HEMOGLOBIN A1c AND MORTALITY IN INSURANCE APPLICANTS: A 5-YEAR FOLLOW-UP STUDY

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Executive Summary: A 5-year follow-up study of mortality among non-smoking insurance applicants based on hemoglobin A1c level found that the mortality risk increases for everyone in a consistent linear pattern above 5.9%, irrespective of age and gender. The magnitude of the relative risk is different by age group, but the pattern of increased risk is similar at all ages. There is no difference in relative mortality risk by hemoglobin A1c level between men and women of the same age. Because this study looked only at insurance applicants, and because it is large (280,000+ subjects and 9,000+ deaths), underwriters can place greater reliance on these results for their underwriting approach to diabetes.

Introduction

Hemoglobin A1c (HbA1c), also called glycohemoglobin, is a reliable indicator of long term blood glucose control. Insurance companies typically consider those with elevations of HbA1c to be at higher mortality risk, and consider the risk to increase further as HbA1c values increase inside the diabetic range. However, both the level of HbA1c where risk begins to increase and the steepness of that risk slope beyond that point are unclear from current clinical literature.

The study most often used currently to define mortality risk associated with HbA1c is the British EPIC-Norfolk study, but it has only 521 deaths and divides HbA1c values from <5% to 7+% only.[1] This results in very wide and overlapping confidence intervals, and provides little guidance regarding mortality for HbA1c values above 7%. Another recent study from Australia divides the groups only by diagnosis, and has even fewer (298) deaths.[2]

This article describes a follow-up study performed by Clinical Reference Laboratory that looks at the mortality of insurance applicants according to their level of HbA1c. It has been recently published in the *Journal of Insurance Medicine*.[3] This study is unprecedented in that:

- The people studied were insurance applicants,
- They were followed for a fairly long period of time, and
- There were so many studied that reliable results were available both for borderline elevations of HbA1c and for values as high as 11%.

How the Study Was Done

Clinical Reference Laboratory (CRL) performs testing on a substantial proportion of U.S. insurance applicants. When screening insurance applicants for diabetic risk, HbA1c is typically performed as a reflex test if personal medical history, blood glucose, fructosamine or other screen for abnormal blood glucose suggests possible increased risk.

This study includes 286,443 applicants age 40 years and up who were tested for HbA1c between 1993 and 2004. These applicants were also known to be negative for urine cotinine (<.25 ng/mL), a metabolite of nicotine, indicating they were non-smokers. We excluded the cotinine-positive applicants (smokers) from this study because their overall mortality was substantially higher, thus complicating any conclusions that we could make from their HbA1c experience.

The Social Security Administration keeps a database (the Death Master File) that lists the deaths of U.S. citizens, and allows this to be used for research purposes. This database was used in 2006 by CRL to determine who in our study had died. The mean duration of follow-up was 5.6 years, with a median of 5 years.

Because of the study size, we were able to split the HbA1c values into relatively small ranges (2% to 4.9%, 5% to 5.9%, 6% to 6.9%, 7% to 7.9%, 8% to 8.9%, 9% to 9.9%, 10% to 10.9%, and 11% and up). We also were able to split the study into subgroups by gender and age (40 to 59 years, 60 to 69 years, 70 years and up).

To compare mortality results among the different HbA1c, gender and age groups, we calculated mortality rates for each subgroup based on the number of people who died (numerator) and the years of exposure that everyone in that subgroup experienced (denominator). These years of exposure are also called "person-years" because they represent the total duration of years studied for all the people in a subgroup. We used this approach because not all of our applicants had the same duration of follow-up; years of exposure were a better indicator of the true mortality experience than using individual lives.

From these rates we then calculated mortality ratios and their 95% confidence intervals. Our mortality ratios compared the mortality rate of a subgroup of interest divided by the rate of the reference group. Reference mortality was taken from the HbA1c subgroup that represented the healthiest risks (5% to 5.9%). The resulting mortality ratios consistently compared the mortality in the "healthiest" group of insurance applicants against the mortality of insurance applicants with other values of HbA1c. These ratios provide the relative risk associated with each HbA1c value subgroup.

No outside reference group was needed; the internal group that we used was no different than other subgroups by any characteristic other than HbA1c level. As a result, we can rely on the mortality results that we found as being a true indication of the effect of HbA1c level.

