Evaluating the Risk of Renal Disease Using Urine Proteinuria or Urine Albuminuria in the Applicant with HbA1c Elevation.

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Executive Summary:

Our study examined the mortality impact of HbA1c elevation for insurance applicants when the presence or absence of proteinuria is taken into account, showing differences from earlier studies when proteinuria was not accounted for. It also compared the use of urine albumin vs. urine protein creatinine ratio in determining the presence of proteinuria and additional risk. The urine protein creatinine ratio delivered near identical risk reduction as urine albumin, with many fewer false positives and much lower cost in the setting of insurance screening.

Introduction

In our prior research, we looked at the impact of the full range of HbA1c values on mortality risk but did not examine the risk by level of proteinuria.[1] In other work, we also showed that using a urine protein creatinine ratio (p/c) <0.11 mg/mg (110 mg/gram) as a cut-off for "normal" rather than <0.21 mg/mg substantially improved risk assessment for those with normal fructosamine values.[2] We have not, however, reported on both HbA1c elevation and degree (or absence) of proteinuria in combination to determine the independent mortality impact of each finding.

In addition to the urine p/c performed on all tested applicants, most insurers perform urine albumin testing (often referred to as "microalbumin" which actually describes test results ≥3 mg/dL to 30 mg/dL) for applicants with elevated HbA1c beginning somewhere between HbA1c 6.0 to 7.0%. Adverse action typically occurs for albumin values ≥3 mg/dL. A few insurers and many clinicians use the urine albumin creatinine ratio (ACR) instead of albumin concentration, with microalbuminuria considered to begin at the roughly equivalent ≥30 mg/g of creatinine. However, prior studies have not consistently shown ACR to improve risk discrimination as compared to the simple albumin concentration.[3]

Urine albumin (or ACR) has two potential problems. The first is simply the additional cost of up to $10 per test. Because (depending on testing approach) 10% or more of applicants age 40+

may end up being tested based on elevated HbA1c level, the average laboratory charge per applicant for these ages may increase by approximately $1. The second problem is that normal adults periodically spill small amounts of albumin into the urine (with exercise, viral illness or other benign causes) which commonly exceed 3 mg/dL (or 30 mg/g of creatinine). For example, 39% of specimens positive for microalbuminuria during the NHANES III general population survey were negative for albumin on a second collection.[4] Because of this limitation, the clinical and research diagnosis of microalbuminuria is usually based on 2 or more urine albumin tests done weeks to months apart, with all or most urine results being positive, an approach not possible for insurance screening based on a single examiner visit.

Both the degree to which risk associated with HbA1c elevation is modified by the presence or absence of albuminuria or proteinuria, and whether urine p/c can substitute for urine albumin are questions to be answered by our study.

How the Study Was Done

Applicants tested at CRL from 1992 to 2007 were matched to the Social Security Death Master File to obtain mortality status in September, 2011 and then de-identified. Applicants were limited to those age 40 to 79 with HbA1c values of 5.0% or higher and with urine p/c results present. This resulted in 456,097 lives and 25,711 deaths with a median follow-up of 7 years (range 0 to 19). The degree of proteinuria was limited to <1 mg/mg (eliminating 1.3% of those in the potential pool) to avoid inflating risk ratios of urine p/c or urine albumin by inclusion of the small number of individuals with very high levels of proteinuria.

Analysis for age 40 to 59 and for 60 to 79 was split by HbA1c range and either urine p/c value or urine albumin level. Urine albumin test results were available for 70.3% of the studied applicants with HbA1c 6.0% or higher; this subgroup was analyzed by albumin specific results as well as by urine p/c.

Analysis of relative mortality utilized Cox regression methodology in IBM SPSS 22 with age, sex and smoking status (defined as urine cotinine >200 ng/mL indicating use of tobacco or nicotine delivery device) included as covariates for all relative mortality calculations. The group

with HbA1c of 5 to 5.9% and urine p/c <0.11 was the (normal) reference group for all relative mortality analyses (whether based on urine p/c or urine albumin) to allow direct comparison of risk between urine p/c and urine albumin for increasing levels of HbA1c.

