Invited review

New cardiovascular risk markers in the general population and in hypertension. Do they improve risk prediction and influence treatment?

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Abstract

We have tested the additive prognostic value of three relatively new, but established cardiovascular risk markers: N-terminal pro-brain natriuretic peptide (Nt-proBNP), related to haemodynamic cardiovascular risk factors, high sensitivity C-reactive protein (hsCRP), related to metabolic cardiovascular risk factors, and urine albumin/creatinine ratio (UACR), related to haemodynamic as well as metabolic risk factors. Furthermore, we have tested the prognostic importance of reduction of UACR during antihypertensive treatment. In healthy subjects with a 10-year risk of cardiovascular death lower than 5% based on HeartScore and therefore not eligible for primary prevention, the actual 10-year risk of cardiovascular death exceeded 5% in a small subgroup of subjects with UACR higher than the 95th percentile of approximately 1.6 mg/mmol. Combined use of high UACR or high hsCRP identified a larger subgroup of 16% with high cardiovascular risk in which primary prevention may be advised despite low-moderate cardiovascular risk based on HeartScore. Furthermore, combined use of high UACR or high Nt-proBNP in subjects with known cardiovascular disease or diabetes identified a large subgroup of 48% with extremely high cardiovascular risk who should be referred for specialist care in order to optimize treatment. Finally, reduction in UACR during antihypertensive treatment was associated with improved prognosis independently of changes in blood pressure and left ventricular hypertrophy. UACR and hsCRP improved risk stratification in low-risk subjects whereas UACR and Nt-proBNP improved risk stratification in high-risk subjects. Changes in UACR during antihypertensive treatment carried additive prognostic information.

Key words: cardiovascular risk prediction, albumin/creatinine ratio, high sensitivity C-reactive protein, N-terminal pro brain natriuretic peptide, antihypertensive treatment.

Introduction

Due to increasing life expectancy and an obesity epidemic in Western countries the demand for prevention and treatment of cardiovascular diseases is growing. In order to prioritize limited health resources cardiovascular risk stratification is essential. Several years ago the Framingham Risk Score was developed based on a large American population survey in Framingham [1] and less than a decade ago the HeartScore was developed based on several European population surveys [2]. These risk scores were only based on traditional cardiovascular risk factors because newer risk markers were not measured in these large population surveys. New risk markers, more closely related to cardiovascular disease, have been developed and successfully tested in well defined groups of patients [3]. However, this multiple risk marker approach has only been done systematically in a few general populations with rather disappointing results [4]. Furthermore, the prognostic importance of reducing these new risk markers was until recently unknown.

We wanted to test the additive prognostic value of three relatively new but established cardiovascular risk markers: N-terminal pro-brain natriuretic peptide (Nt-proBNP) [5], high sensitivity C-reactive protein (hsCRP) [6] and urine albumin/creatinine ratio (UACR) [7]. These three risk markers were chosen because we expected them to have additive prognostic importance as Nt-proBNP was primarily related to haemodynamic cardiovascular risk factors [8, 9], hsCRP was primarily related to metabolic cardiovascular risk factors [10, 11], and UACR was related to haemodynamic as well as metabolic risk factors [12] (Figure 1). Furthermore, in patients with hypertension and left ventricular (LV) hypertrophy enrolled in the LIFE study we measured UACR yearly during either losartan- or atenolol-based antihypertensive treatment to test whether changes in UACR had prognostic importance independently of changes in blood pressure and LV hypertrophy.

Material and methods

In the clinical setting it is recommended to evaluate hsCRP [13], Nt-proBNP [14, 15] and UACR [16, 17] on at least two occasions separated by a few weeks to reduce the intra-individual variations and to exclude ongoing infection to avoid measuring false elevations of hsCRP and UACR. However, in our population study we had only one measurement and could not exclude subclinical infection.

Results and discussion

In the general population, UACR, Nt-proBNP and hsCRP above or below the gender-adjusted median values had additive predictive value (Figure 2). As logarithmic transformed continuous variables, UACR, Nt-proBNP and hsCRP predicted the composite cardiovascular endpoint (CEP) of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke independently of traditional cardiovascular risk factors including left ventricular mass and pulse wave velocity [18], supporting a recent study [19].

