Metabolic syndrome and the risk of new vascular events and all-cause mortality in patients with coronary artery disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm

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Aims
To investigate the vascular risk associated with Metabolic Syndrome (MetS) according to different clinical criteria with subsequent vascular events and all-cause mortality in patients with coronary artery disease, cerebrovascular disease, peripheral artery disease or abdominal aortic aneurysm and to examine whether patients with MetS at treatment goals for systolic blood pressure (SBP) or low density lipoprotein-cholesterol (LDL-c) level are still at elevated risk.

Methods and results
Prospective study of 3196 patients with a history or recent diagnosis of clinically manifest vascular disease. During a median follow-up of 3.2 years (interquartile range 1.4–5.4 years), 331 patients died and 373 patients experienced a first vascular event. National Cholesterol Education Program (NCEP) and revised NCEP (NCEP-R)-defined MetS were related to increased risk of vascular events [HR – hazard ratio 1.50 (95% CI – confidence interval 1.22–1.84) and 1.50 (1.22–1.87)] and all-cause mortality [HR 1.49(1.20–1.84) and 1.43 (1.14–1.78)]. Results were similar in the 2472 patients without type 2 diabetes (DM2) and localization of vascular disease; SBP-category (≥140 or <140 mmHg) or LDL-category (<2.5 or ≥2.5 mmol/L) did not affect this relation.

Conclusion
In patients with various manifestations of atherosclerosis, presence of NCEP and NCEP-R-defined MetS is associated with increased risk of cardiovascular events and all-cause mortality, independently of the presence of DM2. This risk is significantly higher than the risk associated with International Diabetes Federation-defined MetS. Also in patients at treatment goals for SBP (<140 mmHg) or LDL-c (<2.5 mmol/L) according to current guidelines, presence of NCEP-R-defined MetS points to a higher vascular risk.

Keywords
Metabolic syndrome • Cardiovascular risk • Localization of atherosclerosis • Systolic blood pressure • LDL-cholesterol • Treatment goals

Introduction
The clustering of several cardiovascular risk factors as hypertension, dyslipidemia and disturbed glucose metabolism associated with central obesity is often referred to as Metabolic Syndrome (MetS). Patients with MetS have a two- to three-fold increased risk for the development of type 2 diabetes mellitus and cardiovascular morbidity and mortality.1–4 In nearly 20–25% of apparently healthy individuals and in 45% of patients with clinical manifestations of atherosclerosis MetS is present.5,6

Presently various definitions for MetS are being used, based on different criteria, among them the definition proposed by the...
World Health Organization (WHO), the National Cholesterol Education Program (NCEP) definition and the definition of the International Diabetes Federation (IDF).7–10 In 2005, the NCEP definition was revised11 by lowering the threshold for fasting glucose from 6.1 to 5.6 mmol/L, in concordance with the American Diabetes Association criteria for impaired fasting glucose.12 Although the various MetS definitions identify different individuals,5,13 the risk for cardiovascular morbidity and mortality was similar in the general population.14–18

A recent subanalysis of the TNT study reported that patients with coronary heart disease (CHD) and MetS particularly derive incremental benefit from intensive lipid-lowering therapy with high-dose atorvastatin in contrast to patients without MetS.19 Patients with manifest atherosclerotic vascular disease are at increased risk for recurrent vascular events and mortality. Current European and US guidelines recommend a low density lipoprotein-cholesterol (LDL-c) level <2.6 mmol/L and a systolic blood pressure (SBP) level <140 mmHg in these high-risk individuals.20,21 In 2004 the National Heart, Lung and Blood Institute’s Adult Treatment Panel (ATP) III suggested an optional further lowering of LDL-c target levels to below 1.8 mmol/L for very high-risk CHD patients, including those with CHD and MetS.22

In patients with manifest vascular disease presence of MetS is associated with advanced vascular damage.23 Among patients with CHD, those with MetS are at increased risk of subsequent vascular events as compared with those without.24

In the present prospective cohort study, we investigated the risk of the NCEP, NCEP-R and IDF-definition of MetS for future vascular events and total mortality in patients with different manifestations of atherosclerotic disease. Furthermore, we investigated whether patients with MetS and clinically manifest atherosclerotic disease with optimal low LDL-c or SBP levels at baseline were still at higher risk of recurrent vascular events or all-cause mortality compared with patients without MetS.

Methods

Study population

Patients originated from the SMART study (Secondary Manifestations of ARTerial disease), an ongoing prospective cohort study at the University Medical Centre Utrecht designed to establish the prevalence of concomitant arterial diseases and risk factors for atherosclerosis in a high-risk population. Study patients were newly referred to the University Medical Centre Utrecht (UMCU) with manifest atherosclerotic disease or a cardiovascular risk factor and were screened non-invasively for manifestations of atherosclerotic diseases and risk factors other than the qualifying diagnosis. A detailed description of the study has been published previously.25 The Ethics Committee of the University Medical Centre Utrecht approved the study and all participants gave their written informed consent.

