Diabetologia (2010) 53:2079–2085
DOI 10.1007/s00125-010-1864-z

EDITORIAL

Intensified glucose lowering in type 2 diabetes: time for a reappraisal

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Received: 16 July 2010 / Accepted: 16 July 2010 / Published online: 5 August 2010

Keywords Cardiovascular disease · Glycaemic control · Guidelines · Type 2 diabetes · Risk factors · Risk reduction

Abbreviations

CHD	Coronary heart disease
CONTROL	Collaborators on Trials of Lowering Glucose
HMG-CoA	3-Hydroxy-3-methyl-glutaryl-CoA
NNT	Number needed to treat
QALY	Quality-adjusted life years
UKPDS	UK Prospective Diabetes Study

Background

Obesity, urbanisation and an ageing population combine to drive a dramatic increase in the global prevalence of type 2 diabetes [1], a condition in which the morbidity and mortality from cardiovascular disease substantially outweigh the risk of microvascular complications such as renal disease [2]. Statins and antihypertensive agents lower cardiovascular risk in type 2 diabetes, but the benefits of intensified glucose-lowering remain controversial in this context—management recommendations tend to be based on extrapolation from surrogate endpoints. Recent studies have shown that intensified glycaemic control has limited impact on cardiovascular disease, but there is little indication that entrenched positions in the debate have been affected.

Intensified glucose-lowering is more difficult to achieve, and has a greater negative impact on quality of life, than lowering cholesterol or blood pressure [3]. Nonetheless, and despite questionable benefits to the individual, substantial pressure has been exerted on patients and practitioners to achieve rigorous glycaemic targets. This article examines the evidence for and against intensified glucose-lowering therapy in type 2 diabetes.

From magic bullets to risk reduction

Insulin was justifiably regarded as a near-miracle when first introduced [4], and antibiotics were equally life-saving [5]. These were true ‘magic bullets’, with a number needed to treat (NNT) of close to one. The scenario changed when drugs were given to people with no symptoms or evidence of vascular disease in order to reduce the possibility of future vascular events. Even drugs that reduce cardiovascular risk by 25%, such as the 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors [6], would (assuming a 20% risk of a CVD event in 10 years), require 20 such people to be treated for 10 years to prevent one event. For any given year of treatment, 199 of 200 people would have an identical outcome with or without the drug.

Electronic supplementary material The online version of this article (doi:10.1007/s00125-010-1864-z) contains supplementary material, which is available to authorised users.

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The benefits of such therapy are therefore more apparent at a public health level than at the level of an individual patient, a point that may be disregarded in clinical decision-making and in promotional material. Furthermore, there may be a substantial change in the risk–benefit ratio if the intervention is complex, inconvenient or associated with troublesome side effects.

Hyperglycaemia: risk marker or risk factor for cardiovascular disease?

Symptoms of type 2 diabetes are relatively easy to bring under control, and glucose-lowering treatment beyond this point is designed to reduce the risk of a variety of unwanted outcomes [2]. Let us emphasise that there are no arguments in favour of poor glucose control, since mortality increases substantially in those with HbA_{1c} levels over 8–9%, regardless of therapy [7], and there can be no doubt that the burden of complications would be greatly reduced if all patients could maintain an HbA_{1c} levels at around 7.5%. The point at issue relates to the benefits, costs and risks of lowering HbA_{1c} levels from about 8%, a relatively achievable target, to about 7% or below in type 2 diabetes.

The observation that cardiovascular events are quantitatively related to a given variable does not necessarily mean that regulating the marker of risk will reduce the number of events [8]. The risk marker may be an innocent fellow-traveller, with no impact upon aetiological pathways, as has been argued for C-reactive protein and cardiovascular disease [9]. Alternatively, established damage to the vessel wall may be poorly reversible, as with blood pressure lowering in atherosclerotic vascular disease [10]. Finally, the treatment may, while lowering the level of its target risk factor, enhance cardiovascular or other risks through different mechanisms, as with clofibrate treatment for hypercholesterolaemia [11]. Risk factor interventions that completely cancel out the excess level of risk are correspondingly rare. Collins, MacMahon and co-workers compared the influence of blood pressure on coronary heart disease (CHD) risk in observational and interventional studies, and such analyses suggested that some two-thirds of the excess CHD risk conferred by elevated blood pressure is reversed by treatment in intervention trials of about 5 years (Fig. 1) [10, 12, 13].

