Novel Biomarkers for Change in Renal Function in People With Dysglycemia

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Diabetes Care 2020;43:433–439 | https://doi.org/10.2337/dc19-1604

OBJECTIVE

Diabetes is a major risk factor for renal function decline and failure. The availability of multiplex panels of biochemical markers provides the opportunity to identify novel biomarkers that can better predict changes in renal function than routinely available clinical markers.

RESEARCH DESIGN AND METHODS

The concentration of 239 biochemical markers was measured in stored serum from participants in the biomarker substudy of Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial. Repeated-measures mixed-effects models were used to compute the annual change in eGFR (measured as mL/min/1.73 m^2/year) for the 7,482 participants with a recorded baseline and follow-up eGFR. Linear regression models using forward selection were used to identify the independent biomarker determinants of the annual change in eGFR after accounting for baseline HbA_{1c}, baseline eGFR, and routinely measured clinical risk factors. The incidence of the composite renal outcome (i.e., renal replacement therapy, renal death, renal failure, albuminuria progression, doubling of serum creatinine) and death within each fourth of change in eGFR predicted from these models was also estimated.

RESULTS

During 6.2 years of median follow-up, the median annual change in eGFR was −0.18 mL/min/1.73 m^2/year. Fifteen biomarkers independently predicted eGFR decline after accounting for cardiovascular risk factors, as did 12 of these plus 1 additional biomarker after accounting for renal risk factors. Every 0.1 mL/min/1.73 m^2 predicted annual fall in eGFR predicted a 13% (95% CI 12, 14%) higher mortality.

CONCLUSIONS

Adding up to 16 biomarkers to routinely measured clinical risk factors improves the prediction of annual change in eGFR in people with dysglycemia.

Diabetes is a common cause of decline in kidney function with time and accounts for ~45% of all people requiring dialysis (1). Many risk factors for a decline in renal function have been identified and include age, blood pressure, glucose levels, albuminuria, dyslipidemia, cardiovascular disease, and genetic predisposition (2–4). Despite the utility of those risk factors in identifying many people who are at risk for a decline in renal function, many others remain unidentified. The recent availability of large panels of biomarkers that can be measured in small aliquots of serum provides a unique opportunity to identify novel biomarkers for renal function decline.

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Received 12 August 2019 and accepted 27 October 2019

Clinical trial reg. no. NCT00069784, clinicaltrials.gov.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-1604/-/DC1.

The Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial followed 12,537 people with dysglycemia for a median of 6.2 years, during which both insulin glargine–mediated normoglycemia and 1 g of n-3 fatty acid had a neutral effect on cardiovascular outcomes (5). Serum that was stored and frozen in a subset of 8,401 participants at the time of randomization and that was subsequently analyzed for a panel of 239 biomarkers as part of the ORIGIN biomarker substudy and the availability of estimated glomerular filtration rate (eGFR) measurements in most of these participants at baseline and during follow-up provided a unique opportunity to identify novel biomarkers for renal decline. The results of these analyses are reported herein.

RESEARCH DESIGN AND METHODS

The design and results of the ORIGIN trial (5) and biomarker substudy (6,7) have been previously reported. After randomization, participants were followed at regular intervals in 573 sites located in 40 countries for the development of cardiovascular and other serious health consequences. Serum creatinine was measured at each site's local laboratory at baseline, 2 years, and the end of the study after a median of 6.2 years and an eGFR was calculated (8). Because this analysis was designed to identify the subset of biomarkers predicting a decline in renal function over time when added to baseline clinical risk factors, it was restricted to those biomarker substudy participants with both a recorded baseline eGFR and at least one follow-up eGFR at either 2 years or the end of study. As such, data from people who were censored before the 2-year visit because of death or loss to follow-up were not used to identify relevant biomarkers for the decline in eGFR and were only used to estimate the relationship between the clinical and biomarker models that predicted this decline and outcomes. All participants provided written informed consent for the ORIGIN trial and storage of serum for subsequent analyses in the biomarker substudy. The ORIGIN trial and biomarker substudy were funded by Sanofi.

