptomatic patients. Values below the minimal value were coded as lightest gray and values above the maximal value were coded as darkest gray. Exceptions to this rule were the ankle brachial index, the peripheral heart rate at standing position, the creatinine clearance and the hemoglobin concentration. For these 5 parameters, the patients with symptomatic arteriosclerosis had lower median values compared to the asymptomatic patients, and therefore color coding followed the opposite rule: the highest quartile range was assigned to the lighter gray shading (or green color), the 3rd to the light gray shading (or yellow color), the 2nd to the dark gray shading (or orange color) and the lowest quartile range to the darker gray shading (or red color) (Figure 1).

The phenotypical correlation plot

Correlation profiling is used by physiologists to assess the influence of genotype on cardiovascular phenotype (19, 20). In a similar way, we used this approach to comprehensively compare the phenotype of patients with symptomatic arteriosclerosis and patients without cardiovascular events (Figure 6). The 61 parameters, for which a complete dataset was available, were correlated linearly with each other and the linear correlation coefficient R was calculated. Again, color coding was applied to visualize different and opposite degrees of correlation (Figure 6-1, 6-2, legend). Correlation coefficients of 0 +/- 0.01 are shown in black, increasingly positive correlations are turning into gray and light gray, whereas increasingly negative correlations are turning into light scattered and strong scattered.

Statistical analysis

All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago IL, USA). The numeric data which were obtained in the group of patients with symptomatic arteriosclerosis were compared to the patients without cardiovascular events using the Mann-Whitney U test. The presence or absence of cardiovascular risk factors was compared between the two groups using the χ^2 -test. Linear correlation coefficients were determined by the least squares method and correlations were tested for significance using the Spearman's test. P-values < 0.05 were supposed to indicate a significant difference between the groups.

Receiver operating characteristic (ROC) curve for the assessment of diagnostic suitability of the disease activity score

The disease activity score for arteriosclerosis was analyzed and compared to a number of conventional risk factors as well as to the Framingham score as used as diagnostic tool for arteriosclerosis.

Evolution of the disease activity score

The prospective evolution of the disease activity score depending on the state of the disease was assessed by determining the disease activity score in a individual in a two year interval.

Results*The clinical bedside examination identified patients with symptomatic arteriosclerosis*

Of the 269 patients who participated in this study, 100 (37%) had symptomatic arteriosclerosis, i.e. they had suffered from cardiovascular events in the past. 110 (41%) had no history of cardiovascular events such as myocardial infarction, stroke, intermittent claudication, revascularization procedures or other disease defining conditions (Table 1). For 59 (22%) patients, the definite

allocation to one of these two groups was not possible. The characteristics of the patients without cardiovascular events in the past and of the patients with proven symptomatic arteriosclerosis are summarized in Table 1. On average, patients with symptomatic arteriosclerosis were older, and all conventional risk factors were significantly more common in this group. Smoking, a positive family history of cardiovascular events and arterial hypertension were the most prevalent risk factors for both patient groups (Table 1). 60% of the patients with symptomatic arteriosclerosis had coronary heart disease, 26% had cerebrovascular disease, 26% peripheral arterial occlusive disease, 7% aortic and 7% renal arteriosclerosis. For about a quarter of these patients, more than one vascular bed was affected by the disease.

For 15 of the 76 numerical variables tested, the dataset was incomplete (**Appendix II**) and they were therefore excluded from the further statistical analysis. Of the remaining 61 parameters, 25 (43%) showed a consistent difference (P-value < 0.1 in the Mann-Whitney U test) when they were compared between the two patient groups. The majority was obtained in the bedside examination: 7 (28%) from the interview, 11 (44%) from the clinical examination, only 5 (20%) from laboratory tests and 3 (12%) from chest X-ray or electrocardiogram. For these 25 variables, the quartile distribution was calculated (Table 2) and the normalized interquartile limits are shown as color coded columns in Figure 1. These interquartile limits define the range for color coding of the individual patient's data: depending on the value for age, number of pack years, number of children etc which are displayed as a white circle (Figure 1), either green, yellow, orange or red color is assigned to the variable. The color coded values obtained for the 25 variables are then used for the calculation of the disease activity score: a green value adds 0, a yellow value 1, an orange value 2 and a red value 3 points. The sum is divided by the total number of variables assessed which is ideally 25 (Figure 1). Therefore, the scale for the score ranges from a minimal value of 0 to a maximal value of 3. Each of the 25 variables contributes one 25th part of the score value. Accordingly, in this example, the formula to calculate the disease activity score is $\Sigma [\alpha_1 + \alpha_2 + \alpha_3 + \dots + \alpha_{25}] / (25 - [\text{missing variables}])$.

Reproducibility of the data-based clinical disease profile

Since 18 of the 25 variables which contributed to the disease activity score were obtained by a physician during the clinical examination and therefore could be subject to interobserver variability, it was tested whether two independent observers would obtain similar results during two consecutive study periods. During the first period lasting 11 months and during the second period, lasting 8 months, the median values for the 75 numeric variables showed on average excellent correlation (Figure 2A). When the variables were compared during the two study periods using non-parametric tests, only four parameters showed a significant difference in the group of symptomatic patients: the hemoglobin concentration, the monocyte count and the waist and hip circumference (**Appendix III**). In contrast, for the patients who did not suffer from cardiovascular events, 16 variables were different between the two study periods. This suggests that a more heterogeneous collection of diseases in this second group could explain the more pronounced diversity of clinical findings. This observation gives additional support for choosing the symptomatic patients to set the reference for the data-based clinical disease profile and for the disease activity score. The percentile distribution of the disease activity score was also calculated between the two study periods (Figure 2B). It showed a reproducible, normal distribution when it was obtained from different patients and by different investigators.

The data-based clinical disease profile: a rational basis for the individual assessment and classification of arteriosclerosis

Most of the 25 variables which were significantly different in this systematic and comprehensive comparison of clinical information from symptomatic and asymptomatic patients reflect important clinical signs of arteriosclerosis: the anthropometric data reveal abdominal obesity (21), the elevated systolic blood pressure (22) and the reduced ankle brachial index (15) are the consequence of reduced wall compliance and stenotic arteries, cardiomegaly identifies left ventricular hypertrophy (23), QT prolongation may correlate with electric vulnerability (3), diminished creatinin clearance and

glucosuria reflect kidney injury (17). Anemia, monocytosis and elevated blood sedimentation rate are signs of chronic inflammation (24) and finally, the high number of drugs and repetitive hospitalizations are health economic aspects of symptomatic arteriosclerosis (Figure 1). These categories which emerged from the data analysis have immediate implications for the individual classification of the disease. For example, the male patient whose data are shown in Figure 1 (white circles) had a myocardial infarction three years ago. His disease profile is drawing the physician's attention to abdominal obesity as the only remaining, clinically apparent sign of the disease under combined anti-hypertensive and lipid lowering treatment.

When the color coded disease profiles obtained from each individual patient are aligned in an array format (Figure 3) the patient cohort can be divided into the following four groups: female patients without cardiovascular events (upper left quadrant), female patients with symptomatic arteriosclerosis (upper right quadrant), male patients without cardiovascular events (lower left quadrant) and male patients with symptomatic arteriosclerosis (lower right quadrant). Within the quadrants, the data-based clinical disease profile is shown first and it is followed by the disease activity score. The conventional risk factors identified by gray boxes are shown next, and the sum of risk factors which are normalized to the symptomatic patients are shown in a color coded, visually weighed manner. Within each of the four groups, the patients are sorted according to their disease activity score. For the asymptomatic patients, this sorting strategy reveals a cluster of both female and male patients with the metabolic syndrome (Figure 2, brackets): they have abdominal obesity, elevated systolic blood pressure and often diabetes (25). For the symptomatic patients shown on the right panel, this clustering of the metabolic syndrome is less evident. However, the array of the symptomatic patients reveals a gender-specific, distinct profile of the disease: whereas the female patients, despite of taking the same number of drugs, have on average higher, uncontrolled systolic blood pressure (145 (125-160) mmHg versus 130 (115-148) mmHg, $P=0.02$) the male patients are rather obese having a higher body mass index (27.7 (24.6-30.7) kg/m^2 versus 25.4 (23.3-28.1) kg/m^2 ,

$P=0.04$ and a higher waist hip ratio (1.02 (1.0-1.07) versus 0.91 (0.88-0.97), $P<0.001$) than female patients.

The data-based disease activity score correlates with the 10-year risk for cardiovascular events, with the severity of the disease and with age.

For 40 of the 110 patients without cardiovascular events the dataset was complete to calculate the Framingham risk score (ref). This was translated into the 10-year risk to suffer from cardiovascular events. This 10-year risk showed a weak but significant correlation with the disease activity score (Figure 4A). Furthermore, patients with extensive arteriosclerosis which affects more than one vascular bed had a significantly higher disease activity score than patients who had only one organ involved or patients without cardiovascular events in the past (Figure 4B). Finally, the disease activity score is significantly correlated with age for both asymptomatic and symptomatic patients (Figure 5). However, the rate of progression of the disease with time as identified by the linear curve fit of the disease score with the patient's age is faster in symptomatic patients (Figure 5). For the patients older than 70 years, the disease activity score was significant higher in the symptomatic than in the asymptomatic group (1.65 (1.33-1.84) versus 1.23 (1.05-1.53), $P<0.001$).

The phenotypical correlation plot is a tool to identify other conditions linked with symptomatic arteriosclerosis.

The phenotypical correlation plots for the asymptomatic (Figure 6A) and symptomatic (Figure 6B) patients reveal a good association between the anthropometric data and the blood pressure measurements, for both groups of patients. Within the symptomatic patients, body height was negatively correlated with age and with all the four systolic blood pressure measurements (Figure 6B, insert, arrows) whereas in patients without cardiovascular events, there was no obvious or consistently negative correlation observed. This unexpected finding could be translated into the concept (Figure 7) that symptomatic arteriosclerosis is linked with osteoporosis (as measured by an age dependent decrease in body size), and that for an individual patient with symptomatic arteriosclerosis, a

smaller size is linked to stiffening and loss of compliance of the arterial wall (as measured by an elevated systolic blood pressure).

The receiver operating characteristic (ROC) curve for the assessment shows that the disease activity score is highly suitable for the assessment of disease activity

As can be seen from Figures 8 and 9, the area under the curve is 0.688 for the Framingham score, 0.756 for the number of risk factors in the individuals and 0.839 for the disease activity score.

The disease activity score increases significantly over time in individuals with the disease but not in individuals without the disease

It was tested how the disease activity score evolves prospectively in patients suffering from symptomatic arteriosclerosis compared to individuals free of cardiovascular events.

It was demonstrate that within two years, the disease activity scores increases significantly in patients with symptomatic arteriosclerosis but not in individuals without active disease Figure 10. The significance test used to determine the difference between disease activity score during visit 1 and visit 2 was the Wilcoxon test.

Table 1: Patient characteristics

	No cardiovascular events (n=110)	Symptomatic arteriosclerosis (n=100)	P-values [#]
Cardiovascular risk factors n (%)			
Male sex	51 (46.4)	57 (57)	0.095
Age (years)	56.00	72.00	<0.001
Body mass index (kg/m ²)	25.6	26.40	0.085
Arterial hypertension	40 (36.4)	67 (67)	<0.001
Diabetes mellitus	12 (10.9)	30 (30)	0.005
Dyslipidemia	9 (8.2)	50 (50)	<0.001
Smoking	57 (51.8)	61 (61)	0.017
Family history of cardiovascular disease	48 (43.6)	61 (61)	0.038
Drugs at examination n (%)			
Antiplatelet drugs	7 (6.4)	69 (69)	<0.001
Anticoagulants	27 (24.6)	36 (36)	0.07
Nitrates	1 (0.9)	18 (18)	<0.001
Betablockers	19 (17.3)	60 (60)	<0.001

<i>Diuretics</i>	17 (15.5)	48 (48)	<0.001
<i>ACE inhibitors</i>	14 (12.7)	56 (56)	<0.001
<i>Angiotensin II receptor blockers</i>	8 (7.3)	11 (11)	0.347
<i>Ca²⁺ channel blockers</i>	7 (6.4)	26 (26)	<0.001
<i>Oral glucose-lowering agents</i>	9 (8.2)	14 (14)	0.178
<i>Insulin</i>	5 (4.6)	21 (21)	<0.001
<i>Statins</i>	14 (12.7)	68 (68)	<0.001
<i>Other drugs</i>	5 (4.6)	8 (8)	0.299
Cardiovascular events defining symptomatic arteriosclerosis %			
<i>Coronary heart disease</i>	-	60	
Myocardial infarction	-	49	
Significant stenosis of coronary arteries (angiographic findings)	-	23	
Angina pectoris with signs of myocardial ischemia (e.g. exercise testing)	-	9	
History of revascularization	-	14	
<i>Cerebrovascular disease</i>	-	26	
Ischemic stroke	-	26	
<i>Peripheral arterial occlusive disease</i>	-	27	
Ankle-brachial-index<0.9 and symptoms of claudicatio intermittens	-	14	
Angiographically proven and symptoms of claudicatio intermittens	-	5	
History of revascularization	-	17	
<i>Arteriosclerosis of the aorta</i>	-	7	
<i>Arteriosclerosis of the kidney</i>	-	11	
Number of organs affected by cardiovascular events			
1	-	72	
2	-	26	
≥ 3	-	2	

