Review

Glycaemic control and cardiovascular morbi-mortality: The contribution of the 2008 studies

Équilibre glycémique et morbimortalité cardiovasculaire apport des études 2008

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Résumé

L’année 2008 a été riche d’enseignements et fournie en rebondissements en diabétologie. Les études antérieures, l’United Kingdom Prospective Diabetes Study (UKPDS) chez les diabétiques de type 2 et le Diabetes Control and Complications Trial (DCCT) chez les diabétiques de type 1, ont montré qu’un traitement intensif à court terme réduisait les complications microvasculaires et à long terme diminuait les complications micro- et macrovasculaires du diabète. Les conclusions brutes d’Action to Control Cardiovascular risk in Diabetes (ACCORD) relèvent une surmortalité chez les diabétiques de type 2 intensivement traités, tandis que l’étude Action in Diabetes and Vascular disease, Perindopril and Indapamide Controlled Evaluation (ADVANCE) objective une réduction des complications microvasculaires et que Veterans Affairs Diabetes Trial (VADT) montre l’absence d’effet significatif du traitement intensif. L’analyse réfléchie des études parues en 2008 (ACCORD, STENO 2 à cinq ans, ADVANCE, VADT, UKPDS à dix ans, EDIC) est particulièrement informative et permet de souligner l’existence d’une mémoire glycémique, l’absence de mémoire tensionnelle, la nécessité de contrôler l’ensemble des facteurs de risque cardiovasculaires et de traiter précocement le diabète en évitant les hypoglycémies. L’objectif glycémique reposant sur l’HbA1c doit tenir compte de l’âge, de l’ancienneté du diabète, ainsi que de la tolérance aux hypoglycémies et à un contrôle rigoureux des autres facteurs de risque cardiovasculaires.

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Abstract

The year 2008 was rich in teachings and suspense in diabetology. Past studies, i.e. United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetic patients and Diabetes Control and Complications Trial (DCCT) in type 1 diabetic patients, have shown that in the short term, intensive treatment reduces the incidence of microvascular complications linked to diabetes and in the long term that of both microvascular and macrovascular ones. The in-the-raw conclusions of the recent Action to Control Cardiovascular risk in Diabetes (ACCORD) study note an increase in mortality in type 2 diabetic patients treated intensively, while the Action in Diabetes and Vascular disease, Perindopril and Indapamide Controlled Evaluation (ADVANCE) study evidences a reduction in microvascular complications and the Veterans Affairs Diabetes Trial (VADT) study shows that intensive treatment has no significant effect. A well thought-out analysis of the studies published in 2008 (ACCORD, STENO 2 post-trial, ADVANCE, VADT, UKPDS post-trial, Epidemiology of Diabetes Interventions and Complications [EDIC]) is particularly instructive and highlights the existence of glycemic memory, the non-existence of blood pressure memory, the need to control all cardiovascular risk factors and to treat diabetes early while avoiding hypoglycaemic incidents. The glycaemic target based on HbA1c must take into account the patient’s age and the duration of his diabetes, as well as his cardiovascular risk.

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1. Introduction

The year 2008 was rich in teachings and new developments in diabetology. The results of the major studies were impatiently awaited. Indeed, for diabetologists, the connection between the degree of hyperglycaemia and diabetes-linked complications seemed well established. In everyone’s mind, a decrease in HbA1c allows a reduction of the complications related to diabetes and particularly microangiopathy. But an unknown persisted regarding the ideal level of HbA1c with a view to further reducing microangiopathic complications, as well as concerning the actual effectiveness of that approach in relation to microangiopathic complications and mortality. The year 2008 brought contradictory evidence regarding these important topics, which concern especially type 2 diabetics (T2D). The results of the Action to Control Cardiovascular risk in Diabetes (ACCORD), Action in Diabetes and Vascular disease, Perindopril and Indapamide Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT) trials were widely circulated and were the subject of very many comments. Following the publication of these studies, we can now stand back and delineate the reasonable conclusions to be drawn by integrating the results of prior studies (United Kingdom Prospective Diabetes Study [UKPDS], Diabetes Control and Complications Trial [DCCT]) and of observational follow-up studies (UKPDS at 10 years, Epidemiology of Diabetes Interventions and Complications [EDIC]).