Biomarker Panel

Serum samples sent to Myriad RBM (Austin, TX) were assayed for 237 biomarkers using a customized Human Discovery Multi-Analyte Profile 250+ panel on the Luminex 100/200 platform (6). In addition, the Clinical Research Laboratory and Biobank at Hamilton Health Sciences assayed high-sensitivity troponin I (Abbott ARCHITECT; Abbott Diagnostics, Longford, Ireland) and anti-GAD antibodies (ELISA Test Kit; KRONUS, Star, ID). Therefore, a total of 239 biomarkers was assessed. As previously described (6), before any analyses of biomarkers, *1*) outliers were winsorized, *2*) nonnormal right-skewed distributions were natural log-transformed, *3*) those analyzed as continuous variables were standardized to a mean of 0 and SD of 1, and *4*) those analyzed as variables were analyzed according to five ordinal groups.

Statistical Analyses

Repeated-measures, longitudinal, multilevel (mixed-effects) models with follow-up time as a fixed effect were used to compute the annual change in eGFR (measured as mL/min/1.73 m^2/year) for each participant. Linear regression models were used to identify the independent biomarker determinants of the annual change in eGFR (expressed for every unit or category increase) after accounting for baseline HbA_{1c}, baseline eGFR, and routinely measured clinical risk factors. Two sets of clinical risk factors were forced into the model. The cardiovascular risk factor set used the validated INTERHEART risk score (9) and included sex, age (men >55 years, women >65 years), a previous cardiovascular event, previous diabetes, previous hypertension, current smoking, clinical history or laboratory evidence of microalbuminuria or macroalbuminuria, and LDL/HDL cholesterol ratio. The renal risk factor set included sex, age, log_2-transformed albumin-to-creatinine ratio, cholesterol, smoking status, BMI, and mean arterial pressure (10). For each set of clinical risk factors, a forward selection approach was used to identify those biomarkers that independently and cumulatively predicted the change in eGFR, with a *P* value for inclusion set to <0.05 divided by 239 (i.e., 0.00021) to account for the 239 comparisons. The possibility of an interaction between glargine and each identified biomarker on the dependent variable was assessed with a *P* value divided by the number of identified biomarkers. Model fit was assessed by estimating R^2, and models were compared using the likelihood ratio test. R^2 and the difference in log-likelihood were internally validated with 1,000 samples of the data using bootstrapping with replacement. Model calibration was evaluated by plotting the predicted versus observed change in eGFR per year.

The predicted annual change in eGFR on the basis of the two final linear regression models (i.e., the cardiovascular

Table 1—Annual change in eGFR and outcomes during follow-up of 7,482 participants

Characteristic	Value
Annual eGFR change (mL/min/1.73 m^2/year), mean (SD)	−0.13 (1.02)
Annual eGFR change (mL/min/1.73 m^2/year), median (IQR)	−0.18 (−0.71, 0.40)
Composite cardiovascular outcome[a]	1,058 (14.1)
Expanded composite cardiovascular outcome[b]	2,011 (26.9)
Renal outcome[c]	1,646 (22.0)
Renal replacement therapy, renal failure, or renal death	44 (0.60)
Albuminuria progression	1,526 (20.4)
Doubling of serum creatinine	149 (2.0)
Renal outcome excluding progression of albuminuria	174 (2.3)
Renal outcomes at or before 2 years	370 (4.9)
Death	864 (11.5)
Death at or before 2 years	0 (0)[d]

Data are *n* (%) unless otherwise indicated. [a]The first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. [b]The first occurrence of the first coprimary or heart failure hospitalization or revascularization. [c]Renal replacement therapy, renal death, renal failure, albuminuria progression, or doubling of serum creatinine. [d]This analysis was restricted to participants who had a baseline eGFR and at least one follow-up eGFR at either 2 years or end of study; those who died before 2 years were therefore excluded from this analysis.

and renal models described above) was then estimated for all participants in the ORIGIN trial for whom the variables in these models were available. This estimate for each model was used to divide the population into four groups using quartiles (in which the first quartile included participants with the smallest decline over time). The occurrence of death and the renal composite outcome of the ORIGIN trial (i.e., renal replacement therapy, renal death, renal failure, albuminuria category progression, doubling of serum creatinine from baseline) during follow-up was plotted for each of the four groups on the basis of the clinical variables alone and these variables plus the biomarkers.