The two patient groups were compared using the Mann-Whitney-U-Test (for numerical data) or the χ^2 -test (for non-numerical data)

Table 2. The numerical data selected for the data-based clinical disease profile and the disease activity score

Parameter	Method §	No cardiovascular events (n=110)					Symptomatic atherosclerosis (n=100)					P-value #
		Maximum value	75. percentile	Median	25. Percentile	Minimum value	Maximum value	75. percentile	Median	25. percentile	Minimum value	
Age (years)	H	88.0	67.75	56.0	46.25	18.0	92.0	76.0	72.0	66.75	39.0	<0.001
Smoking (packyears)	H	150.0	25.0	1.0	0.0	0	150.0	50.0	15.0	0.0	0.0	0.018
Number of children	H	7.0	2.0	2.0	1.0	0	6.0	3.0	2.0	1.0	0.0	0.028
Body mass index (kg/m ²)	C	40.1	27.75	25.6	23.25	14.5	42.40	29.73	26.4	24.07	16.59	0.085
Waist circumference (cm)	C	120.0	101.0	95.0	82.0	56.0	140.0	109.0	99.5	90.0	71.0	0.006
Hip circumference (cm)	C	126.0	105.0	100.0	91.0	71.0	124.0	110.0	101.5	94.0	78.0	0.078
Waist hip ratio	C	1.20	1.00	0.94	0.88	0.75	1.20	1.04	1.00	0.91	0.78	0.006

Systolic blood pressure left arm supine (mmHg)	C	180.0	140.0	130.0	110.0	85.0	195.0	160.0	140.0	120.0	90.0	0.003
Systolic blood pressure right arm supine (mmHg)	C	190.0	140.0	130.0	110.0	90.0	200.0	160.0	135.0	120.0	85.0	0.005
Systolic blood pressure left arm standing (mmHg)	C	180.0	140.0	120.0	100.0	80.0	225.0	155.0	130.0	120.0	80.0	0.001
Systolic blood pressure right arm standing (mmHg)	C	200.0	140.0	120.0	110.0	80.0	190.0	150.0	130.0	120.0	80.0	0.007
Heart diameter (cm)	X	17.7	14.9	13.5	12.5	9.40	19.8	16.6	15.6	13.9	11.3	<0.001
Heart lung ratio	X	0.61	0.49	0.47	0.43	0.35	0.71	0.56	0.51	0.48	0.38	<0.001
Ankle brachial index right *	C	1.46	1.24	1.14	1.06	0.76	1.50	1.15	1.00	0.95	0.42	<0.001
Ankle brachial index left *	C	1.45	1.21	1.15	1.07	0.70	1.50	1.13	1.02	0.86	0.43	<0.001
QT time (sec)	E	0.50	0.40	0.37	0.35	0.27	0.55	0.43	0.40	0.37	0.21	<0.001
Peripheral heart rate standing (bpm)	C	120.0	92.0	80.0	72.0	48.0	160.0	88.0	78.0	68.0	44.0	0.02
Creatinin clearance (mL/min per 1.73 m ²)	L	242.2	137.1	103.8	79.5	16.91	158.1	93.3	72.4	54.6	15.2	<0.001
Glucosuria (negative=0, +=1, ++=2, +++=3)	L	1.0	0.0	0.0	0.0	0.0	3.0	0.0	0.0	0.0	0.0	0.003
Hemoglobin (g/dL)	L	17.1	14.4	13.6	12.0	5.7	16.3	14.0	12.6	11.2	8.4	0.011
Monocytes (10 ⁹ /L)	L	3.41	0.87	0.47	0.29	0.05	2.78	0.86	0.59	0.40	0.00	0.079
Blood sedimentation rate (mm/h)	L	105.0	27.5	10.0	4.0	2.0	114.0	31.5	13.0	6.0	1.0	0.086
Number of drugs (on admission)	H	10.0	4.0	2.0	1.0	0	14.0	8.0	6.0	4.0	0.0	<0.001
Number of medication (current)	O	11.0	5.0	4.0	2.0	0	14.0	9.0	7.0	5.0	2.0	<0.001
Number of admissions to this hospital	H	8.0	1.0	0.0	0.0	0	15.0	3.0	1.0	0.0	0.0	0.002
Disease activity score	O	1.83	1.22	0.92	0.67	0.25	2.67	1.79	1.49	1.27	0.41	<0.001

* Patients (7 without cardiovascular events, 6 with symptomatic atherosclerosis) who had incompressible ankle arteries (=ABI>1.5) were excluded from this analysis.

The numeric data obtained during the two study periods were compared using Mann-Whitney-U-Test.

§ Method by which the data was obtained: H=history, C=clinical examination, L=laboratory test, X=chest X-ray, E=electrocardiography, O=others.

Once give the disclosure provided herein, many features, modifications, and improvements will become apparent to the skilled artisan. Such features, modifications, and improvements are therefore considered part of the present invention.

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What is claimed is:

1. An assessment tool for a disease comprising:

- (a) a first set of data recorder said first set of data comprising data of measurable indicator parameters and/or variables collected from a first group of individuals having said disease;
- (b) a second set of data recorder, said second set of data comprising data of said measurable indicator parameters and/or variables in (a), but collected from a second group of individuals without said disease;
- (c) a comparing unit/function which compares said first set of data with said second set of data; and
- (d) a selecting unit/function which selects a profiling set from said measurable indicator parameters and/or variables, wherein a coding, such as color, shade or value coding, attributed to each of said measurable parameters and/or variables of said profiling set reflects a disease activity measured by said measurable parameters and/or variables.

2. The assessment tool of claim 1, wherein said coding contributes to a data-based clinical disease profile and/or an activity score of said disease, and wherein, optionally, said selecting unit/function or a further selecting unit/function selects a correlation set, wherein said coding correlates at least two different of said measurable indicator parameters and/or variables of the correlation set.

3. The assessment tool of claim 1 or 2, wherein an attribution unit/function calculates the percentile distribution of each measurable indicator

parameter and/or variable of said profiling set of said first and/or second group, wherein said coding reflects this percentile distribution.

4. The assessment tool of claim 3, wherein said coding is based on percentile ranges such as tertile, quartile, quintile, sextile, septile, octile or nonile ranges of said percentile distribution.
5. The assessment tool of claims 3 and 4, wherein said first group serves as a standard reference.
6. The assessment tool of claim 2 to 5, wherein the selecting unit/function selects said profiling set from parameters and/or variables having a P-value of less than 0.5, preferably less than 0.4, more preferably less than 0.3, even more preferably less than 0.2, even more preferably less than 0.1, 0.05, 0.025, 0.01, 0.005, 0.0025 or 0.001 in a statistical test comparing two groups such as a Mann Whitney U test, a student t-test, or a χ^2 test when compared in (c).
7. The assessment tool of claim 1 to 6, wherein said first recorder, said second recorder, optionally the comparing unit/function, and/or optionally the selecting unit/function and/or optionally the disease activity calculating unit/function and/or the attribution unit/function are a single unit/function.
8. The assessment tool of claim 7, wherein the single unit is a computer readable unit such a CD or DVD, or a processing unit.
9. The assessment tool of claim 8, wherein said processing unit is remotely accessible such as via the internet.
10. The assessment tool of any of the preceding claims, wherein at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%,

about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75% or about 80% of measurable parameters and/or variables of said profiling set are amenable to detection via bedside examination and/or patient interviewing and/or laboratory tests.

11. The assessment tool of any of the preceding claims, wherein the data sets of (a) and (b) were collected approximately within the last 5 years, 4 years, 3 years, 2 years, 1 year, 9 months, 6 months, 3 months, 2 months, 1 months, 2 weeks, 1 week, 5 days, 2 days or 24 hours.

12. The assessment tool of any of the preceding claims, wherein the groups of individuals of (a) and (b) stem from the same population.

13. A method for determining measurable parameters and/or variables correlated to a condition and/or disease comprising:

(a) compiling measurable indicator parameters and/or variables;

(b) collecting and/or storing a first set of data for each of said measurable parameters and/or variables collected from a first group of individuals having said disease;

(c) collecting and/or storing a second set of data for each of said measurable parameters and/or variables collected from a second group of individuals without said disease,

wherein said individuals of (b) and (c) are selected from the same population and, optionally, the first and second set of data were collected approximately within the last 5 years, 4 years, 3 years, 2 years, 1 year, 9 months, 6 months, 3 months, 2 months, 1 months, 2 weeks, 1 week, 5 days, 2 days or 24 hours;

- (d) selecting a profiling set from said measurable parameters and/or variables; and
- (e) optionally, selecting a correlating set from said measurable parameters and/or variables.

14. The method of claim 13, further comprising assigning said measurable indicator parameters and/or variables a coding, such as a color, shade or value coding, wherein said coding reflects a disease activity measured by the measurable parameters and/or variables to the disease and/or condition.

15. The method of claim 14, further comprising calculating a percentile distribution of each measurable indicator parameter and/or variable of said profiling set and/or correlation set, wherein said coding reflects this percentile distribution for said first and/or second group.

16. The method of claim 15, wherein said coding is based on certain percentile ranges such as tertile, quartile, quintile sextile, septile, octile or nonile ranges of said percentile distribution.

17. A method for determining an activity score for at least one condition and/or disease in an individual and/or in a population comprising measuring the measurable indicator parameters and/or variables of the profiling set of claim 13 to 15 in said individual; and determining the activity score of said disease in said individual or a population from an average of the sum of said coding.

18. The method of claim 17, wherein the activity score for more than one disease, preferably at least 30, at least 15, at least 10, 9, 8, 7, 6, 5, 4, 3 or at least 2 diseases is determined.

19. The method of claim 17, wherein said activity score is established in an individual or in a population over time, such as every 3 month, every six month, every year or every other year, to assess changes in said population for said disease over time, and optionally correlating said changes to environmental difference between points in time at which said activity score is established.

20. The method of claim 17, further comprising correlating the coding of said measurable indicator parameters and/or variables of the correlation set of claim 14; and determining positive and/or negative correlations between different of said a indicator parameters and/or variables.

21. The assessment tool of claims 1 to 12 or the method of claims 13 to 20, wherein said condition and/or disease is arteriosclerosis, chronic obstructive pulmonary disease, asthma, severe bacterial infections including pneumonia, sepsis, meningitis, endocarditis, and acute or chronic viral infections, osteoporosis, an autoimmune disease, osteoarthritis, heart failure, drug dependency, alcoholism, an allergy, cancer, diabetes mellitus Type 2 and metabolic syndrome, arterial hypertension, obesity, smoking, venous thrombosis or pulmonary embolism.

22. The assessment tool or method of claim 21, wherein said disease is arteriosclerosis.

23. The assessment tool or method of claim 22, wherein the measurable indicator parameters and/or variables of the profiling set are selected from a group comprising myocardial infarction, significant stenosis of coronary arteries as assessed by angiography, angina pectoris with signs of myocardial ischemia, history of coronary bypass surgery, ischemic stroke, history of carotid surgery, ankle brachial index < 0.9, symptoms of

claudicatio intermittens, significant stenosis of arteries and symptoms of claudicatio, history of peripheral bypass surgery, symptomatic aortic aneurysm, infrarenal diameter > 3cm, renal artery stenosis, impaired renal function with normal urine analysis, history of renal artery revascularization procedures, male sex, arterial hypertension, diabetes mellitus, dyslipidemia, smoking and positive family history for cardiovascular disease.