For the current study we used the data of 3196 consecutive patients, enrolled between January 1996 and March 2005, with either a history or a recent diagnosis of clinically manifest vascular disease: 1750 patients had coronary artery disease (CAD), 935 cerebrovascular disease (CVD), 832 peripheral arterial disease (PAD) and 373 abdominal aortic aneurysm (AAA). A total of 694 patients fell into more categories because they had more than one localization of the clinical manifestation of vascular disease. CAD was defined as either a history or recent diagnosis of angina pectoris, myocardial infarction (MI), cardiac arrest or coronary revascularization (coronary bypass surgery or coronary angioplasty). Patients with CVD had had a transient ischaemic attack, cerebral infarction, amaurosis fugax or retinal infarction, or had a history of carotid surgery. PAD was defined as a symptomatic and documented obstruction of distal arteries of the leg or surgery of the leg (percutaneous transluminal angioplasty, bypass or amputation). Patients with AAA had a suprarenal aneurysm of the aorta (distal aortic anteroposterior diameter ≥3 cm, measured with ultrasonography) or a history of AAA surgery.

Data collection

At inclusion, patients were asked to complete a standardized questionnaire on medical history, symptoms of and risk factors for cardiovascular disease, presence of vascular disease in first-degree relatives and current medication use. Furthermore, a standardized diagnostic protocol was performed including physical examination (height, weight, waist circumference, systolic, and diastolic blood pressure) and laboratory tests to determine fasting serum lipid, glucose and insulin levels. The techniques used for the laboratory tests have been described previously.25 Waist circumference was measured halfway between the lower rib and iliac crest.

Definitions

MetS was defined according to NCEP-criteria,7 revised NCEP (NCEP-R)-criteria11 and IDF-criteria.1 IDF-defined MetS includes ≥3 of the following metabolic abnormalities: abdominal obesity (waist circumference >102 cm in men and >88 cm in women), elevated blood pressure (≥130 mmHg systolic and/or ≥85 mmHg diastolic and/or use of blood pressure lowering agents), hypertriglyceridemia [serum triglycerides ≥1.70 mmol/L (150 mg/dL)], low high-density lipoprotein (HDL) cholesterol (serum HDL-cholesterol <1.04 mmol/L (40 mg/dL) in men and <1.29 mmol/L (50 mg/dL) in women), high fasting glucose (fasting serum glucose ≥6.1 mmol/L (110 mg/dL) and/or use of glucose lowering agents).7 According to the NCEP-R definition, MetS was diagnosed using NCEP criteria except for a lower threshold for fasting glucose (≥5.6 mmol/L).11

Using IDF criteria, MetS was diagnosed in patients who had central obesity (waist circumference >94 cm in men and >80 cm in women) plus two or more of the following abnormalities: high fasting glucose (fasting serum glucose ≥5.6 mmol/L (100 mg/dL) and/or use of glucose lowering agents), hypertriglyceridemia [serum triglycerides ≥1.77 mmol/L (150 mg/dL)], low HDL cholesterol (serum HDL-cholesterol <1.04 mmol/L (40 mg/dL) in men and <1.29 mmol/L (50 mg/dL) in women), high blood pressure (≥130 mmHg systolic and/or ≥85 mmHg diastolic and/or use of blood pressure lowering agents). The use of specific medications as fibrates or nicotinic acid for elevated triglycerides and low HDL-cholesterol was also considered as fulfilling these criteria.7

In the present study, waist circumference was not measured in patients included in the SMART cohort in the period between January 1996 and January 1999. If waist circumference was not available a body mass index (BMI) >30 kg/m² was used as determinant for obesity.8 Diabetes mellitus was defined as either a referral diagnosis of diabetes, self-reported diabetes (use of glucose-lowering agents), a known history of diabetes mellitus at the time of enrolment or a fasting plasma glucose ≥7 mmol/L.8 Fasting plasma glucose measurements were available in 3178 (99%) of 3196 patients.
Table 1 Definitions of fatal/non-fatal vascular events and all-cause mortality

| Event Type                  | Definition                                                                                     |
|----------------------------|-----------------------------------------------------------------------------------------------|
| Vascular death             | Sudden death: unexpected cardiac death occurring within 1 h after onset of symptoms, or within 24 h given convincing circumstantial evidence |
|                            | Death from ischaemic stroke                                                                    |
|                            | Death from intracerebral haemorrhage (haemorrhage on CT-scan)                                   |
|                            | Death from congestive heart failure                                                            |
|                            | Death from myocardial infarction                                                               |
|                            | Death from rupture of abdominal aortic aneurysm                                                |
|                            | Vascular death from other cause, such as sepsis following stent placement                      |
| Ischaemic stroke           | Definite: relevant clinical features that have caused an increase in impairment of at least one grade on the modified Rankin scale, accompanied by a fresh ischaemic infarction on a repeat brain-scan |
|                            | Probable: clinical features that have caused an increase in impairment of at least one grade on the modified Rankin scale; without a fresh ischaemic infarction on a repeat brain-scan |
| Myocardial infarction      | Fatal or non-fatal myocardial infarction: at least two of the following criteria                |
|                            | (i) chest pain for at least 20 min, not disappearing after administration of nitrates          |
|                            | (ii) ST-elevation >1 mm in two following leads or a left bundle branch block on the electrocardiogram |
|                            | (iii) Creatinine kinase (CK) elevation of at least two times the normal value of CK and a myocardial band-fraction >5% of the total CK |
| All-cause mortality        | Death from any cause (both vascular and non-vascular causes)                                   |

Follow-up

Patients were biannually asked to complete a questionnaire on hospitalizations and outpatient clinic visits. Outcomes of interest for this study were MI, ischaemic stroke, vascular death, and a composite of these events (all vascular events). All-cause mortality was recorded as well. Definitions of events are shown in Table 1. When a possible event was reported, hospital discharge letters and results of relevant laboratory and radiology examinations were collected. Death was reported by relatives of the participant, the general practitioner or the vascular specialist. Based on the information from the questionnaire and/or the family, all events were audited by three members of the SMART study Endpoint Committee, comprising physicians from different departments. Follow-up duration (years) was defined as the period between study inclusion and first cardiovascular event or death from any cause, date of loss to follow-up or the preselected date of 1 March 2005. Fifty of the 3196 participants (1.6%) were lost to follow-up due to migration or discontinuation of the study.