1.1. Facts established before 2008

1.1.1. The Diabetes Control and Complications Trial (DCCT)

The DCCT was the first major study carried out in diabetology in type 1 diabetics (T1D) (Fig. 1) [1]. It took place from 1983 to 1993 and included 1441 T1D aged 13 to 39 years, in whom the average course of diabetes was 6 ± 4 years. The patients taking part in the study were randomized into two groups: intensive treatment (three insulin injections or a subcutaneous insulin pump) with a fasting glycaemia target between 0.7 g/L and 1.2 g/L and standard treatment (one or two insulin injections), the objective being to avoid episodes of hypoglycaemia and hyperglycaemia. The average duration of follow-up in that multicentric study was 6.5 years. The HbA1c level differed between the two groups at the end of the study: it averaged 7.4% in the intensive group as compared with 9.1% in the standard treatment group. Intensive insulin treatment reduced the risk of developing retinopathy by 76%, that of finding that retinopathy had progressed by 54% and that of observing the occurrence of diabetic nephropathy by 39% and of a neuropathy by 60%. That study made it possible to conclude that intensive insulin treatment in T1D delayed and slowed the progression of microangiopathic complications. On the other hand, such intensive treatment did not lead to any statistically significant drop in the risk of macroangiopathic complications. The DCCT study was prolonged between 1993 and 2004 in the form of observational follow-up without any intervention: this was the EDIC study (Fig. 1) [2]. In practice, in that study, 1394 T1D from the DCCT’s initial cohort (i.e. 97%) were followed up for 11 additional years. The T1D from the standard treatment group and intensive treatment group then received optimal care, the consequence being identical HbA1c findings in both groups at the end of follow-up (7.8 ± 1.3% in the former standard treatment group versus 7.9 ± 1.3% in the former intensive treatment group). In spite of this, in the group formerly treated intensively macroangiopathic complications were reduced by 42% as regards cardiovascular events and by 57% as regards the occurrence of myocardial infarction (MI), cerebral vascular accidents (CVA) or cardiovascular mortality. The long-term (at 11 years) beneficial effect of intensive insulin treatment on macrovascular complications was demonstrated in the T1D of the DCCT. At the same time, during that DCCT/EDIC study, the benefit was maintained in the case of microvascular complications (retinopathy and nephrophathy) 4 years after intensive insulin treatment [3]. For the first time, the concept of glycaemic memory makes its appearance in the history of diabetology.

1.1.2. The United Kingdom Prospective Diabetes Study (UKPDS)

The UKPDS was the second major study taking place between 1977 and 1998, with a cohort of 4209 T2D aged between 48 and 60 years (Fig. 1, Table 1) [4,5]. The purpose of this randomized study was to compare the effects of intensive treatment of diabetes with hypoglycaemic sulfamides, insulin or metformin (in overweight subjects) with standard treatment as regards the risk of micro- and macrovascular complications in recently diagnosed T2D. At 10.5 years of follow-up, HbA1c was 7% in the intensive treatment group (sulfamides/insulin) and 7.9% in the conventional treatment group ($p < 0.0001$). This study evidenced a significant 12% reduction in diabetes-linked events and a 25% reduction in microvascular complications in the intensive treatment group. On the other hand, macrovascular complications were not significantly reduced, in spite of a trend towards reduction of MI in the intensive group ($−16\%, p = 0.052$). An additional analysis carried out within the framework of the UKPDS showed that a 1% reduction in HbA1c allowed a 37% reduction in microvascular complications, a 14% reduction in MI and a 12% reduction in CVA. This fact
suggests that any decrease in HbA1c is beneficial in terms of reduction of diabetes-linked complications [6]. At the end of the UKPDS in 1997, the T2D and their physicians were left free as to their course of treatment and the patients were included in a 10-year observational study, with an annual evaluation at the initial investigational centre (Fig. 1). The results at 5 years evidenced an 11% reduction in mortality (p = 0.03) and a 14% reduction in MI (p = 0.04). These data prove that intensive treatment of T2D has beneficial effects on the risk of MI at 5 years, whatever the subsequent control and course. Therefore, a certain “memory” of the initial good glycaemic control exists.

