Chapter 2

Clinical characteristics, cardiac events and coronary angiographic findings in the prospective PREVEND cohort: an observational study


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Abstract

Background
The use of invasive procedures has mostly been studied in retrospective (multi)national registries. Limited evidence exists on the association between microalbuminuria and coronary artery disease (CAD).

Methods and results
The incidence of major adverse cardiac events (MACE) and invasive cardiac procedures was registered between 1997-2003 in 8,139 subjects, without prior documented CAD, in the PREVEND cohort study (the Netherlands), which focus is on microalbuminuria and cardiovascular risk. Qualitative coronary angiographic analysis was performed. During 5.5 years of follow up, a first MACE occurred in 271 (3.3%), and a first coronary angiography (CAG) was performed in 264 (3.2%) subjects. Of these, 216 CAGs were available for qualitative angiographic analysis. Indications for CAG were stable angina in 129, acute coronary syndrome (ACS) in 55 and ST-elevation myocardial infarction (STEMI) in 32 subjects. Obstructive coronary artery disease was present in respectively 61, 53 and 30 subjects. A revascularization was performed in, respectively, 50 (39%), 50 (91%) and 25 (78%) subjects. Microalbuminuria was associated with a first MACE, after adjustment for established risk factors. Microalbuminuria was present at baseline in 9% of subjects with normal coronary arteries, in 21% of subjects with 1- and 2-vessel CAD and in 39% of subjects with 3-vessel or left main CAD at CAG during follow up (P<0.005).

Conclusions
This large cohort study shows that two-thirds of diagnostic CAGs for stable angina were not followed by a revascularization, in contrast to CAGs for STEMI or ACS. Furthermore, this study shows that microalbuminuria is associated with CAD.
Introduction

Most of our knowledge related to the incidence and consequences of invasive procedures in patients with suspected coronary artery disease (CAD) is derived from large (multi)national registries or randomized controlled trials, which are based on a retrospective design and selection of participating hospitals or patient groups. These registries have shown that the increase in numbers of percutaneous coronary interventions (PCI) has been almost two times the increase in the number of coronary angiographies (CAG). In spite of this increase, an underuse of coronary revascularizations has been reported in appropriate candidates for a revascularization procedure. Furthermore, it was shown that up to 50% or more of CAGs is not followed by a revascularization procedure. A prospective cohort analysis may provide additional information, since it allows insight in baseline clinical variables and the assessment of events and procedures in patients with suspected CAD, reflecting routine clinical practice. We therefore performed an additional analysis of the prospective Prevention of REnal and Vascular ENdstage Disease (PREVEND) cohort study, which focus is on microalbuminuria and cardiovascular risk in the general population, to assess the number of invasive procedures following major adverse cardiac events (MACE). Our second purpose was to assess the indications for CAGs and the incidence of subsequent revascularization procedures in subjects with suspected CAD. Thirdly, we assessed the association between microalbuminuria and CAD.

Methods

Study population

The principle purpose of the Prevention of REnal and Vascular ENdstage Disease (PREVEND) study is to assess the value of microalbuminuria in relation to cardiovascular and renal risk in the general population. During the period 1997–1998, all inhabitants of the city of Groningen, The Netherlands aged between 28 and 75 years were asked to answer a short questionnaire and to send in a morning urine sample. Insulin treatment and pregnancy were exclusion criteria. Altogether 40,856 subjects responded. All subjects with a morning urinary albumin concentration of at least 10 mg/L (n=7,768) and a random sample of subjects with a morning urinary albumin concentration less than 10 mg/L were invited to an outpatient clinic. The screening program was completed by 8,592 subjects, including 6,000 subjects with and 2,592 subjects without an elevated morning urinary albumin concentration. Collected baseline data at the outpatient clinic included medical history, demographics, biometric data, urine- and blood collections and laboratory measurements. For the current analysis, only subjects without prior documented CAD were included. Prior documented CAD was defined as history of myocardial infarction, revascularization procedure or obstructive coronary artery disease prior to inclusion in the PREVEND
study. A history of myocardial infarction was based on a subjects’ medical history, including structured questionnaire, and the information on previous CAD was complemented by review of the medical report. In tables baseline demographics and laboratory parameters from the baseline visit of the PREVEND cohort are given. For details on the PREVEND study design we refer to earlier publications. The PREVEND study was approved by the medical ethics committee and conducted in accordance with the guidelines of the declaration of Helsinki. All subjects gave written informed consent.