All testing was performed at CRL using Roche reagents on Hitachi chemistry analyzers for urine protein and urine creatinine with Hitachi P Modular used for urine albumin and Hitachi Integra for HbA1c. All testing followed Roche recommended, FDA approved guidelines.

What the Study Found

Table 1 provides the percentage of applicants with urine p/c ≥0.11 mg/mg and/or urine albumin ≥3 mg/dL for each band of HbA1c, split into age 40 to 59 and age 60 to 79. No values are shown for urine albumin in the HbA1c 5 to 5.9% band, as such testing is not routinely done for "normal" HbA1c values. The percentage of applicants who were positive for each measure of proteinuria increased as HbA1c increased, but the percentage positive for urine albumin elevations overall was >1/3 higher than those for urine p/c.

Figures 1 and 2 show the relative risk by HbA1c value, split by level of urine p/c and by urine albumin for age 40 to 59 and 60 to 79 respectively. As expected, the relative risk of an elevated HbA1c was higher for younger as compared to older applicants, but both age groups showed a steady, near-linear, increasing risk as HbA1c increased. The increase in relative risk when proteinuria was present was similar for those with normal and with elevated HbA1c.

The level of risk (both relative to same reference group) for each band of HbA1c when identified as negative for albuminuria or proteinuria is nearly identical for both younger and older ages as shown in Figures 1 and 2. Both urine p/c and urine albumin have near equal ability to exclude additional risk associated with albuminuria or proteinuria.

The risk associated with elevations of urine albumin ≥3 mg/dL was very similar to that for urine p/c 0.11 to 0.20 mg/mg for each age group. The risk increased by an excess of roughly 125% of the risk for the same HbA1c with p/c <0.11 for younger and by 75% of the risk without

proteinuria for older lives. This resulted in parallel lines of risk that increase according to the HbA1c value. Those with urine p/c 0.21 to 0.99 mg/mg showed additional risk.

We also studied ACR (data not shown) using a cut-off of <30 mg/g creatinine (equivalent to urine albumin concentration of <3 mg/dL). The relative mortality was almost identical to that shown in Figures 1 and 2 for urine albumin concentration while the percent of applicants identified as having proteinuria was reduced by approximately 2% for age 40 to 59, and 1% at age 60 to 79.

What Do the Study Results Contribute to Risk Assessment?

Increasing HbA1c is associated with a linear increasing relative risk in the absence and in the presence of albuminuria or proteinuria at HbA1c of 6.0% or higher. If one compares the increase in relative mortality per unit of HbA1c (steepness of the curves) shown in Figures 1 and 2 as compared to that shown in our earlier study (where no analysis was done by level of proteinuria), the risk increase is less in our current study.[1] A likely explanation for that is apparent in Table 1 where higher levels of HbA1c are associated with more proteinuria (and likely with more vascular damage or other diabetic findings). This new study better reflects the (lower) relative risk related to HbA1c when proteinuria is assessed independently (using urine p/c or albumin) as compared to our prior study when proteinuria was not evaluated.

The risk associated with low levels of proteinuria or albuminuria can be accounted for by adding approximately 125% or 75% (depending on younger or older age respectively), of the risk associated with the same HbA1c value without proteinuria.

For applicants with elevated HbA1c, both urine p/c and urine albumin identify a “no albuminuria or proteinuria” group with nearly identical low risk. However, urine albumin testing identifies >1/3 more applicants overall as higher risk without corresponding mortality improvement in the "no albuminuria" group. This is the result of a high false positive rate for albuminuria when only one urine specimen is collected and persistence is not determined by repeat testing. Substituting ACR (albumin creatinine ratio) results in only a very small reduction relative to using urine albumin concentration. Because of similar sensitivity to risk but many fewer (false) positives

requiring underwriting review as well as much lower cost, the urine p/c is the superior measure of risk related to albuminuria or proteinuria for all levels of HbA1c.