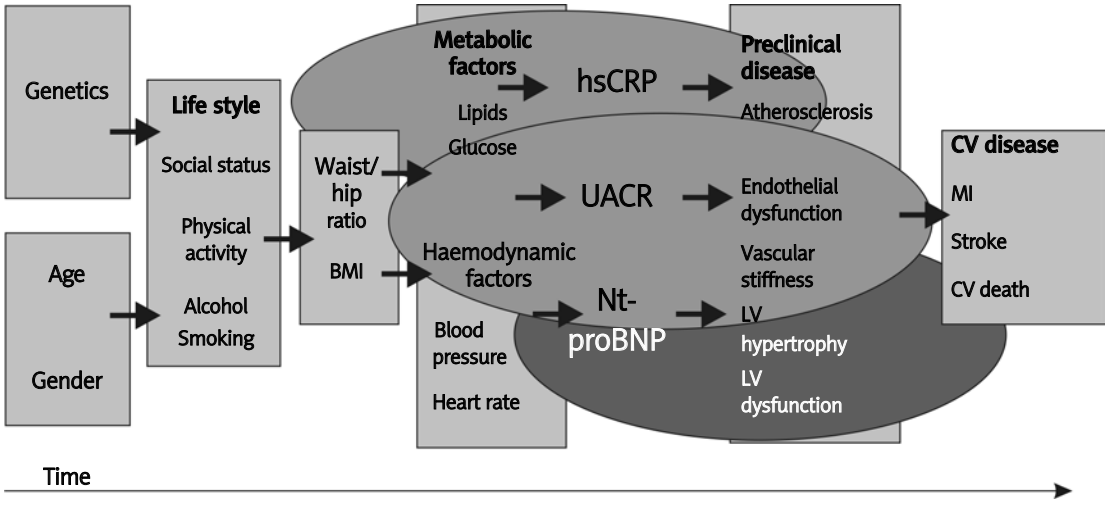

Figure 1. Pathogenesis of cardiovascular disease
High sensitivity C-reactive protein (hsCRP) is related to the metabolic risk factors early in the pathogenesis of cardiovascular disease; N-terminal pro-brain natriuretic peptide (Nt-proBNP) is closely related to preclinical cardiovascular disease later in the pathogenesis; and urine albumin/creatinine ratio (UACR) is related to risk factors early in the pathogenesis as well as preclinical vascular disease later in the pathogenesis

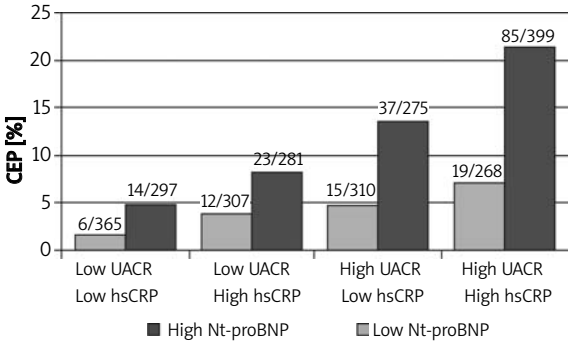

Figure 2. Nt-proBNP, UACR and hsCRP have additive prognostic information

Incidence of the composite endpoint in the general population after a median follow-up of 9.4 years in subjects with Nt-proBNP above vs. below 32 pg/ml in men and 66 pg/ml in women, UACR above vs. below 0.20 mg/mmol in men and 0.30 mg/mmol in women and hsCRP above vs. below 1.81 mg/l

All three risk markers were associated with increased cardiovascular risk even at low values and the risk increased continuously [18] (Figure 3). Due to lack of consensus regarding cut-off values for these apparently continuous risk markers we decided to test different age- and gender-specific cut-off values [20]. Pre-specified 90% specificity, gender-adjusted (men/women) cut-off values of 110/164 pg/ml for Nt-proBNP, 6.0/7.3 mg/l for hsCRP, and 0.73/1.06 mg/mmol for UACR lead to the highest positive predictive values without compromising the necessarily high negative predictive values [20].