What the Study Found

A total of 286,443 applicants age 40 years and up who were tested by CRL between 1993 and 2004 were found to have urine cotinine values between 0 and .24 ng/mL; they also had a HbA1c performed either initially or as a reflex test. Mortality follow-up in 2006 via the Social Security Death Master File found 9,235 deaths within 1,591,418 person-years of experience.

As shown in Table 1 (for ages 40 to 59), Table 2 (for ages 60 to 69) and Table 3 (for ages 70 and up), sufficient person-years and deaths were available for all values of HbA1c to support mortality analysis when divided by gender and the three age subgroups. Since HbA1c is usually performed based on a positive screening result or history of diabetes, people with HbA1c values of 5% to 5.9% (typically considered normal or optimal) contributed only 36.5% of the study's total person-years of exposure.

Table 4 shows the mortality ratios within the HbA1c 5 to 5.9% subgroup when split into 5 to 5.4% and 5.5 to 5.9%. Here, the 5 to 5.4% band is the reference group (mortality = 100%). We found no significant difference in the mortality between the upper and lower halves of the HbA1c 5 to 5.9% range, so we used this subgroup in its entirety as the reference group.

Figure 1 shows mortality ratios for other bands of HbA1c compared to 5% to 5.9%, defined as the reference group with a mortality ratio of 100%. We combined both genders for this graph because we found no meaningful differences between the mortality ratio results when each gender was analyzed separately.

Our tables and figure show increasing 5-year mortality risk with increasing HbA1c values at 6% and higher. This risk increases regardless of whether it is viewed as mortality rates (as shown in Tables 1, 2 and 3), or as mortality ratios with the 5% to 5.9% HbA1c group as the reference (as shown in Figure 1). The impact of increasing HbA1c on mortality is greatest at the youngest ages, and least within the oldest group. However, the impact on mortality is seen at all ages; each unit of increase in HbA1c is associated with a consistent percentage increase in mortality.

We also found that HbA1c values less than 5% are also associated with increased mortality. This trend is even more dramatic as HbA1c values fall below 4%–we did not show the data here because the numbers were small.

What Do the Study Results Contribute to Risk Assessment?

Hemoglobin A1c values of 6% and higher show a steady progressive increase in 5-year mortality risk, with a different rate of increase for different ages (Figure 1). Each 1% increase in HbA1c values is associated with approximately a 50% increase in the mortality ratios for ages 40 to 59, a 30% increase in the mortality ratios for ages 60 to 69, and a 17% increase in the mortality ratios ages 70 and up. This increase begins at HbA1c of 6% and continues at a uniform rate as HbA1c values increase, even as high as 11%.

We did not have diagnoses available for this study, only the actual HbA1c results. Underwriters will encounter diagnostic labels such as "impaired glucose tolerance" and "pre-diabetes." Although these diagnoses are not defined based on HbA1c results, most often these individuals will have HbA1c values in the 6% to 6.9% range; the diagnosis of "diabetes" most often includes those with HbA1c values of 7% and higher.

Table 1. Mortality Rates and Ratios for Ages 40 to 59 Years

Hemoglobin A1c (%)	Deaths	Total Applicants	Person-Years	Mortality Rate	Mortality Ratio (%)	95% CI
Males						
2-4.9	111	7,807	56,110	0.0020	118	96 - 145
5-5.9 (reference)	552	58,496	329,232	0.0017	100	89 - 113
6-6.9	421	29,572	162,220	0.0026	155	136 - 176
7-7.9	314	16,886	93,397	0.0034	201	175 - 230
8-8.9	296	11,594	66,046	0.0045	267	232 - 308
9-9.9	244	8,416	49,092	0.0050	296	255 - 345
10-10.9	194	6,009	35,877	0.0054	323	274 - 380
11 up	353	9,505	57,575	0.0061	366	320 - 418
Total	2,485	148,285	849,549			
Females						
2-4.9	18	2,906	18,246	0.0010	92	56 - 151
5-5.9 (reference)	125	22,407	116,601	0.0011	100	78 - 128
6-6.9	93	10,769	56,076	0.0017	155	118 - 202
7-7.9	90	6,083	31,778	0.0028	264	201 - 346
8-8.9	61	4,082	22,173	0.0028	257	189 - 349
9-9.9	61	2,987	16,742	0.0036	340	250 - 462
10-10.9	65	2,295	13,058	0.0050	464	344 - 627
11 up	150	4,015	23,118	0.0065	605	477 - 767
Total	663	55,544	297,792			
Grand Total	3,148	203,829	1,147,341			