Data analysis

Cox proportional hazards analysis was performed to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the occurrence of vascular events and all-cause mortality associated with presence of MetS. If a patient had multiple events, the first recorded event was used in the analyses. The age and gender adjusted association of NCEP-, NCEP-R- and IDF-defined MetS with vascular events was examined in model I. In order to study the prognostic value of MetS taking into account traditional risk factors for atherosclerosis, LDL-c levels and current smoking were additionally included in model II. Other risk factors for atherosclerosis (elevated BMI and triglycerides and low HDL-cholesterol) were not included in this model because they are components of MetS. Subgroup analyses were performed in patients with and without diabetes and in patients with CAD, CVD, PAD, and AAA separately. Because of the fact that some patients fell into more than one vascular disease manifestation category, adjustments were made for the presence of other vascular diseases in each category. Furthermore, the association of NCEP-R-defined MetS with vascular events was studied in different categories of SBP (<140 mmHg and ≥140 mmHg) and LDL-c levels (<2.5 mmol/L and ≥2.5 mmol/L).

To investigate whether the relation between MetS and vascular events was modified by the presence of diabetes, by the localization of vascular disease or by SBP- or LDL-c category, we included these interaction terms in the Cox model. If the P-value of the interaction term was ≤0.05 effect-modification was considered to be present.

We assessed proportionality by inspecting the Kaplan–Meier graphs and formal testing was done in the STATA package with the Schoenfeld test (P = 0.8 for the NCEP definition, P = 0.8 for the NCEP-R definition and P = 0.7 for the IDF definition).

Analyses were performed in SPSS version 12.0.1 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics

From the total study population, 1362 patients (43%) met NCEP criteria, 1601 patients (50%) NCEP-R criteria and 1375 patients (43%) IDF criteria for MetS. Baseline characteristics of the study population according to MetS status are presented in Table 2. NCEP-R-defined MetS was most prevalent in patients with PAD (55%). In patients with CAD, CVD or AAA, MetS was present in 50, 49, and 53% of patients, respectively. From the total study population, 691 patients (22%) had type 2 diabetes.

Impact of different metabolic syndrome definitions on the incidence of new vascular events and all-cause mortality

During a median follow-up of 3.2 years (interquartile range 1.4–5.4 years), 331 patients of the 3196 patients died (of whom 215 from a vascular cause), 95 had an ischaemic stroke and 195 patients had an MI. The composite of MI, ischaemic stroke or vascular death occurred in 373 patients. The cumulative 5-year risk was 13.2% (95% CI 11.7–14.8) for all-cause mortality, 8.9% (95% CI 7.6–10.2) for vascular death, 3.9% (95% CI 3.0–4.7) for ischaemic stroke, 7.8% (95% CI 6.6–9.0) for MI and 15.0% (95% CI 13.4–16.6) for the composite of vascular events.

As shown in Table 3, both the NCEP and NCEP-R definition for MetS were related to an increased risk of subsequent vascular events [HR 1.50 (95% CI 1.22–1.84) and HR 1.50 (95% CI 1.22–1.85),
Table 2  Baseline characteristics of study population according to metabolic syndrome (MetS) status by different diagnostic criteria

