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# Serum Uric Acid Predicts Vascular Complications in Adults with Type 1 Diabetes: the Coronary Artery Calcification in Type 1 Diabetes Study

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## Abstract

**Hypothesis—**Epidemiologic evidence support a link between serum uric acid (SUA) and vascular complications in diabetes, but it remains unclear whether SUA improves the ability of conventional risk factor to predict complications. We hypothesized that SUA at baseline would independently predict the development of vascular complications over 6 years, and that the addition of SUA to American Diabetes Association's ABC risk factors (HbA1c, BP, LDL-C) would improve vascular complication prediction over 6-years in adults with type 1 diabetes.

**Methods—**Study participants (N=652) were 19–56 year old at baseline and re-examined 6-years later. Diabetic nephropathy (DN) was defined as incident albuminuria or rapid GFR decline (>3.3%/year) estimated by the CKD-EPI cystatin C. Diabetic retinopathy (DR) was based on self-reported history, proliferative diabetic retinopathy (PDR) was defined as laser eye therapy; coronary artery calcium (CAC) was measured using electron-beam computed-tomography. Progression of CAC (CACp) was defined as a change in the square-root transformed CAC-volume ≥ 2.5. Predictors of each complication were examined in stepwise logistic regression with subjects with complications at baseline excluded from analyses. C-statistics, integrated-discrimination indices and net-reclassification improvement were utilized for prediction performance analyses.

**Results—**SUA independently predicted development of incident albuminuria (OR: 1.8, 95% CI 1.2–2.7), rapid GFR decline (1.9, 1.1–3.3), DR (1.4, 1.1–1.9), PDR (2.1, 1.4–3.0) and CACp (1.5

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**Author Contributions**

PB researched, wrote, contributed to discussion, and reviewed/edited the manuscript; DMM researched, contributed to discussion, and reviewed/edited the manuscript; MR designed the CACTI Study, researched, contributed to the discussion and reviewed/edited the manuscript; RJJ contributed to the discussion and reviewed/edited the manuscript; JKSB researched, contributed to the discussion, reviewed/edited the manuscript.

**Duality of interest**

RJJ has patent applications related to the lowering of uric acid and or blocking fructose metabolism as a means for slowing diabetic nephropathy or improving insulin resistance, and has shares with XORT Therapeutics related to these patents. Drs. Bjornstad, Snell-Bergeon and Maahs have no conflict of interest to disclose.

(1.1–1.9). SUA improved the discrimination and net-classification risk of vascular complications over 6-years.

**Conclusion—**SUA independently predicted the development of vascular complications in type 1 diabetes, and also improved the reclassification of vascular complications.

### Keywords

serum uric acid; type 1 diabetes; microvascular complications; macrovascular complications

## Introduction

Vascular complications are responsible for significant morbidity and mortality in type 1 diabetes [1–3]. Vascular complications occur in both the macro- (e.g. coronary artery disease (CAD)) and microvasculature (e.g. diabetic retinopathy (DR), proliferative diabetic retinopathy (PDR) and diabetic nephropathy (DN)), with CAD and DN continuing to be the major causes of mortality in patients with type 1 diabetes [4,5,3].

Recent data from NHANES showed that less than 19% of subjects with type 1 and 2 diabetes achieved all three of the American Diabetes Association (ADA)'s ABC goals (A; HbA1c <7.0%, B; BP <130/80 mm Hg, C; LDL-C <100mg/dL) [2]. Moreover, addressing these conventional risk factors lowers, but does not abolish the risk of developing vascular complications [6,7]. For that reason, there is a need for improved methods of identifying people at risk of vascular complications at an early stage, in addition to novel therapeutic targets to supplement conventional risk factors in preventing the development and progression of these complications. Insulin sensitivity and serum uric acid are increasingly recognized as important risk factors for vascular complications in type 1 and 2 diabetes [8–11]. In type 1 diabetes, in contrast to type 2 diabetes, insulin sensitivity and serum uric acid are very weakly associated and may represent two independent pathogenic mechanisms [12].