High sensitivity C-reactive protein predicted CEP primarily in 41- or 51-year old men, Nt-proBNP in 61- or 71-year old subjects and UACR independently of age and gender [20]. This is probably because hsCRP and UACR are elevated early in the development of atherosclerosis [21, 22] secondarily to metabolic risk factors and endothelial dysfunction [10], and because Nt-proBNP and UACR are elevated later in the process in connection with subclinical cardiovascular damage [8]. Consistent with this we also found: 1) that hsCRP primarily predicted CEP in low-risk subjects without any elements of the metabolic syndrome [23, 24], 2) that Nt-proBNP primarily predicted CEP in high-risk subjects with the metabolic syndrome, diabetes or known cardiovascular disease [23, 24], and 3) that UACR predicted CEP independently of cardiovascular risk assessed by elements of the metabolic syndrome or by HeartScore [23, 24]. In patients with hypertension and LV hypertrophy, Nt-proBNP, but not hsCRP, predicted CEP independently of traditional cardiovascular risk factors and UACR, which supports the idea that hsCRP primarily predicts outcome in low-risk subjects.

In healthy subjects with a 10-year risk of cardiovascular death lower than 5% based on HeartScore [2] and therefore not eligible for primary prevention [25], the actual 10-year risk of cardiovascular death exceeded 5% in a small subgroup of subjects with hsCRP higher than 5.6 mg/l [24], which was close to the pre-specified 90% specificity, gender-adjusted cut-off value of 6.0/7.3 mg/l [20] (Figure 4). As hsCRP ≥6.0/7.3 mg/l was found only in 124 subjects predicting only 6 CEPs and as 82% of the subjects in the low-moderate risk group were 41 or 51 years old [24], one could argue for a lower cut-off value accepting intervention at a lower absolute 10-year cardiovascular risk if the relative risk was high. That would be especially relevant in subjects with moderate cardiovascular risk as recommended by

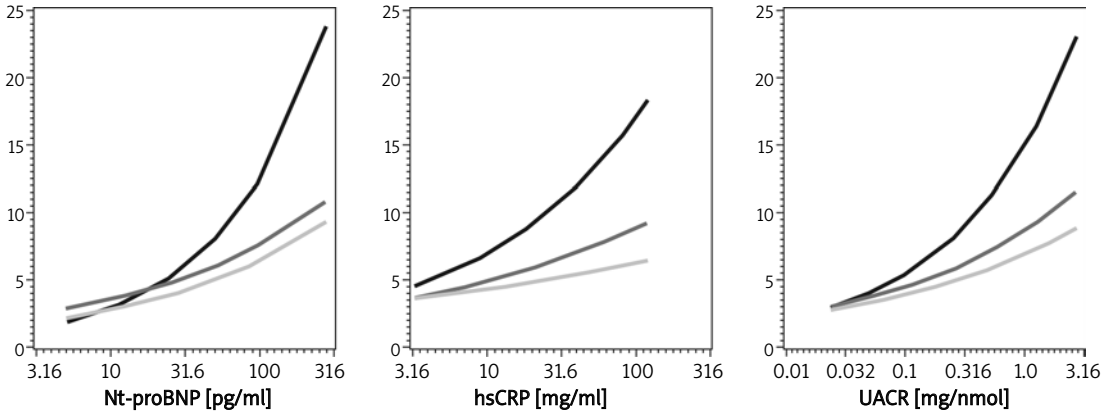

Figure 3. The risk of the composite endpoint increases with increasing levels of the three new risk markers in the general population

The calculated absolute risk of the composite endpoints as functions of log (Nt-proBNP), log (hsCRP) or logUACR unadjusted (black), adjusted for prior stroke or myocardial infarction, known diabetes, CV medication, gender and mean age (dark grey), and further adjusted for smoking and mean heart rate, systolic blood pressure, plasma glucose and serum low density lipoprotein (light grey)

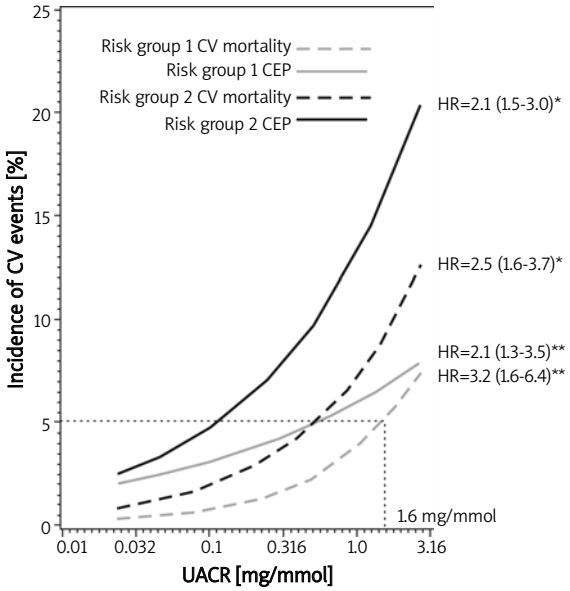

Figure 4. The importance of UACR for the actual absolute risk of cardiovascular (CV) events in apparently healthy subjects

