# GLYCATED HEMOGLOBIN A1C AND ALL-CAUSE MORTALITY:

Dave Rengachary, MD
**SVP, Chief Medical Director**
US Mortality Markets
RGA Reinsurance Company
**Chesterþeld, MO**
drengachary@rgare.com

Yunus Piperdy, BSc, FCII
**VP, Head of Underwriting**
Innovation Strategy UK
RGA UK Services Ltd.
London, UK
ypiperdy@rgare.com

[illegible]

More recently, underwriters have begun looking at whether HbA1c test results could also be used to

UH¿QH PRUWDOLW\ ULVN DVVHVVPHQW IRU SHRSOH ZLWK SUH GLDEHWHV DQG HYHQ WR ¿QH- WXQH PRUWDOLW\ ULVN DVVHVV

ment for people in good health. With HbA1c testing on the rise, an increasing number of underwriters are starting to look more closely at the mortality implica - tions of its results.

Sweet Memories

The A1c component of hemoglobin and its relation-

VKLS ZLWK GLDEHWHV ZDV ¿UVW GLVFRYHUHG LQ WKH ODWH

1960s, and using it as a diagnostic test for diabetes came into clinical practice during the 1970s and 1980s. Since then, the HbA1c test has become the

HbA1c Levels in People With Diabetes

HbA1c tests are useful to assess how well people with diabetes control their condition and if they are being adequately treated. As we mentioned, HbA1c tests can give an indication of a diabetic's blood sugar levels over the past 2 to 3 months. In addition, serial HbA1c test results, which are generally available from an applicant's attending physician or from clinical lab WHVW UHSRUWV FDQ KHOS FRQ¿UP ORQJHU WHUP GLDEHWHV control.

Although routine HbA1c testing for insurance applicants can detect non-disclosure of diabetes, newer types of medical evidence, such as pharmacy, medical billing and electronic health reports, are increasingly being used by insurers to do so. These forms of evidence are often inexpensive, readily available at the policy point-of-sale, and do not require insurance applicants to submit to a blood draw. Given the success these reports have been having in revealing undisclosed diabetes, they reduce the exclusive protective value of HbA1c testing to detect non-disclosure. However, access and procurement of the newer information sources currently remains variable by product and carrier.

Our analysis of the NHANES data found that 32% of the men and 37% of the women with diabetes GH¿QHG DV DQVZHULQJ ³\HV´ WR WKH TXHVWLRQ RI KDYLQJ been previously told by doctors they have diabetes) KDG +E$ F OHYHOV EHORZ WKH GLDJQRVWLF FXW R point for diabetes (see Figure 1). For women age 40 or younger, 54% had HbA1c levels below 6.5%. This suggests HbA1c tests can miss a proportion of people who non-disclose diabetes.

HbA1c testing can be used to detect undiagnosed Type 2 diabetes as well. Historically, HbA1c testing ZDV GRQH DV D UHÀH[ WHVW 7RGD\ WKDQNV WR ORZHU ODE costs, HbA1c tests are done routinely. The protective value of HbA1c testing to detect undiagnosed diabetes depends mainly on the underlying prevalence of undiagnosed diabetes in the population being tested. According to a 2017 report from the CDC, the average undiagnosed diabetes rate in the US population is 2.9% (see Table 3)[6].

Sources: 2011-2014 NHANES and 2015 US Census Bureau data (CDC 2017).

In countries such as the US, with high levels of routine medical testing, the HbA1c test may be of lower value to insurers. This is particularly the case with younger people, due to the low prevalence of undiagnosed Type 2 diabetes in individuals under age 45 or in populations where annual health screening is customary.

**Figure 1. Prevalence of HbA1c levels by sex and** age in people diagnosed with diabetes in NHANES 1988-2015

GLDJQRVWLF FXW Rc

Raised HbA1c Levels in People Without Diabetes

In people without diabetes, increased HbA1c levels can be indicative of pre-diabetes (see Table 2, page IRU FXW Rc OHYHOV $ GLDJQRVLV RI SUH GLDEHWHV FDQ include people with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and metabolic syn- GURPH *LYHQ WKH YDULRXV GH¿QLWLRQV RI SUH GLDEHWHV DQG FXW Rc SRLQWV WKDW YDU\ IURP FRXQWU\ WR FRXQWU\ it is not surprising researchers report wide variations in terms of both prevalence rates and prognostic implications of pre-diabetes.