The predicted annual change in eGFR on the basis of the two final linear regression models was then included as an independent variable in two Cox models to estimate the hazard of death and the renal outcome for every 0.1 mL/min/1.73 m^2 change in eGFR. The discriminative ability of the clinical variables plus biomarkers versus clinical variables alone for each model was estimated with C statistics, the net reclassification improvement on the basis of classifying people into four categories of risk for developing the outcomes (<0.20, 0.20 to <0.30, 0.3 to <0.40, and ≥0.40), and the integrated discrimination improvement.

RESULTS

A total of 7,482 (59.7%) of 12,537 ORIGIN participants in the biomarker substudy (mean age 63.5 years, 66% men) who had a recorded eGFR at baseline and at either the 2-year visit or the end of follow-up were analyzed to identify the independent biomarkers predicting change in eGFR with time. The median follow-up for these analyses was 6.2 years (interquartile range [IQR] 5.8, 6.8) and the median annual change in eGFR (IQR) was −0.18 mL/min/1.73 m^2/year (−0.71, 0.40) (Table 1). As noted in Supplementary Table 1, 6,073 (81%) had established diabetes, 5,901 (79%) had hypertension, 2,290 (31%) had microalbuminuria or macroalbuminuria, 1,405 (19%) had an eGFR <60 mL/min/1.73 m^2, and 4,402 (59%) had a prior cardiovascular event. At baseline, the mean blood pressure was 146/85 mmHg, mean HbA_{1c} was 6.5%, mean BMI was 30.1 kg/m^2, and mean eGFR was

Table 2—Independent biomarkers of annual change in eGFR adjusted for baseline eGFR (*n* = 7,482)

Risk factor	Cardiovascular clinical model, β (95% CI)[a]	Renal clinical model, β (95% CI)[a]
Clinical factors forced into the model		
Prior cardiovascular event	−0.019 (−0.068, 0.030)	NA
Albuminuria	−0.119 (−0.169, −0.069)	NA
Men	0.194 (0.137, 0.250)	NA
Men ≥55, women ≥65 years of age	−0.104 (−0.160, −0.048)	NA
LDL/HDL	−0.011 (−0.031, 0.009)	NA
Current smoking	0.070 (0.001, 0.138)	NA
Prior diabetes	−0.072 (−0.132, −0.011)	NA
Hypertension	−0.029 (−0.083, 0.025)	NA
Log_2-transformed ACR	NA	−0.030 (−0.045, −0.015)
Women	NA	−0.117 (−0.172, −0.063)
Age	NA	−0.007 (−0.010, −0.004)
Cholesterol	NA	−0.039 (−0.060, −0.019)
Current/former smoker	NA	−0.007 (−0.055, 0.041)
BMI	NA	0.001 (−0.003, 0.005)
Mean arterial pressure	NA	−0.003 (−0.005, −0.001)
HbA_{1c}	0.008 (−0.016, 0.033)	0.002 (−0.022, 0.025)
eGFR	−0.009 (−0.010, −0.007)	−0.008 (−0.010, −0.007)
Biomarkers identified by forward selection		
α-1-Microglobulin	−0.129 (−0.159, −0.099)	−0.157 (−0.185, −0.128)
NT-proBNP	−0.094 (−0.114, −0.074)	−0.081 (−0.101, −0.062)
IGF BP4	−0.112 (−0.144, −0.080)[a]	−0.110 (−0.142, −0.078)[b]
Growth/differentiation factor 15	−0.080 (−0.109, −0.052)	−0.091 (−0.118, −0.064)
RAGE	−0.053 (−0.077, −0.029)	−0.052 (−0.077, −0.027)
Myoglobin	−0.077 (−0.102, −0.052)	−0.073 (−0.098, −0.048)
Growth-regulated α-protein	0.059 (0.034, 0.083)	0.058 (0.033, 0.082)
Fibulin-1C	−0.060 (−0.085, −0.034)	−0.048 (−0.073, −0.023)
Urokinase-type plasminogen activator	0.034 (0.010, 0.059)	NA
Apolipoprotein A-IV	−0.054 (−0.078, −0.030)	−0.057 (−0.081, −0.032)
Kidney injury molecule-1	−0.035 (−0.052, −0.018)	NA
Apolipoprotein A-II	0.063 (0.038, 0.087)	0.065 (0.041, 0.089)
Retinol-binding protein 4	−0.054 (−0.082, −0.027)	NA
Fas ligand	−0.086 (−0.124, −0.048)	−0.099 (−0.138, −0.060)
Eotaxin-1	−0.047 (−0.070, −0.023)	−0.052 (−0.075, −0.028)
β-Amyloid 1–40	NA	−0.057 (−0.081, −0.032)