For insurance applicant screening, our suggested urine p/c cut-off for those not requiring additional review is <0.11 mg/mg (110 mg/g) for all applicants including those with and without HbA1c elevations. This cut-off value is derived from our earlier research in non-diabetics.[2] It is very close to the suggested value of 0.09 mg/mg from Yamamoto et al when looking at non-diabetics and at diabetics in predicting albuminuria based on p/c.[5,6] Note that while urine creatinine is well standardized between laboratories, urine protein is not, so that different (insurance and clinical) laboratories using different equipment or reagents may often find a slightly different ratio gives equivalent performance as a cut-off level.

Conclusion

The relative risk associated with increasing HbA1c increases in a near linear manner; the degree of increase (slope) is reduced when the presence or absence of proteinuria is accounted for. The presence of albuminuria or proteinuria increases that risk by a fixed percentage (which is higher at younger ages) of the age-specific risk for the same HbA1c without proteinuria.

Urine protein creatinine ratio is equivalent to urine albumin (microalbumin) in identifying those with the lowest risk. It is superior overall (based on use of a single urine sample) because it has over 1/3 fewer false positives potentially leading to adverse underwriting actions and because it is far less expensive.

The potential value of urine albumin when HbA1c is elevated is not for initial screening, but possibly for confirmation that elevated urine p/c represents albuminuria. Exploring this usage will be the subject of a future study.

Figure 1. Relative mortality by HbA1c and urine p/c or urine albumin for age 40 to 59 (reference: HbA1c 5 to 5.9% and urine p/c <0.11)

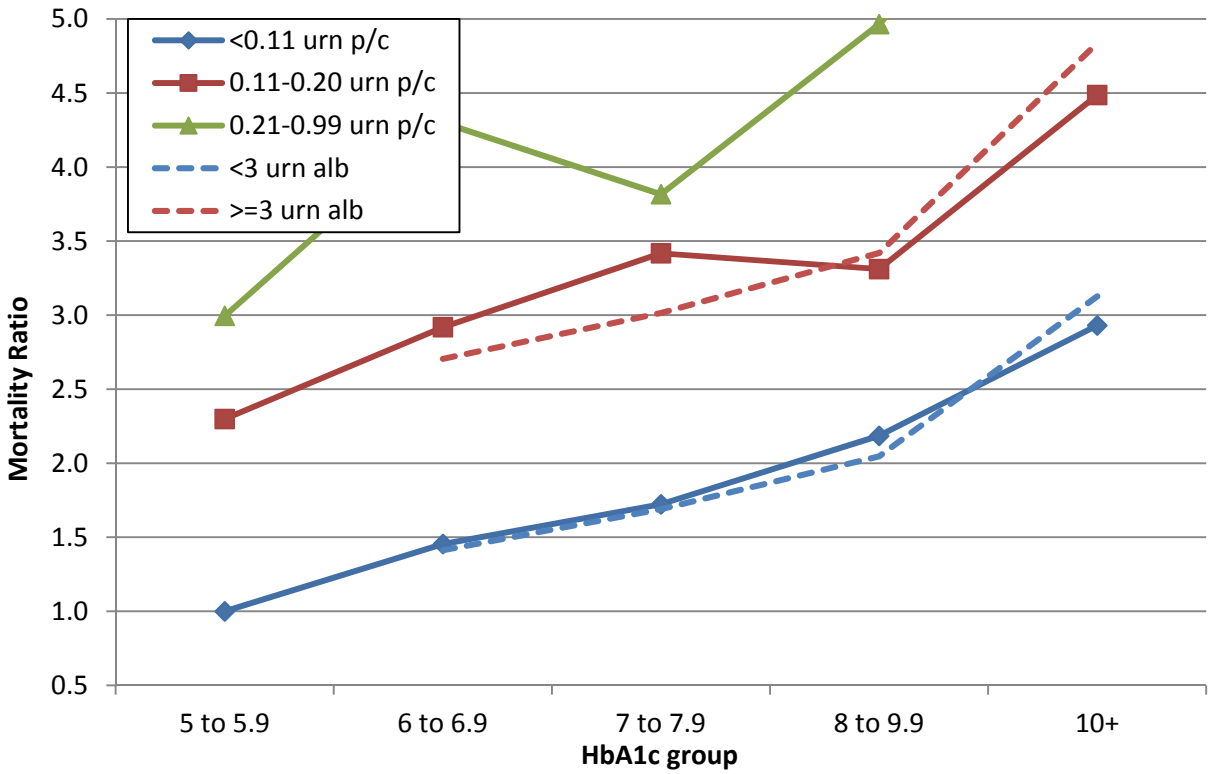

Figure 2. Relative mortality by HbA1c and urine p/c or urine albumin for age 60 to 79 (reference: HbA1c 5 to 5.9% and urine p/c <0.11)