The actual 10-year absolute risk of the composite cardiovascular (CV) endpoint (CEP) (full lines) and CV death (dotted lines) in subjects with an estimated (HeartScore) 10-year risk of CV death below (grey lines) or above (black lines) 5% at different levels of UACR. Hazard ratios (HR) and their 95% confidence intervals are calculated using Cox regression analyses

**P<0.001, **P<0.01*

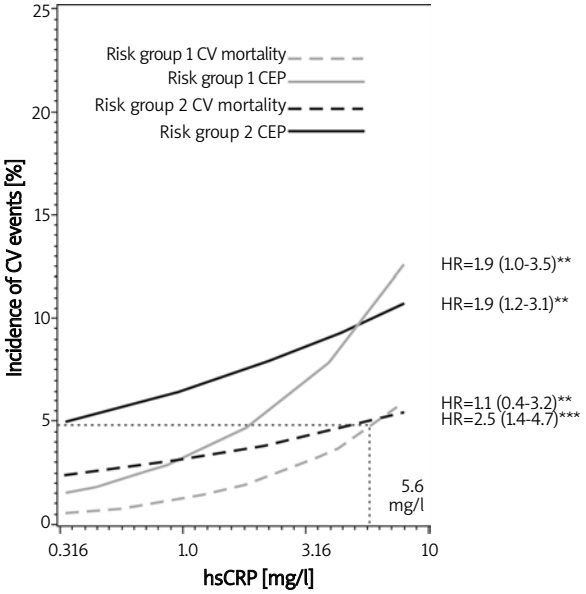

Figure 5. The importance of hsCRP for the actual absolute risk of cardiovascular (CV) events in apparently healthy subjects

The actual 10-year absolute risk of the composite cardiovascular (CV) endpoint (CEP) (full lines) and CV death (dotted lines) in subjects with an estimated (HeartScore) 10-year risk of CV death below (grey lines) or above (black lines) 5% at different levels of hsCRP. Hazard ratios (HR) and their 95% confidence intervals are calculated using Cox-regression analyses

** p<0.01, *** p<0.05*

the Centers for Disease Control and Prevention and the American Heart Association in 2003 [26]. However, our data also suggested that hsCRP did not add new prognostic information in subjects with low-moderate cardiovascular risk, if younger subjects were regarded as being 60 years of age when calculating cardiovascular risk [24] in order to avoid withholding intervention that would be recommended only if the subjects were older [25]. However, this method almost doubled the number of subjects eligible for primary prevention due to high cardiovascular risk based on HeartScore, which is not rational. The impact of measuring hsCRP is still controversial. Ridker et al. [27] and others [28] have previously found hsCRP to predict cardiovascular events independently of Framingham risk score and recently claimed that a new risk score using hsCRP as a continuous variable together with traditional cardiovascular risk factors in subjects with moderate cardiovascular risk can reclassify 40-50% of the subjects to either higher or lower CV risk [29], whereas Danesh et al. [30] have questioned the additive predictive value of hsCRP.

In the same low-moderate risk group, the actual 10-year risk of cardiovascular death exceeded 5% for UACR >1.6 mg/mmol (Figure 5), giving indication for primary prevention [25] in a small subgroup of 61 subjects (4.3%) [24]. However, as most of the subjects were 41 or 51 years old with an overrepresentation of women [24], intervention might be relevant at a lower absolute 10-year risk of cardiovascular death. UACR above the pre-specified gender-adjusted cut-off value of 0.73/1.06 mg/mmol (90% specificity), which was found in 120 subjects with low-moderate cardiovascular risk, identified as many as 10 CEPs with a very high negative predictive value of 98% [24]. High UACR still predicted CEP in subjects with low-moderate cardiovascular risk if younger subjects were regarded as being 60 years when calculating cardiovascular risk [24]. This suggested that primary prevention in subjects with low-moderate cardiovascular risk may be relevant already at levels of UACR around 1 mg/mmol, which represents a practical round cut-off value close to the value at which cardiovascular risk clearly begins to increase in patients with hypertension [31]. However, others