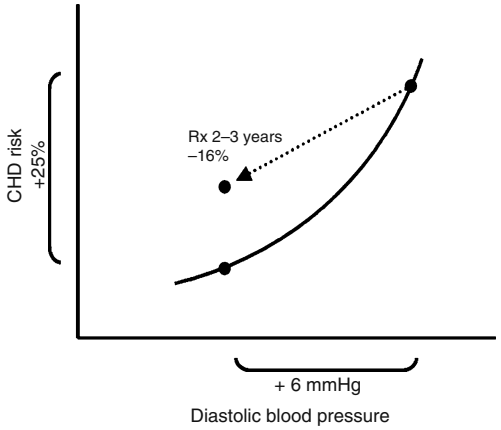

Fig. 1 Cardiovascular risk factors and their reduction. Data from the major observational studies of the relationship between blood pressure and CHD risk have shown that an increase in usual diastolic blood pressure of 6 mmHg is associated with a 25% increased risk of CHD [12]. Overviews of randomised drug trials for the treatment of mild to moderate hypertension published before 1993 showed a reduction in CHD events of 16% [10, 13]. The reduction of diastolic blood pressure in these studies was about 6 mmHg. The usual duration of these trials was about 5 years, implying that the mean duration of treatment before the event occurred was 2–3 years. Rx, treatment

Cardiovascular disease and glucose control

There is a clear epidemiological relationship between levels of HbA_{1c} and the risk of cardiovascular disease in patients with type 2 diabetes. Epidemiological data from the UK Prospective Diabetes Study (UKPDS) showed a 14% decrease in risk of myocardial infarction and 12% decrease in risk of stroke for each 1% decrease in usual mean level of HbA_{1c} [14]. The meta-analysis of Selvin et al. reported comparable reductions of 13% and 17%, respectively, per 1% change in HbA_{1c} [15]. Questions regarding the reversibility of this risk, first raised by publication of the University Group Diabetes Program Study [16], have taken some 40 years to resolve. To take one example, the UKPDS [2] showed a borderline significant 16% reduction in risk of myocardial infarction with intensive therapy, but a non-significant 11% increase in stroke risk, implying that even a study of 3,867 individuals treated for 10 years was insufficiently powered to enable a clear conclusion.

Three further major cardiovascular outcome studies of intensive glycaemic control in patients with type 2 diabetes have appeared over the past 2 years: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [17], the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial [18] and Veterans Affairs Diabetes Trial (VADT) [19]. None found a significant reduction in cardiovascular events in intensively treated patients, and the ACCORD study actually reported a 22% increase in total deaths in this group. The availability of data on 140,278 person-years of treatment does, however, allow more precise estimates of the impact on individual endpoints.

When the studies are combined, there is consensus that non-fatal coronary episodes are reduced by intensive control, whereas stroke, cardiovascular mortality and total mortality are unaffected [20–23]. Differences between the

point estimates reached by the various meta-analyses derive from study selection and the definition of endpoints—for example whether 'unexplained or presumed cardiovascular disease' [17] is included as a cause of death in the category of CHD [20] or myocardial infarction [23]. Using the data from the four studies explored by the Collaborators on Trials of Lowering Glucose (CONTROL) group [23], the authors estimate that intensified glycaemic control, with a mean reduction of about 0.9% in HbA_{1c}, is associated with a significant 9.7% reduction in CHD events, and a non-significant 4% reduction in the risk of stroke (Table 1; Electronic supplementary material [ESM] Table 1). Estimates for total and cardiovascular mortality are unchanged with intensified glycaemic control (ESM Table 1). These analyses concur with observational data suggesting that the nadir of mortality in people with type 2 diabetes occurs at an HbA_{1c} level of 7.5% [7]. They also do not allow for the possibility that therapies such as metformin might produce substantial reductions in cardiovascular events and in all-cause mortality independent of glucose lowering [24].

Cholesterol, blood pressure and hyperglycaemia, the three major continuously distributed risk factors for cardiovascular disease, were compared in terms of their epidemiological associations and their reversibility [22]. Table 1 shows the observed relationship between these three variables and the incidence of CHD and stroke in major reviews [25–27]. Table 1 also provides data on the effect of risk factor lowering, obtained from meta-analyses of interventions for cholesterol [26], blood pressure [27] and glycaemia ([23]; ESM Table 1). Since the benefits of intervention are generally dependent on the degree of risk factor reduction, the units used for comparison in each case are the approximate mean changes in the variable achieved in intervention studies. The data in the table suggest that glycaemia is a substantially weaker risk factor for CHD than cholesterol or blood pressure, and very much weaker than blood pressure when it comes to stroke. All three interventions cancelled out most of the excess risk for CHD, but this was not the case with respect to stroke, for which cholesterol and blood pressure lowering appear fully to reverse the excess risk, whereas intensive glycaemic control is without significant benefit. This suggests that the benefits of cardiovascular risk reduction with antihypertensive and lipid-lowering therapies greatly outweigh the benefits of intensive glucose-lowering, especially in older patients with type 2 diabetes whose main risk is that of macrovascular complications [2].