There was a significant interaction between IGF BP4 and glargine allocation. ACR, albumin-to-creatinine ratio; NA, not applicable. [a]For the cardiovascular model after accounting for this interaction ($P = 0.002$), β (glargine) = −0.177 (−0.225, −0.129) and β (standard care) = −0.058 (−0.100, −0.015). [b]For the renal model after accounting for this interaction ($P = 0.0008$), β (glargine) = −0.168 (−0.215, −0.121) and β (standard care) = −0.060 (−0.103, −0.018).

78 mL/min/1.73 m^2. Because participants had to have survived at least until the 2-year visit to have one follow-up eGFR measured (and therefore be included in this analysis), all deaths occurred between 2 years and the end of the study ($n = 864$). During follow-up, 1,646 (22.0%) participants developed the renal composite outcome, 174 (2.3%) developed the renal composite outcome that excluded albuminuria progression, and 864 (11.5%) died.

After forcing in baseline HbA_{1c}, eGFR, and eight clinical cardiovascular risk factors from the previously validated INTERHEART risk model (9), the linear regression model using a forward selection approach identified 15 of 239 biomarkers as independent predictors of the decline in eGFR during follow-up (Table 2). When the analyses were repeated after substituting previously identified clinical risk factors for renal decline (10) for the cardiovascular risk factors, 12 of these 15 biomarkers were again included, and 1 additional biomarker was identified (Table 2). Forcing in both the cardiovascular and the renal risk factors eliminated one biomarker from the list identified when just the renal risk factors were forced in (Supplementary Table 2). Moreover, there was a significant interaction ($P = 0.0010$ for cardiovascular clinical model and $P = 0.0006$ for renal clinical model) of one biomarker (IGF BP4) with glargine allocation such that the relationship was stronger for participants allocated to glargine versus standard care (Table 2). For both the cardiovascular and the renal model, the identified biomarkers significantly explained more of the variance of the annual change in eGFR than the clinical biomarkers alone (Supplementary Table 3). Moreover, the predicted change in eGFR per year was strongly correlated with the observed change (Supplementary Fig. 1).