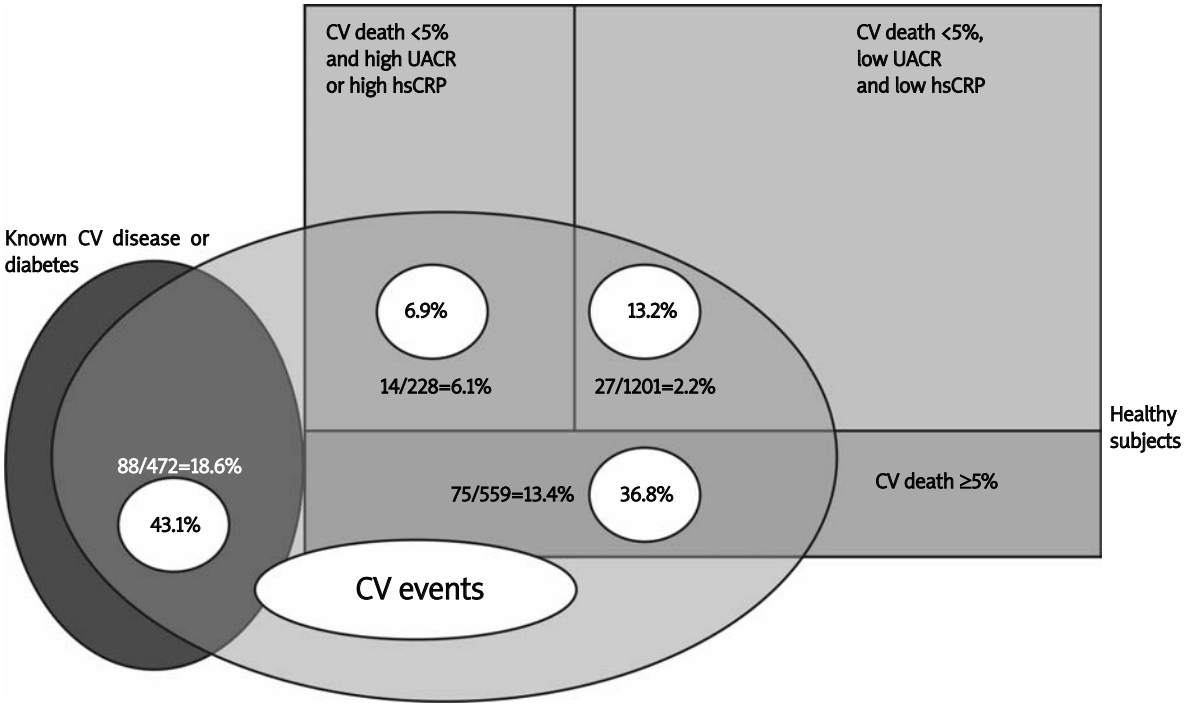

Figure 6. The actual distribution of the composite endpoint according to risk profile
In our population 43% of cardiovascular (CV) events occurred in subjects with known CV disease or diabetes, 37% in subjects with high CV risk as estimated by HeartScore and 20% in subjects with low-moderate CV risk. One third of the events in subjects with low-moderate CV risk could be predicted by high UACR or high hsCRP

have suggested a somewhat higher cut-off value [32]. Combined use of UACR ≥0.73/1.06 mg/mmol or hsCRP ≥6.0/7.3 mg/l identified a larger subgroup of 228 subjects (16%) with high cardiovascular risk in which primary prevention may be advised [24] despite low-moderate cardiovascular risk based on HeartScore [2] (Figure 6). Measuring UACR and hsCRP in subjects with low-moderate CV risk seems to be a clinically relevant supplement to HeartScore as 34% are reclassified correctly versus 15% wrongly. However, in daily clinical practice, we do not suggest that these two new risk markers be measured routinely in subjects with low-moderate CV risk, but measured on an individual basis either in subjects with moderate CV risk or in subjects especially afraid of developing CV disease.