A 2017 meta-analysis of 24 studies reported a preva lence of pre-diabetes in Caucasian and Asian cohorts. The authors estimated prevalence of impaired fasting glucose at 36% using WHO guidelines and at 53% using ADA guidelines. This estimate, however, ap- pears high when compared with prevalence rates for individuals who have both impaired fasting glucose and impaired glucose tolerance, which was 16% using WHO guidelines and 20% using ADA guidelines.[7]

In the US, an estimated 33.9% of adults had pre- diabetes in 2015. For adults age 65 and older, the estimate was 48.3%. Only 11.6% of adults with pre- diabetes reported being aware of their condition. These prevalence rates are based on fasting plasma glucose values of 100 to 125 mg/dL or HbA1c values of 5.7% to 6.4%. (Table 4, below, gives a full breakdown.)

Source: Health Survey for England.

Our analysis of the NHANES subjects who had not previously been told by their doctors they had dia- betes found that 22% of men (11%-38% depending on age) and 20% of women (7%-40% depending on DJH KDG SUH GLDEHWHV DFFRUGLQJ tion (see Figure 2).

**Figure 2. Prevalence of HbA1c groups by sex** and age in people without diabetes in NHANES 1988-2015

Source: 2011-2014 NHANES and 2015 US Census Bureau data (CDC 2017).

Meanwhile, according to the Health Survey for England, prevalence of pre-diabetes in England has increased markedly since 2003, rising from 11.6% to 35.3% in 2011.[8] This 2014 survey used the ADA's +E$ F FXW Rc SRLQWV RI WR DJH DQG WLPH SHULRGV PDNH LW GLIILFXOW WR PDNH GLUHFW comparison with US data, the overall prevalence of pre-diabetes in approximately one-third of the popu - lation is consistent. (See Table 5 for a full breakdown.)

Long-term mortality implications of pre-diabetes are not yet clear-cut. The current literature shows FRQÀLFWLQJ HYLGHQFH DERXW WKH OR gression to overt diabetes vs. the potential to reverse WKH FRQGLWLRQ ZLWK OLIHVW\OH PRG healthier diet and increased physical activity. Table 6 (page 48) summarizes mortality results from recent studies.

| | | |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

| **Table 7: Conditions where low RBC turnover can decrease HbA1c** levels |
|---|
| Increased RBC production due to high altitudes, pregnancy |
| Hemorrhage or chronic bleeding |
| Hemolytic anemia |
| Chronic kidney failure |
| Liver cirrhosis, chronic hepatitis, ribavirin use |
| Alcoholic liver disease |
| )ROLF DFLG GH¿FLHQF\ |
| Hemoglobinopathies; e.g., thalassemia major |
| Spherocytosis |
| Aplastic anemia |

Source: What Clinical Laboratorians Should Do in Response to Extremely Low HbA1c Results.

Several studies have reported slightly increased mortality risk for those with low or very low HbA1c levels. It was not always possible for studies to adjust for underlying confounding factors, which can include age, gender, race/ethnicity, smoker status, alcohol consumption, BMI, blood pressure, biomarkers of LURQ GH¿FLHQF\ DQHPLD DQG OLYHPUDLXQVFWWRQWLDQGFKLOG\ VLJQL¿FDQW tory of chronic diseases. A 2016 study by Schottker et al.[13] used NHANES III data (a subset of NHANES data limited to subjects older than age 50) to adjust for all known confounding risk factors, and found WKDW PRUWDOLW\ ULVN ZDV QRW VLJ Other studies have shown controlling for confounding factors may attenuate the low HbA1c impact, but it

| **Table 8: Mortality data for low HbA1c levels in people without diabetes** | | |
|---|---|---|
| Study | Description | Findings |
| Health and Retirement Study, Li et al. (2019)[9] | 15,869 participants, median age 64 (range 50-101); median follow-up 5.8 years | Hazard ratio 1.60 (1.21-2.07, 95% CI) and 1.30 (1.02-1.65, 95% CI) for very low (<4.88%) and low (4.88%-5.02%) HbA1c where reference HbA1c is > 5.02% and < 5.38% |
| Systematic review and meta-analysis, Cavero-Redondo et al. (2017)[11] | 46 studies, age range 25 to 90; sample sizes ranged from 78 to 548,808 | Hazard ratio 1.19 (1.04-1.36, 95% CI) for HbA1c level < 5% where reference HbA1c is 5.0% to 6.0% |
| Meta-analysis from six cohort studies, Schottker et al. (2016)[13] | 6 population-based cohort studies; 28,681 participants, age ≥ 50 | After adjusting for confounding factors (race/ ethnicity, alcohol consumption, %0, DQG ELRPDUNHUV RI LURQ GH¿FI anemia and liver function), very low HbA1c (< 5%) was not found to be associated with increased mortality with a HR of 1.1 (0.9-1.2, 95% CI) |
| NHANES study, Carson et al. (2010)[15] | NHANES III, 14,099 participants, age ≥ 20 | An HbA1c < 4.0% vs. 5.0% to 5.4% was associated with an increased risk of all-cause mortality, hazard ratio 2.9 (1.45 to 9.63, 95% CI) |

