

**Evidence Tables**

**TARG 2: In people with type 2 diabetes, what should be the target value for HbA1c?**

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention	Comparison	Length of follow-up	Outcome measures	Effect size	Source of funding
Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. <i>Ann Intern Med</i> 2004; 141(6):421-431. Ref ID: 3197	Meta-analysis of prospective cohort studies 2+	N=13 studies N=10 groups of type 2 diabetic persons and 3 of type 1 (Only the results for the type 2 studies presented here). Sample sizes ranged from fewer than 100 to more than 5000 in the largest study. Studies included for type 2 were: Adler 2002 (UK-PDS), Agewall 1997, Florkowski 1998, Gall 1995,	Studies of those with type 2 diabetes. Mean age at baseline in the type 2 studies ranged from 53 to 69 years. The proportion of men included ranged from just 32% to 100% in one study (although in most studies approximately 55% were male). Studies were undertaken in the UK, Sweden, New Zealand, Denmark, Finland the US and Germany.	Prospective cohort studies were selected that examined the cardiovascular outcomes of interest (peripheral arterial disease, coronary heart disease and stroke) and reported a measure of glycosylated haemoglobin .	N/A	Maximum follow-up was 3.5 to 14 years.	Cardiovascular disease endpoints were fatal and nonfatal coronary heart disease (myocardial infarction, angina and ischaemic heart disease); cerebrovascular disease (fatal and non-fatal stroke); peripheral arterial disease (lower extremity peripheral arterial disease, amputation and claudication) and a	<p>The pooled relative risk for total cardiovascular disease (combining 10 independent studies of coronary heart disease alone, stroke alone, and stroke and coronary heart disease combined) was 1.18 (95%CI 1.10 to 1.26) for each 1 percentage point increase in glycosylated haemoglobin.</p> <p>The pooled relative risk of the 5 independent studies that examined glycosylated haemoglobin and the risk for coronary heart disease in persons with type 2 diabetes was 1.13 (95% CI 1.06 to 1.20) for each 1 percentage point increase in glycosylated haemoglobin.</p> <p>The pooled relative risk combining 5 studies of fatal coronary heart disease was 1.16 (95%CI 1.07 to 1.26).</p> <p>Only 3 studies examined glycosylated haemoglobin and risk for stroke; the pooled relative risk for these 3 studies was 1.17 (95%CI 1.09 to 1.25).</p> <p>The pooled relative risk for the 3 studies of glycosylated haemoglobin and peripheral arterial disease was 1.28 (95%CI 1.18 to 1.39).</p>	Agency for health care research and quality

		Kuusisto 1994, Lehto 1996, 1996, 1997, Mattock 1998, Moss 1994, 1999, Roselli della Rovere 2003, Standl 1996 and Stratton 2000 (UK-PDS)					combined cardiovascular disease outcome that included studies of coronary heart disease and stroke (but no peripheral arterial disease).		
Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. <i>BMJ</i> 2000; 321(7258):405-412. Ref ID: 3198 <i>NB This study is included in the meta analysis but has additional information on non-cardiovascular complications</i>	Prospective observational study of participants from 23 hospital based clinics in England, Scotland and Northern Ireland. 2++	N=4585 UKPDS patients included in the analysis of incidence and N=3642 included in the analysis of relative risk (complete data for potential confounders were available in these participants).	Newly diagnosed type 2 diabetes patients. Very old or ill patients were excluded. Mean age 53 years, 60% male, 82% white, 10% Asian Indian, 8% Afro Caribbean, mean BMI 27.7kg/m <sup>2</sup> , median FBG 7.9mmol/l, mean HbA1c 7.1%.	Independent variable: Glycaemic exposure. This was firstly measured at baseline as haemoglobin A1c concentration and secondly over time as an updated mean of annual measurements of haemoglobin A1c concentration, calculated for each individual	N/A	Median 10 years of follow-up	Primary predefined aggregate clinical outcomes: any end point or deaths related to diabetes and all cause mortality. Secondary aggregate outcomes: myocardial infarction, stroke, amputation (including death from peripheral vascular disease) and microvascul	The incidence rates for any end point related to diabetes, adjusted for age, sex, ethnic group and duration of diabetes, increased with each higher category of updated mean HbA1c, with no evidence of a threshold and with a three-fold increase over the range of updated mean HbA1c of <6% (adjusted rate per 1000 person years 35.9, 95%CI 29.9 to 43.1) to equal to or more than 10% (124.9, 95%CI 97.3 to 160.3).  Adjusted incidence rates per 1000 person years for other complications were: Deaths related to diabetes: updated mean HbA1c of <6% (8.9, 95%CI 6.3 to 12.7) to equal to or more than 10% (33.0, 95%CI 19.8 to 55.1). All-cause mortality: updated mean HbA1c of <6% (8.9, 95%CI 6.3 to 12.7) to equal to or more than 10% (33.0, 95%CI 19.8 to 55.1). Fatal or non-fatal MI: updated mean HbA1c of <6% (16.0, 95%CI 12.1 to	Funding by various public and private organisations

