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Earlier intervention in type 2 diabetes: The case for achieving early and sustained glycaemic control

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SUMMARY

In type 2 diabetes, the onset and progression of complications is significantly delayed by improving glycaemic control. However, the proportion of patients reaching and sustaining guideline recommendations for glycaemic targets remains unacceptably low. Recent clinical trials and predictive physiologically based mathematical simulations (Archimedes model) indicate that benefits can be enhanced with earlier intervention and timely achievement of glycaemic targets. This article reviews the evidence for early intervention, showing that intensive approaches, including earlier introduction of combination therapy, allow more patients to achieve glycaemic targets and hence reduce complications and delay disease progression.

Keywords: Type 2 diabetes; glycaemic control; Archimedes model; early intervention; combination therapy

INTRODUCTION

Chronic hyperglycaemia, which often precedes diagnosis of type 2 diabetes for more than a decade, causes extensive vascular damage and leads to the early development of clinical complications. Up to 50% of individuals with type 2 diabetes have complications at diagnosis (1,2), with, for example, nephropathy and retinopathy being present in approximately 20% of subjects (2,3). Progression of complications can be rapid: diabetic nephropathy is a leading cause of end-stage renal disease (ESRD) (4), and diabetic retinopathy is the leading cause of new cases of blindness among adults (5). In addition, peripheral neuropathy is associated with an increased risk of non-traumatic lower extremity amputations (6), and the high incidence of macrovascular complications leads to deaths in 75% of type 2 diabetes patients (7).

This burden of complications increases with severity and duration of hyperglycaemia, but there is now substantial evidence that good glycaemic control reduces the risk of complications (8,9). It is essential therefore to address the management of type 2 diabetes by increasing the proportion of patients who achieve the glycaemic targets outlined in current guidelines (10–15). In this article, we report on the importance of intensive glycaemic control and explore strategies that might help to achieve this objective.

THE IMPORTANCE OF GOOD GLYCAEMIC CONTROL

Epidemiological analysis of the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that a 1% decrease in glycosylated haemoglobin (HbA_{1c}) was associated with a risk reduction of 37% for microvascular disease and 14% for myocardial infarction (MI). These data also indicate that there is no lower threshold to the benefits of glycaemic

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control (16). The Norfolk Cohort of the European Prospective Investigation into Cancer and Nutrition also noted that higher HbA_{1c} level predicts higher risk of death from cardiovascular disease (CVD), ischaemic heart disease (IHD), and all cause mortality. Of particular note in this study was the strikingly greater risk of these events when the HbA_{1c} level rose above 7% (Figure 1) (17). These findings suggest that glycaemic-control strategies should aim to achieve HbA_{1c} as close to normal as possible and as soon as possible, although the benefits of reaching this target should always be weighed against the risk of hypoglycaemia (10,13).

The inadequacy of the current management of glycaemia is exemplified by reports that the majority of individuals with type 2 diabetes in both the US and Europe (63% and 69%, respectively) do not achieve a 7% HbA_{1c} target (18,19). National Health And Nutrition Examination Study (NHANES) data also indicate that the proportion of individuals achieving $HbA_{1c} < 7\%$ has not improved over time (18). The Steno-2 study found poor attainment of HbA_{1c} targets compared with greater attainment of targets for blood pressure and lipids amongst individuals with type 2 diabetes. In the Steno-2 study, blood pressure and lipid values improved gradually over the 8-year study period, whereas mean HbA_{1c} tended to level out (20). Similarly, in NHANES, there were continued improvements over time in the proportion of individuals achieving goals for blood pressure and total cholesterol (18).