Multiple studies link serum uric acid (SUA) to vascular complications and epidemiologic evidence suggests lowering SUA as a novel intervention to prevent renal function loss in type 1 diabetes [13,14]. SUA levels in adult patients with type 1 diabetes tend to be lower than in the general population, but are still strongly related to development of vascular complications [13,15]. The Coronary Artery Calcification in Type 1 diabetes (CACTI) cohort provided the opportunity to examine the associations between SUA and macro- (defined as progression of coronary artery calcification (CAC)) and microvascular (defined as DN, DR and/or PDR) complications in a prospective cohort of adults with type 1 diabetes. We hypothesized that SUA at baseline would independently predict the development of both micro- and macrovascular complications over 6 years in adults with type 1 diabetes. Furthermore, we hypothesized that the addition of SUA to ABC risk factors would improve the vascular event prediction over 6-years in adults with type 1 diabetes.

## Materials and Methods

The CACTI Study enrolled 1416 subjects between the ages of 19–56; 652 with type 1 diabetes and 764 without diabetes, who were asymptomatic for cardiovascular disease (CVD) at the baseline visit in 2000–02 and then were re-examined 3 and 6 years later, as previously described [16]. Only the 652 participants with type 1 diabetes were included in this analysis. The study was approved by the Colorado Multiple Institutional Review Board and all participants provided informed consent.

We measured height and weight, and calculated BMI in $kg/m^2$. Resting systolic (SBP) and fifth-phase diastolic blood pressure (DBP) were measured three times while the patient was seated, and the second and third measurements were averaged. The blood samples for laboratory measurements were all collected at the same baseline visit. After an overnight fast, blood was collected, centrifuged, and separated. Plasma was stored at 4°C until assayed. Serum uric acid levels were measured on stored baseline samples via the Clinical Analyzer utilizing a uricase-based commercial kit in the laboratory of Dr. Richard J. Johnson. These samples had been previously thawed twice. The results were reported in milligrams per deciliter. Total plasma cholesterol and triglyceride levels were measured using standard enzymatic methods, HDL cholesterol (HDL-C) was separated using dextran sulfate and LDL cholesterol (LDL-C) was calculated using the Friedewald formula. High performance liquid chromatography was used to measure HbA1c (HPLC, BioRad variant). Anti-hypertension medication use (including beta-blockers, calcium channel blockers, diuretics, ACE inhibitor (ACEi) and/or angiotensin receptor blockers (ARB) use were self-reported and were combined for our analyses.

### Diabetic nephropathy

We defined DN as incident albuminuria or rapid GFR decline. Albuminuria was defined as AER ≥ 20 μg/min if timed urine samples were obtained, or ACR ≥ 30 mg/g for spot samples (if timed urine was not available). Two timed overnight urine samples were collected in duplicate and urine creatinine and albumin were measured (RIA, Diagnostic Products) and averaged. At both visits, urinary albumin excretion rate (AER) and/or albumin/creatinine ratio (ACR) were measured. Of the 27 subjects who developed incident albuminuria all had AER calculated, and all but two (n=326/328) of those who did not develop incident albuminuria had AER calculated. GFR ($mL/min/1.73m^2$) was determined using the CKD-EPI cystatin C equation [17]. Rapid GFR decline was defined as annual GFR loss > 3.3% [18]. Cystatin C was measured in the University of Colorado Hospital Clinical Lab using the commercially available Dade-Behring assay following package insert instructions on a BNII or Prospec instrument as previously described in detail [19].

### CAC progression

CAC measurements were obtained in duplicate using an ultrafast Imatron C-150XLP electron beam computed tomography scanner (Imatron, San Francisco, CA). The average of the two scores was used as the CAC score for that visit. Scans were repeated on follow-up, an average of 6.1 years after the baseline exam. Presence of CAC was defined as a CAC score > 0. Progression of CAC was defined as an increase in volume of CAC of ≥ 2.5 square

root transformed units. This definition of progression has previously been shown to represent significant progression of atherosclerosis [7,20].