The clinical significance of an intervention is better expressed in terms of absolute rather than relative risk reduction, and absolute risk will depend upon the background risk of the population [28]. Table 1 shows the same data translated into NNT [22] by assuming, as an example, a 5 year risk similar to those of individuals in the conventional treatment limb of the authors' meta-analysis of glucose lowering (7.4% CHD, 3.3% stroke). In terms of overall cardiovascular risk, the number of individuals who would require 5 years of treatment to prevent one event would be 44 with cholesterol lowering, 34 with blood

Table 1 The epidemiological and interventional relationships of cholesterol, blood pressure and HbA_{1c} with cardiovascular disease

Variable	CHD[a]	Stroke (all)	Cardiovascular disease
Cholesterol (1 mmol/l)			
Epidemiological (%)	−30	−10	
Intervention (%)	−23	−17	
NNT for 5 years	59.2	177.7	44.4
Blood pressure (10/5 mmHg)			
Epidemiological (%)	−25	−36	
Intervention (%)	−22	−41	
NNT for 5 years	61.8	73.7	33.6
Glycaemia (HbA_{1c} 0.9%)			
Epidemiological (%)	−12	−15	
Intervention (%)	−9.7	−4.0	
NNT for 5 years	140.3	767.7	118.5

Epidemiological data are derived from overviews of published studies on cholesterol [25], blood pressure [12] and glycaemia [15]

For each variable, the data are shown for a change corresponding to the mean change of the variable in intervention studies. Interventional data for cholesterol and blood pressure are derived from published meta-analyses [26, 27] and for glycaemia from the meta-analysis of the CONTROL Group [23] and ESM Table 1

NNT are calculated by assuming a 5 year level of risk equivalent to that of the conventional treatment limb of the meta-analysis (CHD 7.4%, stroke 3.3%, see ESM Table 1), applying a factor of 5/4.4 (1.136) to derive these from the 4.4 year data

[a] CHD is defined as fatal and non-fatal myocardial infarction and sudden death

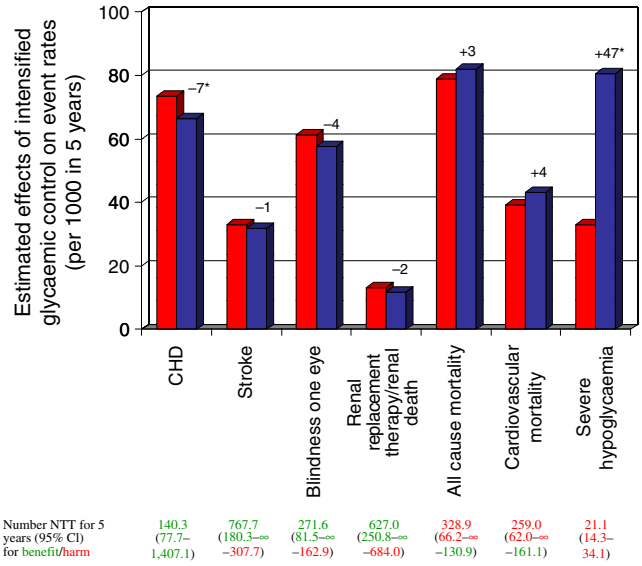

Fig. 2 The influence of intensified glycaemic control on rates of macrovascular and microvascular events, mortality and serious hypoglycaemia per 5 years, and NNT, in type 2 diabetic patients. Rates of events on conventional glycaemic control regimens are derived from those for 12,729 participants of mean age 62 years with type 2 diabetes in the meta-analysis based on data from the CONTROL Group [23] and shown in ESM Table 1. These rates are indicated in red as per cent incidence during 5 years. The effects of intensified glycaemic control on macrovascular and microvascular events and on hypoglycaemia are estimated from this meta-analysis ([23] and ESM Table 1). The calculated effects of glucose lowering are shown in blue, and absolute risk reductions/increases are shown at the top of these bars per 1,000 participants treated for 5 years. NNT for benefit or harm for 5 years is shown in green and red, respectively. *Statistically significant treatment effects (CHD $p=0.03$; severe hypoglycaemia $p<0.00001$)