The reason for these differences is likely to be multifactorial. For example, there appears to be a much greater awareness in the general population of the risks associated with hypertension and hypercholesterolaemia than the harmful effects of hyperglycaemia. In addition, hyperglycaemia has been perceived by too many for too long as a benign condition, stemming from an unhealthy lifestyle and not requiring treatment. Another influential component may be the increasing use of more efficacious treatments or rapid progression to management with combinations of treatments for hypertension and dyslipidaemia. In comparison, procedures for managing hyperglycaemia have seen relatively little change in recent years. These generally focus on the traditional stepwise approach, in which a period of lifestyle modification is followed by a slow process of uptitration of monotherapy and eventually combination therapy (21). When adopting this conservative approach, there is often a reluctance to switch from traditional methods and habits, despite the recognition that glycaemic targets are not being achieved (22).

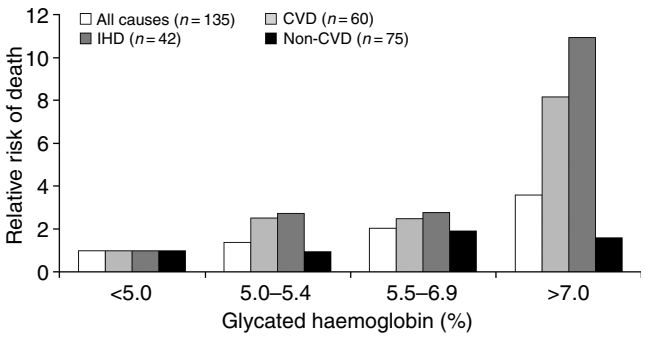

Figure 1 Effect of HbA_{1c} on cause of death (17). CVD, cardiovascular disease; IHD, ischaemic heart disease. $p < 0.001$ (χ^2 linear trend)

BENEFITS OF GLYCAEMIC CONTROL

It would not be possible to review all the evidence relating to the benefits of glycaemic control on micro- and macrovascular complications in diabetes. However, in this section, we highlight two seminal studies that we feel are particularly relevant to the issue of early aggressive therapy of diabetes and its long-term benefits.

The Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications – Evidence from Type 1 Diabetes

It is well established from studies in type 1 diabetes that intensive therapy to reduce HbA_{1c} will delay the onset, and reduce the progression, of microvascular complications. For example, in the Diabetes Control and Complications Trial (DCCT), a large type 1 diabetes outcome study, intensive diabetes management with three or more daily insulin injections or insulin pump therapy, aiming for an HbA_{1c} target of $\leq 6.05\%$, was compared with conventional insulin treatment with once- or twice-daily insulin injections. In addition, intensively treated participants had more frequent clinical visits and performed self-monitoring of blood glucose at least four times per day. A 2% difference in HbA_{1c} was maintained between the two treatment groups. The study was stopped early, because intensive therapy significantly reduced the risk of nephropathy and retinopathy by 54% and 76%, respectively, after 6.5 years (23). In the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study to the DCCT, all patients were encouraged to adopt intensive insulin therapy in their usual clinical setting (24). As a result, glycaemic control in the patients previously in the conventional arm of the DCCT improved, while in the intensive group, it deteriorated somewhat. After 8 years of follow-up, HbA_{1c} levels stabilised to around 8% in patients from both the former-intensive and former-conventional groups (Figure 2A) (25).

However, despite similar HbA_{1c} levels during this follow-up period, some important differences remained. The cumulative incidence of retinopathy remained much lower in those previously receiving intensive therapy (Figure 2B) (26), and the benefits of early intensive therapy in reducing the risk of microalbuminuria were also maintained (25). In addition, the progression of carotid intima-media thickness was significantly less in the intensively treated group after 6 years of follow-up (27). The persistent benefits from earlier intensive