### Diabetic retinopathy and proliferative diabetic retinopathy

Diagnosis of DR and PDR were based on self-reported history of DR and laser eye treatment respectively. Self-reported DR and laser eye treatment have been respectively validated as both sensitivity and specific tools for determining DR and PDR [21,22].

### Statistical Analysis

Analyses were performed in SAS (version 9.3 for Windows; SAS Institute, Cary, NC). Post-hoc power calculations for SUA were provided by PROC POWER in SAS and based on Shieh-O'Brien approximation for logistic regression with an alpha value set at 0.05, response probability based on incidence of dependent outcome (e.g. 0.425 for CACp) and with odds ratios from the multivariable analyses. These analyses yielded a power >0.99 for CACp, >0.99 for rapid GFR decline, >0.99 for incident albuminuria, 0.92 for incident DR and >0.99 for incident PDR. Differences between men and women were assessed using Chi-Square for categorical variables and t-test for continuous variables. Logistic regression was performed to evaluate the associations between variables at baseline and development of incident albuminuria, incident DR, incident PDR and rapid GFR decline and CACp. For that reason, we excluded subjects with albuminuria, DR and PDR at baseline in the respective analyses with incident albuminuria, DR or PDR as the outcomes. For rapid GFR decline and CACp, however, we examined progression and therefore did not exclude baseline disease. Variables considered for inclusion in the multivariable models were based on *a priori* criteria: significance in previous work, significant contribution to the model (p-value of <0.1), or confounding between the main variable of interest and the outcome by >10%. The following variables were considered for inclusion in the models: SUA, HDL-C, LDL-C, SBP, DBP, antihypertensive medications, HbA1c, diabetes duration, sex and age. Stepwise logistic regression was used to determine which variables remained in multivariable models predicting DR, PDR, albuminuria, rapid GFR decline and CACp, respectively. Only variables with P<0.1 in stepwise selection were included in the models. We also ran fully adjusted models adjusting for all of the above covariates.

Prediction metrics for microvascular (incident albuminuria, rapid GFR decline, incident DR and incident PDR) and macrovascular (CACp) events over 6-years were investigated with C-statistics, integrated discrimination index (IDI), relative integrated discrimination index (relative IDI) and continuous net reclassification improvement. Subjects without data at baseline and follow-up were excluded from the analyses. The C-statistic has been criticized for insensitivities to changes in clinical decisions yielded for information gained [23–25]. Therefore, we also utilized IDI, relative IDI and NRI. NRI estimates correct changes in clinical classification across risk thresholds [23–25], and IDI, and relative IDI, use probability differences instead of categories [23–26]. For incident albuminuria and CACp we also examined categorical net reclassification improvement (NRI); estimating the ability of SUA to appropriately reclassify 6-year risk of experiencing CACp or incident albuminuria from a categorical model using risk cutoffs derived from the Framingham studies [27–30]. We did not have well established risk cut-offs for the other outcomes and

thus could not calculate categorical NRI. Event re-classification describes the percentage of events (i.e. CACp) correctly reclassified by the addition SUA to the ABC model. Similarly, non-event reclassification reports the percentage of non-events (i.e. no CACp) correct reclassified by the addition SUA to the ABC model. Significance was based on an α-level of 0.05.

## Results

In CACTI, 7.6% of adults with type 1 diabetes experienced incident albuminuria, 10.6% rapid GFR decline, 18.2% DR, 8.3% PDR and 42.5% CACp over 6-years as previously reported in detail [31]. SUA at baseline was significantly higher in men than women (5.6±1.0 vs 4.6±1.0 mg/dL, p<0.0001), but overall within the low-normal range (3.5–7.0 mg/dL [32]), and lower than the cohort's non-diabetic controls as previously described [12]. Baseline subject characteristics stratified by gender are shown in Table 1.