The degree to which the predicted annual change in eGFR (estimated using the baseline variables and biomarkers in Table 2) also predicted either death or

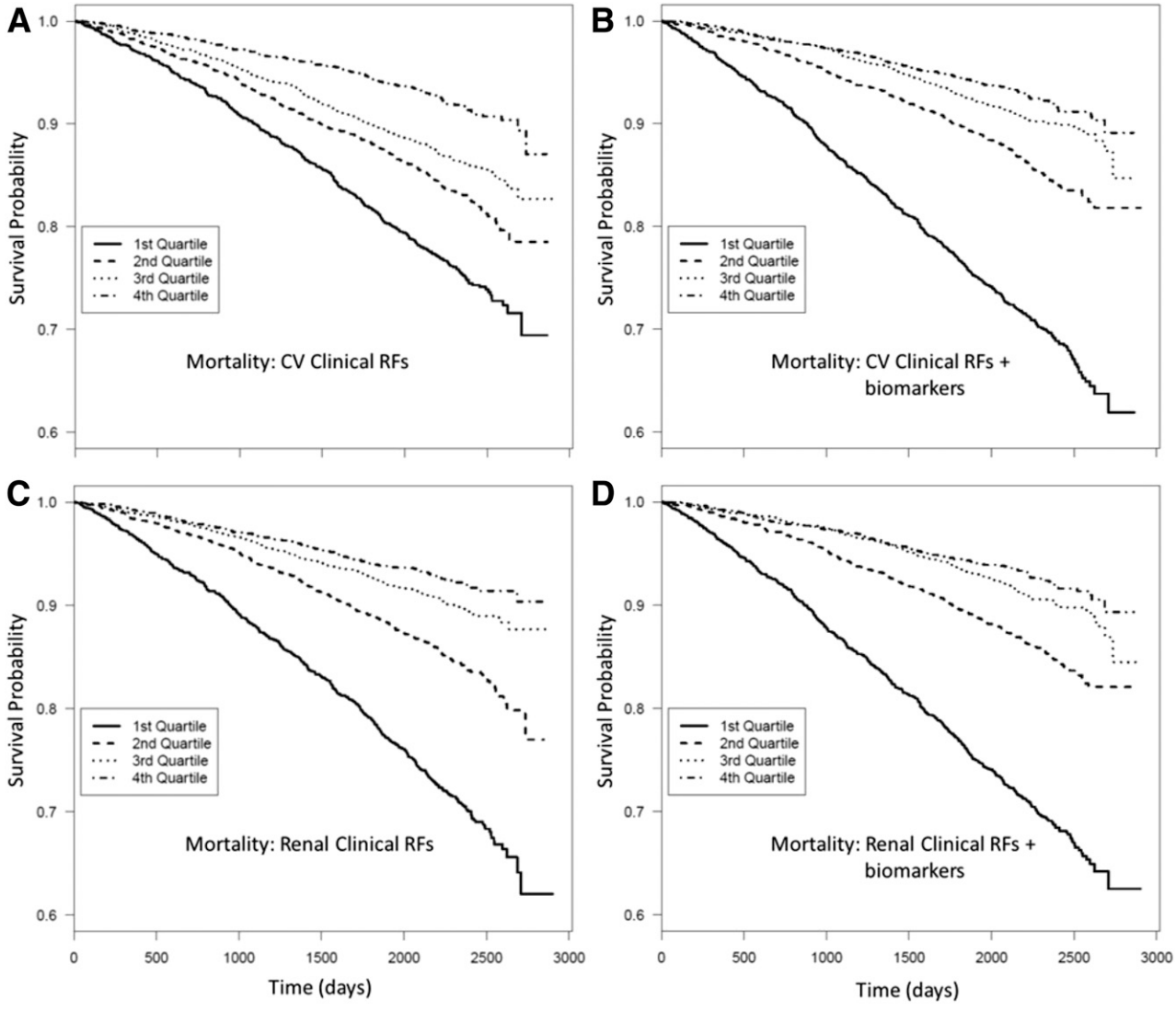

Figure 1—Kaplan-Meier curves illustrating the time to death in participants grouped according to fourths of the predicted annual change in eGFR. The annual change in eGFR was predicted by the clinical risk factors (RFs) alone and these plus the identified biomarkers for both the cardiovascular (CV) model (*A* and *B*) and the renal model (*C* and *D*) in 7,945 participants for whom all baseline clinical and biomarker data were available in the ORIGIN database. Annual change in eGFR quartile cut points for model B are first less than −0.40, second −0.40 to −0.11, third −0.12 to 0.13, and fourth ≥0.14 mL/min/1.73 m^2/year and for model D, first less than −0.39, second −0.39 to −0.11, third −0.12 to 0.135, and fourth ≥0.135 mL/min/1.73 m^2/year.