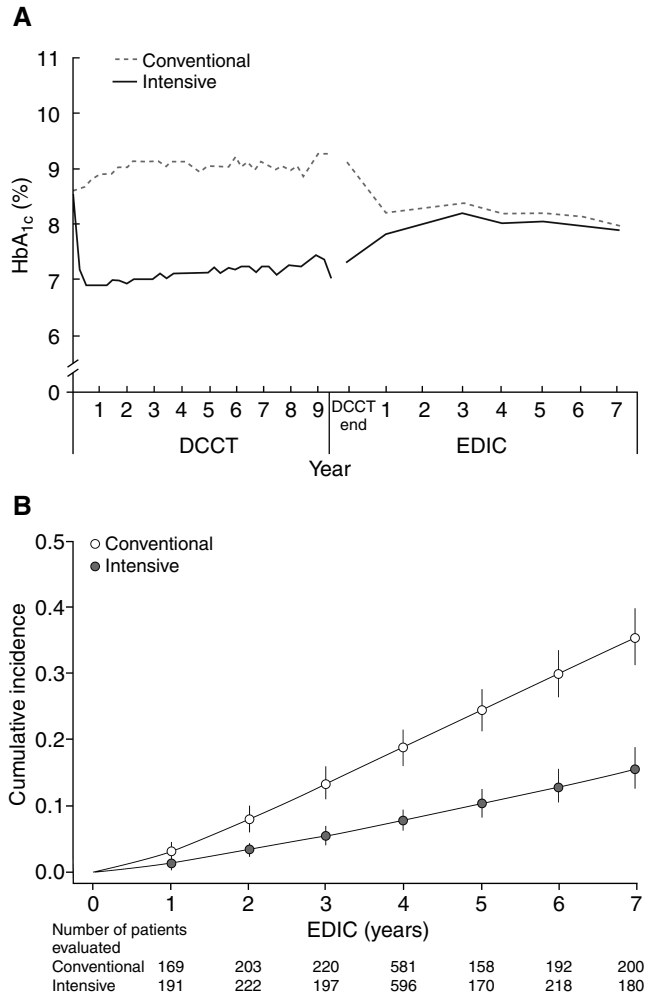

Figure 2 Effect of early intensive therapy in the Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Intervention and Complications (EDIC) (A) on glycaemic control (23,26) and (B) on progression of retinopathy (26). Reproduced with permission, 2 A) Copyright © American Medical Association, 2002, All rights reserved. 2 B) Adapted with permission from Diabetes Control and Complications Trial Research Group *N Engl J Med* 1993; **329**: 977–986. Copyright © 1993 Massacheusetts Medical Society. All rights reserved

intervention are consistent with the hypothesis of a long-lasting effect of an earlier physiological improvement, and the investigators called this 'metabolic memory' (25). The observation that benefits extend beyond the initial period of intervention support a policy of implementing intensive treatment in patients with type 1 diabetes as early as is safely possible after diagnosis (26).

The UKPDS – Evidence from Type 2 Diabetes

The UKPDS was the first large trial in type 2 diabetes to compare the effect of intensive treatment (using sulphonylurea, metformin or insulin) with that of conventional treatment (lifestyle management) on the development of micro- and macrovascular complications. Although glycaemic control gradually deteriorated in both the groups over 10 years, mean HbA_{1c} was 11% lower in the intensive group over this period compared with that in the conventional group. Intensive treatment significantly reduced the risk of microvascular disease by 25%, more specifically with 21% and 34% reductions in the risk of retinopathy and albuminuria, respectively. Intensive treatment produced a 16% reduction in the risk of MI ($p = 0.052$) compared with conventional treatment (8,9).

At the end of the UKPDS study, patients and clinicians were advised of the need for good glycaemic control. However, unlike in the DCCT, there was no attempt to influence therapy choice, and patients returned to community-based or hospital-based care. A deterioration in glycaemic control occurred in the patients who had received intensive therapy during the study, and after 3 years poststudy monitoring (PSM) the mean HbA_{1c} levels were similar in the groups previously receiving conventional or intensive therapy. Importantly, however, and similar to results in EDIC, it has recently been reported that the risk reductions provided by intensive therapy during the UKPDS were maintained at 5 years PSM. These results suggest that the benefits of early improvements in glucose control also persist in the longer term in type 2 diabetes (28).