| Total population, n = 3196 | NCEP MetS | NCEP-R MetS | IDF MetS |
|----------------------------|-----------|-------------|---------|
|                             | Yes       | No          | Yes     | No     | Yes   | No     |
| N (%)                      |           |             |         |        |       |        |
| Age (years)                | 60 ± 10   | 60 ± 11     | 60 ± 10 | 60 ± 11 | 60 ± 10 | 60 ± 11 |
| Male gender, n (%)         | 983 (72)  | 1441 (79)   | 1174 (73) | 1250 (78) | 991 (72) | 1431 (79) |
| Smoking, n (%)             | 131 (10)  | 174 (10)    | 146 (9)  | 159 (10) | 154 (11) | 150 (8)    |
| Body mass index (kg/m²)    | 29 ± 4    | 25 ± 3      | 28 ± 4  | 25 ± 3  | 29 ± 4  | 25 ± 3    |
| Diabetes mellitus type 2, n (%) | 529 (39)  | 162 (9)     | 531 (33) | 160 (10) | 431 (31) | 259 (14)  |
| Fasting serum insulin (mIU/L) |           |             |         |        |       |        |
| HOMA-IR                    | 3.5 (2.4–4.9) | 1.9 (1.3–2.7) | 3.3 (2.3–4.7) | 1.9 (1.2–2.6) | 3.1 (2.3–4.6) | 1.9 (1.2–2.7) |
| Cholesterol (mmol/L)       | 5.4 (4.6–6.2) | 5.1 (4.4–5.9) | 5.4 (4.6–6.2) | 5.1 (4.4–5.8) | 5.2 (4.5–6.0) | 5.2 (4.5–6.0) |
| LDL-cholesterol (mmol/L)   | 3.3 (2.6–4.0) | 3.1 (2.5–3.9) | 3.3 (2.6–4.0) | 3.1 (2.5–3.9) | 3.2 (2.5–3.9) | 3.2 (2.5–3.9) |
| Use of lipid lowering agents, n (%) | 637 (47)  | 849 (46)     | 763 (48) | 723 (45) | 704 (51) | 780 (43)  |
| Use of glucose lowering agents, n (%) | 329 (24)  | 119 (7)      | 331 (21) | 117 (7)  | 261 (19) | 187 (10)  |
| Use of blood pressure lowering agents, n (%) | 684 (50)  | 600 (33)     | 782 (49) | 502 (32) | 685 (50) | 599 (33)  |
| Glucose (mmol/L)           | 6.3 (5.7–7.6) | 5.5 (5.2–5.9) | 6.2 (5.7–7.3) | 5.4 (5.1–5.9) | 6.1 (5.6–7.1) | 5.5 (5.2–6.1) |
| Triglycerides (mmol/L)     | 2.16 (1.71–2.86) | 1.29 (1.01–1.61) | 2.10 (1.61–2.77) | 1.24 (0.98–1.55) | 1.88 (1.40–2.60) | 1.39 (1.05–1.96) |
| HDL-cholesterol (mmol/L)   | 0.99 (0.86–1.17) | 1.29 (1.10–1.53) | 1.00 (0.87–1.21) | 1.32 (1.12–1.55) | 1.09 (0.91–1.30) | 1.22 (0.99–1.47) |
| Waist circumference (cm)   | 102 ± 11  | 92 ± 10     | 101 ± 11 | 91 ± 9  | 102 ± 9  | 89 ± 9    |
| Systolic blood pressure (mmHg) | 146 ± 20  | 138 ± 20    | 145 ± 20 | 140 ± 22 | 145 ± 21 | 141 ± 22  |
| Diastolic blood pressure (mmHg) | 82 ± 11   | 79 ± 10     | 82 ± 11  | 80 ± 11 | 83 ± 11  | 80 ± 11   |

Components of metabolic syndrome

- Hypertension, n (%)  
  - NCEP MetS: 1240 (91)  
  - NCEP-R MetS: 1273 (69)  
  - IDF MetS: 1433 (90)  
- Hyperglycemia, n (%)  
  - NCEP MetS: 893 (66)  
  - NCEP-R MetS: 324 (18)  
  - IDF MetS: 1345 (84)  
- Low HDL cholesterol, n (%)  
  - NCEP MetS: 971 (71)  
  - NCEP-R MetS: 371 (20)  
  - IDF MetS: 1073 (67)  
- Hypertriglyceridemia, n (%)  
  - NCEP MetS: 1033 (76)  
  - NCEP-R MetS: 367 (20)  
  - IDF MetS: 1147 (72)  
- Central obesity, n (%)  
  - NCEP MetS: 742 (55)  
  - NCEP-R MetS: 196 (11)  
  - IDF MetS: 811 (51)  

Localization of vascular disease

- Cerebrovascular disease, n (%)  
  - NCEP MetS: 390 (29)  
  - NCEP-R MetS: 545 (30)  
  - IDF MetS: 459 (29)  
- Coronary artery disease, n (%)  
  - NCEP MetS: 743 (55)  
  - NCEP-R MetS: 1007 (55)  
  - IDF MetS: 877 (55)  
- Peripheral arterial disease, n (%)  
  - NCEP MetS: 418 (31)  
  - NCEP-R MetS: 414 (23)  
  - IDF MetS: 460 (29)  
- Abdominal aortic aneurysm, n (%)  
  - NCEP MetS: 169 (12)  
  - NCEP-R MetS: 204 (11)  
  - IDF MetS: 198 (12)  

HOMA-IR: homeostasis model assessment determined insulin resistance (fasting serum glucose × fasting serum insulin)/22.5; LDL-cholesterol: low density lipoprotein-cholesterol; HDL-cholesterol: high-density lipoprotein cholesterol; NCEP: National Cholesterol Education Program; NCEP-R: revised NCEP; IDF: International Diabetes Federation.

 Mean ± standard deviation.

 Median with interquartile range.

 Currently smoking.

 Documentation of type 2 diabetes based on referral diagnosis, medical history (use of glucose-lowering agents) or fasting plasma glucose ≥ 7 mmol/L.

 Patients on glucose-lowering agents excluded from analyses.
respectively] and all-cause mortality [HR 1.45 (95% CI 1.17–1.80) and HR 1.43 (95% CI 1.15–1.78)]. IDF-defined MetS was less strongly associated with the occurrence of vascular events [HR 1.31 (95% CI 1.06–1.61)] and all-cause mortality [HR 1.13 (95% CI 0.89–1.42)].

Although it was not the primary aim of this study, the risk associated with each individual component of MetS was analysed as well. Central obesity was weakly associated with an increased risk of all vascular events but none of the other MetS components was (Table 4).

The relation between NCEP-R MetS and subsequent vascular events and between NCEP-R MetS and all-cause mortality was not modified by the presence of diabetes (P-values for interaction 0.90 for all vascular events and 1.03 for all-cause mortality). As shown in Table 5, the associations of NCEP-R-defined MetS with the various endpoints in the 2472 patients without diabetes mellitus were similar as compared with the total study population.