24. Use of the assessment tool of claims 1 to 12 or the method of claim 13 to 23 in disease profiling.

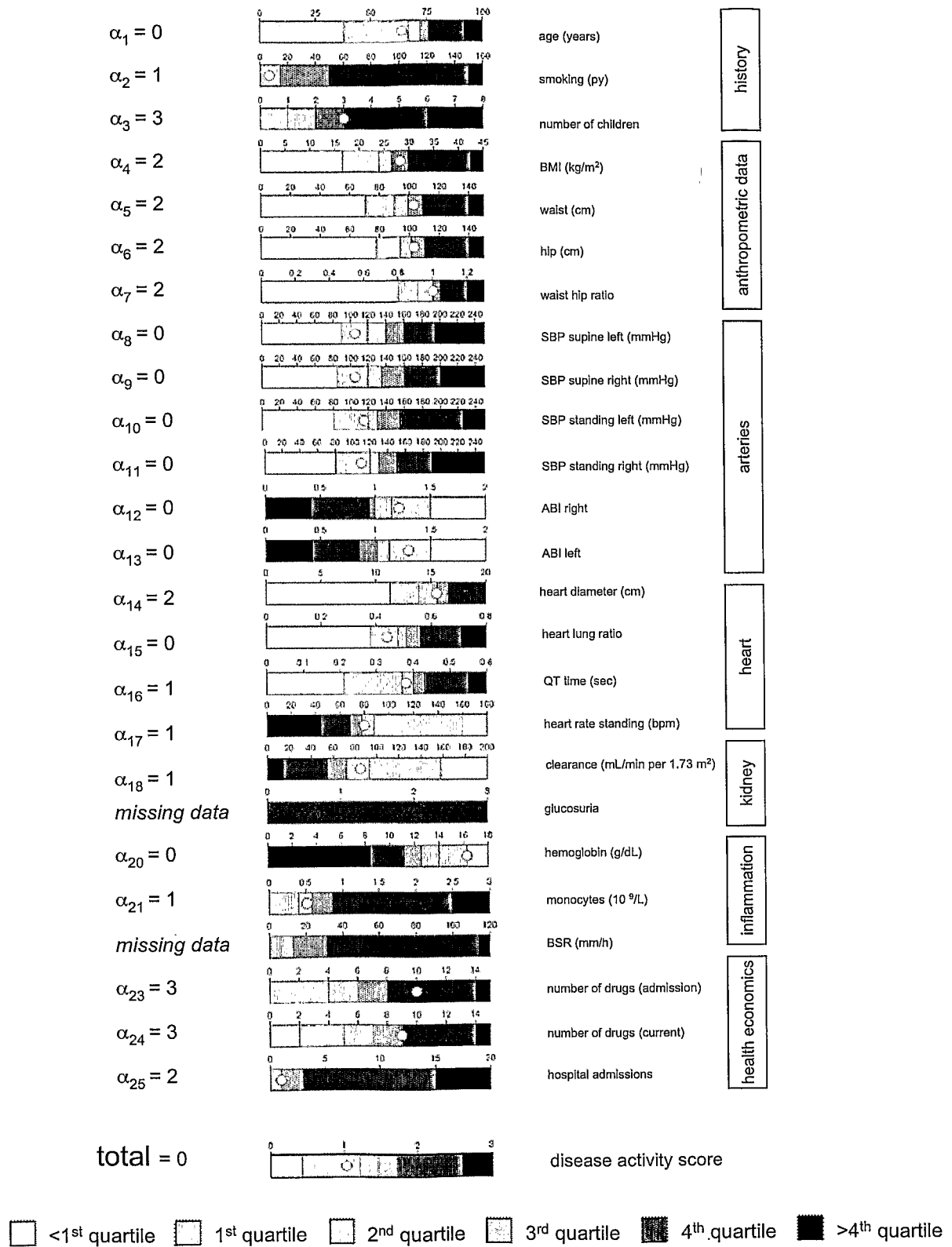


Figure 1

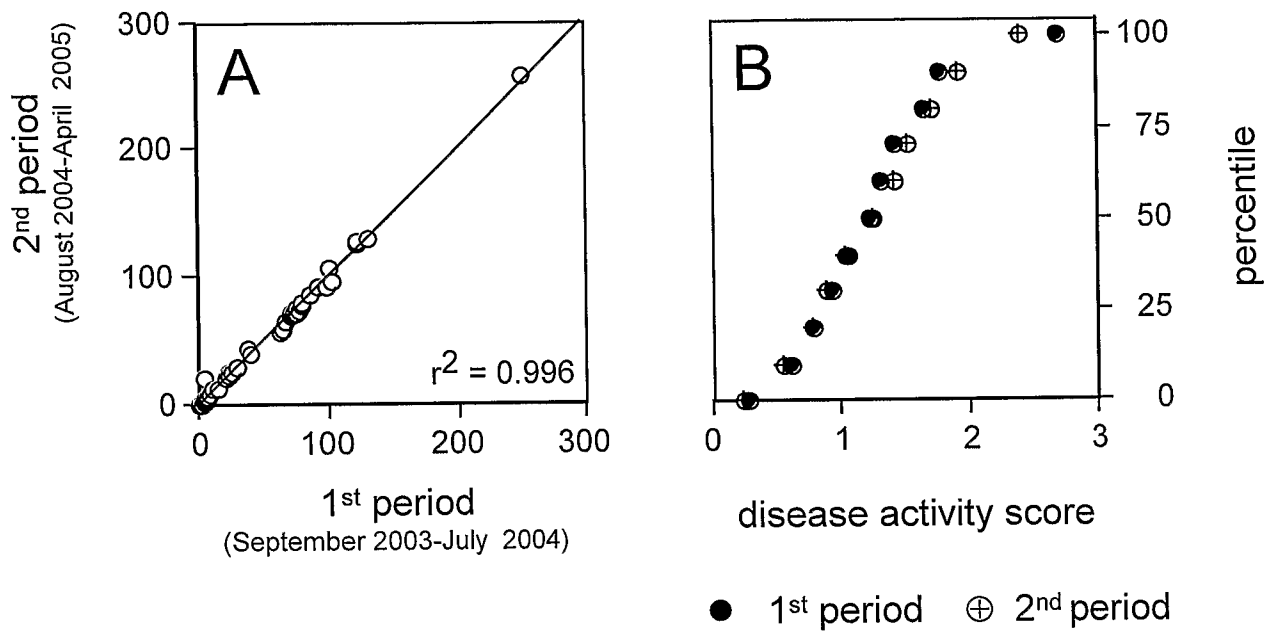
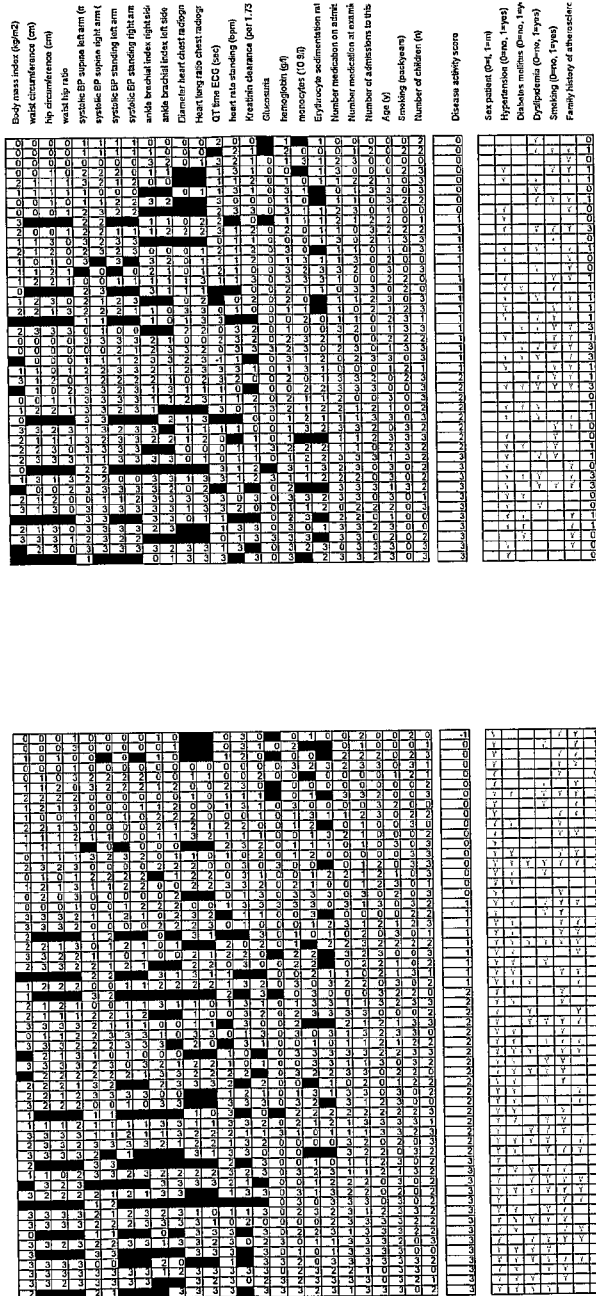
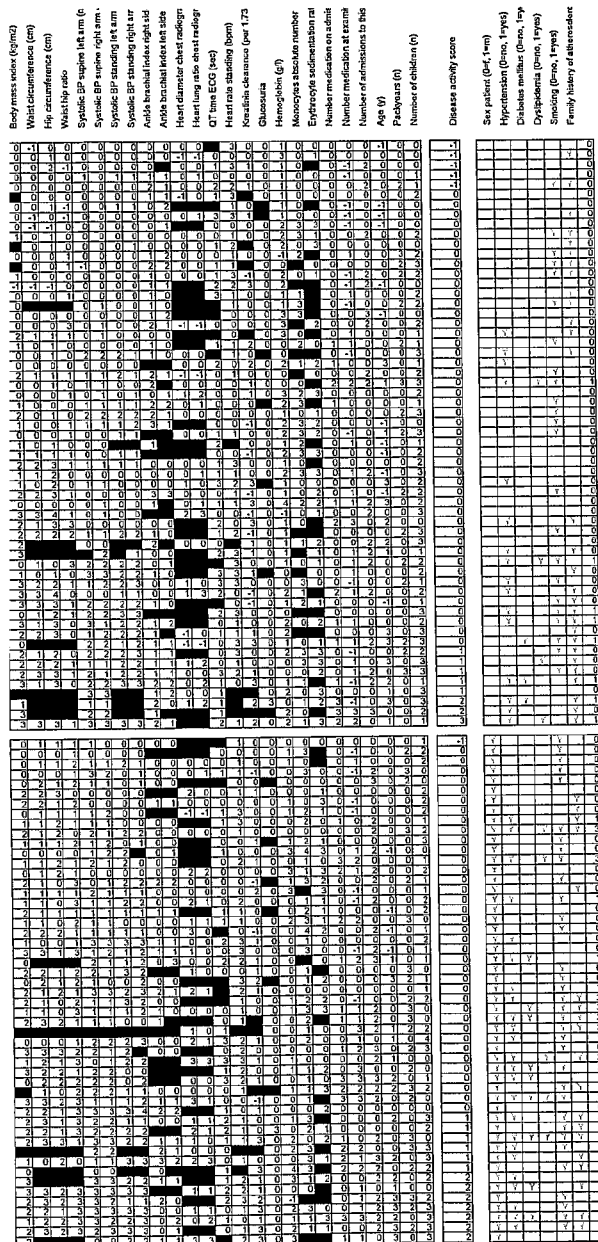


Figure 2

no cardiovascular events

symptomatic arteriosclerosis



female patients

male patients

Code legend
 Y risk factor present
 N risk factor absent
 1 < 1st quartile
 2 1st quartile
 3 2nd quartile
 4 3rd quartile
 5 4th quartile
 6 > 4th quartile
 7 missing value
 dark green or lightest gray
 green or lighter gray
 yellow or light gray
 orange or dark gray
 red or darkest gray
 dark red or darkest gray