STRATEGIES FOR ACHIEVING EARLY GLYCAEMIC CONTROL: THE ROLE OF COMBINATION THERAPY

Several studies have shown that deterioration in β-cell function precedes the development of type 2 diabetes by many years (29–33). In the UKPDS, loss of glycaemic control was mirrored by a progressive decline in β-cell function, which had already deteriorated by 50% in the majority of individuals at the time of diagnosis (29). Extrapolation of data from the UKPDS and Belfast diet study has revealed that β-cell dysfunction could be commencing up to 15 years prior to diagnosis (29,31). Thus, intervention, whether with lifestyle modification or with pharmacological treatment, is invariably warranted from the time of diagnosis.

Intensive lifestyle intervention is effective in reducing the rate of progression from impaired glucose tolerance to type 2 diabetes over 2.8 years by almost 60% (34,35). It is also an initial recourse after diagnosis of type 2 diabetes. While intensive lifestyle regimens are maintained successfully by some subjects, there will be many who need additional support, and early pharmacological intervention is indicated if lifestyle measures are not effective. Moreover, the UKPDS demonstrated the difficulty in maintaining glycaemic control with monotherapy using traditional agents. After only 3 years in this study, over 50% of subjects were inadequately controlled with one antidiabetic agent, and after 9 years only 25% of patients on monotherapy achieved the HbA_{1c} target of $< 7\%$ (36). Thus, combination therapy is often required as an earlier option in the management of type 2 diabetes.

Earlier Intervention in Other Areas

The clinical success seen with early intervention strategies has been recognised in other therapeutic areas, leading to changes in guidelines, such as the management of hypertension and dyslipidaemia (37,38). In the case of blood pressure control, recommended targets are rarely achieved with monotherapy. In fact, overwhelming evidence indicates that optimal blood pressure control can only be achieved with combination treatment using two to four antihypertensive agents (Table 1) (39–42).

There is also evidence that earlier blood pressure control improves outcomes. For example, in the Systolic Hypertension in Europe trial, immediate antihypertensive treatment prevented strokes and major cardiovascular (CV) events compared with delayed treatment (43). Mounting evidence for the benefits of combination therapy and earlier treatment has led to the incorporation of recommendations for early combination therapy in recent hypertension guidelines from the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, which note that more than two-thirds of hypertensive individuals cannot be controlled on one drug and will require two or more antihypertensive agents (37).

A similar strategy of earlier use of combination therapy in type 2 diabetes has a number of potential advantages. These include more rapid achievement of therapeutic goals, reduced side-effects associated with the use of submaximal doses of drugs, the opportunity to combine oral antidiabetic agents with complementary modes of action and the potential to delay disease progression and defer, or prevent, the development of complications. The potential benefits of this approach are highlighted in the Canadian Diabetes Association 2003 Clinical Practice Guidelines. These caution that, as with the treatment of hypertension, late combination therapy makes the task of achieving glycaemic targets more difficult, and these guidelines advocate the use of multiple therapies because of the progressive nature of glycaemic deterioration (44).

Combination Therapy Using Agents with Complementary Modes of Action

Several classes of agents with different modes of action are now available, and the advantages of earlier combination with several of these agents have recently been demonstrated. For example, studies have evaluated the efficacy and tolerability of sulphonylurea/metformin combination therapy compared with sulphonylurea or metformin monotherapy as initial pharmacological treatment for type 2 diabetes (45–48). These have shown that initial therapy with glyburide/metformin (glibenclamide/metformin) consistently produces greater improvements in glycaemic control than either glyburide or metformin monotherapy and can bring more patients – up to 80% – to $HbA_{1c} < 7\%$ (45,46). Glyburide/metformin combination therapy was also associated with improvements in gastrointestinal tolerability vs. metformin monotherapy, although a higher incidence of hypoglycaemia was observed with higher doses of glyburide/metformin (45,46). Other studies have reported that 45–70% of patients with type 2 diabetes achieve the HbA_{1c} target $< 7\%$ with combination of the insulin secretagogue nateglinide and metformin, and suggest that this combination is suitable as initial therapy and in therapy-experienced patients (49–51).

