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Review

Use of insulin in type 2 diabetes: What we learned from recent clinical trials on the benefits of early insulin initiation

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Abstract

The majority of people with type 2 diabetes mellitus (T2DM) require insulin therapy to maintain HbA_{1c} levels < 7% during the first decade of diagnosis. Large prospective trials investigating the cardiovascular (CV) benefits of intensive glycaemic control have produced inconsistent results; however, meta-analyses have suggested that intensive glycaemic control provides both micro- and macrovascular benefits. The ORIGIN study investigated the impact of basal insulin glargine therapy targeting ≤ 5.3 mmol/L for fasting plasma glucose compared with standard care on CV outcomes in people with pre- or early diabetes, and demonstrated a neutral effect on CV outcomes with long-term use of insulin glargine early in the course of diabetes, with a low rate of severe hypoglycaemia and modest weight gain. The EARLY, GLORY and EASIE studies also demonstrated that insulin use earlier in the treatment pathway led to improved glycaemic control, reduced weight gain and fewer hypoglycaemic episodes than when insulin was added later in the course of disease. The beneficial effect of early transient intensive insulin therapy (TIIT) at diagnosis has been demonstrated in a number of trials; it rapidly limits the damage caused by gluco- and lipotoxicity, improving residual β-cell function and potentially slowing disease progression. The evidence suggests that people newly diagnosed with T2DM and HbA_{1c} > 9% should be given early TIIT to achieve normoglycaemia within weeks, after which standard care should then be adopted. Insulin use earlier in the treatment pathway should be considered, as it reduces the risk of hypoglycaemia as well as allows β-cell rest, which can help preserve β-cell function.

Keywords: Type 2 diabetes mellitus; Insulin; Early medical intervention; Residual β-cell function; Transient intensive insulin therapy

1. Introduction

Since the development of insulin therapy in the early 20th century, insulin has been a key component of diabetes management, with the majority of people with type 2 diabetes mellitus (T2DM) requiring insulin therapy to maintain HbA_{1c} levels < 7% within nine years of diagnosis [1,2]. This glycaemic target (HbA_{1c} < 7%) is recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) in their consensus statement on the management of hyperglycaemia, which also emphasizes the need for a patient-centred approach to diabetes management [3]. The management strategy outlined by these guidelines reduces the incidence of microvascular disease, but does not reduce the risk of macrovascular disease to the same extent [4,5]. Therefore, at present a key unmet need for patients with T2DM is the prevention of cardiovascular (CV) disease, the major cause of mortality in those with T2DM, with the risk of heart disease-related death being two to four times higher in people with diabetes [6]. Indeed, T2DM is a CV risk factor comparable to previous myocardial infarction (MI) in people without diabetes aged 30 years or older [7].

T2DM develops over a number of years, with changes in glucose levels, insulin sensitivity and insulin secretion happening 3–6 years before diagnosis and a deficit in β-cell capacity up to 12 years before diagnosis [8–10]. Initial insulin resistance is accompanied by a deficit in early-phase insulin secretion as a result of loss of β-cell mass [11–14]. This results in mild hyperglycaemia, which is termed 'impaired glucose tolerance' (IGT) [15], and defined as fasting plasma glucose (FPG) < 7.0 mmol/L and postprandial plasma glucose (PPG) 7.8–11.1 mmol/L following a 75-g oral glucose challenge [15]. When people are

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identified as having IGT, they can be treated with diet, exercise and drugs to reduce their mild hyperglycaemia, which reduces conversion to T2DM [16]. As glucose levels rise, glucotoxicity further damages β cells, while increased free fatty acid levels during IGT also damage β cells (lipotoxicity) [17]. At some point, gluco- and lipotoxicity will damage β cells to the extent that the production of insulin becomes inadequate, resulting in a relatively rapid rise of blood glucose levels and the development of T2DM [11]. Nevertheless, endogenous insulin may still be produced by the remaining β-cells, and blood glucose levels may be stabilized at much higher levels, with the remaining β-cell mass becoming damaged more slowly [11]. This slow damage results in the progressive nature of T2DM, and studies have suggested that achieving glycaemic targets early in the disease course can improve outcomes, including CV outcomes, owing to less damage from hyperglycaemia [4,5].