**Definition of end points and follow up**
Cardiac events and revascularization procedures during follow up were counted in PREVEND subjects without prior documented CAD at baseline. The end point of this study was defined as cardiovascular death (ICD-10 I01-99), cardiac events (ICD-9 410, 411), PCI and coronary artery bypass graft surgery (CABG). The vital status of all subjects was evaluated through the municipal register until December 31\textsuperscript{st} 2003. Causes of death were obtained from the Central Bureau of Statistics according to ICD-10 codes (I01-199 for cardiovascular disorders). Information related to cardiac events and revascularization procedures were obtained from the national hospital information system (Prismant, Utrecht, the Netherlands). Cardiac events were reviewed by a clinical event committee and divided into ST-elevation myocardial infarctions (STEMI) or non-ST-elevation acute coronary syndromes (ACS). ST-elevation myocardial infarction was defined as chest pain and ST-elevation over 1 mm in at least 2 contiguous leads. To evaluate therapeutic consequences after STEMI, subjects with STEMI were divided into those presenting within or over 24 hours after the onset of chest pain. Non-ST-elevation acute coronary syndrome was defined as chest pain with positive cardiac markers (troponin or creatinin kinase) and/or dynamic ST-segment changes. Major adverse cardiac event was defined as cardiovascular death, STEMI, ACS or revascularization procedure.

**Assessment of coronary angiography**
The incidence of coronary angiographies was obtained from the Catheterisation Laboratory registries of the two hospitals in the Groningen region, namely the University Medical Center Groningen (UMCG) and the Martini Hospital Groningen (MHG) and was completed with information on CAG obtained from the national hospital information system (Prismant, Utrecht, the Netherlands). In case a PCI was performed during the same session as the CAG, PCI and CAG were counted as separate procedures. All CAGs performed in the UMCG or MHG were requested in order to perform qualitative angiographic analysis and to evaluate the therapeutic consequences as decided by the UMCG Thoraxcenter multidisciplinary team. For all subjects in whom CAG is performed in the UMCG or MHG, the UMCG Thoraxcenter multidisciplinary team takes decisions to perform revascularization procedures or to continue conservative treatment. The team has extensive experience with the RAND-UCLA criteria and takes decisions in accordance with the European Society of Cardiology guidelines. Indications for CAG were divided into STEMI presenting...
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within or over 24 hours after the onset of chest pain, ACS or stable angina. Stable angina was defined as angina or angina-like symptoms. Indications for CAG and peri- and post-procedural events were reviewed by a senior cardiologist.

Qualitative angiographic analysis
We performed qualitative angiographic analysis of all available first CAGs for all indications (STEMI, ACS or stable angina). Qualitative coronary angiographic analysis was performed by a senior cardiologist (RT), who had no knowledge of the clinical indications for CAG or of the subjects’ clinical status. Analysis of CAGs included the identification of obstructive lesions (at least 50% stenosis) or minor lesions (less than 50% stenosis) in the left main stem, left anterior descending artery, left circumflex artery and/or right coronary artery. In case an obstructive lesion was found in a coronary vessel, additional minor lesions present in this vessel were not recorded. In case of absence of any lesion, the coronary arteries were graded as normal. An interobserver agreement of 95% was found in a random sample of 44 coronary angiographies (20%) which were analysed by a senior cardiologist (FZ) unaware of the prior analyses.

Data handling and definitions
Risk factors were defined as follows or as given in tables. Hypertension was defined as blood pressure equal to or above 140/90 mm Hg or use of antihypertensive medication. Hypercholesterolemia was defined as total cholesterol above 6.5 mmol/L or use of lipidlowering treatment. Abdominal obesity was defined as waist circumference equal to or above 102 cm in men and equal to or above 88 cm in women. Low HDL cholesterol was defined as HDL-cholesterol below 1.04 mmol/L in men and below 1.30 mmol/L in women. Diabetes was defined as fasting plasma glucose levels above 6.9 mmol/L, or non-fasting plasma glucose levels above 11.0 mmol/L or the use of oral anti-diabetic drugs. High age was defined as age >60 years. High hs-C-reactive protein (CRP) was defined as hs-CRP>3.0 mg/L.

