

Hemoglobin A1C levels in nondiabetics

What underwriters should know

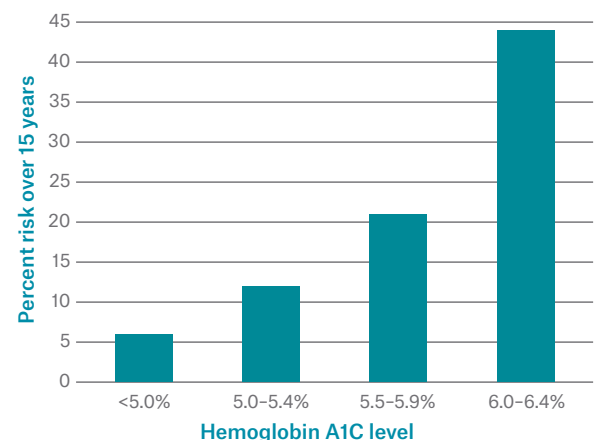
- Hemoglobin A1C (HbA1C) levels below 6.5 percent in nondiabetic individuals may also be helpful in the underwriting assessment of insurance applicants.
- Risk of developing diabetes mellitus over the ensuing fifteen years approximately doubles for each band of HbA1C from 5.0–5.4 percent, 5.5–5.9 percent and 6.0–6.4 percent.
- Hemoglobin A1C levels above 5.4 percent in nondiabetics are associated with increased relative risk for developing coronary atherosclerotic heart disease (CAD), ischemic stroke (CVA) and mortality from any cause, as compared to those with HbA1C levels in the 5.0–5.4 percent range.

It has been demonstrated that the development of microvascular complications of diabetes mellitus, especially diabetic retinopathy, can be delayed by establishing more strict glycemic control. As a result, methods of monitoring glycemic control by measuring the amount of glucose attached to various proteins in the blood have been developed. Determination of the amount of glucose that becomes attached to red blood cell hemoglobin – the hemoglobin A1C (HbA1C) level – has become well-established. The attachment of glucose to the hemoglobin molecule is irreversible, is proportional to the amount of plasma glucose, and begins when a new red blood cell enters the circulation. Approximately one percent of red blood cells are destroyed daily, and the average life span of a red blood cell is about 120 days. This means that, at any point in time, the HbA1C level reflects the average blood glucose level over the prior 120 days. However, the level actually correlates best with the

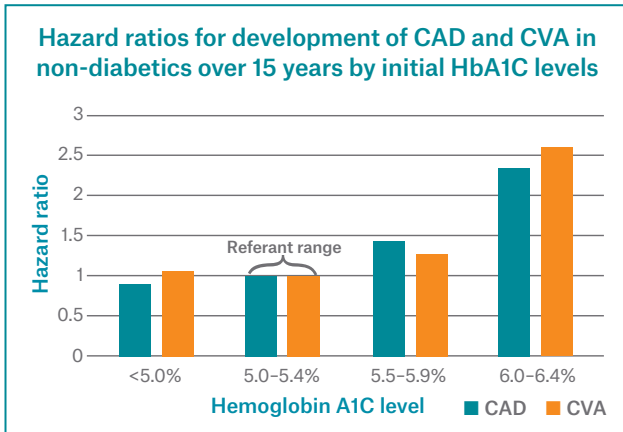
period covering the previous eight to twelve weeks. Since its introduction, HbA1C testing has been found useful not only in determining the level of diabetic control but also, because of efficiency, has become an accepted method for establishing the diagnosis of diabetes mellitus. Hemoglobin A1C levels of 6.5 percent and greater are now considered to be diagnostic for diabetes mellitus.

Hemoglobin A1C levels below 6.5 percent have also been found indicative of risk for future morbidity and mortality in those who are nondiabetic. Hemoglobin A1C levels in nondiabetic participants in the Atherosclerosis Risk in Community Study (ARIC) have been found to indicate future risk for developing not only diabetes, but also coronary atherosclerotic heart disease (CAD), ischemic stroke (CVA) and mortality from all causes.¹ After a follow up period of 15 years HbA1C levels of <5.0 percent, 5.0–5.4 percent, 5.5–5.9 percent and 6.0–6.4 percent were found to represent respectively the following risks for developing diabetes: 6 percent, 12 percent, 21 percent and 44 percent.