				from baseline to each year of follow-up.			<p>ar disease (predominantly retinal photocoagulation). Single end points: non-fatal heart failure and cataract extraction. Risk reduction associated with a 1% reduction in updated mean HbA1c adjusted for possible confounders at diagnosis of diabetes.</p> <p>21.2) to equal to or more than 10% (38.6, 95%CI 24.4 to 61.0). Fatal or non-fatal stroke: updated mean HbA1c of &lt;6% ( 4.3, 95%CI 2.6 to 7.0) to equal to or more than 10% (12.0, 95%CI 5.7 to 25.3). Amputation or death from peripheral vascular disease: updated mean HbA1c of &lt;6% ( 1.2, 95%CI 0.4 to 3.2) to equal to or more than 10% (12.2, 95%CI 4.6 to 32.4). Fatal or non-fatal microvascular disease: updated mean HbA1c of &lt;6% ( 6.1, 95%CI 4.1 to 9.0) to equal to or more than 10% (57.8, 95%CI 39.3 to 85.1). Heart failure: updated mean HbA1c of &lt;6% ( 2.3 95%CI 1.2 to 4.5) to equal to or more than 10% (11.9, 95%CI 5.5 to 25.8). Cataract extraction: updated mean HbA1c of &lt;6% ( 4.1, 95%CI 2.5 to 6.5) to equal to or more than 10% (14.4, 95%CI 8.1 to 25.7).</p> <p>Each 1% reduction in updated mean HbA1c was associated with reductions in risk of:  21% for any endpoint related to diabetes (95%CI 17% to 24%, p&lt;0.0001),  21% for deaths related to diabetes (15% to 27%, p&lt;0.0001),  14% for all cause mortality (9% to 19%, p&lt;0.0001)  14% for myocardial infarction (8% to 21%, p&lt;0.0001)  12% for stroke (95%CI 1% to 21%,</p>
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								<p>p=0.035) 43% for peripheral vascular disease (amputation or death from PVD) (95%CI 31% to 53%, p&lt;0.0001). 37% for microvascular complications (33% to 41%, p&lt;0.0001)</p> <p>For the single endpoints each 1% reduction in updated mean HbA1c was associated with reductions in risk of: 16% for heart failure (95%CI 3% to 26%, p=0.016) 19% for cataract extraction (95%CI 11% to 26%p&lt;0.0001)</p> <p>The association with glycaemia was less steep for stroke and heart failure, for which blood pressure is a major contributing factor.</p> <p>No threshold of risk was observed for any endpoints.</p>	
<p>Gerstein HC PJ. The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiological analysis. Diabetologia 2005; 48(9):1749-1755. Ref ID: 1487</p>	<p>Prospective observational study of participants in the Heart Outcomes Prevention Evaluation (HOPE) study. 2+</p>	<p>N=3529 diabetic participants recruited in 19 countries</p>	<p>All participants had a history of diabetes (type 1 or 2 not specified). Mean age was 65.4 years ± 6.5, 37% were female, mean duration of diabetes 11.46 ± 10.5 years, mean glycated haemoglobin (GHb) levels 7.40% ± 1.87%.</p>	<p>Independent variable: GHb was measured in all participants with self-reported diabetes as either total GHb or HbA1c. The results of baseline and annual measureme</p>	<p>N/A</p>	<p>Median 4.5 years</p>	<p>The primary outcome was the first occurrence of one or more of the following: non-fatal myocardial infarction, stroke or CV death. Key secondary outcomes included total</p>	<p>There was a consistent and progressive relationship between the GHb level (both baseline and updated) and the age and sex adjusted relative hazard of the following outcomes: the primary outcome (non-fatal myocardial infarction, stroke or CV death), hospitalisation for congestive heart failure, total mortality and overt nephropathy. All showed significant trends with the strongest relationships being seen with the updated GHb level.</p> <p>A 1% absolute rise in the updated GHb predicted future CV events (RR=1.07, 95%CI 1.01 to 1.13; p=0.014), death</p>	<p>MRC Canada, Aventis, Astra Zeneca, the Natural Source vitamin E Association, NEGMA and King Pharm-</p>