A similar approach can be taken by the combination of metformin with a thiazolidinedione (52,53). For example, addition of rosiglitazone to submaximal metformin therapy significantly improved glycaemic control and was associated with an increase in the proportion of individuals achieving HbA_{1c} goals compared with uptitration of metformin. Also, 41% of patients receiving metformin/thiazolidinedione reached the target of $\leq 6.5\%$ compared with 28% of patients in the metformin monotherapy group. In addition, insulin sensitivity improved significantly in the metformin/thiazolidinedione group compared with the uptitrated metformin group (52). Importantly for compliance, fewer gastrointestinal symptoms were reported in individuals taking the thiazolidinedione added to submaximal dose metformin compared with those on uptitrated metformin alone (53).

There is also evidence that combination therapy using agents with complementary modes of action can exert additive effects on glycaemic control at maximal doses as well as submaximal. For example, in a 2-year study, early addition of rosiglitazone to sulphonylurea therapy significantly reduced disease progression, enabling an increased proportion of patients to achieve HbA_{1c} goals compared with uptitration of sulphonylurea (Figure 3A, 3B), without any increase in

Table 1 Number of antihypertensive agents required to achieve target blood pressure (39–42)

	MDRD (39)	*ABCD (40)*	*HOT (41)*	*UKPDS (42)*
Target BP (mmHg)	< 92 MAP*	< 75 DBP	< 80 DBP	< 85 DBP
Achieved BP (mmHg)	93	~75	81	82
Average number of drugs per patient	3.6	2.7	3.3	2.8

ABCD, appropriate blood pressure control in diabetes; BP, blood pressure; DBP, diastolic blood pressure; HOT, Hypertension Optimal Treatment; MDRD, Modification of Diet in Renal Disease; UKPDS, UK Prospective Diabetes Study.
*The goal mean arterial pressure (MAP) of < 92 mmHg specified in the MDRD trial corresponds to a systolic/diastolic blood pressure of approximately 125/75 mmHg.

adverse events (54). Furthermore, medical resource utilisation decreased with combination therapy (Figure 3C) (55).

Insulin also has a role in combination therapy in getting patients to target, and the benefits of this approach have been demonstrated in several studies (56–58). For example, in the Treat-to-Target Trial, subjects inadequately controlled ($HbA_{1c} > 7\%$) on one or two oral agents (sulphonylureas, metformin or thiazolidinediones) were randomised to receive either addition of human neutral protamine hagedorn (NPH) insulin or glargine. In both the groups, the majority of patients (around 60%) reached the HbA_{1c} target of $\leq 7\%$ after 24 weeks (56). Thus, with vigilance against hypoglycaemia, combinations of antidiabetic agents with different mechanisms of action can be used effectively to enhance glycaemic control.