The present review is an overview of recent large clinical trials, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [18], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE), [19] the Veterans Affairs Diabetes Trial (VADT) [20,21] and the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study, as well as other smaller trials (including EASIE, EARLY and GLORY). Here the particular focus is on the earlier use of insulin as first-line treatment and as part of early transient intensive insulin therapy (TIIT) for the treatment of T2DM. The potential impact of these studies on clinical practice to improve the management of the disease is also discussed.

2. Impact of glycaemic control on CV risk factors

Diabetes is an independent risk factor for CV disease, and a positive correlation has been demonstrated between the risk of CV disease and level of glycaemic control [7,22,23]. Several large prospective trials – the Diabetes Intervention Study (DIS) [24], United Kingdom Prospective Diabetes Study (UKPDS) [4,25], ACCORD [18], ADVANCE [19] and VADT [20,21] – have investigated whether intensive glycaemic control can help to reduce CV risk in people with T2DM.

Even though the results of the individual trials were inconsistent, a meta-analysis of UKPDS, ACCORD, ADVANCE and VADT by Turnbull et al. [26] found that allocation to more-intensive glycaemic control reduced the risk of major CV events by 9% compared with less-intensive glycaemic control (Fig. 1). This reduction in the risk of major CV events was primarily the result of a 15% reduced risk for MI [26]. There was no difference in mortality between the more and less intensively treated groups [26]. Findings from meta-analyses of other trials where differences in glycaemic control have been observed also concluded that intensive glycaemic control provides macrovascular benefits [27–29]. It is, therefore, essential to determine which people are likely to experience the best outcomes from intensive control [26–29].

A substudy of the UKPDS investigated the β-cell function of those treated with either sulphonylurea, diet or metformin during the UKPDS [8]. It found that even though β-cell function continued to decline despite intervention – with similar declines seen with diet and sulphonylurea treatment after one year – an increase in β-cell function was seen with intensive therapy with sulphonylurea during the first year (Fig. 2) [8,30]. This meant that, after 6 years of treatment, there was a greater degree of β-cell function remaining in the intensive-treatment group [8]. This greater degree of β-cell function indicates that more endogenous insulin is being produced, which helps to limit glycaemic excursions, thereby reducing damage from hyperglycaemia and potentially reducing the risk of hypoglycaemia as well.

3. The ORIGIN study and impact of early insulin treatment

The early use of therapy targeting FPG $\leq$ 5.3 mmol/L, to reduce the risk of conversion from IGT to T2DM as well as to lower the risk of longer-term complications, was investigated in the ORIGIN study [31]. This study investigated the impact of basal insulin glargine therapy targeting FPG $\leq$ 5.3 mmol/L compared with standard care on CV outcomes in 12,537 people with CV risk factors and impaired fasting glucose (IFG), IGT or T2DM [31]. Compared with the ACCORD, ADVANCE and VADT, the ORIGIN study enrolled people with a shorter mean duration of T2DM and lower mean baseline HbA_{1c} levels [31]. The early use of basal insulin maintained HbA_{1c} at < 6.5% over the 6.2 years of the trial, which was achieved with a stable dose of insulin glargine, while adherence remained high throughout the study [31]. The dose of insulin glargine remained low throughout the study, with the median dose increasing from 0.31 U/kg at year 1 to 0.40 U/kg at year 6 [31]. During the study, the rate of CV outcomes was similar with both insulin therapy and standard care [31].

At the start of the ORIGIN study, 11.7% of people in the insulin glargine group and 11.4% of those in the standard-care group had either IGT or IFG [31]. Such people who were receiving insulin glargine were 20% less likely to develop T2DM after 6.2 years than those receiving standard care [31]. One possible explanation for this reduced risk of progression is that the group receiving insulin glargine had lower HbA_{1c} levels throughout the trial; thus demonstrating the importance of optimal glycaemic control early in the course of disease [31]. In addition, people receiving insulin glargine typically required fewer additional antidiabetic agents at the end of the study than those receiving standard care, with 35.1% requiring no oral antidiabetic drugs (OADs) compared with 19.2% among those receiving standard care [31]. Overall, the ORIGIN study demonstrated that long-term use of insulin glargine is safe, with a low risk of severe hypoglycaemia and only moderate weight gain, as well as a reduced need for additional OADs or complex insulin regimens. The relationship between frequency of episodes of hypoglycaemia and CV outcomes is shown in Table 1 [32].