### Diabetic nephropathy

In stepwise multivariable logistic regression models, SUA predicted increased odds of developing incident albuminuria (odds ratio (OR): 1.8, 95% CI: 1.2–2.7, p=0.004) and rapid GFR decline by $eGFR_{CYSTATIN\ C}$ (OR 1.9, 95% CI: 1.1–3.3, p=0.03) after adjustment for age, diabetes duration, HbA1c, HDL-C, SBP, DBP and antihypertensive medications, the only other variables entering the stepwise models (Table 2). HbA1c also predicted increased odds of developing albuminuria, and antihypertensive medication use predicted rapid GFR decline in the multivariable models (Table 2). Male gender appeared protective against rapid GFR decline (Table 2). To further test the independence of the association between SUA and DN – we ran models where all variables (SUA, age, diabetes duration, sex, HbA1c, SBP, DBP, LDL-C, HDL-C and antihypertensive medications) were adjusted for and the associations between SUA and albuminuria (p=0.02) and rapid GFR decline by $eGFR_{CYSTATIN\ C}$ (p=0.03) remained significant.

Of all the variables in the fully adjusted model, SUA and age were the strongest single predictors of incident albuminuria, C-statistic = 0.70 (95% CI 0.63–0.76), and rapid GFR decline, C-statistics = 0.66 (0.59–0.74) respectively. C-statistics for baseline models including ABC risk factors with and without SUA are shown in Table 3. The addition of SUA to the ABC model did improve the relative IDI by 35% (p=0.02) for incident albuminuria, but did not reach statistical significance for rapid GFR decline (6.5%, p=0.11) (Table 3). For category free NRI, 23% and 40% of non-events were correctly reclassified by the addition of SUA to the ABC model for incident albuminuria and rapid GFR decline respectively (Table 4). For incident albuminuria, we also built a categorical NRI, based on 3 risk cut-offs categories from the Framingham studies for incident albuminuria (cut-offs of <3%, 3–6% and >6%) [27,28]. The addition of SUA to the ABC model significantly improved non-event classification of incident albuminuria based on the pre-defined risk categories (Table 4).

### Diabetic retinopathy and peripheral diabetic retinopathy

In stepwise multivariable logistic regression models, SUA predicted increased odds of developing incident DR (OR 1.4, 95% 1.1–1.9, p=0.01) and incident PDR (OR 2.1, 95% 1.4–3.0, p=0.0001) after adjustment for age, diabetes duration, HbA1c, HDL-C, SBP, DBP and antihypertensive medications, the only other variables entering the stepwise models (Table 2). HbA1c and diabetes duration also predicted increased odds of developing DR and PDR in multivariable models (Table 2). Moreover, older age appears protective for DR (Table 2), but when removing the collinear variable diabetes duration from the model – the association became insignificant (OR 1.01, 95% 0.91–1.04, p=0.77). To further test the independence of the association between SUA and retinopathy – we ran models where all variables were adjusted for and the associations remained significant between SUA and PDR (p=0.02) and almost significant for DR (p=0.053).

Of all the variables in the fully adjusted model, diabetes duration and HbA1c were the strongest single predictors of DR; C-statistic 0.62 (95% CI 0.55–0.69) and PDR; C-statistics 0.70 (0.60–0.79) respectively. SUA was the second strongest single predictor of both DR; C-statistics 0.60 (0.52–0.68) and PDR; C-statistics 0.67 (0.58–0.77). C-statistics for baseline models including ABC risk factors with and without SUA are shown in Table 3. The addition of SUA to the ABC model improved the relative IDI by 14% (p=0.01) for incident DR and 38% (p=0.01) for incident PDR (Table 3). For category free NRI, 15% and 30% of non-events were correctly reclassified by the addition of SUA to the ABC model for incident DR and incident PDR respectively (Table 4).