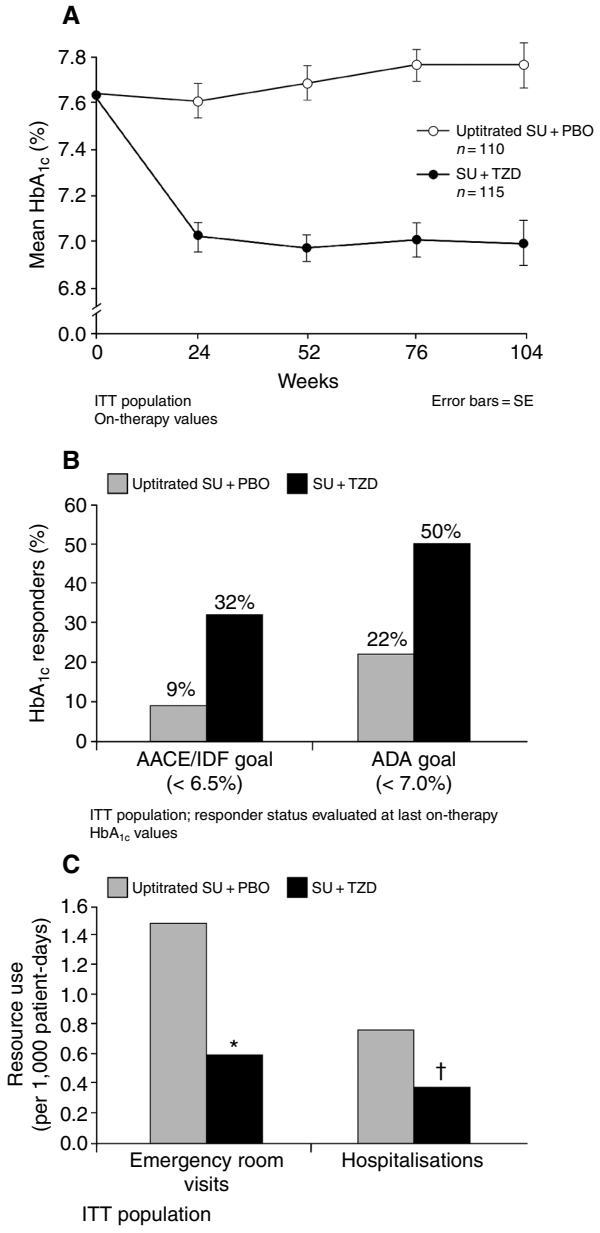

Figure 3 Effect of addition of rosiglitazone to a sulphonylurea (A) on long-term glycaemic control, (B) on HbA_{1c} targets (54) and (C) on emergency room visits and hospitalisations (55). SU, sulphonylurea; PBO, placebo; TZD, thiazolidinedione. *$p < 0.001$ for number of emergency room visits, †$p < 0.05$ for number of hospitalisations. 3 A and 3 B, Redrawn with permission from Rosenstock J et al. Effect of early addition of rosiglitazone to sulphonylurea therapy in older type 2 diabetes patients (> 60yrs): The Rosiglitazone Early vs. SULphonylurea Titration (RESULT) study. *Diabetes Obes Metab* (doi: 10.1111/j.1463-1326.2005.00541.x) Blackwell Publishing Ltd

Predictive Modelling Supports the Case for Early Glycaemic Control

Further support for an approach that brings patients to target as early as possible is provided by the physiologically based Archimedes model (59). The model is continuous in nature and therefore distinct from other models, such as Markov models, and has been validated comparing the results predicted by the model with actual trial results, including those from the UKPDS (8), the DCCT (23) and the Diabetes Prevention Program (DPP) (34,60). The Archimedes model has been used to conduct a simulated clinical trial of a randomly selected population of individuals in the US who have type 2 diabetes that is currently uncontrolled ($HbA_{1c} > 7\%$). It projected the effects of four programmes (i) *status quo* in which no change was made to existing levels of compliance and control; (ii) control to HbA_{1c} levels $< 7\%$ over 6 months; (iii) control to HbA_{1c} levels $< 7\%$ over 12 months and (iv) control to HbA_{1c} levels $< 7\%$ over 24 months (Figure 4A). The simulation assumed good control of other risk factors, such as hypertension and dyslipidaemia (61).

The model predicted that getting patients to target would confer many benefits on microvascular endpoints when compared with the *status quo*. For example, the model predicted that albuminuria, proteinuria, retinopathy, eye surgery, blindness and foot ulcers would be reduced by better glycaemic control (Figure 4B). Moreover, these benefits were enhanced when patients were brought to $HbA_{1c} < 7\%$ earlier (Table 2). Of note, treatment to target within 6 months would reduce the risk of ESRD by 44% compared with *status quo*, thus theoretically preventing around 20,000 cases of ESRD per annum in the US. In contrast, compared with achieving control within 6 months, a delay in achieving control until 24 months would result in almost 4000 more cases of ESRD. Similarly, compared with the *status quo*, achieving control to $HbA_{1c} < 7\%$ within 6 months would reduce both the eye surgery and the incidence of blindness by 73%, which would be the equivalent of preventing around 17,500 cases of blindness. However, delaying control to 24 months would result in an additional 3000 cases of blindness per annum compared with the number of cases that would occur with the achievement of control within 6 months.