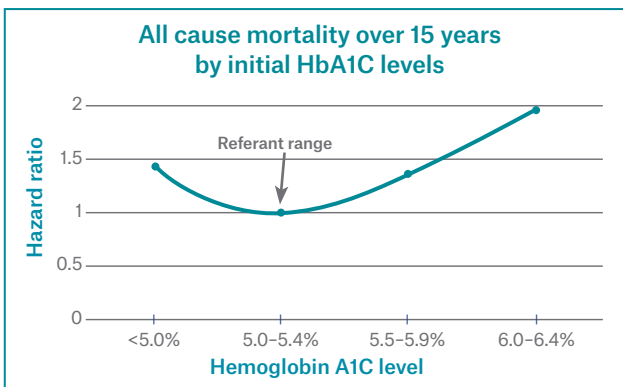
Risk for developing diabetes over subsequent years by HbA1C level



Hemoglobin A1C also appears to be an indicator of risk for development of macrovascular disease (both CAD and ischemic stroke) in nondiabetics.



Although minimal, relative risk for mortality from all causes begins to rise at HbA1C levels above 5.5 percent in a roughly linear fashion. Interestingly, those with HbA1C levels below 5 percent also appear to have a higher risk of mortality from all causes relative to those in the HbA1C 5.0 percent to 5.4 percent range. This results in a J-shaped mortality curve.



Since red blood survival time affects determination of HbA1C levels, alterations in the life of red blood cells may distort HbA1C values. Rapid red blood cell turnover due to hemolysis or situations resulting in production of many new red blood cells through the treatment of anemia with iron, vitamin B 12, folic acid or erythropoietin will result in falsely depressed HbA1C levels. Recent blood transfusion and splenomegaly also may result in falsely depressed levels. Obviously, such processes that are associated with rapid red blood cell turnover, necessity for blood transfusion or splenomegaly may well be due to conditions associated with increased

mortality. However, the J-shaped mortality curve remains after hematologic problems are excluded, suggesting that further evaluation of health problems associated with the low-normal glycemic state need to be investigated. A study on insurance applicants that evaluated mortality results associated with various levels of HbA1C obtained between 1993 and 2004 found that relative mortality was increased for HbA1C levels below 5.0 in the insurance applicant population as well.² Specific diseases associated with the increased mortality found in low HbA1C levels have not been well defined but there appears to be an increase in cancer related deaths.³ An association between low HbA1C values and hospitalization for liver disease has also been found.

Since HbA1C reflects attachment of glucose to red blood cells it is logical that some hematologic problems may also result in falsely elevated HbA1C levels. When red blood cell production is depressed in some anemic states (e.g., untreated iron deficiency, vitamin B 12 deficiency or folate deficiency) a disproportionate number of older red blood cells may result in a false elevation of HbA1C levels. Values may also be falsely high in the presence of abnormal hemoglobin (e.g., HbF or HbS). Chronic kidney disease may result in either falsely depressed or falsely elevated values.

Key points

- Mortality from all causes in nondiabetics with HbA1C levels below 6.5 percent is expressed as a J-shaped curve with increased relative risk not only for those with HbA1C levels above 5.4 percent also but also those with HbA1C levels below 5.0 percent.
- Since HbA1C quantifies glycosylation of red blood cells, alterations in red blood cell metabolism or diseases with a hematologic component may falsely skew HbA1C levels.
- Mortality causes for those having HbA1C levels below 5.0 percent have not yet been well worked out.

References

1. Selvin E, et al, [Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults](#), *NEJM* 2010;362(9):800-11.
2. Stout R, et al, [Relationship of Hemoglobin A1c to Mortality in Nonsmoking Insurance Applicants](#), *Journal of Insurance Medicine* 2007;39:174-81.
3. Aggarwal V, et al, [Low Hemoglobin A1c in Nondiabetic Adults](#), *Diabetes Care* 2012;35:2055-2060.



Dr. Robert Lund,
Vice President & Medical
Director, Munich Re, US (Life)