Table 2. Mortality Rates and Ratios for Ages 60 to 69 Years

Hemoglobin A1c (%)	Deaths	Total Applicants	Person-Years	Mortality Rate	Mortality Ratio (%)	95% CI
Males						
2-4.9	68	1,019	7,570	0.0090	124	96 - 160
5-5.9 (reference)	491	11,934	67,960	0.0072	100	88 - 113
6-6.9	491	10,984	58,483	0.0084	116	103 - 132
7-7.9	438	6,787	36,762	0.0119	165	145 - 188
8-8.9	304	4,199	23,286	0.0131	181	157 - 208
9-9.9	230	2,500	14,700	0.0156	217	185 - 253
10-10.9	187	1,517	8,914	0.0210	290	245 - 344
11 up	230	1,937	11,647	0.0197	273	234 - 320
Total	2,439	40,877	229,322			
Females						
2-4.9	25	378	2,764	0.0090	166	109 - 254
5-5.9 (reference)	150	5,012	27,590	0.0054	100	80 - 125
6-6.9	188	4,423	22,921	0.0082	151	122 - 187
7-7.9	120	2,630	13,619	0.0088	162	127 - 206
8-8.9	112	1,719	9,295	0.0120	222	174 - 283
9-9.9	92	1,079	6,137	0.0150	276	213 - 357
10-10.9	39	663	3,785	0.0103	190	133 - 270
11 up	110	1,171	6,945	0.0158	291	228 - 373
Total	836	17,075	93,056			
Grand Total	3,275	57,952	322,378			

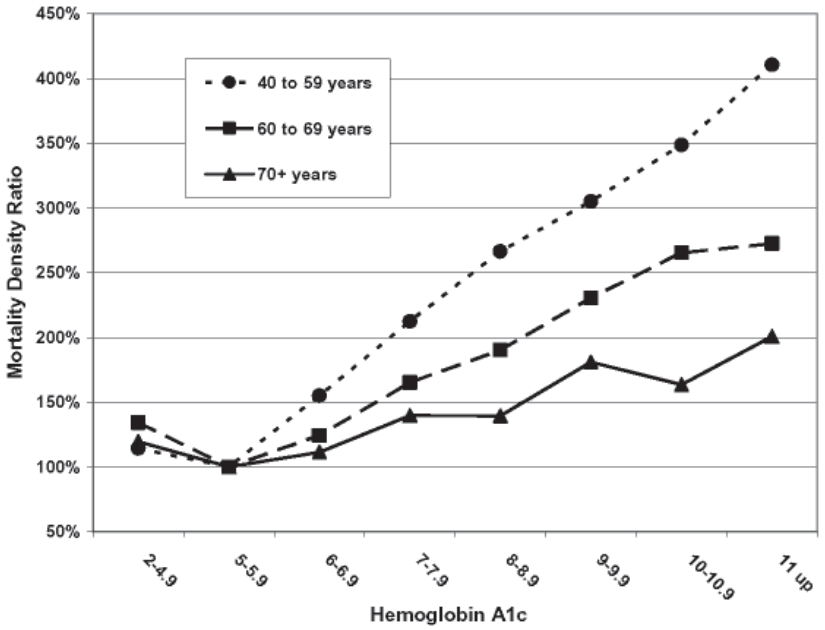
Table 3. Mortality Rates and Ratios for Ages 70 and Up Years

Hemoglobin A1c (%)	Deaths	Total Applicants	Person Years	Mortality Rate	Mortality Ratio (%)	95% CI
Males						
2-4.9	54	399	2,688	0.0201	96	72 - 127
5-5.9 (reference)	495	4,754	23,612	0.0210	100	88 - 113
6-6.9	503	4,722	22,243	0.0226	108	95 - 122
7-7.9	352	2,608	12,782	0.0275	131	115 - 151
8-8.9	207	1,339	7,074	0.0293	140	119 - 164
9-9.9	122	622	3,357	0.0363	173	142 - 211
10-10.9	59	320	1,781	0.0331	158	121 - 207
11 up	99	360	2,036	0.0486	232	187 - 288
Total	1,891	15,124	75,573			
Females						
2-4.9	32	175	1,115	0.0287	181	125 - 261
5-5.9 (reference)	254	3,376	15,988	0.0159	100	84 - 119
6-6.9	247	2,908	13,328	0.0185	117	98 - 139
7-7.9	168	1,412	6,912	0.0243	153	126 - 186
8-8.9	78	733	3,734	0.0209	131	102 - 169
9-9.9	64	399	2,079	0.0308	194	147 - 255
10-10.9	37	241	1,322	0.0280	176	125 - 249
11 up	41	294	1,648	0.0249	157	113 - 218
Total	921	9,538	46,126			
Grand Total	2,812	24,662	121,699			