Analytical methods
Systolic and diastolic blood pressure measurements were calculated as the mean of the last two out of ten consecutive measurements with an automatic Dinamap XL model 9300 series device (Johnson-Johnson Medical INC, Tampa, Florida). Serum total cholesterol were determined by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, New York, U.S.A.). HDL-cholesterol was determined by MEGA (Merck, Darmstadt, Germany). The urinary albumin excretion was measured as the mean of two 24h-urine collections. Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg l\(^{-1}\) and intra- and inter-assay coefficients of variation of less than 2.2% and 2.6%, respectively (Dade Behring Diagnostic, Marburg, Germany). High sensitive CRP was measured by nephelometry with a threshold of 0.18 mg/L and intra-and interassay coefficients of variation of <4.4 and <5.7% respectively (BNII, Dade Behring Diagnostic, Marburg, Germany).
Statistical analysis
Continuous data are given as means (standard deviation). In case of a skewed distribution the median (interquartile range) was used. Differences between groups were evaluated by Chi-square tests, when appropriate. P-values were two-sided and needed to be <0.05 to be significant. Probability weighted Cox’ proportional hazard analyses were performed to adjust for the survey weights based on non-random inclusion of subjects with and without elevated morning urinary albumin concentration levels at the PREVEND cohort study entry. Models were fitted to evaluate the univariate impact of microalbuminuria, and after adjustment for age and sex, and after adjustment for established risk measures, namely smoking status, diabetes, obesity, hypertension, hypercholesterolemia, low HDL-cholesterol and high hs-CRP. Event-free survival time for subjects was defined as the period from the date of the outpatient clinic baseline assessment to the date of first MACE or CAG, or death from any cause until 31 December 2003, or 31 December 2002 until which date information regarding specific causes of death follow up information was available. If a person had moved away from the city of Groningen or to an unknown destination, or died due to a non-cardiovascular cause, the person was censored on the last available contact date or date of death. All calculations were performed with SPSS version 11.0 software (SPSS, Chicago, IL, USA).

Results
Baseline characteristics
Of the initial 8,592 subjects included, 8,139 had no prior documented CAD (94.7%), and were included in the current analysis. The population consisted of middle-aged subjects and included an equal number of males and females. More than one third were current smokers and only a small number had diabetes (table 1).

Incidence of MACE
During a mean of 5.5 years of follow up, 271 subjects (3.3%) experienced a first MACE. During follow up, 747 subjects (9%) left the area and 186 subjects (2%) died from a non-cardiovascular cause and were therefore censored. Incidence of all and first MACEs, respectively, are shown in table 2. Kaplan Meier survival curves for subjects who remained free from cardiovascular death, STEMI, ACS or revascularization procedures show a gradual decrease in event free survival (figure 1).

Number of invasive procedures following a first MACE
The number of invasive procedures and therapeutic consequences after a first MACE is shown in figure 2a (flowchart). Of the 50 patients presenting with STEMI as a first cardiac event, 37 subjects presented within 24 hours after onset of symptoms. Twenty-two of these subjects (59%) received thrombolytic therapy. In 2 subjects (5%) contraindications for thrombolytic therapy were present, but primary PCI was
Table 1. Baseline characteristics of 8,139 PREVEND participants without prior documented CAD.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=8,139</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>49 (12)</td>
</tr>
<tr>
<td>Male gender, No. (%)</td>
<td>3,979 (49)</td>
</tr>
<tr>
<td>Body mass index, mean (SD) kg/m²</td>
<td>26 (4)</td>
</tr>
<tr>
<td>Blood pressure, mean (SD), mm Hg</td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>129 (20)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74 (10)</td>
</tr>
<tr>
<td>Smoking status, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>2,786 (34)</td>
</tr>
<tr>
<td>Past</td>
<td>2,880 (35)</td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>270 (3)</td>
</tr>
<tr>
<td>Cholesterol, mean (SD), mmol/L</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.6 (1.1)</td>
</tr>
<tr>
<td>HDL</td>
<td>1.33 (0.40)</td>
</tr>
<tr>
<td>Albuminuria, median (interquartile range), mg/24h</td>
<td>9.17 (6.24-16.88)</td>
</tr>
<tr>
<td>hs-CRP, median (interquartile range), mg/L</td>
<td>1.24 (0.54-2.87)</td>
</tr>
<tr>
<td>Medication, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Lipidlowering</td>
<td>875 (5)</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>389 (11)</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; hs-CRP, high sensitivity-C-reactive protein; HDL, high density lipoprotein.
SI conversion factor: to convert mg/dL tot mmol/L, divide values for total cholesterol and HDL cholesterol by 0.0259.

