Haemoglobin A$_{1c}$ concentrations were associated with increased cardiovascular disease and all cause mortality

Khaw KT, Wareham N, Bingham S, *et al.* Association of hemoglobin A$_{1c}$ with cardiovascular disease and mortality in adults: the European Prospective Investigation into Cancer in Norfolk. *Ann Intern Med* 2004;**141**:413–20.

Clinical impact ratings GP/FP/Primary care ★★★★★☆ IM/Ambulatory care ★★★★☆☆ Cardiology ★★★★★☆
Endocrine ★★★★☆☆
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Q What is the relation between haemoglobin (Hb) A$_{1c}$ concentrations and coronary heart disease (CHD) events, cardiovascular disease (CVD) events, and all cause mortality?

METHODS

Design: cohort study (European Prospective Investigation into Cancer in Norfolk [EPIC-Norfolk]) with a mean follow up of 6 years.

Setting: Norfolk, UK.

Patients: 10 232 patients 45–79 years of age (54% women, 2.4% with diabetes) who were recruited from general practice registers and had baseline data on a health and lifestyle questionnaire and HbA$_{1c}$ concentrations.

Risk factors: HbA$_{1c}$ concentrations, known diabetes, age, body mass index, waist-to-hip ratio, systolic blood pressure, cholesterol concentrations, triglyceride concentrations, cigarette smoking, and history of heart attack or stroke.

Outcomes: CHD events (hospital admission or death from CHD), CVD events (hospital admission or death from CHD, stroke, or other vascular causes), and all cause mortality.

MAIN RESULTS

Persons with known or undiagnosed diabetes had a greater risk of all cause mortality and CVD or CHD events than those without diabetes. A gradient of increasing rates of all cause mortality, CHD, and CVD was found for the entire distribution of HbA$_{1c}$ concentrations in men and women (p<0.001 for linear trend).

Regression analyses adjusted for age and other risk factors (except for HbA$_{1c}$ concentration) showed that compared with persons without diabetes, men with diabetes had a higher risk of CHD events, CVD events, and all cause mortality, and women with diabetes had an increased risk of CHD events and CVD events (table). In a regression analysis that did not adjust for diabetes, HbA$_{1c}$ concentrations predicted an increased risk of CHD, CVD, and all cause mortality in both men and women. A 1% increase in HbA$_{1c}$ concentration was associated with a 20–30% increase in event rates. When the regression model included both diabetes and HbA$_{1c}$
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concentrations, similar relative risks for an increase in HBA$_{1c}$ were noted, but diabetes was no longer a significant risk factor.

CONCLUSIONS

A 1% increase in haemoglobin A$_{1c}$ concentrations was associated with a 20–30% increase in cardiovascular events and all cause mortality in men and women 45–79 years of age. This relation was independent of diabetes status.

Abstract and commentary also appear in ACP Journal Club

Commentary

Diabetes mellitus is a major risk factor of CVD, and unlike hypertension, smoking, and dyslipidaemia, it is becoming more common over time.

The diagnostic criteria for diabetes include fasting plasma glucose concentrations ≥7.0 mmol/l or 2 hour postload plasma glucose concentrations ≥11.1 mmol/l, values above which the risk of *microvascular* complications of diabetes, such as retinopathy, neuropathy, and nephropathy, increases. These values correspond approximately to an HbA$_{1c}$ concentration of 7%. However, there is considerable epidemiological evidence that the risk of CVD begins to increase at lower glycaemic concentrations than would be considered ''abnormal''—levels that would not be associated with increased microvascular disease risk.[1] The study by Khaw *et al* adds to this evidence because of its large study population and particularly large number of female participants.

In this study, 72% of the excess CVD risk that was attributable to higher HbA$_{1c}$ concentrations occurred in patients with HbA$_{1c}$ concentrations of 5.0–6.9%. In light of this evidence, perhaps the cut point for a ''normal'' HbA$_{1c}$ concentration should be revised downward, as has been done for cholesterol and blood pressure. It would also be desirable to develop and validate cardiovascular risk calculators that include HbA$_{1c}$ concentration as a predictor variable, as has been done for patients with type 2 diabetes in the UKPDS Risk Engine.[2] In the meantime, HbA$_{1c}$ concentrations provide an additional measure of an individual patient's CVD risk.

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1 Selvin E, Marinopoulos S, Berkenblit G, *et al.* Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004;**141**:421–31.
2 Stevens RJ, Kothari V, Adler AI, *et al.* The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci (Lond)* 2001;**101**:671–9.

Adjusted relative risks (RRs) for coronary heart disease events, cardiovascular disease events, and all cause mortality by haemoglobin A$_{1c}$ concentrations and history of diabetes*

Outcomes at mean 6 y	Adjusted RR (95% CI) per 1% increase in HbA$_{1c}$ concentration		Adjusted RR (CI) for diabetes history (yes vs no)	
	Men	Women	Men	Women
Coronary heart disease	1.25 (1.16 to 1.34)	1.20 (1.07 to 1.34)	1.87 (1.30 to 2.71)	2.71 (1.48 to 4.98)
Cardiovascular disease	1.21 (1.13 to 1.29)	1.21 (1.11 to 1.31)	1.81 (1.31 to 2.49)	1.89 (1.09 to 3.23)
All cause mortality	1.24 (1.14 to 1.34)	1.28 (1.06 to 1.32)	1.94 (1.31 to 2.87)	0.71 (0.26 to 1.93)†

*Adjusted for age and cardiovascular risk factors (systolic blood pressure, serum cholesterol concentration, body mass index, waist-to-hip ratio, cigarette smoking, and history of myocardial infarction or stroke). †Not significant.