In summary, these first two major studies demonstrated (Fig. 1):

- the rapid effectiveness of intensive treatment as regards microvascular complications in T1D and T2D;
- the long-term beneficial effect of such intensive treatment as regards the occurrence of micro- and macrovascular complications;
- the presence of a glycaemic memory.

However, doubts were raised early in 2008, when the ACCORD study was stopped, regarding the value and safety of intensifying the treatment of diabetes with a view to reducing cardiovascular events and mortality.

### 1.2. Morbi-mortality studies in 2008

#### 1.2.1. The Action to Control Cardiovascular risk in Diabetes study (ACCORD Study Group)

The purpose of the ACCORD study was to determine, in T2D, whether a level of HbA1c below 6% would allow a decrease in cardiovascular events as compared with a treatment strategy whose HbA1c objective was between 7 and 7.9% (Table 1) [7]. This randomized study was conducted in the United States in a cohort of 10,251 T2D with a high cardiovascular risk, with a mean age of 62.2 years and a diabetes duration of 10 years. HbA1c was initially 8.1% in both groups. The study had been planned to last 5 years. All treatment combinations could be used and insulin could be prescribed if the HbA1c target was not reached. Only the treatment objective in terms of HbA1c differed between the intensive group and the standard group.

In February of 2008, an early interruption, 17 months prior to the end of the study, was decided on account of excess mortality in the intensive treatment group, with a relative risk of 1.22 (1.01–1.46; p = 0.04), i.e. a 22% increase in mortality. Cardiovascular mortality accounted for over 50% of the overall mortality. The cardiovascular mortality was 2.6% in the intensive group as compared with 1.8% in the standard group (p = 0.02). Half the cases of cardiovascular mortality were secondary to presumed or unexplained cardiovascular events. It should be explained that the mortality rate observed was very low as compared with previous studies, suggesting that the patients were

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**Table 1**

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<th>ADVANCE</th>
<th>VADT</th>
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especially well treated as regards the other risk factors. The primary endpoint including MI, CVA and cardiovascular mortality in this study did not, however, differ between the two groups. A 24% reduction in non-fatal MI in the intensive group was even noted \((p=0.004)\). HbA1c averaged 6.4% in the intensive group, as compared with 7.5% in the standard group. The frequency of hypoglycaemic episodes was distinctly higher in the intensive group as compared with the standard group: 10.5% of these iatrogenic complications required medical assistance, as compared with 3.5% in the standard group \((p<0.001)\).

Thus, in view of these results, uncertainties appeared as to the value of normalising HbA1c. Doubtless, the UKPDS and DCCT studies had demonstrated a benefit as regards microvascular complications, but the ACCORD study raised doubts by evidencing an increase in mortality in the event of intensive treatment.

However, other studies published or presented in 2008 nuance these negative conclusions and provide further data concerning the value of intensifying glycaemic control.

1.2.2. Observational and follow-up studies with no intervention: DCCT/EDIC in T1D and UKPDS in T2D

The results of the EDIC study (1993 to 2008) presented at the EASD congress in Rome in September 2008, which concerned 92% of the T1D of the initial cohort of the DCCT, evidence the persistence of a long-term beneficial effect of the intensive insulin treatment followed during the 6.5 years of the initial period of the study \([8]\). The cumulative incidence of cardiovascular events is in fact distinctly lower in the group initially treated intensively, even though glycaemic control subsequently became identical. This confirms the presence of a glycaemic memory as regards cardiovascular events.

The data of the observational study 10 years after the end of the UKPDS, carried out on 78% of the initial cohort, also evidences the presence of glycaemic memory in T2D (Table 1)\([9]\). Indeed, diabetes-linked events were reduced by 9%, microvascular complications by 24% and mortality by 13% in the initial intensive treatment group (sulfamide–insulin) in spite of the fact that HbA1c levels had become similar and close to 7.8% in both groups. Macrovascular complications and MI were also significantly reduced by 15% in the former intensive group (sulfamide–insulin) and by 33% in the former intensive group (metformin). These facts therefore demonstrate the long-term value of strict and early glycaemic control in T2D.