Table 2. Incidence of MACE in 8,139 PREVEND participants without prior documented CAD (1997-2003).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>All Events, No.</th>
<th>(%)</th>
<th>First Events, No.</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major adverse cardiac event</td>
<td>419†</td>
<td>(5.1)</td>
<td>271‡</td>
<td>(3.3)</td>
</tr>
<tr>
<td>Revascularization procedure</td>
<td>181</td>
<td>(2.2)</td>
<td>70</td>
<td>(0.9)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>115</td>
<td>(1.4)</td>
<td>40</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>66</td>
<td>(0.8)</td>
<td>30</td>
<td>(0.5)</td>
</tr>
<tr>
<td>Non-ST-elevation acute coronary syndrome</td>
<td>133</td>
<td>(1.6)</td>
<td>118</td>
<td>(1.4)</td>
</tr>
<tr>
<td>ST-elevation myocardial infarction, time delay after onset of chest pain</td>
<td>51</td>
<td>(0.6)</td>
<td>50</td>
<td>(0.6)</td>
</tr>
<tr>
<td>&lt; 24 hours</td>
<td>38</td>
<td>(0.5)</td>
<td>37</td>
<td>(0.5)</td>
</tr>
<tr>
<td>&gt; 24 hours</td>
<td>13</td>
<td>(0.2)</td>
<td>13</td>
<td>(0.2)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>54</td>
<td>(0.7)</td>
<td>33</td>
<td>(0.4)</td>
</tr>
</tbody>
</table>

Abbreviations: MACE, major adverse cardiac event; CAD, coronary artery disease.
Major adverse cardiac event is defined as a composite end point comprising, respectively, any (†) and the first of any (‡) of these events: revascularization procedure, non-ST-elevation acute coronary syndrome, ST-elevation myocardial infarction, or cardiovascular death.
Figure 1. Kaplan Meier survival curves of 8,139 PREVEND subjects without prior documented CAD who remained free from cardiovascular death, ST-elevation myocardial infarction, non-ST-elevation acute coronary syndrome, or revascularization procedure.

Figure 2. Flow chart for the incidence of first major adverse cardiac events and subsequent invasive procedures (A) and for the incidence and indications of first coronary angiographies and subsequent revascularization procedures (B).

Abbreviations: CAD, coronary artery disease; MACE, major adverse cardiac event; STEMI, ST-elevation myocardial infarction; ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; CAG, coronary angiography.
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not performed. In 13 subjects (35%) primary PCI was performed.

Of the 118 subjects with ACS, in 57 subjects (48%) CAG was performed within 3 months, which was followed by a revascularization procedure in 54 subjects (46%). In a later stadium, more invasive procedures were performed in an additional number of subjects. This resulted in a total of 76 CAGs (64%) and 67 revascularization procedures (57%), including 45 PCIs (38%) and 32 CABGs (27%), during the entire follow up period.

Incidence of coronary angiographies

Two-hundred-and-sixty-four subjects (3.2%) underwent a first CAG after inclusion in the PREVEND study (incidence 0.6% per year). In 48 subjects (18.2%) this was followed by a second CAG (incidence 0.1% per year). The incidence of CAGs was stable during follow up (data not shown). Indications for 264 first CAGs were STEMI in 39 subjects (15%), following an ACS in 73 subjects (28%) and stable angina in 152 subjects (58%), respectively, as shown in figure 2b (flowchart).

Coronary angiographic findings and subsequent revascularization procedures

Of 264 first CAGs, 240 CAGs were performed in the UMCG or MHG and 216 of these were available for angiographic analysis (90%). The angiographic findings and revascularization procedures following these 216 first CAGs according to indications are given in table 3.