### Risk of new vascular events and all-cause mortality in patients with and without metabolic syndrome according to the localization of clinically manifest vascular disease

The relation between NCEP-R MetS and future vascular events and between NCEP-R MetS and all-cause mortality was not modified by the localization of clinically manifest atherosclerosis (P-values for interaction 0.93 for all vascular events and 0.97 for all-cause mortality). As shown in Table 6, presence of NCEP-R-defined MetS was related to an increased risk of subsequent vascular events and

### Table 3 Risk of different metabolic syndrome (MetS) diagnostic criteria on the occurrence of new vascular events and all-cause mortality

|                          | Number of events | Model | Hazard ratio (95% CI) |
|--------------------------|------------------|-------|-----------------------|
|                          |                  |       | NCEP MetS | NCEP-R MetS | IDF MetS |
| **Total population (n = 3196)** |                  |       |           |            |         |
| Myocardial infarction    | 195              | I     | 1.54 (1.16–2.04) | 1.60 (1.20–2.14) | 1.34 (1.00–1.80) |
|                          |                  | II    | 1.61 (1.21–2.15) | 1.68 (1.25–2.26) | 1.32 (0.97–1.78) |
| Ischemic stroke           | 95               | I     | 1.66 (1.10–2.49) | 1.75 (1.15–2.66) | 1.32 (0.88–1.99) |
|                          |                  | II    | 1.73 (1.13–2.65) | 1.77 (1.14–2.75) | 1.36 (0.88–2.01) |
| Vascular death            | 215              | I     | 1.71 (1.31–2.24) | 1.69 (1.28–2.22) | 1.36 (1.03–1.81) |
|                          |                  | II    | 1.65 (1.25–2.17) | 1.61 (1.22–2.14) | 1.34 (1.00–1.43) |
| All vascular events*     | 373              | I     | 1.50 (1.22–1.84) | 1.50 (1.22–1.85) | 1.31 (1.06–1.61) |
|                          |                  | II    | 1.53 (1.24–1.89) | 1.51 (1.22–1.87) | 1.30 (1.05–1.62) |
| All-cause mortality       | 331              | I     | 1.45 (1.17–1.80) | 1.43 (1.15–1.78) | 1.13 (0.89–1.42) |
|                          |                  | II    | 1.43 (1.14–1.78) | 1.40 (1.12–1.75) | 1.13 (0.89–1.43) |

Model I: adjusted for age and gender; Model II: Model I with additional adjustments for low density lipoprotein-cholesterol and current smoking; NCEP: National Cholesterol Education Program; NCEP-R: revised NCEP; IDF: International Diabetes Federation; CI: confidence interval.

*Composite of myocardial infarction, ischaemic stroke, and vascular death.

### Table 4 Risk of different metabolic syndrome (MetS) definitions and its components on the occurrence of any vascular event

| MetS definitions                  | Prevalence (%) | Hazard ratio* (95% CI) |
|----------------------------------|----------------|-----------------------|
| NCEP-defined MetS                | 43             | 1.50 (1.22–1.84)      |
| NCEP-R-defined MetS              | 50             | 1.50 (1.22–1.85)      |
| IDF-defined MetS                 | 43             | 1.31 (1.06–1.61)      |
| **MetS components**              |                |                       |
| Waist ≥ 102 cm (F), >88 cm (C)²  | 29             | 1.15 (0.99–1.33)      |
| Waist ≥ 94 cm (F), >80 cm (C)²   | 52             | 1.16 (1.00–1.33)      |
| Blood pressure ≥ 130/85 mmHg and/or medication | 79 | 1.02 (0.91–1.16) |
| Fasting glucose ≥ 5.6 mmol/L and/or medication³ | 62 | 1.01 (0.91–1.12) |
| Fasting glucose ≥ 6.1 mmol/L and/or medication³ | 38 | 1.04 (0.96–1.13) |
| Triglycerides ≥ 1.7 mmol/L       | 44             | 1.00 (0.89–1.11)      |
| HDL < 1.03 mmol/L (C), < 1.29 (F) | 42             | 1.02 (0.92–1.13)      |

CI: confidence interval; HDL: high-density lipoprotein.

*Age and gender adjusted hazard ratio.
³National Cholesterol Education Program (NCEP) and revised NCEP (NCEP-R) definition.
²International Diabetes Federation (IDF) definition.
†NCEP-R and IDF definition.
○NCEP definition.
all-cause mortality in all vascular disease-manifestation categories (CAD, CVD, PAD, and AAA).

Risk of new vascular events and all-cause mortality in patients with and without metabolic syndrome according to treatment goals for low density lipoprotein-cholesterol or blood pressure

The relation between NCEP-R MetS and subsequent vascular events and between NCEP-R MetS and all-cause mortality was not modified by SBP category (P-values for interaction 0.23 for all vascular events and 0.21 for all-cause mortality). As shown in Table 7, both in patients with low SBP (<140 mmHg) or high SBP (≥140 mmHg), NCEP-R-defined MetS was related to an increased risk of new vascular events [HR 1.75 (95% CI 1.15–2.66)] and all-cause mortality [HR 1.77 (95% CI 1.14–2.75)] for low or high SBP respectively and all-cause mortality [HR 1.77 (95% CI 1.14–2.75)] and all-cause mortality [HR 1.77 (95% CI 1.14–2.75)] for low or high SBP respectively. The relation between NCEP-R MetS and future vascular events and between NCEP-R MetS and all-cause mortality was not modified by LDL-c category (P-values for interaction 0.19 for all vascular events and 0.49 for all-cause mortality). As shown in Table 7, both in patients with low LDL-c levels (<2.5 mmol/L) or high LDL-c levels (≥2.5 mmol/L), NCEP-R-defined MetS was related to an increased risk of future vascular events [HR 1.29 (95% CI 0.77–2.18)] and HR 1.50 (95% CI 1.20–1.89) for low and high LDL-c respectively and all-cause mortality [HR 1.67 (95% CI 0.86–3.22)] and HR 1.39 (95% CI 1.10–1.75) for low and high LDL-c, respectively.