The Glucose Reduction and Atherosclerosis Continuing Evaluation (GRACE) [33] substudy of ORIGIN evaluated the impact of insulin glargine treatment during ORIGIN on carotid intima-media thickness (CIMT) [33]. Intima-media thickness is a measurement of the innermost two layers of the arterial wall, and the CIMT is a surrogate endpoint for atherosclerosis

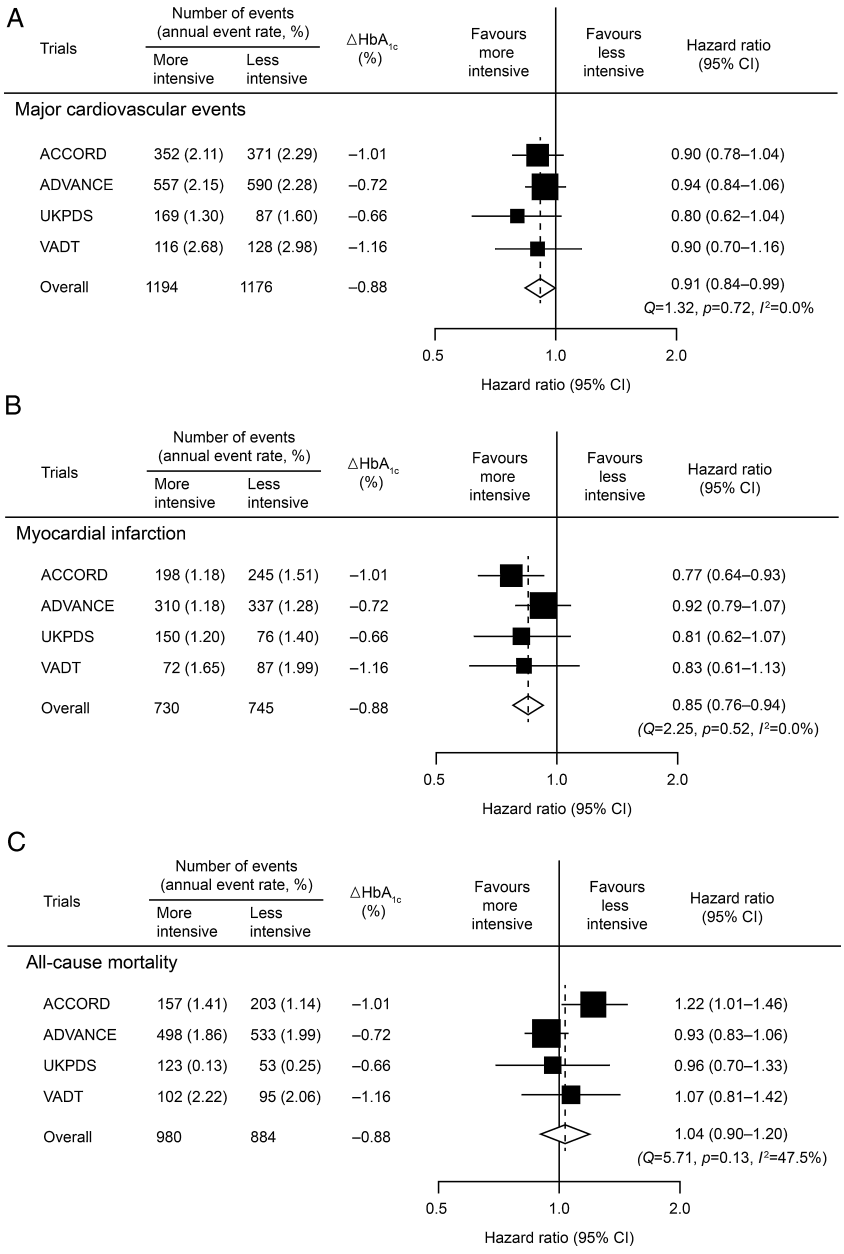

Fig. 1. Probabilities of (A) major cardiovascular events, (B) myocardial infarction and (C) all-cause mortality with intensive glucose-lowering *vs.* standard treatment [26]. The diamond incorporates the point estimate (vertical dashed line) and the 95% confidence interval (CI) of the overall effect for each outcome. Hazard ratios (HR) are provided for more-intensive *vs.* less-intensive glucose control. ΔHbA_{1c} = mean HbA_{1c} of more-intensive group minus mean HbA_{1c} of less-intensive group. UKPDS follow-up truncated at 5 years from randomization.