data-based clinical disease profile

risk factors

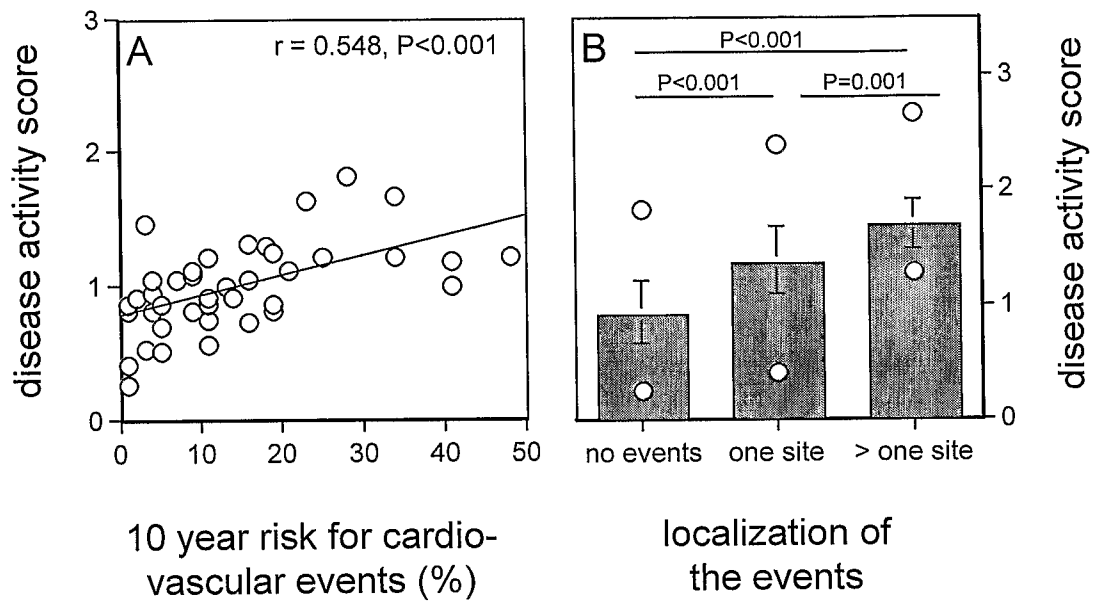
disease activity score

data-based clinical disease profile

risk factors

disease activity score

Figure 3



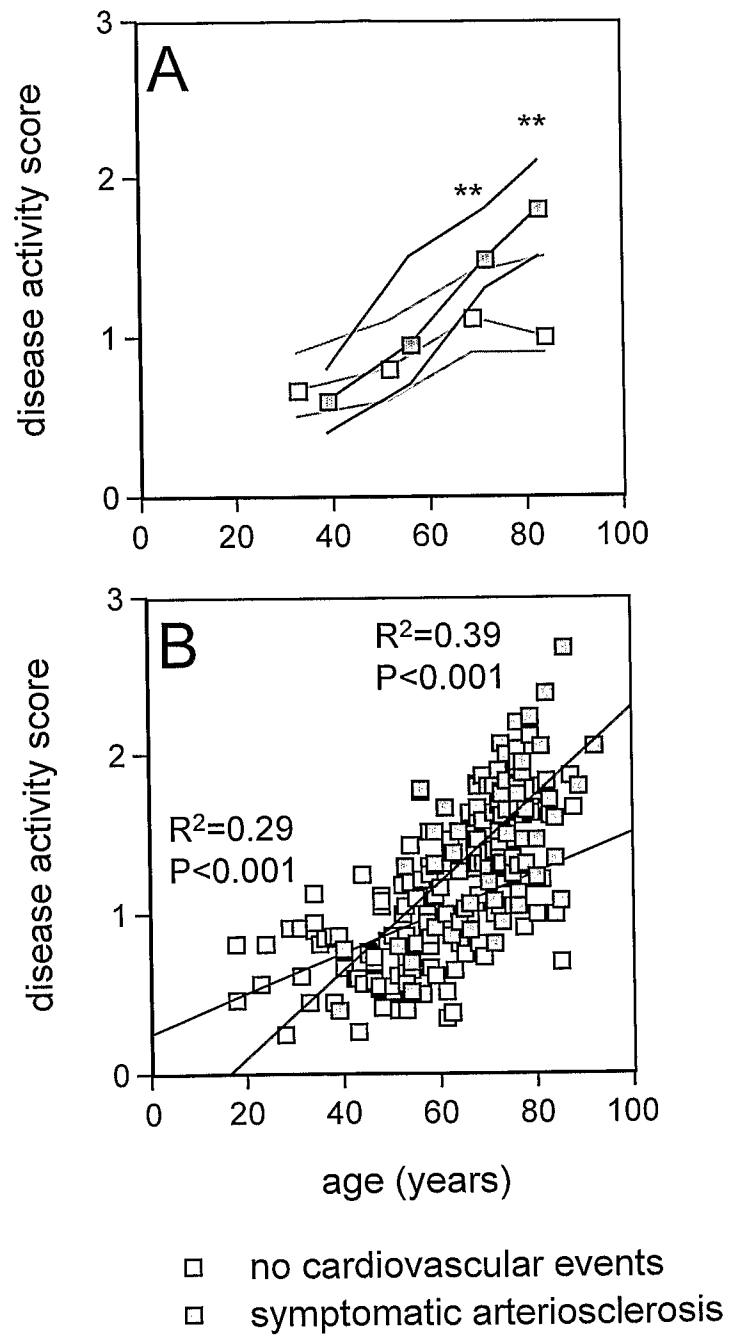


Figure 5

[illegible]

R-value-

0.91-1
0.81-0.9
0.71-0.8
0.61-0.7
0.51-0.6
0.41-0.5
0.31-0.4
0.21-0.3
0.11-0.2
0.01-0.1
-0.01-(-0.1)
-0.11-(-0.2)
-0.21-(-0.3)
-0.31-(-0.4)
-0.41-(-0.5)
-0.51-(-0.6)
-0.61-(-0.7)
-0.71-(-0.8)
-0.81-(-0.9)
-0.91-(-1.0)

Figure 6-1



0.91-1
0.81-0.9
0.71-0.8
0.61-0.7
0.51-0.6
0.41-0.5
0.31-0.4
0.21-0.3
0.11-0.2
0.01-0.1
0.01-(-0.1)
0.11-(-0.2)
0.21-(-0.3)
0.31-(-0.4)
0.41-(-0.5)
0.51-(-0.6)
0.61-(-0.7)
0.71-(-0.8)
0.81-(-0.9)
0.91-(-1.0)

Figure 6-2

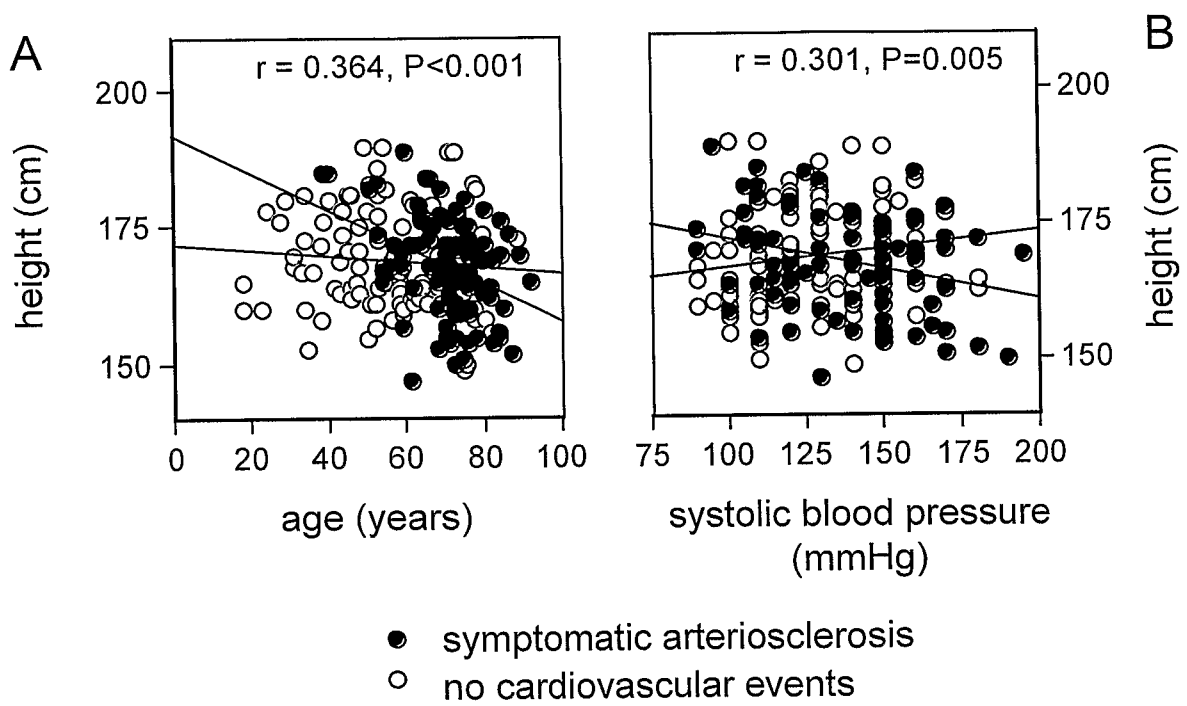


Figure 7

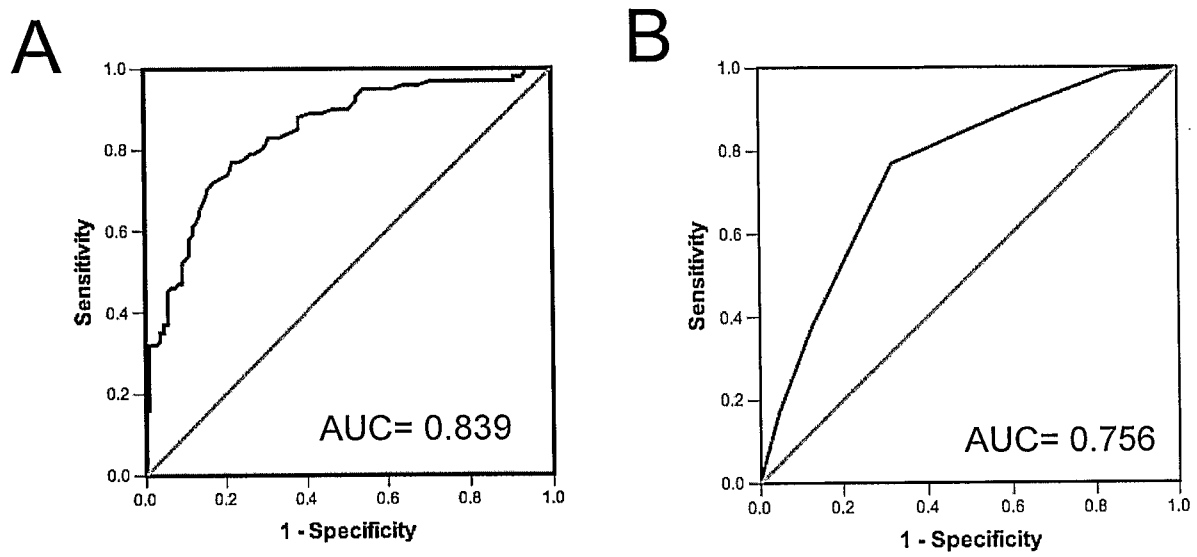


Figure 8

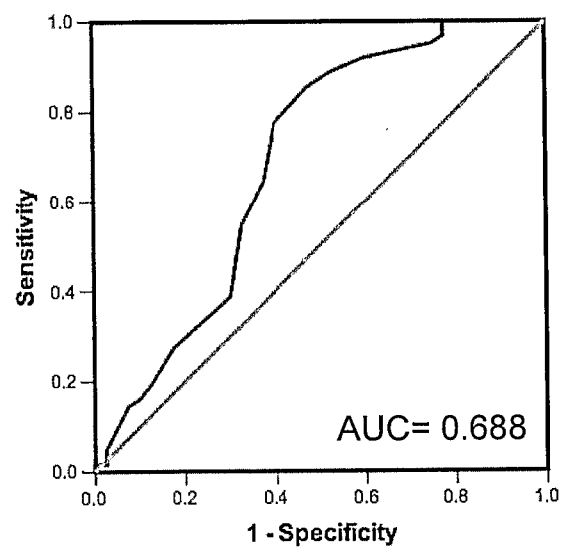


Figure 9

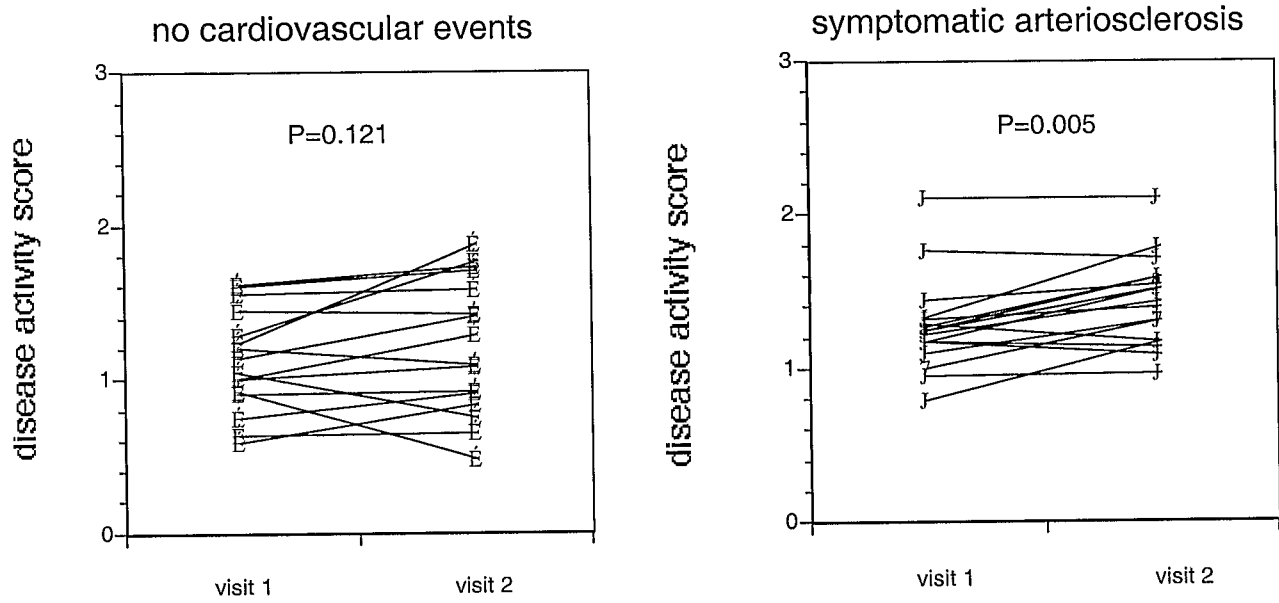


Figure 10

Appendix I: General questionnaire for databased clinical disease profiling

number	area	question	data type			
	personal data				default	multiple choice
1.1.1		patient id	number		empty space	
1.1.2		hospital patient id	text		empty space	
1.1.3		date of examination	date		00.00.0000	
1.1.4		date of birth	date		00.00.0000	
1.1.5		last name	text		empty space	
1.1.6		first name	text		empty space	
1.1.7		address	text		empty space	
1.1.8		phone number	text		empty space	
1.1.9		cell phone	text		empty space	
1.1.10		fax number	text		empty space	
1.1.11		e-mail	text		empty space	
1.1.12		professional status (last)	text		empty space	
1.1.13		retired	yes/no		not assessed	yes, no
1.1.14		since when?	date		00.00.0000	
1.1.15		family physician	text		empty space	
1.1.16		health insurance	text		empty space	
1.1.17		insurance class	multiple choice, simple		not assessed	
1.1.18		additional comments	text		empty space	
	history of hospitalizations					
1.1.19		date of first hospitalization in the current hospital	date		00.00.0000	
1.1.20		date of first hospitalization in	date		00.00.0000	

		the department of medicine							
1.1.21		last hospitalization in the department of medicine	date						
1.1.22		total number of hospitalizations	number				00.00.0000		
1.1.23		number of hospitalizations in the department of medicine	number				empty space		
1.1.24		type of current hospitalization	multiple choice, simple				empty space		emergency, regular admission
1.1.25		admitted by	multiple choice, simple				empty space		family physician, emergency physician, ambulance, other hospital, others
1.1.26		admitted to the department of	multiple choice, simple				empty space		depends on local setting
1.1.27		current ward	multiple choice, simple				empty space		depends on local setting
1.1.28		date of current hospitalization	date				00.00.0000		
1.1.29		date of discharge	date				00.00.0000		
1.1.30		out-patient visit	yes/no				empty space		yes, no
1.1.31		additional comments	text				empty space		
	Current history								
		reason for the current hospitalization	text				empty space		
1.1.32		additional comments	text				empty space		
	Personal history								
1.1.34		former diseases	yes/no				empty space		yes, no; if no, forward to 1.1.42
1.1.35		date of the event	date				00.00.0000		