				nts were recorded throughout the study as an assessment of diabetes control. Updated GHb levels were calculated for each diabetic individual as the mean of all of the available measurements for that individual during the entire period of follow-up. The GHb results were expressed and analysed as a "derived HbA1c".			mortality, hospitalisation for congestive heart failure and overt nephropathy .	(RR=1.12, 95%CI 1.05 to 1.19; p=0.0004), heart failure (RR=1.20, 95%CI 1.08 to 1.33; p=0.0008) and overt nephropathy (RR=1.26, 95%CI 1.17 to 1.36; p=0.0001), after adjusting for age, sex, diabetes duration, blood pressure, WHR, hyperlipidaemia and ramipril.	aceutica ls
Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S et al. Glycemic control and heart failure among adult patients with diabetes. Circulation 2001; 103(22):2668-	Observational study of participants on the Kaiser Permanente Medical	N=48,858	The cohort excluded those who had a previous hospitalisation with primary or secondary diagnosis of heart failure during the 5 years before baseline. Mean age of the whole	Independent variable: HbA1c. The study cohort had at least one measurement of HbA1c	N/A	Median 2.2 years	The primary study endpoint was a composite of hospitalisation for heart failure or death with	Age adjusted incidence rates of heart failure increased with increasing levels of HbA1c in a monotonic fashion (p for linear trend 0.0001).  In the fully adjusted analysis, the relative risk associated with a 1% increase in HbA1c was 1.08 (95%CI	Kaiser Foundation Research Institute and the

<p>2673. Ref ID: 487</p>	<p>Care Program of Northern California diabetes registry. 2+</p>		<p>cohort was 58 years.</p> <p>Of the men (53%): 52% were white, 9% were black, 11% were Hispanic, 11% Asian and Pacific Islander and 17% unknown 75% had type 2 diabetes, 4% had type 1 and 20% were unknown. Mean duration of diabetes 9 ± 10 years Mean HbA1c 8.5% ± 1.9</p> <p>Of the women (47%): 49% were white, 12% were black, 12% were Hispanic, 11% Asian and Pacific Islander and 16% unknown 75% had type 2 diabetes, 5% had type 1 and 19% were unknown Mean duration of diabetes 9 ± 10 years Mean HbA1c 8.6% ± 1.9</p>	<p>between January 1 1995 and June 30 1996. For patients with more than one measurement during this period only the last measurement was used.</p>			<p>heart failure as the underlying cause.</p>	<p>1.05 to 1.12). This model was adjusted for age, sex, ethnicity, education level, smoking, alcohol consumption, self-reported hypertension, obesity, cardioprotective medicine used at baseline, type of diabetes and treatment, duration of diabetes and incidence of myocardial infarction during follow-up.</p> <p>A concentration of HbA1c more than or equal to 10% relative to HbA1c less than 7%, was associated with a 1.6 fold increased heart failure risk (for hospitalisation or death).</p>	<p>American Diabetes Association</p>
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