and associated CV disease [34,35]. The ORIGIN–GRACE substudy included 1184 people who underwent carotid ultrasound at baseline and then yearly until 1–1.3 years prior to the final ORIGIN study visit [33]. Over a median duration of 4.9 years, a statistically non-significant reduction in CIMT progression was observed with insulin glargine compared with standard care [33]. The authors highlight that this modest decrease in carotid atherosclerosis is consistent with what was observed in the Epidemiology of Diabetes Interventions and Complications (EDIC) study/Diabetes Control and Complications Trial (DCCT), where benefits were observed after long-term follow-up [33]. However, further follow-up is needed to determine whether the decrease in CIMT observed in the GRACE substudy persists and whether this difference leads to a clinically significant impact on CV outcomes. Monnier et al. [36] examined the relationship between insulin and atherosclerosis, and concluded that early insulin initiation may have a protective function. However, while further study is needed to determine the relationship between insulin and atherosclerosis, the authors acknowledge that smaller doses of insulin earlier on in the disease course are preferable to higher doses later on.

Overall, the ORIGIN study demonstrated that, in people with dysglycaemia and CV risk factors, insulin is safe and effective for controlling blood glucose levels, even though no CV benefits were observed. This might have been because long-term follow-up is required to observe macrovascular benefits; it is hoped

Table 1
Adjusted propensity scores for the relationship between frequency of hypoglycaemic episodes and cardiovascular (CV) outcomes.

	Composite	Death	CV death	Arrhythmia death
Non-severe hypoglycaemia				
1 or more episodes	0.51 (0.45–0.57)[a]	0.64 (0.57–0.71)[a]	0.57 (0.49–0.66)[a]	0.57 (0.47–0.71)[a]
2 or more episodes	0.44 (0.38–0.51)[a]	0.62 (0.54–0.71)[a]	0.54 (0.45–0.65)[a]	0.54 (0.41–0.69)[a]
3 or more episodes	0.47 (0.40–0.56)[a]	0.66 (0.57–0.78)[a]	0.60 (0.49–0.74)[a]	0.61 (0.46–0.81)[a]
4 or more episodes	0.48 (0.39–0.58)[a]	0.66 (0.55–0.79)[a]	0.63 (0.50–0.80)[a]	0.63 (0.46–0.87)[c]
5 or more episodes	0.50 (0.40–0.62)[a]	0.64 (0.53–0.79)[a]	0.67 (0.52–0.86)[c]	0.72 (0.51–1.01)
Severe hypoglycaemia				
1 or more episodes	0.79 (0.62–1.00)[b]	0.93 (0.74–1.16)	0.89 (0.67–1.19)	0.92 (0.62–1.37)
2 or more episodes	0.77 (0.44–1.33)	1.13 (0.74–1.75)	1.05 (0.59–1.85)	1.56 (0.80–3.03)
3 or more episodes	1.16 (0.48–2.79)	1.05 (0.44–2.54)	1.37 (0.51–3.68)	2.65 (0.99–7.12)
4 or more episodes	1.24 (0.31–4.98)	1.96 (0.63–6.08)	2.08 (0.52–8.36)	3.83 (0.95–15.4)
5 or more episodes	1.30 (0.18–9.21)	2.88 (0.72–11.5)	2.21 (0.31–15.8)	3.94 (0.55–28.1)