the renal composite outcome was then estimated in all 7,945 ORIGIN trial participants for whom these baseline variables were available. Kaplan-Meier curves illustrating the incidence of these two outcomes within each fourth (estimated using quartiles) of the predicted annual change in eGFR for each model are shown in Fig. 1 for death and Fig. 2 for the renal composite outcome. As shown in Supplementary Table 4, for every 0.1 mL/min/1.73 m^2 predicted annual fall in eGFR using the cardiovascular model, the hazard of death increased 1.13-fold (95% CI 1.12, 1.14), the hazard of the renal composite outcome increased 1.11-fold (1.10, 1.12), and the hazard of the renal composite outcome that excluded albuminuria progression increased 1.28-fold (1.25, 1.31). For every 0.1 mL/min/1.73 m^2 predicted annual fall in eGFR using the renal model, the hazard of death increased 1.13-fold (1.12, 1.14), the hazard of the renal composite outcome increased 1.10-fold (1.09, 1.12), and the hazard of the renal composite outcome that excluded albuminuria progression increased 1.27-fold (1.25, 1.31). However, as noted in Supplementary Table 5, the addition of the biomarkers only marginally improved the models' ability to discriminate between participants who did and did not die or experience a renal outcome.

CONCLUSIONS

These analyses show that the addition of up to 16 biochemical markers to routinely measured clinical markers clearly improves the ability to predict the decline in eGFR in middle-aged and older patients with either early diabetes or