1.2.3. The Veterans Affairs Diabetes Trial (VADT) study

The VADT study, presented at the ADA congress in June 2008 and at the EASD congress in September 2008, was carried out with 1791 American army veterans whose type 2 diabetes was out of control. The average HbA1c upon inclusion in the study was 9.5%, age was 60 years and the duration of diabetes averaged 11.5 years (Table 1). The aim of this randomized prospective study was to evaluate the effect of intensive treatment (HbA1c below 7%) in T2D with a high cardiovascular risk, inadequately controlled in spite of maximum oral therapy or of insulin therapy, while the management of the lipid parameters and arterial blood pressure was intensified in both groups.

The duration of this study was 6 years. At the end of the study, HbA1c was 6.9% in the intensive group as compared with 8.4% in the standard group. The main criterion of judgment in this study was based on the recording of major cardiovascular events, including cardiovascular mortality, MI, CVA, severe cardiac insufficiency and indications for cardiac or peripheral arterial revascularisation. In this study, those events proved less frequent in the intensive group (25.9% as compared with 29.3%), but the difference was not significant. It must be stressed that in both groups the incidence of cardiovascular events was two to three times lower than predicted. Neither does the VADT evidence any difference as regards mortality from all causes or cardiovascular mortality. Finally, no significant effect on microvascular complications was noted, aside from a trend towards a decrease in the progress of evidenced retinopathy and from a reduction of progression from normal albuminuria to micro- or macroalbuminuria (38.6% in the standard group and 31.6% in the intensive group, \(p=0.02)\). A supplementary analysis evidenced a relationship between cardiovascular events and the duration of diabetes in the intensive treatment group (Fig. 2). When the duration of diabetes was less than 15 years, intensive treatment had a beneficial effect on cardiovascular events. On the other hand, intensive treatment proved rather deleterious if the diabetes was over 15 years old. As in the ACCORD studies, hypoglycaemic episodes were more frequent in the intensive group as compared with the standard group. The main predictive factor of the main judgment criterion was the occurrence of episodes of hypoglycaemia. Finally, in that same study, hypoglycaemic episodes increased the risk of major cardiovascular events \((p=0.02)\) and cardiovascular mortality \((p=0.008)\).

1.2.4. The Action in Diabetes and Vascular disease, Perindopril and Indapamide Controlled Evaluation (ADVANCE) study

The ADVANCE study concerns T2D randomized into four groups with a twofold aim, i.e. control of blood pressure and glycaemic control. The results of the blood pressure arm,
which were published in 2007, showed that a set combination of perindopril–indapamide followed for 4.3 years reduced diabetes-linked complications by 9%, cardiovascular mortality by 18%, mortality from all causes by 14% and nephropathy by 21% [10].

The aim of the glycaemic arm was to evaluate the effect of intensive treatment of diabetes on micro- and macrovascular complications (Table 1) [11]. Thus, 11,240 T2D patients with a high cardiovascular risk were randomized into two groups: either an intensive treatment group receiving modified-release gliclazide with an HbA1c target below 6.5%, or the usual management of the patients’ diabetes. The average age of the participants was 66 years and their diabetes duration averaged 8 years. The initial HbA1c level, which was 7.5%, fell, after a median follow-up time of 5 years, to 6.5% in the intensive treatment group as compared with 7.3% in the standard group. The occurrence of macro- and microangiopathic events, which was the main judgment criterion, was decreased by 10% in the intensive group. On the other hand, although a favourable trend existed, no significant reduction was noted as regards macrovascular complications, whether as concerns deaths from cardiovascular causes or coronary heart disease or cerebral vascular disease. The beneficial effect noted on the main judgment criterion was secondary to the reduction in microvascular complications (−14%; IC 95%: 3 to 23%; p = 0.015) and was especially related to the decrease in the incidence of nephropathy (4.1% versus 5.2%, relative risk = 0.79, p = 0.006). Finally, it must be stressed that, in contrast with the ACCORD study, mortality from all causes was not increased in the intensive group.

1.3. Why the excess mortality noted in the ACCORD study?

Several explanations were put forward by various authors [12,13].

The decline in HbA1c was very rapid in the intensive group in the ACCORD study, i.e. 1.4% over a period of 4 months as compared with 0.6% in the standard group.

Severe hypoglycaemic episodes were very frequent in the intensive group.