### Coronary artery calcification progression

In stepwise multivariable logistic regression models, SUA predicted increased odds of developing CACp (1.5, 95% CI: 1.1–1.9, p=0.004) after adjustment for age, diabetes duration, HbA1c, HDL-C, SBP, DBP and antihypertensive medications, the only other variables entering the stepwise models (Table 2). HbA1c, diabetes duration and antihypertensive medication use also predicted increased odds of developing CACp in multivariable models (Table 2). To further test the independence of the association between SUA and vascular complications – we ran models where all variables were adjusted for and the associations remained significant between SUA and CACp (p=0.02).

Of all the variables in the fully adjusted model, CACp was most strongly predicted by diabetes duration; C-statistics 0.72 (95% CI: 0.67–0.77). However, the addition of SUA to the ABC model predicting CACp did statistically improve the C-statistics (ΔAUC= 0.05, p=0.005, Table 3). The addition of SUA to the ABC model also improved the relative IDI by 12% (p<0.0001) for CACp (Table 3). For category-free NRI, 19% of events and 25% of non-events were correctly reclassified by the addition of SUA to the ABC model for CACp (Table 4). Building a categorical NRI for CACp, we employed 3 risk cut-offs based on risk categories from the Framingham studies for CACp (cut-offs of <20%, 20–50%, and >50%) [27–30]. The addition of SUA to the ABC model, also improved non-event re-classification of CACp based on the predefined risk categories (Table 4).

## Discussion

We report that SUA was independently associated with increased odds of developing incident albuminuria, rapid GFR decline, DR, PDR and CACp over 6-years in adults with type 1 diabetes. Notably, these relationships were evident despite most subjects having low to normal levels of SUA. Furthermore, SUA at baseline added information to ABC risk factors in predicting vascular complications. Epidemiologic evidence links SUA and DN, with a clinical trial underway exploring the role of allopurinol as a renoprotective agent in type 1 diabetes [33], but SUA may be an equally important target in the prevention of DR, PDR and atherosclerosis, and deserves further research.

SUA has previously been shown to be associated with both the development of DN [13,14,34] and CAC [15] in subjects with type 1 diabetes. The novel finding of this study is that we demonstrate that SUA also improves the ability of conventional risk factors to predict incident vascular complications in adults with type 1 diabetes. Furthermore, SUA at baseline is associated with DR and PDR independent of other established risk factors. In support of this, Krizova et al. recently demonstrated that increased intra-vitreous levels of UA may be involved in the pathogenesis and progression of DR [35]. Moreover, micro and macrovascular complications cluster; DR is associated with atherosclerosis [36] and cardiorenal complications remain strongly interrelated in diabetes [37], suggesting possible common underlying risk factors.

SUA as a unified risk factor for the development of both micro- and macrovascular complications does not necessarily imply causation, but increasing evidence implicates SUA in the pathogenesis of vascular complications in type 1 diabetes. For example, raising SUA in rats with a uricase inhibitor induces renal microvascular disease [38]. Elevated SUA was associated with oxidative stress, systemic inflammation and endothelial dysfunction induced by decreased endothelial nitric oxide production [39]. SUA is also associated with arterial stiffness by pulse wave velocity [40] and carotid intima media thickness [41,42] in adults, and predicted myocardial small vessel dysfunction following myocardial infarction [43], suggesting it may play role in causing small vessel arteriolar disease in multiple organs [44].

The Preventing Early Renal Function Loss (PERL) Allopurinol Study [33] is an ongoing multi-center double-blind randomized clinical trial with allopurinol to lower SUA in subjects with type 1 diabetes in an attempt to prevent early DN [33]. If PERL produces promising results, similar studies could be conducted with other microvascular and macrovascular complications as endpoints. The recent discovery that fructose-mediated generation of SUA may contribute to vascular complications provides an additional opportunity for important diet and lifestyle modifications [45].