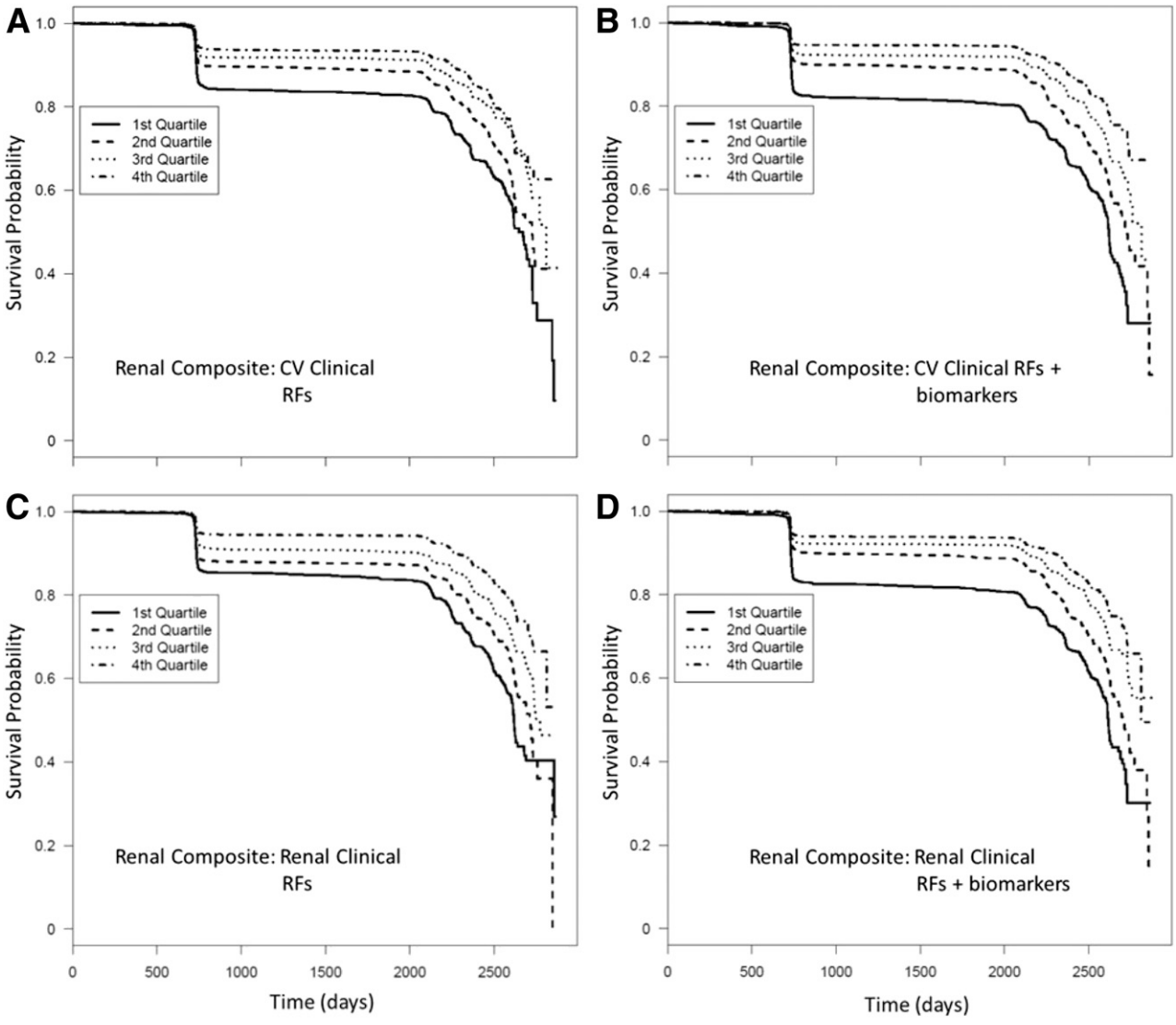

Figure 2—Kaplan-Meier curves illustrating the time to the renal composite outcome (i.e., renal replacement therapy, renal death, renal failure, albuminuria category progression, doubling of serum creatinine from baseline) in participants grouped according to fourths of the predicted annual change in eGFR. The annual change in eGFR was predicted by the clinical risk factors (RFs) alone and these plus the identified biomarkers for both the cardiovascular (CV) model (*A* and *B*) and the renal model (*C* and *D*) in 7,945 participants for whom all baseline clinical and biomarker data were available in the ORIGIN database. Annual change in eGFR quartile cut points for model B are first < -0.40, second -0.40 to -0.11, third -0.12 to 0.13, and fourth ≥ 0.14 mL/min/1.73 m^2/year and for model D, first less than -0.39, second -0.39 to -0.11, third -0.12 to 0.135, and fourth ≥ 0.135 mL/min/1.73 m^2/year.

prediabetes who have additional cardiovascular risk factors. They also show that the 15 biomarkers that were identified after accounting for previously identified clinical cardiovascular risk factors included 12 of the 13 that were identified after accounting for previously identified clinical renal risk factors. Despite the clear improvement in the prediction of eGFR, the addition of these biomarkers to clinical cardiovascular or renal risk factors only slightly improved the ability to predict death and a renal composite outcome during >6 years of follow-up.

These serum biomarkers were identified by applying an agnostic approach to a set of 239 biomarkers that were measured at baseline in a large proportion of participants in the ORIGIN trial. The statistical analyses were not based on any underlying biologic rationale or mechanistic considerations related to renal decline, and the biomarkers that were available in the database were originally measured in 2014 because they were deemed to be broadly relevant to cardiovascular disease, renal disease, or diabetes (6).

Several possibilities account for the set of biomarkers that were identified in Table 2 as the best independent predictors of the decline in eGFR. These include hypotheses related to causality; however, neither the strength nor the direction of the observed relationships provides reliable information regarding pathophysiology or mechanism. Indeed, a biomarker may be inversely related to the decline in eGFR (e.g., growth-regulated α-protein) because a process that promotes the decline in eGFR may also promote the rise in this biomarker for reasons unrelated to the kidney or because determinants of the level of this biomarker buffer or minimize renal damage over time. Biomarkers may have been identified by these analyses for reasons related to the characteristics of their distribution within the population or their statistical relationship to other biomarkers that are themselves pathophysiologically related to renal decline. Such possibilities may account for some of the differences in biomarkers from those identified in other studies (11,12).