Discussion

In the present study it was shown that in patients with various manifestations of atherosclerotic vascular disease, presence of MetS according to NCEP or NCEP-R criteria was associated with a higher risk of subsequent vascular events and all-cause mortality, independently of the presence of type 2 diabetes. Also in patients at treatment goals for SBP (<140 mmHg) or LDL-c (<2.5 mmol/L) according to current guidelines, presence of NCEP-R-defined MetS points to a higher vascular risk. IDF-defined MetS was less strongly related to an increased risk of new vascular events and all-cause mortality.

In the present study it was shown that although the prevalence of NCEP-defined and IDF-defined MetS were similar in our study population (43%), they appeared to identify different individuals at different risk. These findings are in contrast with a recent study conducted in healthy men, reporting different prevalences but a similar predictive ability for mortality of IDF, NCEP, and NCEP-R-defined MetS. Several other prospective studies have reported similar associations of different MetS definitions with cardiovascular risk in the general population as well. However, a recent study conducted in non-diabetic subjects also reported a lower cardiovascular risk associated with IDF-defined MetS compared with NCEP-defined MetS. In patients referred for coronary angiography NCEP-defined MetS but not IDF-defined MetS predicted future vascular events. The results of that study and of the present study indicate that in patients with clinical manifestations of vascular disease, presence of MetS, according to either
| Table 6 | Risk of metabolic syndrome (revised National Cholesterol Education Program) on the occurrence of new vascular events and all-cause mortality in strata of clinical manifestations of vascular diseases\(^a\) |
|-----------------------------------------------|
| | Model | CAD (n = 1750) | CVD (n = 935) | PAD (n = 832) | AAA (n = 373) |
| | | Number of events | Hazard ratio (95% CI) | Number of events | Hazard ratio (95% CI) | Number of events | Hazard ratio (95% CI) | Number of events | Hazard ratio (95% CI) |
| | Myocardial infarction | I | 116 | 1.62 (1.11–2.35) | 53 | 1.64 (0.94–2.87) | 68 | 1.91 (1.15–3.18) | 39 | 1.11 (0.59–2.09) |
| | | II | 1.79 (1.20–2.66) | 1.63 (0.92–2.89) | 1.99 (1.18–3.37) | 1.22 (0.65–2.32) |
| | Ischemic stroke | I | 38 | 2.37 (1.13–4.94) | 60 | 1.29 (0.77–2.15) | 26 | 2.99 (1.20–7.46) | 11 | 2.35 (0.62–8.96) |
| | | II | 2.21 (1.05–4.66) | 1.12 (0.65–1.91) | 3.32 (1.23–8.98) | 2.13 (0.54–8.40) |
| | Vascular death | I | 105 | 1.59 (1.07–2.36) | 77 | 1.61 (1.02–2.56) | 86 | 1.88 (1.20–2.95) | 71 | 1.38 (0.86–2.22) |
| | | II | 1.47 (0.98–2.21) | 1.40 (0.88–2.23) | 1.77 (1.12–2.80) | 1.35 (0.83–2.21) |
| | All vascular events\(^b\) | I | 189 | 1.57 (1.17–2.11) | 139 | 1.29 (0.92–1.81) | 118 | 1.76 (1.21–2.58) | 88 | 1.18 (0.77–1.81) |
| | | II | 1.65 (1.21–2.24) | 1.19 (0.84–1.68) | 1.80 (1.21–2.66) | 1.19 (0.77–1.84) |
| | All-cause mortality | I | 149 | 1.64 (1.17–2.28) | 118 | 1.16 (0.80–1.66) | 132 | 1.41 (1.00–2.00) | 98 | 1.32 (0.88–1.97) |
| | | II | 1.53 (1.09–2.15) | 1.02 (0.71–1.48) | 1.37 (0.96–1.97) | 1.28 (0.84–1.95) |

Model I: adjusted for age and gender; Model II: Model I with additional adjustments for low density lipoprotein-cholesterol, current smoking, and the presence of other vascular diseases; CI: confidence interval; CAD: coronary artery disease; CVD: cerebrovascular disease; PAD: peripheral arterial disease; AAA: abdominal aortic aneurysm.

\(^a\)No interaction between revised National Cholesterol Education Program metabolic syndrome (NCEP-R MetS) and localization of vascular disease (P-values for interaction 0.93 for all vascular events and 0.97 for all-cause mortality).