There are important limitations of this study worth mentioning. First, DR and PDR were self- reported and could have been affected by poor recall, but self-reported of DR and PDR were recently validated for subjects with type 1 diabetes with sensitivity and specificity greater than 90% [21,22]. Only 27 subjects experienced incident albuminuria over 6-years limiting the power of our analyses. Although we adjusted for a variety of important confounding variables, we cannot rule out the presence of unknown risk factors that may

have biased or confounded the present analyses. The risk categories used for the categorical NRI were derived from Framingham studies with study populations not identical to ours, for which reason we also employed category-free NRI. Results from this study may not be generalizable to significantly younger or older subjects with type 1 diabetes. We also acknowledge that microalbuminuria as a proxy for DN is not without controversy [46], and for that reason added rapid GFR decline by cystatin C to further investigate renal outcomes [18].

In summary, in this study SUA at baseline was associated with the development of vascular complications over 6 years in adults with type 1 diabetes. Furthermore, we show that SUA at baseline can add valuable information to conventional risk factors in risk stratifying individuals for micro- and macrovascular complications. To translate this epidemiologic data into clinical practice adequately powered clinical trials that capture important long-term vascular outcomes are needed.

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Drs. Petter Bjornstad and Janet K. Snell-Bergeon are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

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## Table 1

Baseline Subject Characteristics Stratified by Gender

| | Men (n=298) | Women (n=354) | p-value |
|---|---|---|---|
| **Age (years)** | 37 ± 9 | 36 ± 9 | 0.07 |
| **Diabetes duration (years)** | 24 ± 9 | 23 ± 9 | 0.29 |
| **HbA1c (%)** | 8.0 ± 1.2 | 8.0 ± 1.3 | 0.90 |
| **HbA1c (mmol/mol)** | 64.0 ± 10.8 | 64.0 ± 11.9 | 0.90 |
| **LDL-C (mg/dl)** | 104 ± 30 | 98 ± 28 | 0.007 |
| **HDL-C(mg/dl)** | 51 ± 14 | 60 ± 17 | <0.0001 |
| **Triglycerides (mg/dl)** | 80 (61–113) | 77 (61–104) | 0.23 |
| **SBP (mm Hg)** | 121 ± 14 | 114 ± 14 | <0.0001 |
| **DBP (mm Hg)** | 80 ± 9 | 75 ± 8 | <0.0001 |
| **BMI (kg/m$^2$)** | 26.5 ± 3.9 | 26.0 ± 4.7 | 0.09 |
| **Waist circumference (cm)** | 90.3 ± 11.7 | 80.8 ± 12.0 | <0.0001 |
| **SUA (mg/dl)** | 5.6 ± 1.0 | 4.6 ± 1.0 | <0.0001 |
| **AER (μg/min)** | 7.4 (4.5–23.8) | 5.8 (3.8–11.8) | <0.0001 |
| **ACR (mg/dL)** | 6.3 (3.7–21.3) | 6.2 (4.2–12.5) | 0.86 |
| **eGFRCYSTATIN C** | 107 ± 23 | 106 ± 20 | 0.68 |
| **Insulin therapy** | 100% | 100% | N/A |
| **Metformin** | 2.4% | 3.3% | 0.43 |
| **Pioglitazone** | 0% | 0.6% | 0.19 |
| **On antihypertensive medications (%)** | 41% | 35% | 0.09 |
| **Ever smoker (% yes)** | 18% | 22% | 0.21 |
| **Any CAC (% yes)** | 49 | 28 | <0.0001 |
| **Albuminuria (% yes)** | 27 | 17 | 0.005 |
| **Microalbuminuria (% yes)** | 15 | 12 | 0.19 |
| **Macroalbuminuria (% yes)** | 11 | 6 | 0.01 |
| **PDR (% yes)** | 27 | 19 | 0.02 |
| **Retinopathy (% yes)** | 33 | 26 | 0.07 |

Data are means ± SD, % or median ($25^{th}$ – $75^{th}$ %)