pressure lowering and 119 with intensive glucose-lowering. Figure 2 uses data from this meta-analysis (ESM Table 1) of studies of intensive glycaemic control to quantify likely benefit and harm in a cohort of type 2 diabetic patients treated for 5 years, and using the event rate in the conventional treatment limb of the meta-analysis. The reduction in major cardiovascular event rates of about eight per 1,000, and of (statistically insignificant) serious microvascular events of about six per 1,000, was not accompanied by a reduction in mortality. Furthermore, the approximate 14 per 1,000 reduction in complications was accompanied by an increase of nearly 50 per 1,000 in the rate of serious hypoglycaemia. The fact that studies involving more than 140,000 person-years of follow-up were needed to demonstrate the cardiovascular benefits of glucose lowering indicates the modest degree of reduction in absolute risk that has been achieved. By contrast, the first Veterans Administration study on treatment of hypertension produced a clear result after randomisation of 143 patients for a mean follow-up of about 18 months [29]. The overall lack of effect of improved glucose control is often explained on the grounds that this is of greater benefit in early than in advanced cardiovascular disease [21, 23, 30–32]. From this point of view it can be noted that the 10-year follow-up of the UKPDS, a study performed in recently diagnosed individuals, showed an absolute risk reduction of 3.4% in the incidence of myocardial infarction and stroke [31], with a NNT of 29.4 for 10 years to prevent one event, showing an effect about twice that calculated in Table 1 (NNT of 118.5 for 5 years).

The benefits of intensified glucose control are typically experienced over the longer term. Older patients, or those with a reduced life expectancy, will therefore experience diminishing benefit. This point is often emphasised in current guidelines, but the practical implications have not been explored in any detail. Recent studies, which have used modelling techniques to estimate the impact of glycaemic control on life expectancy, are enlightening in this respect [33, 34]. The UKPDS outcomes model estimated that intensified glucose control would increase quality-adjusted life years (QALY) by 0.27, or about 99 days [33]. Huang et al. [35] estimated that intensive control would add 106 days of life expectancy to an otherwise healthy newly diagnosed diabetic patient aged 60–64 years, decreasing with increasing comorbidities, longer duration of disease, or advancing age to only five to eight additional days. Kahn et al. modelled the impact of cardiovascular prevention in a simulated population matching that of the US [36]. This model estimated that patients with diabetes would gain an additional 2.3 QALY with reduction of HbA_{1c} to below 7% for up to 30 years. All three models estimated life expectancy gains by factoring out the impact of the risk marker under investigation. This approach assumes full reversibility of the impact of that variable on events, an assumption which may be less valid for stroke or cardiovascular mortality than for total coronary events when it comes to glucose control (Table 1) [22, 23]. It might even be suggested on this basis that intensified glycaemic control influences the cause of death more than its rate. An alternative actuarial approach, which makes no such assumptions about reversibility, was used (in the pre-HMG-CoA reductase inhibitor era), to calculate the benefits of lipid and blood pressure treatment [8], but has not been applied to glycaemia. This analysis found that the risk factor that had the greatest impact on life expectancy, and that was most reversible, was smoking cessation. Another study using this approach explored the theoretical impact on absolute risk only of combination therapy [37].

To summarise, four large clinical trials have shown no increase in life expectancy, or indeed quality of life [38], in response to intensified diabetes therapy. Epidemiological estimates do imply relatively modest improvements in life expectancy, but highlight the fact that these will be greatest in younger and healthier patients. No demonstrated benefit is present for those with established CHD. To put this in perspective, some 65% of people with diabetes are aged

60 years or above and 38% are over the age of 70 years [39], and 80% of 65-year-old people suffer three or more chronic conditions, regardless of diabetes status [40]. Current estimates suggest that the benefits of intensified glucose-lowering therapy with respect to life expectancy in this population can be measured in days.

Microvascular complications in type 2 diabetes

A newly diagnosed patient aged 65 years who embarks on intensified glycaemic control is substantially more likely to succumb to a cardiovascular event than to develop serious microvascular complications, but the demonstrated benefits of improved control upon microvascular outcomes must not be ignored. Both the UKPDS [2] and the Diabetes Control and Complications Trial (DCCT) [41] showed that a 1% reduction in HbA_{1c} reduced the risk of these complications by about 25%. These considerations are more relevant for the younger patient with type 2 diabetes, but even by the age of 53 years (the mean age of enrolment for the UKPDS) the combined 10 year incidence of myocardial infarction (17.4%) and stroke (5%) was more than five times greater than the combined risk of renal failure (0.8%) and blindness (3.5%) [2]. A calculation of NNT to prevent these serious microvascular events, quantified using a meta-analysis of data from the same four major studies [2, 17–19, 42], shows that it would be necessary to treat 272 patients with intensified glycaemic control for 5 years to prevent one person developing blindness in one eye, and 627 patients for 5 years to prevent one developing renal failure, although the effect is not statistically significant for either endpoint (Fig. 2; ESM Table 1). Both the lifetime risk of these microvascular outcomes and the added benefit of improved glucose control diminish with age. As an example, a 65-year-old with new-onset diabetes who has an HbA_{1c} of 8.0% has an estimated 2/1,000 lifetime risk of blindness, falling to less than 1/1,000 by reducing HbA_{1c} to 7.0% (NNT 500–1,000) [43]. The authors of this analysis argue that efforts should be focused on those with HbA_{1c} levels greater than 8%, since many more microvascular events will be prevented by this approach. The implication of these observations is that benefits accruing over decades should be taken into account in planning treatment for younger people, but that intensive glycaemic targets should be advised with some caution in older individuals [22].