\(^b\)Composite of myocardial infarction, ischaemic stroke, and vascular death.
### Table 7  Risk of metabolic syndrome (revised National Cholesterol Education Program) on the occurrence of new vascular events and all-cause mortality in patients at guidelines targets for systolic blood pressure or low density lipoprotein-cholesterol levels\(^{a,b}\)

| Total population \((n = 3196)\) | SBP<140 mmHg \((n = 1547)\) | SBP≥140 mmHg \((n = 1649)\) | LDL<2.5 mmol/L \((n = 714)\) | LDL≥2.5 mmol/L \((n = 2455)\) |
|-------------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Model                         | Number of events            | Hazard ratio \((95\% CI)\)  | Number of events            | Hazard ratio \((95\% CI)\)  | Number of events            | Hazard ratio \((95\% CI)\)  |
| Myocardial infarction         | I                           | 92                          | 1.98 \((1.31–3.00)\)        | 103                         | 1.44 \((0.96–2.16)\)        | 32                          | 2.05 \((0.98–4.30)\)        | 163                         | 1.49 \((1.08–2.04)\)        |
|                               | II                          | 1.73 \((1.10–2.72)\)        | 1.51 \((0.98–2.32)\)        | 1.80 \((0.81–4.00)\)        | 1.34 \((0.97–1.87)\)        |
| Ischemic stroke               | I                           | 33                          | 1.78 \((0.89–3.56)\)        | 1.57 \((0.92–2.68)\)        | 0.80 \((0.31–2.11)\)        | 77                          | 2.05 \((1.26–3.32)\)        |
|                               | II                          | 2.06 \((0.99–4.29)\)        | 1.57 \((0.88–2.80)\)        | 0.63 \((0.21–1.85)\)        | 2.17 \((1.32–3.55)\)        |
| Vascular death                | I                           | 78                          | 1.97 \((1.26–3.10)\)        | 1.54 \((1.08–2.19)\)        | 1.48 \((0.65–3.40)\)        | 192                         | 1.69 \((1.26–2.27)\)        |
|                               | II                          | 1.53 \((0.93–2.49)\)        | 1.50 \((1.04–2.18)\)        | 1.25 \((0.49–3.19)\)        | 1.60 \((1.18–2.17)\)        |
| All vascular events\(^c\)     | I                           | 154                         | 1.75 \((1.27–2.41)\)        | 1.34 \((1.02–1.77)\)        | 1.29 \((0.77–2.18)\)        | 314                         | 1.50 \((1.20–1.89)\)        |
|                               | II                          | 1.54 \((1.09–2.17)\)        | 1.32 \((0.96–1.77)\)        | 1.12 \((0.63–1.98)\)        | 1.40 \((1.10–1.77)\)        |
| All-cause mortality           | I                           | 122                         | 1.74 \((1.21–2.48)\)        | 1.25 \((0.95–1.66)\)        | 1.67 \((0.86–3.22)\)        | 294                         | 1.39 \((1.10–1.75)\)        |
|                               | II                          | 1.48 \((1.01–2.18)\)        | 1.23 \((0.91–1.65)\)        | 1.43 \((0.69–2.98)\)        | 1.33 \((1.04–1.69)\)        |

Model I adjusted for age and gender; Model II: Model I with additional adjustments for type 2 diabetes, current smoking, and low density lipoprotein-cholesterol (LDL-c) (in the blood pressure strata) and type 2 diabetes and current smoking (in the LDL-c strata); CI: confidence interval.

\(^{a}\)No interaction between revised National Cholesterol Education Program metabolic syndrome (NCEP-R MetS) and systolic blood pressure (SBP) category \((P\text{-values for interaction }0.23\text{ for all vascular events and }0.21\text{ for all-cause mortality})\).

\(^{b}\)No interaction between NCEP-R MetS and LDL-c category \((P\text{-values for interaction }0.19\text{ for all vascular events and }0.49\text{ for all-cause mortality})\).

\(^{c}\)Composite of myocardial infarction, ischaemic stroke and vascular death.
MetS is entirely due to the high prevalence of type 2 diabetes and all-cause mortality, irrespective of the site of the clinical manifestation of atherosclerosis. Several factors may explain the weaker association of IDF-defined MetS with vascular events. First, the lower cut-off value for waist circumference results in identification of patients with lower abdominal obesity, of which a large proportion is likely not to be insulin resistant. Patients with MetS diagnosed by the IDF definition but not by the NCEP definition had a more favourable cardiovascular risk profile than those classified with the NCEP definition but not with the IDF definition.27 Apparently, the obligatory presence of an increased waist in the IDF definition leads to identification of patients with lower prevalence of other MetS criteria. For example, in the present study the high triglycerides and low HDL cholesterol components of MetS are less prevalent in patients with IDF-defined MetS than in those with NCEP- or NCEP-R-defined MetS. In another study, after modification of the IDF waist criterion using a higher cut-off for abdominal obesity, the cardiovascular risk associated with IDF-defined MetS substantially increased.26 In our study, the difference in risk between MetS criteria cannot only be explained by the difference in cut-off values of individual components (Table 4).

Like several previous studies we found that the prognostic capacity of the different definitions is better for NCEP and NCEP-R-defined MetS than for IDF-defined MetS.24,25 We did not formally test if the different definitions lead to different HR’s and realize that these findings should be replicated in future studies.