Weight gain was 3.5 kg in the intensive group as compared with 0.4 kg in the standard group. Thus, a weight gain of over 10 kg was noted in 28% of the T2D belonging to the intensive group, whereas the initial body mass index already averaged 32 kg/m².

Anti-hypertensive treatments were different from group to group, since the percentage of patients receiving ACE inhibitors was smaller in the intensive group than in the standard group (69.7% versus 71.9%, p = 0.04).

Finally, at the end of the ACCORD study, 92% of the patients in the intensive group were receiving glitazones and 77% were receiving insulin. Although the sub-group analysis did not evidence the responsibility of any treatment in the excess mortality, it appears to be at least possible that the drug associations, the maximum doses used and the frequent changes in treatment had a deleterious effect.

Thus, it appears from a reading of the in-the-raw conclusions of these studies that an intensification of the treatment of diabetes significantly reduces microvascular complications in the short run (UKPDS, ADVANCE), but remains uncertain as regards macrovascular complications (ADVANCE, ACCORD, VADT) and may even increase mortality from all causes under certain circumstances (ACCORD) (Table 1).

1.4. Major lessons to be drawn

The distance necessary for thought now allows us to derive a certain number of teachings from the studies published in 2008.

1.4.1. Glycaemic memory

The existence of a glycaemic memory has in fact been established in T1D thanks to the EDIC study and in T2D thanks to the observational and follow-up study carried on for 10 years after the end of the UKPDS [2,9]. In both studies, the incidence of diabetes-linked events proved to be lower in the intensive group and remained so at a distance from the period during which control was optimal. The incidence of microvascular and macrovascular complications is thus strongly linked to past glycaemic control. Lost time cannot be regained, which implies that diabetics must be cared for early on.

1.4.2. The absence of blood pressure memory

Hypertension is a cardiovascular risk factor frequently associated with diabetes. The UKPDS study demonstrated that “strict” control of arterial blood pressure (ABP) (SAP < 150 mmHg and DAP < 85 mmHg) in T2D as compared with less ambitious control (SAP < 180 mmHg and DAP < 105 mmHg) for a period of 8.5 years allowed a 24% reduction in diabetes-linked events, a 32% reduction in mortality, a 44% reduction in CVA and a 37% reduction in microangiopathic complications [14]. The observational study 10 years after the end of the UKPDS shows that after 1 year the ABP became identical in both groups. At the end of this long period of observation, diabetes-linked events were identical in both populations [15]. The former group strictly treated for arterial blood pressure therefore lost its initial benefit. It can thus be shown that, by contrast with what was observed in the case of glycaemia, current control of ABP is as important as past control and that there is no blood pressure heritage. Blood pressure objectives must therefore be permanently maintained in order to avoid losing the benefit of the normalisation of ABP.

1.4.3. Early and intensive control

The UKPDS is the only study demonstrating a long-term benefit of strict glycaemic control as regards micro- and macroangiopathic complications (Table 1) [4]. This study was carried out in T2D who were relatively young, who had been diagnosed recently and who were treated intensively and early, which sets it off from the ACCORD or ADVANCE studies [7,11]. The VADT study confirmed the importance of the length of the course of the diabetes (Fig. 2). Indeed, in the post-hoc analysis, cardiovascular events were found to be reduced in the
intensive treatment group only when the course of the disease was short upon inclusion in the study.

1.4.4. Not too rapid intensive treatment

In the ACCORD study, in which excess mortality was observed, the T2D belonging to the intensive group experienced a rapid fall in their glycosylated hemoglobin, i.e. 1.4% in 4 months [7]. It is probably preferable to secure a progressive reduction in HbA1C, as in the ADVANCE study, where HbA1c fell by only 0.5% in 6 months [11]. The deleterious effect of a very rapid rate of decline in glycaemia is known in the case of retinopathy in T1D. A similar phenomenon might exist at the level of cardiac microcirculation, as suggested by the results of the ACCORD study.

1.4.5. Avoid hypoglycaemic episodes

In all the studies whose aim is glycaemic control, the frequency of hypoglycaemic episodes is higher in the diabetics belonging to the intensive groups. Nevertheless, the number of hypoglycaemic episodes was distinctly higher in the ACCORD study [7]. Finally, the VADT study showed that hypoglycaemic episodes increased the risk of major cardiovascular events ($p=0.002$) and cardiovascular mortality ($p<0.008$). Thus, the deleterious effect of severe and reiterated hypoglycaemic episodes is in fact highlighted by those two studies.