Intensified glucose control: the costs

A comparison of the cost-effectiveness of intensified control of glucose, blood pressure and cholesterol in type 2 diabetes points strongly to the same conclusion [44]. For example, the cost-effectiveness of lowering HbA_{1c} from about 8% to 7% for a 65-year-old new-onset patient (based on UKPDS data and expressed in 1,997 US$) is $154,376 per QALY, as against $43,331 for cholesterol lowering and –$413 for blood pressure lowering. The costs of glucose control rise to $401,883 per QALY for those aged 75-84 years, and to $2.1 million over that age; in contrast, blood pressure control is cost-saving at every age below 85 years [44].

Intensified glucose control: the risks

Hyperglycaemia differs from cholesterol and blood pressure in another important respect, namely the complexity of glucose-lowering therapy. Management of risk factors implies medication for comparatively healthy individuals. The HMG-CoA reductase inhibitors, and to some degree the newer antihypertensive agents, provide simple regimens with drugs that are relatively free from side effects. Glucose-lowering therapies are, in contrast, associated with a wide range of unwanted consequences, for example weight gain, heart failure and osteopenic fractures for the thiazolidinediones, and weight gain and hypoglycaemia for the sulfonylureas. This side of the equation is rarely taken into consideration when intensified control is advocated. Furthermore, and in stark contrast to lipid-lowering or antihypertensive therapies, intensive glucose-lowering may require several injections each day [45], requires regular fingerprick blood testing and is associated with side effects that include hypoglycaemia and loss of consciousness, and perhaps an increased future risk of dementia [46]. Our data (Fig. 2) suggest that 1,000 patients treated for 5 years would experience 47 additional hypoglycaemic events requiring assistance from another person in order to prevent about eight major (non-fatal) cardiovascular events over the same period. A study of 701 patients with type 2 diabetes assessed for quality of life ‘utilities’, where 1 corresponds to perfect health and 0 to death, rated the utility for intensified glycaemic treatment as 0.67, or the loss of one-third of full quality of life [3]. In other words, this analysis suggests that it would be necessary to treat 119, 272 and 627 diabetic patients for 5 years for each person who benefits in terms of cardiovascular, eye or renal complications, respectively, using a treatment perceived to diminish quality of life by one-third.

Conclusions

Hyperglycaemia is a substantially weaker risk factor for CVD than cholesterol or blood pressure, and glucose-lowering interventions are correspondingly less effective. This awareness has yet to be reflected in standard guide-

lines [47]. Furthermore, little attention has been paid to the unwanted effects of intensified therapy, and its low utility in those with established complications or a limited life expectancy. Treatment strategies that make sense at a population level may offer little advantage to the majority of those whose lives are affected by them, and can bring considerable inconvenience. Good glucose control does indeed offer protection against microvascular complications, cataracts and neuropathy, but the added benefits of an HbA_{1c} of 7%, as against 8%, diminish with age and life expectancy. In such instances efforts and resources would be better directed to those with higher levels of HbA_{1c}, who have much more to gain from attention to their glucose control. Each individual should indeed be encouraged to achieve the best possible compromise between glucose control and vascular risk, but fully informed consent should be the prelude to intensified therapy. This is not achieved when benefits are grossly overestimated, or when trials are presented in terms of relative risk reductions—'25% fewer heart attacks'. Absolute risk reduction, the corresponding NNT, and the potential gain in life expectancy, are much more relevant in such discussions [48, 49], particularly when the recommended treatment impinges upon every aspect of a person's life.

Acknowledgements We would like to express thanks to R. Collins, R. Holman, I. Chalmers, P. Yudkin, C. Stehouwer and H. Price for valuable comments, advice and suggestions, and for provision of data during the process of writing this paper.

Duality of interest The authors declare that there is no duality of interest associate with this manuscript.

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