It has been suggested that in patients with established cardiovascular disease the increased cardiovascular risk associated with MetS is entirely due to the high prevalence of type 2 diabetes among patients with MetS.28 However, in our study population the increased cardiovascular risk associated with MetS was independent from the presence of type 2 diabetes. In patients with CHD this has been reported as well19,24 and is in fact not surprising, since MetS contains as per definition, apart from dysglycemia, several other well-established cardiovascular risk factors such as hypertension and dyslipidemia, but also hypercoagulability, inflammation, low adiponectin plasma levels and small-dense LDL-c may contribute to the increased cardiovascular risk.

In the present study it was shown that NCEP-R-defined MetS was able to identify patients at high risk for new vascular events and all-cause mortality, irrespective of SBP being high (≥140 mmHg) or low (<140 mmHg). This implicates that patients with MetS and manifest vascular disease having an optimal SBP (<140 mmHg) according to current guidelines are at increased risk of cardiovascular events and all-cause mortality compared with those without MetS. This is irrespective of the use of blood pressure lowering agents. These results indicate that by using the fairly simple MetS diagnostic criteria, clinicians are able to identify patients at the highest risk. These patients may benefit from more aggressive cardiovascular risk reduction than recommended by current European and US guidelines. This will need further investigation.

In the present study it was shown that the increased risk of cardiovascular events and all-cause mortality associated with presence of MetS was independent of patients having low (<2.5 mmol/L) or high (≥2.5 mmol/L) LDL-c levels. Patients with MetS and manifest atherosclerotic disease having an optimal low LDL-c (<2.5 mmol/L) according to current guidelines are at increased risk of cardiovascular events and all-cause mortality compared with those without MetS. This was irrespective of the use of lipid-lowering agents. However, due to the small number of events in the low LDL-c category, confidence limits are wide. This has to be taken into account when interpreting these results. NCEP-ATPIII guidelines provide an optional further lowering of LDL-c below 1.8 mmol/L in very high-risk patients, including those with MetS.22 In a recent report from the TNT study, conducted in coronary patients, MetS was found to identify those patients who benefit the most from intensive lipid-lowering therapy.19 In the present prospective study, conducted in a large cohort of patients with various manifestations of atherosclerotic disease, it is shown that among patients with optimal low LDL-c levels, presence of MetS was associated with increased cardiovascular risk.

Some limitations of this study have to be taken into account. The study population consisted of those patients who had survived their first vascular event, so it could be that our patients are healthier than those not referred to our hospital. This may have influenced the estimation of risk. Secondly, stratification of our study population in different disease-manifestation categories and in low and high LDL-c categories resulted in small numbers of events in some categories, attenuating the precision of the risk estimation. Drawing firm conclusions from those results should therefore be done with caution. Thirdly, stratification of our study population in low and high SBP- and LDL-categories was based on baseline measurements of blood pressure and LDL-c. It is not known whether the observed values had been on this level long before enrolment in the study or if they had just been reached, nor whether this level substantially changed during follow-up. This may have influenced the estimation of risk in the different categories. Finally, an oral glucose tolerance test was not performed and could therefore not be included in the definition of diabetes.

In conclusion, the results from the present study show that in patients with different clinical manifestations of vascular disease, presence of NCEP and NCEP-R-defined MetS is associated with an increased risk of cardiovascular events and all-cause mortality, independently of the presence of type 2 diabetes. This risk is significantly higher than the risk associated with IDF-defined MetS and is present irrespective of the site of the clinical manifestation of atherosclerosis. Also in patients at treatment goals for SBP (<140 mmHg) or LDL-c (<2.5 mmol/L) according to current guidelines, presence of NCEP-R-defined MetS points to a higher cardiovascular risk. Patients with clinically manifest vascular disease and MetS may benefit from more aggressive treatment of cardiovascular risk factors than recommended by current guidelines.

Conflict of interest: none declared.

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‘Parachute’ accessory mitral leaflet and pulmonary valve stenosis in an asymptomatic 85-year-old man

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An 85-year-old man underwent transthoracic echocardiography. Anamnesis included hypertension and mild chronic obstructive pulmonary disease. At the age of 18, he had been dispensed from the military service because of a cardiac murmur. Since then, he had not undergone cardiac testing and had been absolutely asymptomatic.

Transthoracic echocardiography showed a moderately dilated, hypertrophic left ventricle with mildly reduced contractile function as well as grade II–III mitral and aortic regurgitation. Within the left ventricular outflow tract, a mobile discrete membrane caused subaortic obstruction with a peak dynamic gradient of 30 mmHg. Transoesophageal echocardiography revealed the membrane to be accessory mitral valve tissue implanted on the anterior mitral annulus and leaflet with a broad systolic (‘parachute’) anterior movement, obstructing a large part of the left ventricular outflow tract. The aortic valve was tricuspid; the cusps, although thickened, showed normal mobility. As a collateral finding, mild right atrial and ventricular enlargement with moderate to severe (peak gradient 50 mmHg) pulmonary valve stenosis were also present. In consideration of the age and of the absence of symptoms, the patient was discharged without further intervention. Accessory mitral valve tissue is an anomaly of the embryologic development of the endocardial cushion. Although very rare, it should always be considered among the possible causes of a subaortic gradient.

Panel A. Transthoracic view of the subaortic membrane attached to the anterior mitral annulus and to chordae tendineae from the anterior papillary muscle. LA, left atrium; LV, left ventricle; AO, ascending aorta; IVS, interventricular septum; PM, papillary muscle.

Panel B. Transoesophageal view of the subaortic membrane attached to the anterior mitral annulus and to chordae tendineae from the anterior papillary muscle.

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