Our analysis of the NHANES data is shown in Figure 3 (page 48). The hazard ratio for HbA1c levels of < 5% for people without diabetes was 1.19 (1.11-1.28, 95% CI). After adjusting for common confounding factors the hazard ratio remained significant in our analysis. (Note: We used NHANES data consisting of nine waves of surveys including the most recent mortality update. The NHANES analyses listed in Table 8 (page 49) covers only the third wave of NHANES.)

hyperlipidemia, low HDL or hypertriglyceridemia. In our analysis using a multivariate Cox model, we found HbA1c levels, systolic blood pressure and BMI all have their own independent impacts on mortality. This supports the idea that the combined mortality impact would be stronger than for each risk factor alone.

Consistent with many other earlier studies, we also found a low HbA1c test result (< 5%) is associated with elevated mortality. The reason for the correlation between low HbA1c and higher mortality is unclear; more studies are needed to better understand the cause. When assessing an applicant with low HbA1c, it is important for underwriters to consider the possibil - ity of serious underlying causes, including liver dis - ease and blood disorders such as thalassemia major, spherocytosis and aplastic anemia. In the absence of any obvious cause, and assuming a well-documented medical history is available, a cautious approach is suggested, given potential mortality implications at these low levels.

**HbA1c: Still Hitting That Sweet Spot**

**The literature review and our analysis con ý rmed** HbA1c testing is indeed a useful blood test for mortality risk assessment. From a mortality perspective, our analysis shows that even after adjusting for commonly recognized confounding factors, mortality increases by 11% for each 1% increase in HbA1c, after excluding subjects with HbA1c < 5%.

While HbA1c is used to detect non-disclosure of diabetes and undiagnosed diabetes, it can also play a role in assessing pre-diabetes. In addition, low HbA1c levels can alert underwriters about the possibility of serious underlying disorders.

HbA1c testing has potential value as a mortality biomarker. When used selectively, HbA1c testing remains a useful tool in an underwriter's armory and continues to provide good value.

Notes

1. Stout RL, et al. Relationship of HbA1c to mortality in nonsmoking

About the Authors

Guizhou Hu, MD, received his medical degree from Beijing Medical University and a PhD in epidemiology from Cornell University. His background and expertise have centered on epidemiological research and predictive analytics in health care and insurance medicine. He joined RGA in the role of Vice President, Head of Risk Analytics, in 2018. He is responsible for supporting RGA's future underwriting initiatives. Prior to joining 5*$ KH VHUYHG DV &KLHI 'HFLVLRQ $QDO\WLF 2dFHU DW *HQ 5H IRU \H WL¿F 2dFHU DW %LR6LJQLD ,QF IRU \HDUV ZKHUH KH SDWHQWHG D Q 'U +X KDV DXWKRUHG PDQ\ SHHU UHYLHZHG VFLHQWL¿F DUWLFOHV DQ

Dave Rengachary, MD, is Senior Vice President and Chief Medical Director for US Mortality Markets at RGA Reinsurance Company. Prior to joining RGA in 2013, he was a general neurologist in practice at Missouri Baptist Medical Center, where he also served as medical director for its Primary Stroke Center. He is the primary author and editor of the Washington University Neurology Survival Guide. He serves on the board of directors of Memory Home Care Solutions and the ABC Brigade, dedicated to Alzheimer's and stroke support, respectively. Dr. Rengachary is a past president of the Midwestern Medical Directors Association, Deputy Director of the Longer Life Foundation, a Medical Consultant for the Academy of Life Underwriting, and a member of the Educational Committee of the American Academy of Insurance Medicine.

**Yunus (Pip) Piperdy, BSc, FCII,** is Vice President and Head of Underwriting Innovation Strategy for RGA UK Services Limited. He specializes in underwriting systems, medical research and product design. His main focus is to ensure underwriters can take advantage of medical and technological advances. With 35 years of medical underwriting experience, Pip has worked in senior underwriting roles both for direct and reinsurance companies. He is the UK editor of ON THE RISK and enjoys writing articles about underwriting. He is an active member of insurance industry committees and currently sits on Select 74's underwriting committee.

**Have you ever considered writing an article for *OTR*?**

**Do you need something extra for your Performance Review? Need to add to your Resume being published in a professional journal? Sharing your expertise and knowledge can help elevate your visibility in your profession.**

***OTR* is looking for narrowly focused articles of 1000 words or articles with a broader focus up to 2500 words.**

Do you have an interest in Financial Underwriting, Technology, Avocations or **Living Beneþts? We are currently looking for editors who would be willing to** commit to these and other topics.

**Visit www.ontherisk.com to review a copy of the Author Guidelines or con**tact an Editor today.