Of 129 subjects with a first CAG for stable angina, 61 subjects had obstructive CAD, while in 68 subjects normal coronary arteries or nonobstructive coronary artery disease was present. Of 61 subjects with obstructive CAD, in 50 subjects a revascularization procedure was performed, while in 11 subjects conservative treatment was continued (due to a coronary anatomy not suitable for intervention in 9 subjects, and angina being secondary to other causes in 2 subjects). Of 68 subjects without obstructive CAD, reasons for CAG were in 13 subjects the evaluation of aortic valve disease, atrial septum defect or electrophysiology. All subjects had angina or angina-like symptoms. In 26 subjects a CAG was performed because of stable angina, without evidence of

Table 3. Indications and findings of first CAG in 216 PREVEND participants without prior documented CAD in whom CAG was available for analysis.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Normal coronary arteries n(%)</th>
<th>Nonobstructive CAD n(%)</th>
<th>1-vessel CAD n(%)</th>
<th>2-vessel CAD n(%)</th>
<th>3-vessel CAD or LM lesion n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI (&lt;24 h)</td>
<td>18 (0)</td>
<td>0 (0)</td>
<td>11 (61)</td>
<td>5 (28)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>STEMI (&gt;24 h)</td>
<td>14 (1)</td>
<td>1 (8)</td>
<td>6 (46)</td>
<td>6 (39)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ACS</td>
<td>55 (0)</td>
<td>2 (4)</td>
<td>24 (44)</td>
<td>16 (29)</td>
<td>13 (24)</td>
</tr>
<tr>
<td>Stable Angina*</td>
<td>129 (26)</td>
<td>34 (26)</td>
<td>21 (16)</td>
<td>23 (18)</td>
<td>17 (13)</td>
</tr>
</tbody>
</table>

Abbreviations: ACS, non-ST-elevation acute coronary syndrome; CAD, coronary artery disease; CAG, coronary angiography; STEMI, ST-elevation myocardial infarction.

* Stable angina is defined as angina or angina-like symptoms.
ischemia based on electrocardiographic exercise testing or myocardial perfusion imaging, in order to eliminate diagnostic uncertainty. In 15 subjects an abnormal electrocardiographic exercise test result, and in 14 subjects a reversible myocardial perfusion defect were the reasons to perform CAG.

All subjects who underwent acute CAG for STEMI <24 hours had obstructive CAD and were treated with primary PCI. In 14 subjects in whom a CAG was performed for STEMI >24 hours, in 12 subjects obstructive CAD was found, followed by a revascularization procedure in 7 and conservative treatment in 5 subjects.

In 53 out of 55 subjects with a first CAG following an ACS obstructive CAD was found. In 50 out of these 55 subjects (91%) a subsequent revascularization procedure was performed. In 3 subjects with obstructive CAD a revascularization procedure was not indicated and conservative treatment was continued.

**The association between microalbuminuria and CAD**
The association between microalbuminurina and the occurrence of a first MACE during follow up is shown in table 4. In univariate analysis and after adjustment for established coronary risk factors, microalbuminuria was associated with a first MACE.
As shown in table 5, microalbuminuria was present at baseline in 9% of subjects with normal coronary arteries, in 21% of subjects with 1- and 2-vessel CAD and in 39% of subjects with 3-vessel or left main CAD at CAG during follow up ($P_{\text{trend}}=0.005$).

**Discussion**

This is the first report to describe the clinical and angiographic characteristics of subjects without a history of CAD undergoing a first CAG after inclusion in a prospective population based cohort study. We performed the current analysis since most of the insight in the incidence of CAGs and revascularization procedures result from registries with a retrospective design. This type of study uses a selection of hospitals and subject groups. A prospective cohort analysis has major advantages, since it allows insight in baseline clinical variables and the assessment of events and procedures in subjects with suspected CAD, reflecting routine clinical practice.

**Invasive procedures after a first MACE**

The low number of primary PCIs in subjects with STEMI, namely in one-third only, reflects the clinical practice between 1997-2003, since in this time period thrombolytic therapy was still accepted as first-line treatment in these subjects. This number will have increased from then, since primary PCI has been accepted as a first line treatment in subjects presenting with STEMI. The number of CAGs in subjects with ACS (48% within 3 months, 64% during total follow up) was in line with the European Heart Survey (52%). The numbers of PCIs and CABGs (27% and 38%) in PREVEND were higher than the rates in European and American Surveys (25-33% and 5-12%, respectively), probably due to a longer follow up time. The number of revascularizations was comparable to the ICTUS trial. In ICTUS, high risk ACS subjects were randomized to an early invasive or conservative strategy under modern antiplatelet therapy. Early CAG was followed by a revascularization procedure in 79%, versus 54% of the "conservative" patients. These data confirm the need for a revascularization procedure in many subjects with ACS in the days or weeks following the acute presentation.