**Table 2**

Predictors of Vascular Complications in Stepwise Logistic Regression Analysis

| | Incident albuminuria (n=330) | Rapid GFR decline (n=236) | Incident DR (n=361) | Incident PDR (n=392) | CACp (n=455) |
|---|---|---|---|---|---|
| **Variable** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** |
| **Age (per 10 years)** | – | **2.0** (1.3–3.0) P=0.001 | **0.7** (0.5–1.0) P=0.04 | – | **1.8** (1.3–2.6) P=0.0004 |
| **Diabetes duration (per 10 years)** | – | – | **2.4** (1.6–3.8) P<0.0001 | **1.8** (1.1–2.8) P=0.01 | **2.2** (1.5–3.0) P<0.0001 |
| **Male sex** | – | **0.3** (0.1–0.9) p=0.03 | – | – | – |
| **HbA1c (per 1%)** | **1.5** (1.2–2.1) P=0.003 | – | **1.5** (1.2–1.8) P=0.0004 | **1.8** (1.4–2.3) P<0.0001 | **1.3** (1.1–1.6) P=0.005 |
| **SBP (per 10 mmHg)** | – | – | – | – | **1.4** (1.2–1.7) P=0.0006 |
| **DBP (per 10 mmHg)** | – | – | **1.6** (1.1–2.2) P=0.009 | – | – |
| **Anti-hypertensive medications** | – | **3.5** (1.4–9.0) P=0.01 | – | – | **2.1** (1.3–3.4) P=0.003 |
| **HDL-C (per 10 mg/dl)** | – | – | – | – | **0.8** (0.6–0.9) P=0.0005 |
| **SUA (per 1 mg/dl)** | **1.8** (1.2–2.7) P=0.004 | **1.9** (1.1–3.3) p=0.03 | **1.4** (1.1–1.9) P=0.01 | **2.1** (1.4–3.0) P=0.0001 | **1.5** (1.1–1.9) P=0.004 |

The odds ratio represents the odds of developing the vascular event per 1-unit increase in the independent variable, unless otherwise specified. Dashes indicate that variable did not enter the model. A separate model was constructed for each outcome.

## Table 3

C-statistics for Models with SUA, SBP, DBP, HbA1c and LDL-C as Continuous Variables

| **Model 1 (HbA1c, SBP, DBP and LDL-C) vs. model 2 (model 1 + SUA)** | | | | |
|---|---|---|---|---|
| **Models** | **AUC (95% CI)** | **ΔAUC** | **IDI (±SE)** | **Relative IDI* (%)** |
| ***CAC progression (n=199)*** | | | | |
| **Model 1** (model 1: HbA1c, SBP, DBP and LDL-C) | **0.67** (0.62–0.73) | | | |
| **Model 1 + SUA** (model 1: HbA1c, SBP, DBP and LDL-C) | **0.72** (0.68–0.77) | | | |
| **SUA + Model 1 vs Model 1** (model 1: HbA1c, SBP, DBP and LDL-C) | | **0.05** (p=0.005) | **0.05**±0.01 (p<0.0001) | **12.2%** (p<0.0001) |
| ***Incident albuminuria (n=27)*** | | | | |
| **Model 1** (model 1: HbA1c, SBP, DBP and LDL-C) | **0.67** (0.55–0.80) | | | |
| **Model 1 + SUA** (model 1: HbA1c, SBP, DBP and LDL-C) | **0.73** (0.61–0.84) | | | |
| **SUA + Model 1 vs Model 1** (model 1: HbA1c, SBP, DBP and LDL-C) | | **0.06** (p=0.20) | **0.04**±0.02 (p=0.02) | **35.1%** (p=0.02) |
| ***Rapid GFR decline (n=50)*** | | | | |
| **Model 1** (model 1: HbA1c, SBP, DBP and LDL-C) | **0.69** (0.60–0.77) | | | |
| **Model 1 + SUA** (model 1: HbA1c, SBP, DBP and LDL-C) | **0.70** (0.62–0.79) | | | |
| **SUA + Model 1 vs Model 1** (model 1: HbA1c, SBP, DBP and LDL-C) | | **0.02** (p=0.27) | **0.01**±0.01 (p=0.11) | **6.5%** (p=0.11) |
| ***Incident diabetic retinopathy (n=71)*** | | | | |
| **Model 1** (model 1: HbA1c, SBP, DBP and LDL-C) | **0.65** (0.58–0.72) | | | |
| **Model 1 + SUA** (model 1: HbA1c, SBP, DBP and LDL-C) | **0.68** (0.61–0.75) | | | |
| **SUA + Model 1 vs Model 1** (model 1: HbA1c, SBP, DBP and LDL-C) | | **0.03** (p=0.19) | **0.02**±0.01 (p=0.01) | **14%** (p=0.01) |
| ***Incident peripheral diabetic retinopathy (n=35)*** | | | | |
| **Model 1** (model 1: HbA1c, SBP, DBP and LDL-C) | **0.73** (0.64–0.82) | | | |
| **Model 1 + SUA** (model 1: HbA1c, SBP, DBP and LDL-C) | **0.77** (0.69–0.86) | | | |
| **SUA + Model 1 vs Model 1** (model 1: HbA1c, SBP, DBP and LDL-C) | | **0.04** (p=0.31) | **0.05**±0.02 (p=0.01) | **38%** (p=0.01) |