1.1.36				multiple choice, simple		empty space	tonsillectomy, appendectomy, cholecystectomy, hysterectomy, birth of child, myocardial infarction, stroke, thrombosis, pulmonary embolism, pneumonia, transurethral resection of the prostate, urinary tract infection, arterial hypertension, diabetes, freetext
1.1.37		type of event		text		empty space	
1.1.38		treating physician		multiple choice, simple		empty space	no, yes
1.1.39		report for the event		text		empty space	
1.1.40		additional comments		yes/no		empty space	yes, no ; if yes, back to 1.1.36
		additional events?					
	System's overview						
1.1.41		weakness, fatigue		multiple choice, simple		empty space	none, freetext
1.1.42		appetite		multiple choice, simple		empty space	normal, reduced, increased, freetext
1.1.43		thirst		multiple choice, simple		empty space	normal, reduced, increased, freetext
1.1.44		body weight		multiple choice, simple		empty space	stable, decreasing, increasing, freetext
1.1.45		urination		multiple choice, simple		empty space	normal, dysuria, pollakisuria, hematuria, incontinence, freetext
1.1.46		bowel movements		multiple choice, simple		empty space	normal, diarrhea, constipation, freetext
1.1.47		nausea		multiple choice, simple		empty space	normal, freetext
1.1.48		vomiting		multiple choice, simple		empty space	normal, freetext

1.1.49		dyspnea	multiple choice, simple		empty space	normal, NYHA 1,2,3,4
1.1.50		coughing	multiple choice, simple		empty space	normal, freetext
1.1.51		expectoration	multiple choice, simple		empty space	none, hemoptoe, freetext
1.1.52		angina pectoris	multiple choice, simple		empty space	none, NYHA 1,2,3,4
1.1.53		edema	multiple choice, simple		empty space	none, feet, ankle, legs, anasarka, freetext
1.1.54		blood pression	multiple choice, simple		empty space	normal, elevated, low, freetext
1.1.55		headache	multiple choice, simple		empty space	normal, freetext
1.1.56		sleep	multiple choice, simple		empty space	normal, freetext
1.1.57		sweating	multiple choice, simple		empty space	normal, freetext
1.1.58		veneral disease	multiple choice, simple		empty space	none, freetext
1.1.59		pregnancies	number		empty space	
1.1.60		births	number		empty space	
1.1.61		menstruation	date		00.00.0000	
1.1.62		menarche	date		00.00.0000	
1.1.63		anticonception	multiple choice, simple		empty space	
1.1.64		vaccinations	multiple choice, simple		empty space	
1.1.65		alcohol	multiple choice, simple		empty space	
1.1.66		smoking	multiple choice, simple		empty space	
1.1.67		allergies	multiple choice, simple		empty space	

1.1.68		drugs	multiple choice, simple	empty space	
1.1.69		illicit drugs	multiple choice, simple	empty space	
1.1.70		additional comments	text	empty space	
	Social history				
1.1.71		marital status	multiple choice, simple	empty space	
1.1.72		children	number	empty space	
1.1.73		profession	text	empty space	
1.1.74		retired since	date	00.00.0000	
1.1.75		hobbies	text	empty space	
1.1.76		military service	yes/no	empty space	yes, no
1.1.77		pets	multiple choice, simple	empty space	none, freetext
1.1.78		travel history	multiple choice, simple	empty space	freetext
1.1.79		dependency	multiple choice, simple	empty space	freetext
1.1.80		living condition	text	empty space	
1.1.81		additional comments	text	empty space	
	Family history				
			data type	default	choice
1.2.1	parents	father	multiple choice, simple	empty space	healthy, sick, died, unknown; if unknown go to 1.2.7
1.2.2		date of birth, father	date	00.00.0000	
1.2.3		date of death, father	date	00.00.0000	
1.2.4		cause of death, father	text	empty space	

1.2.5		diseases, father	multiple choice, multiple		empty space	diabetes, obesity, hypertension, tuberculosis, asthma, allergies, cancer, rheumatoid diseases, mental illness, epilepsy, others
1.2.6		additional comments, father	text		empty space	
1.2.7		mother	multiple choice, simple		empty space	healthy, sick, died, unknown; if unknown go to 1.2.13
1.2.8		date of birth, mother	date		00.00.0000	
1.2.9		date of death, mother	date		00.00.0000	
1.2.10		cause of death, mother	text		empty space	
1.2.11		diseases, mother	multiple choice, multiple		empty space	healthy, cardiovascular events, diabetes, obesity, hypertension, tuberculosis, asthma, allergies, cancer, rheumatoid diseases, mental illness, epilepsy, others
1.2.12		additional comments, mother	text		empty space	
1.2.13	siblings	siblings	yes/no		empty space	yes, no; if no, go to question 1.2.23
1.2.14		number	number		empty space	
1.2.15		1st sibling	multiple choice, simple		empty space	brother, sister, freetext
1.2.16		health state	multiple choice, simple		empty space	healthy, sick, died, unknown
1.2.17		date of birth, sibling	date		00.00.0000	
1.2.18		date of death, sibling	date		00.00.0000	
1.2.19		cause of death, sibling	text		empty space	
1.2.20		diseases	multiple choice, multiple		empty space	healthy, cardiovascular events, diabetes, obesity, hypertension, tuberculosis, asthma, allergies, cancer,

							rheumatoid diseases, mental illness, epilepsy, others
1.2.21		additional comments, siblings	text			empty space	
1.2.22		additional siblings	yes/no			empty space	yes, no; if yes, go to 1.2.15: 2nd sibling. if no, go to 1.2.23
1.2.23	children	children	yes/no			empty space	yes, no ; if no, go to 1.2.33
1.2.24		number of children	number			empty space	
1.2.25		1st child	multiple choice, simple			empty space	son, daughter
1.2.26		health state	multiple choice, simple			empty space	healthy, sick, died, unknown
1.2.27		date of birth, child	date			00.00.0000	
1.2.28		date of death, child	date			00.00.0000	
1.2.29		cause of death, child	text			empty space	
1.2.30		diseases	multiple choice, multiple			empty space	healthy, cardiovascular events, diabetes, obesity, hypertension, tuberculosis, asthma, allergies, cancer, rheumatoid diseases, mental illness, epilepsy, others
1.2.31		additional comment, child	text			empty space	
1.2.32		additional children	yes/no			empty space	yes, no; if yes, go to 1.2.25: 2nd child if no, go to 1.2.33
1.2.33	comments	additional comments	text			empty space	

number	physical examination						
organ	question		data type	unit	default		multiple choice

	system						
2.1.1	vital sign	temperatur peripheral	number	°C	empty space		
2.1.2		temperatur rectal	number	°C	empty space		
2.1.3		blood pressure left, supine systolic	number	mmHg	empty space		
2.1.4		blood pressure left, supine diastolic	number	mmHg	empty space		
2.1.5		blood pressure left, standing systolic	number	mmHg	empty space		
2.1.6		blood pressure left, standing, diastolic	number	mmHg	empty space		
2.1.7		pulse quality	multiple choice, multiple		empty space	normal, durus, celer, altus, tardus, parvus, alternans, paradoxus, freetext	
2.1.8		pulse, left supine	number	bpm	empty space		
2.1.9		pulse, left standing	number	bpm	empty space		
2.1.10		blood pressure right supine systolic	number	mmHg	empty space		
2.1.11		blood pressure right supine diastolic	number	mmHg	empty space		
2.1.12		blood pressure right standing systolic	number	mmHg	empty space		
2.1.13		blood pressure right standing, diastolic	number	mmHg	empty space		
2.1.14		pulse quality	multiple choice, simple		empty space	normal, durus, celer, altus, tardus, parvus, alternans, paradoxus, freetext	
2.1.15		pulse, right supine	number	bpm	empty space		
2.1.16		pulse, right standing	number	bpm	empty space		
2.1.17		respiration	number	bpm	empty space		
2.1.18		general appearance	multiple choice, simple		empty space	well, acutely ill, compromised, severely ill, critically ill, freetext	

2.1.19		orientation	multiple choice, multiple		empty space	fully oriented, desoriented for time, desoriented for place, desoriented for person, hallucinations, obsessions, recent memory impaired, remote memory impaired, freetext
2.1.20		mental state	multiple choice, simple		empty space	normal, depressive, anxious, emotionally labile, freetext
2.1.21		speech	multiple choice, simple		empty space	normal, fluent, aphasia, dysarthria, freetext
2.1.22		nutritional state	multiple choice, simple		empty space	normal, obese, cachectic, freetext
2.1.23		body	multiple choice, simple		empty space	normal, athletic, pycnic, leptosomal, freetext
2.1.24		other comments	text		empty space	
2.1.25					empty space	
2.1.26	anthropometry	age	number	years	empty space	calculated (from date of birth and current date)
2.1.27		gender	multiple choice, simple		empty space	male, female, freetext
2.1.28		ethnic origin	multiple choice, simple		empty space	caucasian, mediterranean, asia, africa, south america, freetext
2.1.29		body weight	number	kg	empty space	
2.1.30		size	number	m	empty space	
2.1.31		body mass index	number	kg/m2	empty space	calculated
2.1.32		waist circumference	number	cm	empty space	
2.1.33		hip circumference	number	cm	empty space	
2.1.34		waist hip ratio	number		empty space	calculated
2.1.35		other comments	text		empty space	
2.1.36	skin	color, pigmentation	multiple choice, multiple		empty space	normal, dark, black, red, icteric, pale, freetext
2.1.37		teleangiectasies	yes/no		empty space	if no, go to 2.1.39

2.1.38		localization	multiple choice, multiple		empty space	generalized, head, neck, trunc, left arm, right arm, left leg, right leg, freetext
2.1.39		lipid storage lesions	yes/no		empty space	if no, go to 2.1.42
2.1.40		type	multiple choice, multiple		empty space	xanthelasma, xanthoma, freetext
2.1.41		localization	multiple choice, multiple		empty space	generalized, head, neck, trunc, left arm, right arm, left leg, right leg, freetext
2.1.42		exanthema	yes/no		empty space	if no, go to 2.1.47
2.1.43		primary lesion	multiple choice, multiple		empty space	none, urticaria, macula, papula, plaque, knods, bulla, vesicle, pustule, scales, freetext
2.1.44		localization	multiple choice, multiple		empty space	generalized, head, neck, trunc, left arm, right arm, left leg, right leg, freetext
2.1.45		secondary lesion	multiple choice, multiple		empty space	none, crusts, erosion, excoriation, ulcer, scar, freetext
2.1.46		localization	multiple choice, multiple		empty space	generalized, head, neck, trunc, left arm, right arm, left leg, right leg, freetext
2.1.47		hematoma	multiple choice, multiple		empty space	none, petechia, ekchymosis, purpura, freetext
2.1.48		localization	multiple choice, multiple		empty space	generalized, head, neck, trunc, left arm, right arm, left leg, right leg, freetext
2.1.49		benign tumors	multiple choice, multiple		empty space	none, naevi, fibroma, verruca senilis, neurofibroma, freetext
2.1.50		localization	multiple choice, multiple		empty space	generalized, head, neck, trunc, left arm, right arm, left leg, right leg, freetext
2.1.51		malignant tumors	multiple choice, multiple		empty space	none, actinic hyperkeratosis, spinalioma, basalioma,

							melanoma, Kaposi sarcoma, freetext
2.1.52		localization		multiple choice, multiple		empty space	generalized, head, neck, trunc, left arm, right arm, left leg, right leg, freetext
2.1.53		primary hair		multiple choice, multiple		empty space	normal, alopecia, abdominal baldness, hypertrichosis, freetext
2.1.54		secondary hair		multiple choice, multiple		empty space	normal, male hairtype, female hairtype, hirsutism, freetext
2.1.55		nails		multiple choice, multiple		empty space	normal, leukonychia, white bands, onychomycosis, splinter hemorrhages, shallow pitting, freetext
2.1.56		hidrosis		multiple choice, multiple		empty space	normal, hyperhidrosis, dry skin, freetext
2.1.57		breast left		multiple choice, multiple		empty space	normal, atrophic, enlarged, nodule, inverted nipple, peau d'orange, freetext
2.1.58		breast right		multiple choice, multiple		empty space	normal, atrophic, enlarged, nodule, inverted nipple, peau d'orange, freetext
2.1.59		scars		yes/no		empty space	if no, go to 2.1.62
2.1.60		number		number		empty space	
2.1.61		localization		text		empty space	
2.1.62		implants		multiple choice, multiple		empty space	none, port-à-cath, pacemaker, defibrillator, artificial joint, freetext
2.1.63		other comments		text		empty space	
	musculoskeletal system			multiple choice, simple		empty space	normal, kyphosis, lordosis, skoliosis, freetext
2.1.64		vertebral column		number		empty space	
2.1.65		Schober		number		empty space	
2.1.66		Ott		number		empty space	