This is illustrated by Mendelian randomization analyses designed to identify causal biomarkers for renal disease. One analysis identified lower serum ferritin and iron as causal factors (13). A more recent analysis that linked the same population of ORIGIN participants with publicly available genetic data demonstrated that uromodulin (also called Tamm-Horsfall glycoprotein) and human EGF receptor 2 (HER 2) were both causally related to renal decline and that the biomarker ACE was causally related to HER 2 levels (14). The fact that these four biomarkers that are causally related to renal disease were not identified by the statistical analyses reported here (despite being included in the biomarker panel that was analyzed) highlights the importance of not assuming causality on the basis of associations.

Uncertainty regarding causality, however, does not preclude the use of these independent factors in risk models to predict outcomes. The fact that the addition of the identified biomarkers clearly improves the prediction of the decline in eGFR means that the panel has clinical utility. This is highlighted by the observation that it can help to differentiate people at risk for other outcomes, such as the composite renal outcome and mortality. Moreover, these biomarkers may both improve the efficiency and reduce the sample size of clinical trials focused on reducing the decline in renal function in people with dysglycemia if they are used as stratification variables or entry criteria.

Strengths of these analyses include the large sample size, long follow-up, measurement of a comprehensive set of 239 biomarkers and a baseline eGFR in 8,154 people, and the availability of at least one follow-up eGFR in 7,482 people. A major limitation is the measurement of eGFR at only two time points during follow-up (2 years and study end) and the resulting exclusion from the analyses of 672 (8.2%) participants who did not provide follow-up eGFR levels because of death or missing blood samples.

These analyses clearly illustrate the value of adding a small panel of biochemical markers to routinely measured clinical risk factors for predicting the decline in GFR with time in patients with dysglycemia. They also show that the selected biomarkers are robust and perform similarly when added to different sets of clinical risk factors. Clinicians can use these biomarkers to more accurately identify patients who would benefit from renal protective approaches and who could be recruited into trials testing the effect of novel agents on eGFR.

Funding and Duality of Interest. This work was funded by Sanofi and received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement no. 115974. The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associations with JDRF. H.C.G. holds the McMaster-Sanofi Population Health Institute Chair in Diabetes Research and Care. He reports research grants from Eli Lilly, AstraZeneca, Merck, Novo Nordisk, and Sanofi; honoraria for speaking from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, and Sanofi; and consulting fees from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Janssen, Sanofi, Kowa, and Cirius. G.P. is a Tier 2 Canada Research Chair in Genetic and Molecular Epidemiology and holds a CISCO Professorship in Integrated Health Biosystems. M.J.M. Directs the Clinical Research Laboratory and Biobank at the Population Health Research Institute. S.I.B. serves as an unblinded data safety and monitoring board reporting statistician for two clinical trials funded by Sanofi. A.K. is employed by Sanofi and receives consulting fees from Sulfateq BV. S.H. is employed by Sanofi and holds Sanofi shares. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. H.C.G. led the ORIGIN trial and ORIGIN biomarker study and prepared the first draft of the manuscript. H.C.G., G.P., M.J.M., S.F.L., S.I.B., A.K., and S.H. reviewed the literature, interpreted the findings, revised the manuscript, and approved the final version. H.C.G., G.P., M.J.M., S.F.L., S.I.B., and S.H. developed the statistical plan for these analyses. S.F.L. did the statistical analyses. S.H. conceptualized the application of Luminex technology to the ORIGIN samples and proposed analyzing the biomarkers predicting eGFR decline. H.C.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented orally at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019, and the 55th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain, 16–20 September 2019.

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