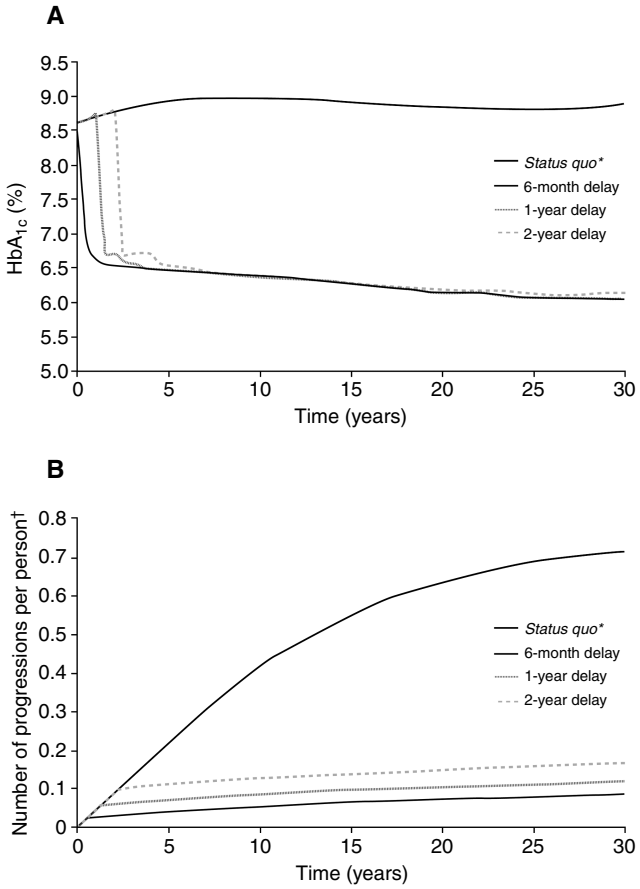

Figure 4 Archimedes model: (A) HbA_{1c} brought to $< 7\%$ at different time periods; (B) effect on retinopathy of delay in controlling glycaemia. **Status quo*, no change to existing levels of compliance and control; †value on *y* axis, cumulative probability of outcome

Evident from this simulation was the decreased risk of developing microvascular complications between the three management periods: 6-month delay < 12-month delay < 24-month delay. This order remained constant over a 30-year time span as illustrated in Figure 3B for retinopathy, supporting the rationale of early intervention. The model also predicted that the benefits of early glycaemic control on microvascular complications would be much greater for patients with high baseline HbA_{1c}, for example, $HbA_{1c} > 9\%$. In addition, controlling HbA_{1c} to $< 7\%$ at 6 months should result in a reduction in the risk of MI and coronary heart disease of 11 and 17%, respectively, i.e. of the same order of risk reduction for these events in the UKPDS (8,9). This relatively small effect may be because of the smaller contribution that hyperglycaemia makes to macrovascular disease compared with microvascular disease, hence the importance of early and effective control of concurrent CV-risk factors such as blood pressure and plasma lipid profile.

Table 2 Archimedes model predictions of the effect of intensive glycaemic control on 20-year risk in microvascular complications

	Control to $HbA_{1c} < 7\%$	
	Achieved promptly (within 6 months) (A) (%)	*Delayed (to 24 months) compared with A (%)*
Proteinuria	↓52	↑15
End-stage renal disease	↓44	↑16
Eye surgery	↓73	↑41
Blindness	↓73	↑47

CONCLUSION

While it is well-established that good glycaemic control plays a key role in reducing diabetes-related complications, current management of glycaemia remains inadequate, and insufficient patients achieve glycaemic goals. There is mounting evidence that earlier intervention, through both lifestyle and pharmacological management, including earlier combination therapy, can alleviate the burden of complications in type 2 diabetes.

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