2.1.67		painful areas		yes/no		empty space	cervical vertebral column, thoracic vertebral column, lumbal vertebral column, sacrum, freetext
2.1.68		localization		multiple choice, multiple		empty space	
2.1.69		joints		multiple choice, simple		empty space	normal, abnormal, freetext
2.1.70		localization		multiple choice, multiple		empty space	left shoulder, right shoulder, left elbow, right elbow, left carporadial, right carporadial, left carpoulnar, right carpoulnar, left carpophalangeal, right carpophalangeal, left proximal interphalangeal, right proximal interphalangeal, left distal interphalangeal, right distal interphalangeal, left distal hip, left knee, right knee, left ankle, right ankle, left tarsophalangeal, right tarsophalangeal, left interphalangeal, right interphalangeal, freetext
2.1.71		mobility		multiple choice, simple		empty space	normal, hypermobile, limited, freetext
2.1.72		localization		multiple choice, multiple		empty space	left shoulder, right shoulder, left elbow, right elbow, left carporadial, right carporadial, left carpoulnar, right carpoulnar, left carpophalangeal, right carpophalangeal, left proximal interphalangeal, right proximal interphalangeal, left distal interphalangeal, right distal

						interphalangeal, left hip, right hip, left knee, right knee, left ankle, right ankle, left tarsophalangeal, right tarsophalangeal, left interphalangeal, right interphalangeal, freetext
2.1.73			effusion		yes/no	empty space
						if no, go to 2.1.75 left shoulder, right shoulder, left elbow, right elbow, left carporadial, right carporadial, left carpoulnar, right carpoulnar, left carpophalangeal, right carpophalangeal, left proximal interphalangeal, right proximal interphalangeal, left distal interphalangeal, right distal interphalangeal, left hip, right hip, left knee, right knee, left ankle, right ankle, left tarsophalangeal, right tarsophalangeal, left interphalangeal, right interphalangeal, freetext
2.1.74			localization		multiple choice, multiple	empty space
2.1.75			inflammation		yes/no	empty space
						if no, go to 2.1.77

2.1.76					localization	multiple choice, multiple				empty space	left shoulder, right shoulder, left elbow, right elbow, left carporadial, right carporadial, left carpoulnar, right carpoulnar, left carpophalangeal, right carpophalangeal, left proximal interphalangeal, right proximal interphalangeal, left distal interphalangeal, right distal interphalangeal, left hip, right hip, left knee, right knee, left ankle, right ankle, left tarsophalangeal, right tarsophalangeal, left interphalangeal, right interphalangeal, freetext
2.1.77					deformation	yes/no				empty space	if no, go to 2.1.79
2.1.78					localization	multiple choice, multiple				empty space	left shoulder, right shoulder, left elbow, right elbow, left carporadial, right carporadial, left carpoulnar, right carpoulnar, left carpophalangeal, right carpophalangeal, left proximal interphalangeal, right proximal interphalangeal, left distal interphalangeal, right distal interphalangeal, left hip, right hip, left knee, right knee, left ankle, right ankle, left tarsophalangeal, right tarsophalangeal, left interphalangeal, right interphalangeal, freetext
2.1.79					other comments	text				empty space	

2.1.80	legs	edema		yes/no		empty space	none, port wine stains left, port wine stains right, branch varicosis left, branch varicosis right, trunc varicosis left, trunc varicosis right, freetext
2.1.81		varicosis		multiple choice, multiple		empty space	
2.1.82		other comments		text		empty space	
2.1.83	lymph nodes			multiple choice, multiple		empty space	normal, enlarged, painful, immobile, freetext
2.1.84		localization		multiple choice, multiple		empty space	generalized, cervical left, cervical right, axillary left, axillary right, supraclavicular left, supraclavicular right, inguinal left, inguinal right, freetext
2.1.85		consistency		multiple choice, multiple		empty space	soft, solid, stony, fluctuating, freetext
2.1.86		other comments		text		empty space	
2.1.87	head	meningism		yes/no		empty space	
2.1.88		face motion		multiple choice, multiple		empty space	normal, hypomimia, amimia, tick, freetext
2.1.89		face muscles		multiple choice, multiple		empty space	normal, facial paresis left, facial paresis right, freetext
2.1.90		eyes		multiple choice, multiple		empty space	normal, diminished visual acuity left, diminished visual acuity right, left bulbus painful, right bulbus painful, left bulbus rockhard, right bulbus rockhard, exophthalmus right, exophthalmus left, freetext
2.1.91		lids		multiple choice, multiple		empty space	normal, ptosis left, ptosis right, freetext
2.1.92		conjunctiva		multiple choice, multiple		empty space	normal, red left, red right, freetext

2.1.93		sklera	multiple choice, multiple		empty space	normal, icteric left, icteric right, blue left, blue right, freetext
2.1.94		cornea	multiple choice, multiple		empty space	normal, opacity left, opacity right, freetext
2.1.95		lenses	multiple choice, multiple		empty space	normal, cataract left, cataract right, artificial lens left, artificial lens right, freetext
2.1.96		visual field	multiple choice, multiple		empty space	normal, hemianopsia left, hemianopsia right, bitemporal hemianopsia, freetext
2.1.97		bulbus motion	multiple choice, multiple		empty space	normal, convergent strabism, divergent strabism, conjugated gaze palsy, freetext.
2.1.98		nystagmus (fast component to left)	yes/no		empty space	
2.1.99		nystagmus (fast component to right)	yes/no		empty space	
2.1.100		pupil left	multiple choice, multiple		empty space	normal, miotic, mydriatic, freetext
2.1.101		pupil right	multiple choice, multiple		empty space	normal, miotic, mydriatic, freetext
2.1.102		pupil motion light left	multiple choice, multiple		empty space	normal, weak, absent, freetext
2.1.103		pupil motion light right	multiple choice, multiple		empty space	normal, weak, absent, freetext
2.1.104		pupil motion convergence left	multiple choice, multiple		empty space	normal, weak, absent, freetext
2.1.105		pupil motion convergence right	multiple choice, multiple		empty space	normal, weak, absent, freetext
2.1.106		eyes fundus left	multiple choice, multiple		empty space	normal, arteriovenous crossings, cotton wool, bleedings, hardexudates, swollen disk, freetext
2.1.107		eyes fundus right	multiple choice, multiple		empty space	normal, arteriovenous crossings, cotton wool,

						bleedings, hard exsudates, swollen disk, freetext
2.1.108		nose		multiple choice, multiple	empty space	normal, rhinophym, freetext
2.1.109		nose breathing		multiple choice, multiple	empty space	normal, obstruction left, obstruction right, freetext
2.1.110		lips		multiple choice, multiple	empty space	normal, cyanotic, strawberry red, perleche, freetext
2.1.111		teeth		multiple choice, multiple	empty space	normal, healthy, loose, missing, prosthesis, erosions, sensitivity, freetext
2.1.112		gums		multiple choice, multiple	empty space	normal, hypertrophic, atrophic, inflamed, freetext
2.1.113		tongue		multiple choice, multiple	empty space	normal, atrophic, strawberry tongue, glossitis, macroglossia, white patches, freetext
2.1.114		mucus membrane		multiple choice, multiple	empty space	normal, ulcers, xerostomia, koplik spots, freetext
2.1.115		palate		multiple choice, multiple	empty space	normal, red, white patches, freetext
2.1.116		gag reflex		multiple choice, multiple	empty space	normal, decreased, absent, increased, freetext
2.1.117		tonsils		multiple choice, multiple	empty space	normal, enlarged, red, stipples, purulent, state after tonsilectomy, freetext
2.1.118		foetor		multiple choice, multiple	empty space	normal, ethylic, nicotinic, uremic, hepatic, anaerobic, freetext
2.1.119		hearing		multiple choice, multiple	empty space	normal, reduced, missing, Weber to left, Weber to right, Rinné abnormal left, Rinné abnormal right, freetext
2.1.120		other comments		text	empty space	
2.1.121	cervical	thyroid		multiple choice,	empty space	normal, homogenous goiter

2.1.122		other comments	multiple			empty space	nodular goiter, freetext
2.1.123	cardio-vascular	peripheral circulation	text multiple choice, multiple			empty space	normal, cold skin, warm skin, freetext
2.1.124		cyanosis	multiple choice, multiple			empty space	none, central, akral, freetext
2.1.125		edema	multiple choice, multiple			empty space	none, generalized, face, legs, left leg, right leg, freetext
2.1.126		jugular veins	multiple choice, multiple			empty space	normal, distended, Kussmaul sign, underfilled, freetext
2.1.127		hepatjugular reflux	negative/positive			empty space	
2.1.128		vein pulsations	yes/no			empty space	
2.1.129		other comments	text			empty space	
2.1.130		left apical impulse	multiple choice, multiple			empty space	normal, enlarged point of maximal impulse, prolonged, lateral displacement, freetext
2.1.131		right apical impulse	multiple choice, simple			empty space	absent, present
2.1.132		rhythm	multiple choice, multiple			empty space	regular, extrasystoles, absolute arrhythmia, freetext
2.1.133		systolic murmur	yes/no			empty space	if no, go to 2.1.139
2.1.134		intensity	multiple choice, multiple			empty space	1/6, 2/6, 3/6, 4/6, 5/6, 6/6
2.1.135		maximal intensity	multiple choice, multiple			empty space	2nd ICS parasternal right, 2nd ICS parasternal left, Erb, PMI, freetext
2.1.136		quality	multiple choice, multiple			empty space	pure, coarse, rumbling, low pitched, medium pitched, high pitched, freetext
2.1.137		duration	multiple choice, multiple			empty space	early, late, holosystolic, freetext
2.1.138		transmission	multiple choice, multiple			empty space	carotids, axilla, freetext

2.1.139		diastolic murmur		yes/no		empty space	if no, go to 2.1.2.1.144
2.1.140		maximal intensity		multiple choice, multiple		empty space	2nd ICS parasternal right, 2nd ICS parasternal left, Erb, PMI, freetext
2.1.141		quality		multiple choice, multiple		empty space	pure, coarse, rumbling, low pitched, medium pitched, high pitched, freetext
2.1.142		duration		multiple choice, multiple		empty space	early, late, holodiastolic, freetext
2.1.143		transmission		multiple choice, multiple		empty space	carotid, axilla, freetext
2.1.144		S1		multiple choice, multiple		empty space	normal, accentuated, split, freetext
2.1.145		S2		multiple choice, multiple		empty space	normal, accentuated, split, freetext
2.1.146		S3		yes/no		empty space	
2.1.147		S4		yes/no		empty space	
2.1.148		right temporal artery		multiple choice, multiple		empty space	normal, weak, painful, absent, freetext
2.1.149		left temporal artery		multiple choice, multiple		empty space	normal, weak, painful, absent, freetext
2.1.150		right carotid artery		multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.151		left carotid artery		multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.152		right radial artery		multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.153		left radial artery		multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.154		right femoral artery		multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.155		left femoral artery		multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.156		right popliteal artery		multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext

2.1.157		left popliteal artery	multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.158		right tibial posterior artery	multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.159		left tibial posterior artery	multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.160		right tibial anterior artery	multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.161		left tibial anterior artery	multiple choice, multiple		empty space	normal, weak, absent, bruit, freetext
2.1.162		aorta	multiple choice, multiple		empty space	normal, enlarged, bruit, freetext
2.1.163		vascular bruits	yes/no		empty space	if no, go to 2.1.165
2.1.164		localization	text		empty space	
2.1.165		ABI resting left	number		empty space	
2.1.166		ABI resting right	number		empty space	
2.1.167		ABI stress left	number		empty space	
2.1.168		ABI stress right	number		empty space	
2.1.169		other comments	text		empty space	
2.1.170	thorax&lungs		multiple choice, multiple			normal, barrel shape, pectus carinatum, pectus excavatum, freetext
		form	multiple choice, multiple		empty space	symmetric, asymmetric, freetext
2.1.171		respiratory motion	multiple choice, multiple		empty space	freetext
2.1.172		periodicity of respiration	multiple choice, multiple		empty space	normal, Kussmaul, Cheyne Stokes, Biot, apnea, freetext
2.1.173		fremitus left	yes/no		empty space	
2.1.174		fremitus right	yes/no		empty space	
2.1.175		whispered voice left	yes/no		empty space	
2.1.176		whispered voice right	yes/no		empty space	
2.1.177		palpation left	multiple choice, simple		empty space	normal, freetext
2.1.178		palpation right	multiple choice, multiple		empty space	normal, freetext

			simple						
2.1.179		percussion left	multiple choice, simple			empty space		normal, hypersonoric, dull, freetext	
2.1.180		percussion right	multiple choice, simple			empty space		normal, hypersonoric, dull, freetext	
2.1.181		auscultation left	multiple choice, multiple			empty space		normal, vesicular, tubular, wheezes, rales, stridor, pleural rub, freetext	
2.1.182		localization	multiple choice, multiple			empty space		upper ventral, mid ventral, lower ventral, upper dorsal, mid dorsal, lower dorsal	
2.1.183		auscultation right	multiple choice, multiple			empty space		normal, vesicular, tubular, wheezes, rales, stridor, pleural rub, freetext	
2.1.184		localization	multiple choice, multiple			empty space		upper ventral, mid ventral, lower ventral, upper dorsal, mid dorsal, lower dorsal	
2.1.185		other comments	text			empty space			
2.1.186	abdomen	tenderness	multiple choice, multiple			empty space		normal, tender, abnormal, freetext	
2.1.187		localization	multiple choice, multiple			empty space		left upper quadrant, left lower quadrant, right upper quadrant, right lower quadrant	
2.1.188		resistance	multiple choice, multiple			empty space		none, guarding, induced guarding, rebound tenderness, referred rebound tenderness, tumor, freetext	
2.1.189		localization	multiple choice, multiple			empty space		left upper quadrant, left lower quadrant, right upper quadrant, right lower quadrant	
2.1.190		maximal intensity	multiple choice, multiple			empty space		left upper quadrant, left lower quadrant, right upper quadrant, right lower quadrant	
2.1.191		ascites	multiple choice, simple			empty space		none, possible, sure	