Table 4. Relative Risks for Hemoglobin A1c 5 to 5.4% vs. 5.5 to 5.9%

Hemoglobin A1c	Males 40 to 59	Males 60 to 69	Males 70+	Females 40 to 59	Females 60 to 69	Females 70+
HbA1c 5 to 5.4% (reference)	100%	100%	100%	100%	100%	100%
HbA1c 5.5 to 5.9%	103%	93%	105%	106%	105%	106%

Figure 1. Mortality Ratios for Hemoglobin A1c, by Age Group



Based on this study and other clinical literature, risk is best assessed by HbA1c values rather than any particular diagnosis or lack of one. The mortality risk increases gradually based on the degree of long-term elevation of blood glucose, not in a stepwise fashion based on diagnosis. Other adverse findings may increase the risk profile of an individual, but it is unclear how much the lack of other adverse findings would improve the level of risk noted in this study.

We also found increased mortality within the small group of individuals with HbA1c values below 5%. This trend is especially strong for values below 4%, but our numbers are too small for firm conclusions. We believe that the increased mortality for these individuals is likely to be related to shortened red blood cell (RBC) life, since hemoglobin contained within the RBC is glycated slowly over its lifespan. This group may include people with hemoglobinopathies or shortened RBC survival associated with blood loss, mechanical trauma or disease. Clearly, HbA1c values below 5% as part of an insurance examination should prompt a health review at the time of underwriting.

Finally, there has been debate as to whether risk is different in the group with HbA1c of 5 to 5.4% vs. 5.5 to 5.9%, and if this could be used as a selection factor for preferred classes. The EPIC-Norfolk study suggested the possibility of a difference, but the number of deaths was small and confidence intervals widely overlapping.[1] In addition, that study was done in the mid 1990s before the current standardization of HbA1c laboratory analysis, so a value of 5.5% then might be significantly higher if measured now.

Table 4 shows the mortality in our study of the HbA1c band of 5.5 to 5.9% relative to 5 to 5.4%, with the latter set as the reference at 100%. Relative mortality in the higher band varies from 93% to 106% of the lower band; on average the 5.5 to 5.9% band has very slightly higher mortality but this difference is far less than necessary to separate a group into different underwriting classes or to be seen as clinically important. We believe that all individuals with HbA1c 5 to 5.9% should be combined to represent the lowest risk subgroup.

Our results indicate that even small elevations of HbA1c above 5.9% are associated with important levels of excess mortality. Typically, HbA1c is reflexed off fructosamine, blood glucose or diabetic history. Mildly elevated HbA1c values in the 6 to 6.9% range are usually discovered only if the fructosamine reflex level is set sufficiently low to detect applicants with impaired glucose tolerance. Higher HbA1c values are commonly associated with elevations in either blood or urine glucose.

The "cost" (number of HbA1c tests done, most of which are normal) and "benefit" (applicants with elevated risk identified) associated with various trigger levels of your screening test should be discussed with your laboratory. The potential benefit of additional HbA1c tests increases with face amount and with age, as more HbA1c elevations occur at older ages.

References

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About the Authors

Vera F. Dolan, MSPH, FALU, Research Associate at Clinical Reference Laboratory, is a consultant specializing in underwriting research and product development. At CRL Vera assists with the analysis and publication of CRL's mortality study data. In her consulting practice, Vera develops risk assessment tools for underwriters, including underwriting manuals, as automated risk assessment systems and underwriter training. Vera provides litigation support for misrepresentation and other underwriting issues, as well as life expectancy calculations for use during litigation.

Vera has a BA in Public Health from the Johns Hopkins University, and a Master's in Public Health in Epidemiology from the University of North Carolina at Chapel Hill. Vera was employed as an underwriting researcher at Lincoln Re and Transamerica Occidental Life before starting her consultancy in 1989. Vera is an Associate Editor of *ON THE RISK*, and regularly speaks to actuaries and underwriters on risk assessment topics.

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