In subjects with known cardiovascular disease or diabetes, Nt-proBNP and UACR above the pre-specified 90% specificity, gender-adjusted cut-off values of 110/164 pg/ml or 0.73/1.06 mg/mmol predicted CEP with very high positive predictive values of approximately 37% and relatively high negative predictive values of 90%. Furthermore, combined use of UACR ≥0.73/1.06 mg/mmol or high Nt-proBNP ≥110/164 pg/ml in subjects with known cardiovascular disease or diabetes identified a larger subgroup of 228 subjects (48%) with extremely high cardiovascular risk who should be referred for specialist care in order to optimize treatment [24]. Measuring UACR and Nt-proBNP seems to be relevant in patients with known CV disease or diabetes as 49% are reclassified correctly vs. 15% wrongly. For pragmatic reasons we recommend using the threshold accepted in heart failure of 125 pg/ml [33] as the cut-off value in cardiovascular risk stratification instead of our gender-adjusted cut-off value of 110/164 pg/ml.

In patients with hypertension and electrocardiographic LV hypertrophy, blood pressure reduction was associated with a significant 30-40% reduction in UACR. However, the reduction was more marked in patients randomized to an angiotensin-II receptor blocker based antihypertensive regime compared to a β-adrenergic receptor blocker based regime [34], suggesting either a more effective reduction of the central blood pressure [35] or a blood pressure independent effect of the renin-angiotensin-aldosterone system on UACR. Furthermore, one year UACR had independent prognostic importance independently of changes in blood pressure [31] and LV hypertrophy assessed by electrocardiography [12] (Figure 7). This supports the concept that albuminuria [36-38] and LV hypertrophy [39-41] are markers of pre-clinical disease in different organs with a possible direct influence on CV risk [42]. Albuminuria reflecting generalized transvascular leakiness [43] may promote lipid insudation, atherosclerosis and thrombosis in coronary as well as cerebral arteries

and thereby contribute to CV events. LV hypertrophy may through myocardial ischaemia [44] compromise LV function and increase the risk of arrhythmia [45]. Therefore, it seems likely that albuminuria and LV hypertrophy are not just markers of CV risk, but also important CV risk factors which need to be addressed directly in the future treatment of patients with hypertension to improve prognosis.

In conclusion, we as well as others have found that UACR, Nt-proBNP and hsCRP have additive predictive value and predict major cardiovascular events independently of traditional cardiovascular risk factors, whereas the clinical impact is less clear. However, in healthy subjects with a 10-year risk of cardiovascular death lower than 5% based on HeartScore, combined use of UACR ≥0.73/1.06 mg/mmol or hsCRP ≥6.0/7.3 mg/l seemed to identify a subgroup of 16% with high cardiovascular risk in which primary prevention with more exercise, healthy diet, smoking cessation, and blood pressure and cholesterol monitoring/lowering according to general guidelines may be advised. Whereas in subjects with known cardiovascular disease or diabetes, combined use of UACR ≥0.73/1.06 mg/mmol or high Nt-proBNP ≥110/164 pg/ml seemed to identify a larger subgroup of 48% with extremely high cardiovascular risk who should be referred for specialist care in order to optimize treatment. However, further studies are needed to confirm this.

Antihypertensive treatment reduces UACR and the reduction carries additive prognostic information independently of changes in blood pressure and LV hypertrophy.

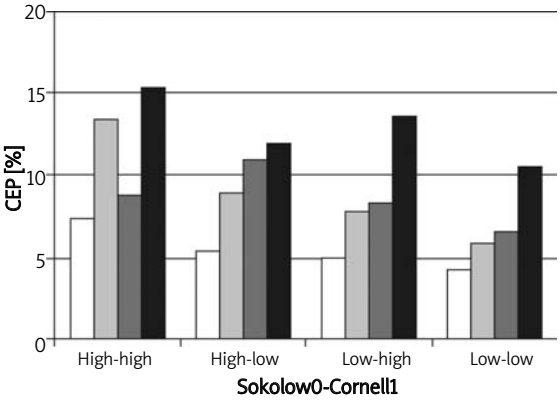

Figure 7. The additive prognostic importance of albuminuria and left ventricular hypertrophy at baseline and after one year of antihypertensive treatment

The additive prognostic importance of baseline Sokolow-Lyon voltage (median 29.9 mm) and one year Cornell Product (median 2484 mm × ms) as well as baseline (median 1.18 mg/mmol) and one year UACR (median 0.65 mg/mmol) on the incidence of the composite endpoint (CEP). High and low correspond to values above or below the median values

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