2.1.192		bowel sounds	multiple choice, multiple		empty space	normal, high pitched, absent, increased, bruits, freetext
2.1.193		liver	number	cm in MCL	empty space	
2.1.194		liver (scratch)	number	cm in MCL	empty space	
2.1.195		liver consistency	multiple choice, multiple		empty space	normal, solid, rockhard, nodular, painful, freetext
2.1.196		spleen	multiple choice, multiple		empty space	absent, freetext
2.1.197		kidney left	multiple choice, multiple		empty space	normal, painful, freetext
2.1.197		kidney right	multiple choice, multiple		empty space	normal, painful, freetext
2.1.198		hernias	multiple choice, multiple		empty space	normal, hernia right, hernia left, freetext
2.1.199		genital organs	multiple choice, multiple		empty space	normal, hydrocele right, hydrocele left, freetext
2.1.200		urinary catheter	yes/no		empty space	
2.1.201		rectal	multiple choice, multiple		empty space	normal, hemorrhoids, marisks, polyps, freetext
2.1.202		prostate	multiple choice, multiple		empty space	normal, solid, painful, enlarged, rockhard, fluctuating, freetext
2.1.203		Courvoisier sign	yes/no			
2.1.204		Mc Burney sign	yes/no			
2.1.205		Psoas sign left	yes/no			
2.1.206		Psoas sign right	yes/no			
2.1.207		other comments	text		empty space	
2.1.208	nervous system	odor	multiple choice, multiple		empty space	normal, absent, freetext
2.1.209		corneal reflex	multiple choice, simple		empty space	normal, absent right, absent left, freetext
2.1.210		palate	multiple choice,		empty space	symmetric, palsy right, palsy

			simple			left, freetext
2.1.211		swallowing	multiple choice, simple		empty space	normal, freetext
2.1.212		trunc motion	multiple choice, simple		empty space	normal, freetext
2.1.213		trunc sensibility	multiple choice, simple		empty space	
2.1.214		upper extremity, right, tonus	multiple choice, simple		empty space	normal, reduced, flaccid, rigor, spasm, freetext
2.1.215		upper extremity, right, strength	multiple choice, simple		empty space	M5 (normal), M4, M3, M2, M1, M0, freetext
2.1.216		upper extremity, right, position	multiple choice, simple		empty space	normal, signe du cinquieme doigt, main creuse, paresis, palsy, freetext
2.1.217		upper extremity, right, diadochokinesis	multiple choice, simple		empty space	normal, dysdiadochokinesis, adiadochokinesis, freetext
2.1.218		upper extremity, right, finger to nose	multiple choice, simple		empty space	normal, dysmetric, freetext
2.1.219		upper extremity, right, touch	multiple choice, simple		empty space	normal, reduced, freetext
2.1.220		upper extremity, right, pain	multiple choice, simple		empty space	normal, reduced, freetext
2.1.221		upper extremity, right, temperature	multiple choice, simple		empty space	normal, reduced, freetext
2.1.222		upper extremity, right, vibration	multiple choice, simple		empty space	normal, reduced, freetext
2.1.223		upper extremity, left, tonus	multiple choice, simple		empty space	normal, reduced, flaccid, rigor, spasm, freetext
2.1.224		upper extremity, left, strength	multiple choice, simple		empty space	M5 (normal), M4, M3, M2, M1, M0, freetext
2.1.225		upper extremity, left, position	multiple choice, simple		empty space	normal, signe du cinquieme doigt, main creuse, paresis, palsy, freetext
2.1.226		upper extremity, left, diadochokinesis	multiple choice, simple		empty space	normal, dysdiadochokinesis, adiadochokinesis, freetext

2.1.227		upper extremity, left, finger to nose	multiple choice, simple		empty space	normal, dysmetric, freetext
2.1.228		upper extremity, left, touch	multiple choice, simple		empty space	normal, reduced, freetext
2.1.229		upper extremity, left, pain	multiple choice, simple		empty space	normal, reduced, freetext
2.1.230		upper extremity, left, temperature	multiple choice, simple		empty space	normal, reduced, freetext
2.1.231		upper extremity, left, vibration	multiple choice, simple		empty space	normal, reduced, freetext
2.1.232		lower extremity, right, tonus	multiple choice, simple		empty space	normal, reduced, flaccid, rigor, spasm, freetext
2.1.233		lower extremity, right, strength	multiple choice, simple		empty space	M5 (normal), M4, M3, M2, M1, M0, freetext
2.1.234		lower extremity, right, position	multiple choice, simple		empty space	normal, paresis, palsy, freetext
2.1.235		lower extremity, right, diadochokinesis	multiple choice, simple		empty space	normal, dysdiadochokinesis, adiadochokinesis, freetext
2.1.236		lower extremity, right, heel to knee	multiple choice, simple		empty space	normal, dysmetric, freetext
2.1.237		lower extremity, right, Lasègue	negative/positive		empty space	
2.1.238		angle	number	°	empty space	
2.1.239		lower extremity, right, inverted Lasègue	negative/positive		empty space	
2.1.240		lower extremity, right, touch	multiple choice, simple		empty space	normal, reduced, freetext
2.1.241		lower extremity, right, pain	multiple choice, simple		empty space	normal, reduced, freetext
2.1.242		lower extremity, right, temperature	multiple choice, simple		empty space	normal, reduced, freetext
2.1.243		lower extremity, right, vibration	multiple choice, simple		empty space	normal, reduced, freetext
2.1.244		lower extremity, left, tonus	multiple choice, simple		empty space	normal, reduced, flaccid, rigor, spasm, freetext

2.1.245		lower extremity, left, strengt	multiple choice, simple		empty space	M5 (normal), M4, M3, M2, M1, M0, freetext
2.1.246		lower extremity, left, position	multiple choice, simple		empty space	normal, paresis, palsy, freetext
2.1.247		lower extremity, left, diadochokinesis	multiple choice, simple		empty space	normal, dysdiadochokinesis, adiadochokinesis, freetext
2.1.248		xtremity, left, heel to knee	multiple choice, simple		empty space	normal, dysmetric, freetext
2.1.249		lower extremity, left, Lasègue	negative/positive		empty space	
2.1.250		angle	number	°	empty space	
2.1.251		lower extremity, left, inverted Lasègue	negative/positive		empty space	
2.1.252		lower extremity, left, touch	multiple choice, simple		empty space	normal, reduced, freetext
2.1.253		lower extremity, left, pain	multiple choice, simple		empty space	normal, reduced, freetext
2.1.254		lower extremity, left, temperature	multiple choice, simple		empty space	normal, reduced, freetext
2.1.255		lower extremity, left, vibration	multiple choice, simple		empty space	normal, reduced, freetext
2.1.256		Romberg	multiple choice, simple		empty space	normal, drop to left, drop to right, undirected dropping, freetext
2.1.257		gait	multiple choice, simple		empty space	normal, small steps, wide-based, steppage, freetext
2.1.258		limping	multiple choice, simple		empty space	normal, Duchenne left, Duchenne right, Trendelenburg left, Trendelenburg right, freetext
2.1.259		Unterberg test	multiple choice, simple		empty space	normal, rotating to left, rotating to right, freetext
2.1.260		biceps (C6) right	multiple choice, simple		empty space	normal, absent, missing, hyperactive, freetext
2.1.261		biceps (C6) left	multiple choice, simple		empty space	normal, absent, missing,

				simple				hyperactive, freetext
2.1.262		triceps (C7) right		multiple choice, simple			empty space	normal, absent, missing, hyperactive, freetext
2.1.263		triceps (C7) left		multiple choice, simple			empty space	normal, absent, missing, hyperactive, freetext
2.1.264		Knips/Trömner right		negative/positiv e			empty space	
2.1.265		Knips/Trömner left		negative/positiv e			empty space	
2.1.266		abdominal right		multiple choice, simple			empty space	normal, absent, missing, hyperactive, freetext
2.1.267		abdominal left		multiple choice, simple			empty space	normal, absent, missing, hyperactive, freetext
2.1.268		knee (L4) right		multiple choice, simple			empty space	normal, absent, missing, hyperactive, freetext
2.1.269		knee (L4) left		multiple choice, simple			empty space	normal, absent, missing, hyperactive, freetext
2.1.270		ankle (S1) right		multiple choice, simple			empty space	normal, absent, missing, hyperactive, freetext
2.1.271		ankle (S1) left		multiple choice, simple			empty space	normal, absent, missing, hyperactive, freetext
2.1.272		babinski right		negative/positiv e			empty space	
2.1.273		babinski left		negative/positiv e			empty space	

Appendix II: Numerical variables obtained from the patients.

Code number	Parameter	Method [§]	No cardiovascular events (total 110 patients)		Symptomatic arteriosclerosis (total 100 patients)		P-value #
			Median	n (%)	Median	n (%)	
I	Age (years)	H	56.00	110 (100)	72.00	100 (100)	<0.001
II	Weight (kg)	C	72.30	109 (99.1)	75.35	98 (98)	0.385
III	Height (m)	C	1.67	103 (93.6)	1.68	89 (89)	0.754
IV	Body mass index ¹ (kg/m ²)	C	25.60	103 (93.6)	26.40	88 (88)	0.0085
V	Waist circumference ² (cm)	C	95.00	97 (88.2)	99.50	84 (84)	0.006
VI	Hip circumference ² (cm)	C	100.00	97 (88.2)	101.50	84 (84)	0.078
VII	Waist hip ratio ²	C	0.94	97 (88.2)	1.00	84 (84)	0.006
VIII	Systolic blood pressure left arm supine (mmHg)	C	130.00	108 (98.2)	140.00	97 (97)	0.001
IX	Diastolic blood pressure left arm supine (mmHg)	C	80.00	108 (98.2)	80.00	97 (97)	0.421
X	Systolic blood pressure right arm supine (mmHg)	C	130.00	109 (99.1)	135.00	95 (95)	0.005
XI	Diastolic blood pressure right arm supine (mmHg)	C	80.00	109 (99.1)	80.00	95 (95)	0.717
XII	Peripheral heart rate supine (bpm)	C	76.00	109 (99.1)	72.00	100 (100)	0.124
XIII	Systolic blood pressure left arm standing (mmHg)	C	120.00	101 (91.8)	130.00	79 (79)	<0.001
XIV	Diastolic blood pressure left arm standing (mmHg)	C	80.00	101 (91.8)	80.00	79 (79)	0.464
XV	Systolic blood pressure right arm standing (mmHg)	C	120.00	100 (90.9)	130.00	78 (78)	0.007
XVI	Diastolic blood pressure right arm standing (mmHg)	C	80.00	101 (91.8)	80.00	78 (78)	0.761
XVII	Peripheral heart rate standing (bpm)	C	80.00	102 (92.7)	78.00	82 (82)	0.02
XVIII	Central heart rate supine (bpm)	C	76.00	109 (99.1)	72.00	100 (100)	0.311
XIX	Ankle brachial index right *	C	1.14	95 (86.4)	1.00	80 (80)	<0.001
XX	Ankle brachial index left *	C	1.15	86 (78.2)	1.02	78 (78)	<0.001

XXI	Hemoglobin (g/dL)	L	13.60	110 (100)	12.55	100 (100)	0.011
XXII	Leukocytes ($10^9/L$)	L	8.50	109 (99.1)	8.30	100 (100)	0.896
XXIII	Thrombocytes ($10^9/L$)	L	253.00	109 (99.1)	259.00	100 (100)	0.738
XXIV	Neutrophile granulocytes ($10^9/L$)	L	5.61	94 (85.5)	5.66	90 (90)	0.991
XXV	Eosinophilic granulocytes ($10^9/L$)	L	0.07	96 (87.3)	0.12	91 (91)	0.077
XXVI	Basophilic granulocytes ($10^9/L$)	L	0.04	96 (87.3)	0.03	90 (90)	0.756
XXVII	Lymphocytes ($10^9/L$)	L	1.70	96 (87.3)	1.60	91 (91)	0.256
XXVIII	Monocytes ($10^9/L$)	L	0.47	96 (87.3)	0.59	89 (89)	0.079
XXIX	HbA1c (%)	L	6.10	18 (16.4)	7.10	33 (33)	
XXX	Blood glucose level after overnight fast (mmol/L)	L	6.20	79 (71.8)	6.00	73 (73)	
XXXI	Cholesterol total (mmol/L)	L	5.00	45 (41)	4.60	68 (68)	
XXXII	LDL cholesterol (mmol/L)	L	3.28	42 (38.2)	2.65	62 (63)	
XXXIII	HDL cholesterol (mmol/L)	L	1.08	44 (40)	1.05	67 (67)	
XXXIV	Triglycerides (mmol/L)	L	1.10	43 (39.1)	1.60	60 (60)	
XXXV	Kreatinin ($\mu\text{mol/L}$)	L	62.00	107 (97.3)	77.00	100 (100)	<0.001
XXXVI	Body surface area (m^2)	L	1.84	103 (93.6)	1.87	89 (89)	0.577
XXXVII	Kreatinin clearance ($\text{mL/min per } 1.73 \text{ m}^2$)	L	103.80	100 (90.9)	72.40	89 (89)	<0.001
XXXVIII	Blood sedimentation rate (mm/h)	L	10.00	79 (71.8)	13.00	80 (80)	0.086
XXXIX	C-reactive protein (mg/L)	L	7.00	104 (94.6)	9.00	97 (97)	0.534
XL	Creatine kinase (U/L)	L	98.50	84 (76.4)	107.00	86 (86)	0.217
XLI	Creatin kinase, MB form (U/L)	L	4.00	25 (22.7)	6.00	52 (52)	
XLII	Troponin I (ng/mL)	L	0.02	26 (23.6)	0.04	43 (43)	
XLIII	GOT/ASAT (U/L)	L	23.00	104 (94.6)	25.00	95 (95)	0.272
XLIV	GPT/ALAT (U/L)	L	24.00	104 (94.6)	23.00	95 (95)	0.903
XLV	Alkaline phosphatase (U/L)	L	67.00	99 (90)	77.00	88 (88)	0.197
XLVI	Gamma glutamyl transpeptidase GGT (U/L)	L	41.00	43 (39.1)	61.50	34 (34)	
XLVII	D-dimer ($\mu\text{g/L}$)	L	1.03	23 (20.9)	2.02	11 (11)	
XLVIII	Brain natriuretic peptide	L	256.50	6 (5.5)	220.00	17 (17)	