**Coronary angiographic findings and subsequent revascularization procedures**

Coronary angiographies in subjects with STEMI or ACS were mostly followed by a revascularization procedure. This was not the case for CAGs in subjects with stable angina, which was defined as angina or angina-like symptoms and the indication for most first CAGs. The high number (61%) of these CAGs not followed by a revascularization procedure is in line with a large European registry. This high number is worrisome, since CAG is associated with considerable costs, and a small, but significant risk of major complications. There are two potential explanations for this phenomenon.

First, it has been reported that some subjects with an indication for a revascularization
procedure, receive conservative treatment. This issue has been evaluated by several studies\textsuperscript{2,8,9,19} in one of which the UMCG Thoraxcenter has also participated.\textsuperscript{8,9} The relevance of this issue has been highlighted by the observation that in appropriate candidates for a revascularization procedure, an underuse of revascularization procedures was associated with a worse clinical outcome.\textsuperscript{2,20} In PREVEND, a decision to perform a revascularization procedure was taken by the UMCG Thoraxcenter multidiciplinary team for 90% of subjects with obstructive CAD. In the other subjects performance of a revascularization procedure was discussed, but conservative treatment was continued, due to presence of contraindications for a revascularization procedure.

Second, current clinical guidelines advise the performance of non-invasive tests for the detection of myocardial ischemia prior to CAG.\textsuperscript{4,21} Although we have not included the results of non-invasive tests in the current analysis, the high number of CAGs for stable angina in the absence of any coronary lesion, which is in line with previous reports,\textsuperscript{22} raises the suspicion that currently available non-invasive tests have a limited ability to differentiate between subjects at high versus low coronary risk. Perhaps that new imaging modalities that provide anatomical information on CAD, such as electron beam computed tomography or multislice detector computed tomography, may improve risk stratification prior to CAG. Future studies are needed to evaluate the implications of such a strategy on the incidence on CAG.

**Impact of microalbuminuria on CAD**

Microalbuminuria has been found to be present in 3–15% of the general population\textsuperscript{23–25} and has been associated with increased coronary risk.\textsuperscript{23,24,26,27} The pathophysiologic link between microalbuminuria and increased coronary risk still needs to be elucidated. Microalbuminuria may imply a vulnerability for atherosclerosis due to its association with inflammatory and prothrombotic changes involved in endothelial dysfunction.\textsuperscript{28–35} There is conflicting evidence that microalbuminuria reflects a systemic transvascular leakage of albumin, which may be associated with leakage of lipoproteins and other macromolecules.\textsuperscript{36–38} Finally, microalbuminuria has been regarded as marker of generalized atherosclerosis, but this hypothesis has been denied previously.\textsuperscript{39} In our study, an association between microalbuminuria and MACE was demonstrated, which confirms earlier evidence on the impact of microalbuminuria on cardiovascular risk. Furthermore, in line with an earlier angiographic study,\textsuperscript{40} microalbuminuria was most frequently present in subjects who had severe CAD at CAG during follow up. Whether microalbuminuria can be regarded as appropriate screening tool in asymptomatic populations is subject to future investigation.

**Limitation**

The generalizability of our results may be somewhat limited since a part of our study population was selected for the presence of microalbuminuria. Our cohort may therefore represent a population with an increased cardiovascular risk profile when compared to a general population based cohort. We realize that the subjects
of the PREVEND study were selected for a different reason than the observation of the incidence and therapeutic consequences of coronary angiographies. Therefore for example the number of diabetes subjects is not representative for a population undergoing CAG. Furthermore, our study was a single center study, and limited by a low number of coronary events. However, the advantage of a cohort study lies in its prospective design and its population based approach may better reflect routine clinical practice than multinational registries on the incidence of invasive procedures. Furthermore, the uniqueness of our study lies herein that we included only subjects without prior documented CAD.

Conclusions

This large cohort study shows that two-thirds of diagnostic CAGs for stable angina were not followed by a revascularization, in contrast to CAGs for STEMI or ACS. Furthermore, this study confirms the association between microalbuminuria and CAD.
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