* Relative IDI – calculated as the ratio of IDI over the discrimination slope of the model without the new variable (i.e. SUA).

## Table 4

Prediction Performance Analyses for Models with SUA, SBP, DBP, HbA1c and LDL-C as Continuous Variables

| **Model 1 (HbA1c, SBP, DBP and LDL-C) vs. model 2 (model 1 + SUA)** | |
|---|---|
| ***CAC progression (n=199)***<br>*Low risk category: <20%*<br>*Intermediate risk category: 20–50%*<br>*High risk category: >50%* | |
| ***Categorical NRI*** | ***0.12 (95% CI 0.03–0.21)*** |
| ■ Percentage of events correctly reclassified | **6%** (p=0.13) |
| ■ Percentage of non-events correctly reclassified | **6%** (p=0.04) |
| ***Category free NRI*** | ***0.44 (95% CI 0.25–0.62)*** |
| ■ Percentage of events correctly reclassified | **19%** (p=0.008) |
| ■ Percentage of non-events correctly reclassified | **25%** (p<0.0001) |
| ***Incident albuminuria (n=27)***<br>*Low risk category: <3%*<br>*Intermediate risk category: 3–6%*<br>*High risk category: >6%* | |
| ***Categorical NRI*** | ***0.30 (95% CI 0.14–0.46)*** |
| ■ Percentage of events correctly reclassified | **7%** (p=0.32) |
| ■ Percentage of non-events correctly reclassified | **23%**(p<0.0001) |
| ***Category free NRI*** | ***0.35 (95% CI −0.04–0.74)*** |
| ■ Percentage of events correctly reclassified | **11%** (p=0.56) |
| ■ Percentage of non-events correctly reclassified | **23%** (p<0.0001) |
| ***Rapid GFR decline (n=50)*** | |
| ***Category free NRI*** | ***0.28 (95% CI −0.01–0.57)*** |
| ■ Percentage of events correctly reclassified | **12%** (p=0.40) |
| ■ Percentage of non-events correctly reclassified | **40%** (p<0.0001) |
| ***Incident diabetic retinopathy (n=71)*** | |
| ***Category free NRI*** | ***0.19 (95% CI −0.07–0.45)*** |
| ■ Percentage of events correctly reclassified | **4%** (p=0.72) |
| ■ Percentage of non-events correctly reclassified | **15%** (p=0.01) |
| ***Incident peripheral diabetic retinopathy (n=35)*** | |
| ***Category free NRI*** | ***0.44 (95% CI 0.10–0.78)*** |
| ■ Percentage of events correctly reclassified | **14%** (p=0.40) |
| ■ Percentage of non-events correctly reclassified | **30%** (p<0.0001) |