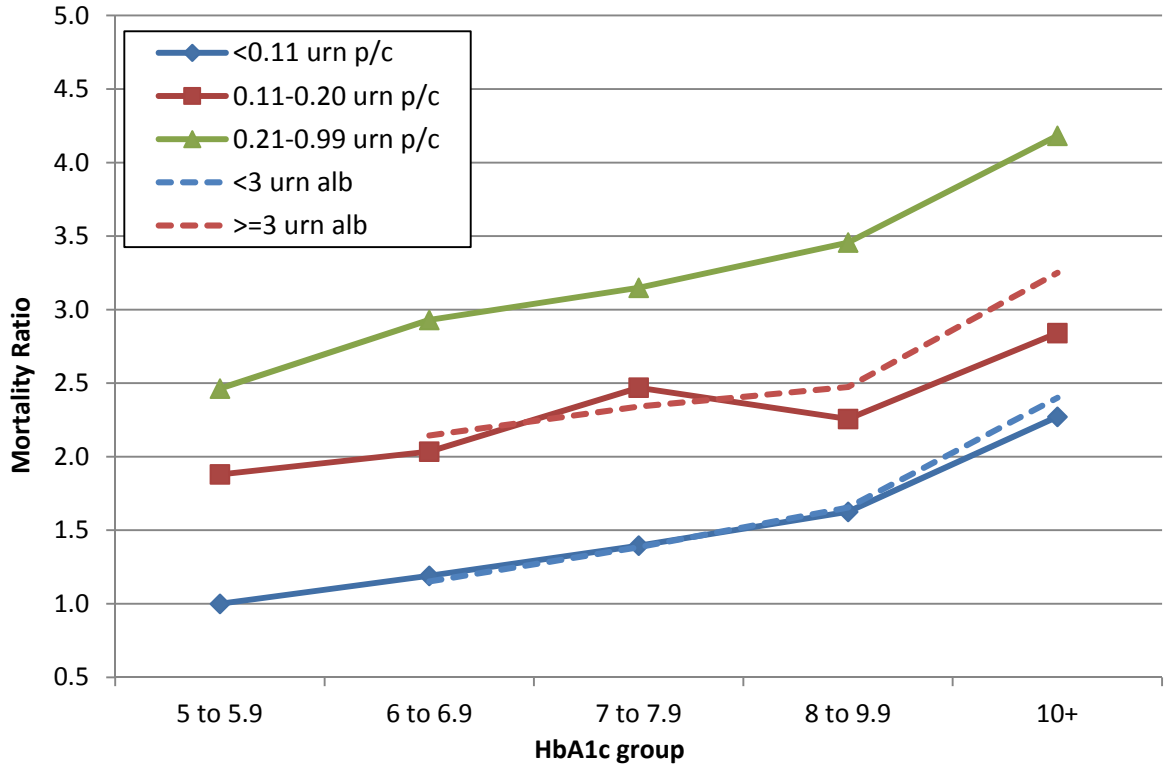

Table 1. Presence of urine p/c ≥0.11 mg/mg or urine albumin ≥3 mg/dL by HbA1c level

	% with p/c ≥0.11		% with albumin ≥3	
HbA1c %	Age 40-59	Age 60-79	Age 40-59	Age 60-79
5-5.9	4.9%	7.9%	------	------
6-6.9	8.9%	12.9%	16.8%	19.7%
7-7.9	13.9%	18.8%	22.7%	26.7%
8-9.9	20.4%	25.4%	31.0%	33.1%
10+	29.7%	36.0%	37.1%	40.6%
6-10+	15.9%	18.8%	24.8%	25.9%

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