	(pg/mL)							
XLIX	Thyroid stimulating hormone (mU/L)	L	1.12	36 (32.7)	1.47	41 (41)		
L	INR	L	1.10	107 (97.3)	1.10	92 (92)		0.316
LI	Proteinuria (negative=0, +=1, ++=2, +++=3)	L	0.00	110 (100)	0.00	100 (100)		0.23
LII	Glucosuria (negative=0, +=1, ++=2, +++=3)	L	0.00	110 (100)	0.00	100 (100)		0.003
LIII	Urine leukocytosis (negative=0, +=1, ++=2, +++=3)	L	0.00	110 (100)	0.00	100 (100)		0.647
LIV	Heart rate in ECG (bpm)	E	77.00	98 (89.1)	73.00	93 (93)		0.187
LV	QT time (sec)	E	0.37	95 (86.4)	0.40	90 (90)		<0.001
LVI	Sokolov index right ventricle (mV)	E	0.30	96 (87.3)	0.40	92 (92)		0.494
LVII	Sokolov index left ventricle (mV)	E	1.70	97 (88.2)	1.60	92 (92)		0.514
LVIII	Maximal exercise capacity stress test (W)	O	137.50	10 (9.1)	100.00	9 (9)		
LIX	Lung diameter (cm)	X	28.55	70 (63.6)	29.60	77 (77)		0.35
LX	Heart diameter (cm)	X	13.50	70 (63.6)	15.60	77 (77)		<0.001
LXI	Heart lung ratio	X	0.47	70 (63.6)	0.51	77 (77)		<0.001
LXII	Left ventricular ejection fraction (%)	O	40.50	14 (12.7)	40.00	37 (37)		
LXIII	Age father at time of death (years)	H	73.00	71 (64.6)	74.00	78 (78)		0.09
LXIV	Age mother at time of death (years)	H	80.00	54 (49.1)	80.00	76 (76)		0.88
LXV	Number of siblings	H	2.00	87 (88.2)	2.00	86 (86)		0.693
LXVI	Number of children	H	2.00	110 (100)	2.00	100 (100)		0.028
LXVII	Number of drugs (on admission)	H	2.00	110 (100)	6.00	100 (100)		<0.001
LXVIII	Number of drugs for the treatment of atherosclerosis	H	0.00	110 (100)	3.50	100 (100)		<0.001

	(on admission)						
LXIX	Number of drugs (current)	O	4.00	110 (100)	7.00	100 (100)	<0.001
LXX	Number of drugs for the treatment of atherosclerosis (current)	O	0.00	110 (100)	4.00	100 (100)	<0.001
LXXI	Number of admissions to this hospital	H	0.00	108 (98.2)	1.00	96 (96)	0.002
LXXII	Packyears	H	1.00	110 (100)	15.00	100 (100)	0.018
LXXIII	Number of standard alcoholic drinks	H	0.00	110 (100)	0.00	100 (100)	0.127
LXXIV	If female: age at menarch (years)	H	14.00	55 (91.7 of female patients)	13.25	40 (93.0 of female patients)	0.873
LXXV	If female: age at menopause (years)	H	48.00	29 (48.3 of female patients)	50.00	35 (81.4 of female patients)	0.354
LXXVI	Number of cardiovascular risk factors	H	2.00	110 (100)	3.00	100 (100)	<0.001
LXXVII	Disease activity score	O	0.92	110 (100)	1.51	100 (100)	<0.001

The data of the patient groups are shown as median values. The two patient groups were compared by Mann-Whitney-U-Test.

Data sets with $P < 0.1$ were selected for the disease activity score.

* Patients (7 without cardiovascular events, 6 with symptomatic arteriosclerosis) who had incompressible ankle arteries ($=ABI > 1.5$) were excluded from this analysis.

§ Method by which the data was obtained: H=history, C=clinical examination, L=laboratory test, X=chest X-ray, E=electrocardiography, O=others.

Appendix III: Test for the reproducibility of the clinical data acquisition. Values with <75 % completion of dataset are excluded from this analysis⁺

Code number	Parameter	Method [§]	No cardiovascular Events (n=110)		P-value [#]	Symptomatic arteriosclerosis (n=100)		P-value [#]
			Median (1st period)	Median (2nd period)		Median (1st period)	Median (2nd period)	
XXI	Hemoglobin (g/dL)	L	13.70	13.20	0.144	13.65	12.25	0.002
V	Waist circumference (cm)	C	97.00	87.50	0.020	105.00	95.00	0.003
VI	Hip circumference (cm)	C	102.00	91.00	<0.001	104.00	98.00	0.007
XXVIII	Monocytes (10 ⁹ /L)	L	0.42	0.64	0.002	0.51	0.70	0.012
VII	Waist hip ratio	C	0.94	0.95	0.717	1.00	0.97	0.069
XLIII	GOT/ASAT (U/L)	L	23.00	24.00	0.847	23.00	26.00	0.102
XVIII	Central heart rate supine (bpm)	C	76.00	76.00	0.794	72.00	76.00	0.117
XVII	Peripheral heart rate standing (bpm)	C	80.00	84.00	0.303	72.00	80.00	0.123
LI	Proteinuria (negative=0, +=1, ++=2, +++=3)	L	0.00	0.00	0.863	0.00	0.00	0.153
XXXVIII	Blood sedimentation rate (mm/h)	L	10.00	8.50	0.482	11.00	15.00	0.175
XXXV	Kreatinin (μmol/L)	L	66.50	56.00	0.023	73.00	79.00	0.206
XVI	Diastolic blood pressure right arm standing (mmHg)	C	80.00	80.00	0.148	75.00	80.00	0.213
XV	Systolic blood pressure right arm standing (mmHg)	C	120.00	125.00	0.231	120.00	130.00	0.219
LIX	Lung diameter (cm)	X	28.60	28.75	0.262	28.80	30.05	0.230
XXIII	Thrombocytes (10 ⁹ /L)	L	233.50	282.00	0.029	267.00	252.50	0.241

LXVII	Number of drugs (on admission)	H	3.00	1.00	0.006	5.00	6.00	0.243
LXI	Heart lung ratio	X	0.47	0.47	0.634	0.52	0.50	0.252
LXXV	If female: age at menopause (years)	H	43.00	53.00	0.046	53.00	50.00	0.254
XIII	Systolic blood pressure left arm standing (mmHg)	C	120.00	122.50	0.424	130.00	130.00	0.267
XXVII	Lymphocytes ($10^9/L$)	L	1.60	2.00	0.057	1.65	1.50	0.271
XII	Peripheral heart rate supine (bpm)	C	76.00	72.00	0.985	70.00	72.00	0.273
LVII	Sokolov index left ventricle (mV)	E	1.80	1.50	0.311	1.45	1.70	0.278
LXXI	Number of admissions to this hospital	H	0.00	0.00	0.055	1.00	1.00	0.280
III	Height (m)	C	1.67	1.67	0.970	1.69	1.67	0.282
XI	Diastolic blood pressure right arm supine (mmHg)	C	80.00	80.00	0.411	80.00	80.00	0.309
I	Age (years)	H	58.00	51.00	0.018	73.50	72.00	0.317
LXXIII	Number of standard alcoholic drinks	H	0.00	0.00	0.991	0.75	0.00	0.347
XXVI	Basophilic granulocytes ($10^9/L$)	L	0.03	0.05	0.019	0.03	0.04	0.383
XLV	Alkaline phosphatase (U/L)	L	67.00	68.00	0.907	77.00	78.00	0.395
LXIII	Age father at time of death (years)	H	74.00	74.50	0.756	73.00	72.00	0.430
LXIX	Number of drugs (current)	O	4.00	3.00	0.040	6.00	7.00	0.435
XXXIX	C-reactive protein (mg/L)	L	4.00	34.00	0.001	8.00	16.00	0.443
LXV	Number of siblings	H	2.00	2.00	0.672	3.00	3.00	0.460
XXXVII	Kreatinin clearance (mL/min per $1.73 m^2$)	L	91.12	122.00	0.009	73.85	70.54	0.533
LXIV	Age mother at time of death (years)	H	80.00	87.00	0.643	82.00	78.00	0.542

LII	Glucosuria (negative=0, +=1, ++=2, +++=3)	L	0.00	0.00	0.711	0.00	0.00	0.550
XXXVI	Body surface area (m ²)	C	1.85	1.81	0.826	1.87	1.86	0.568
XL	Creatine kinase (U/L)	L	98.50	96.00	0.784	99.00	111.00	0.593
LXVI	Number of children	H	2.00	2.00	0.554	2.00	2.00	0.619
LXX	Number of drugs for the treatment of atherosclerosis (current)	O	1.00	0.00	0.001	4.00	4.50	0.641
LVI	Sokolov index right ventricle (mV)	E	0.40	0.30	0.924	0.40	0.40	0.652
II	Weight (kg)	C	73.35	70.10	0.678	75.00	75.70	0.665
LX	Heart diameter (cm)	X	13.55	13.20	0.726	15.60	15.55	0.669
XIX	Ankle brachial index right *	C	1.14	1.14	0.957	1.07	1.00	0.681
LXXVI	Number of cardiovascular risk factors	H	2.00	2.00	0.939	3.00	3.00	0.698
XX	Ankle brachial index left *	C	1.16	1.14	0.349	1.05	1.00	0.710
LIV	Heart rate in ECG (bpm)	E	77.00	77.00	0.658	78.00	72.00	0.720
XXIV	Neutrophile granulocytes (10 ⁹ /L)	L	4.54	7.10	0.020	5.23	6.15	0.746
LXXIV	If female: age at menarch (years)	H	14.00	14.00	0.624	13.00	13.50	0.757
LIII	Urine leukocytosis (negative=0, +=1, ++=2, +++=3)	L	0.00	0.00	0.501	0.00	0.00	0.762
XIV	Diastolic blood pressure left arm standing (mmHg)	C	80.00	82.50	0.099	80.00	80.00	0.765
XXII	Leukocytes (10 ⁹ /L)	L	7.30	9.70	0.023	8.25	8.40	0.800
LXVIII	Number of drugs for the treatment of atherosclerosis (on admission)	H	1.00	0.00	0.001	3.00	4.00	0.806
XLIV	GPT/ALAT (U/L)	L	23.00	25.00	0.218	23.00	22.50	0.816

LV	QT time (sec)	E	0.38	0.37	0.973	0.40	0.40	0.818
L	INR	L	1.10	1.00	0.002	1.10	1.10	0.824
IX	Diastolic blood pressure left arm supine (mmHg)	C	80.00	80.00	0.654	80.00	80.00	0.868
XXV	Eosinophilic granulocytes ($10^9/L$)	L	0.07	0.09	0.222	0.13	0.09	0.907
X	Systolic blood pressure right arm supine (mmHg)	C	130.00	125.00	0.731	140.00	135.00	0.931
IV	Body mass index (kg/m^2)	C	25.68	25.40	0.959	26.20	26.76	0.933
VIII	Systolic blood pressure left arm supine (mmHg)	C	125.00	130.00	0.790	140.00	140.00	0.951
LXXVII	Disease activity score	O	1.00	0.88	0.132	1.49	1.50	0.981
LXXII	Packyears	H	0.00	3.00	0.817	15.00	10.00	0.996

+ Numeric data sorted by P-value for patients with symptomatic arteriosclerosis (low $\rightarrow$ high).

* Patients (7 without cardiovascular events, 6 with symptomatic arteriosclerosis) who had incompressible ankle arteries ($=ABI>1.5$) were excluded from this analysis.

The numeric data obtained during the two study periods were compared using Mann-Whitney-U-Test.

§ Method by which the data was obtained: H=history, C=clinical examination, L=laboratory test, X=chest X-ray, E=electrocardiography, O=others.