1.4.6. Controlling other cardiovascular risk factors

A reduction in blood pressure reduced micro- and macrovascular complications in the UKPDS and ADVANCE studies [10,14]. In the latter study, an analysis of the results of the doubly intensive sub-group relating both to glycaemia and to arterial blood pressure indicates that this strategy reduces overall mortality by one-fifth, cardiovascular mortality by one-quarter and nephropathy by one-third. The effects are therefore additive and there is no interaction between them. These observations confirm the value of acting both on glycaemia and on arterial pressure in order to reduce cardiovascular morbi-mortality.

The STENO2 study perfectly illustrates the value of optimal control of the various cardiovascular risk factors [16]. This study was carried out in 160 patients with type 2 diabetes and persistent microalbuminuria. The patients, whose average age was 55 years, were randomized openly into two groups: either intensive treatment for ABP (SAP<140 mmHg and DAP<85 mmHg), glycaemic control (HbA1c<6.5%), lipid balance (total cholesterol <1.9 g/L and triglycerides <1.5 g/L) and discontinuation of smoking, or standard treatment (SAP<160 mmHg and DAP<95 mmHg; HbA1c<7.5%; total cholesterol <2.5 g/L and triglycerides <1.95 g/L). After 7.8 years of follow-up, a 53% reduction in macroangiopathic complications, a 58% reduction in retinopathy and a 61% reduction in nephropathy were observed in the intensive group in spite of a relatively poor HbA1c level, i.e. 7.9%. The observational study carried out on the 130 surviving T2D, whose duration was 5.5 years, confirmed the beneficial effect of intensive treatment, with a 57% reduction in cardiovascular events and a 59% reduction of the composite criterion (cardiovascular mortality, MI, CVA, revascularisation, amputation) [17].

A reading of these results explains the relative absence of effect of the intensive treatment of glycaemia on macrovascular complications in the ACCORD and VADT studies. Indeed, the control of the other risk factors was excellent, since ABP was below 130/80 mmHg and since 90% of the patients were receiving antihypertensive treatment including an ACE inhibitor in 70% of cases. Finally, treatment with a platelet aggregation inhibitor was prescribed in 70 to 90% of patients, their LDL cholesterol level averaged below 1 g/L and nearly 90%...
were treated with statins. Thanks to this optimal control, cardiovascular events were less frequent than had been predicted.

1.4.7. The HbA1c target

The HbA1c target cannot be below 6% in view of the results of the ACCORD study. Thus, an HbA1c target below 7% is generally proposed in most international recommendations [18]. However, the duration of diabetes may be a parameter to be taken into account. Thus, the UKPDS study has definitely established that intensive treatment begun immediately upon discovery of the diabetes reduced micro- and macrovascular complications. On the other hand, when the duration of diabetes is over 10 years, as in the ADVANCE study, such intensive treatment reduces microvascular complications but has no effect on macrovascular complications.

The beneficial effects of intensive treatment are observed only at a distance from the institution of such a strategy, as in the UKPDS and DCCT studies. This fact may explain that in the ADVANCE and VADT studies the results regarding the incidence of macroangiopathic complications evidence only a favourable but non-significant trend.

When all is said and done, the HbA1c target must therefore be discussed individually depending on the history of the diabetes, on the complications and on the cardiovascular risk factors (Fig. 3).

2. Conclusion

Finally, 2008 has strengthened the convictions of diabetologists by confirming, through the results of the major studies, the value of optimal control of glycaemia and of other cardiovascular risk factors. The HbA1c target must take into account the age of the patient, the duration of the diabetes, the associated risk factors and the previous control of the patient (Fig. 3). The notion of glycaemic memory is in favour of the early institution of an intensive strategy, while avoiding hypoglycaemic episodes and an overly rapid normalisation of glycaemic control. When the diabetic patient has reached the stage of micro- or macrovascular complications, strictness regarding the treatment of other cardiovascular risk factors must be reinforced, whereas the glycaemic target must be individualised by balancing the advantages of treatment against the risks.

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References