[a] $P < 0.001$.
[b] $P < 0.05$.
[c] $P < 0.01$

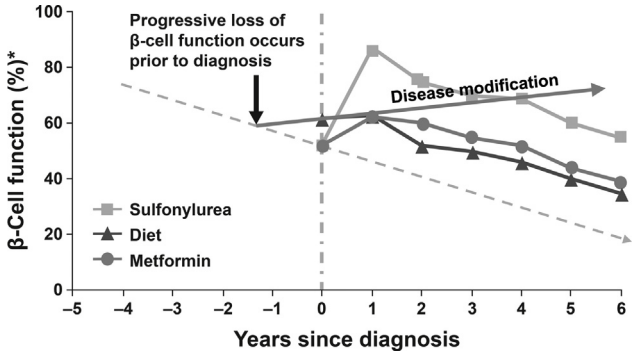

Fig. 2. Impact of intensive therapy with sulphonylurea compared with conventional therapy using metformin or diet on β-cell function, as measured by homoeostasis model assessment (HOMA) in the United Kingdom Prospective Diabetes Study (UKPDS) [8,30]. * β-cell function measured by HOMA.

that the ORIGIN and Legacy Effects (ORIGINALE) study (a long-term follow-up of the ORIGIN trial) will provide further information on this [37]. It is, nevertheless, possible that early insulin treatment provides non-CV benefits, including preservation of β-cell function with lower doses of insulin than would be required later in the disease course, resulting in a lower risk of hypoglycaemia and only moderate weight gain. This should enable longer-term treatment that is less complicated, safer and cheaper. These aspects of early insulin treatment have already been investigated in a number of prospective clinical trials.

4. Studies investigating early insulin for non-cardiovascular benefits

The EARLY study investigated the use of basal insulin as second-line therapy following failure of metformin in 1438 people with T2DM [38,39], and demonstrated that early basal insulin therapy was safe and effective, with HbA_{1c} levels decreasing from 8.69% to 7.39% and a low rate of hypoglycaemia over 24 weeks. Subgroup analyses found that people with lower HbA_{1c} levels at baseline, lower body mass index (BMI) and/or shorter duration of T2DM were more likely to achieve glycaemic targets ($HbA_{1c} < 7\%$) [39]. The GLORY study investigated the use of either metformin or insulin glargine as first-line treatment in 75 people with drug-naïve T2DM over 36 weeks [40]. Insulin glargine treatment was associated with improvements in FPG, overall interstitial glucose load and β-cell function, with no increased risk of hypoglycaemia compared with metformin treatment [40]. However, improvements in PPG and endothelial function were similar with insulin glargine compared with metformin [40]. This suggests that if β-cell function is of interest, then insulin glargine might be the best first-line treatment; however, in terms of overall effects, including microvascular effects, this trial failed to provide enough evidence to suggest changes in clinical practice.

The evaluation of insulin glargine versus sitagliptin in insulin-naive patients (EASIE) trial compared 24 weeks of treatment with either insulin glargine or sitagliptin as add-on treatment in 515 people with T2DM who had not achieved glycaemic targets with metformin monotherapy [41]. Insulin glargine reduced HbA_{1c} to a greater extent than sitagliptin (–1.72% *vs.*–1.13%, respectively) and with a low rate of hypoglycaemia; thereby demonstrating that insulin glargine, as a second-line therapy following metformin failure, may be a good and effective clinical option [41]. Alvarsson et al. [42] compared early use of either insulin or sulphonylurea in 49 people with drug-naïve T2DM over six years and found that good glycaemic control was maintained in both treatment groups; however, β-cell function was preserved to a greater extent in those treated with early insulin therapy [42]. The authors suggested that the beneficial effect of insulin was a result of β-cell rest [42]. This occurs when the provision of exogenous insulin reduces the amount of endogenous insulin the body requires, thus decreasing β-cell stress and reducing the likelihood that they will undergo apoptosis [43]. The use of insulin rather than insulin secretagogues is also likely to provide greater β-cell rest as the provision of exogenous insulin reduces the amount of insulin these cells need to secrete; whereas, the use of sulphonylureas encourages endogenous insulin secretion, further stressing β cells.

A meta-analysis of prospective clinical trials investigating the addition of insulin glargine to either metformin or sulphonylurea, or both, in people with uncontrolled T2DM was performed by Fonseca et al. [44] and included 2171 participants from 11 trials. This meta-analysis found that the addition of insulin to

metformin monotherapy was more effective than adding it to therapy with sulphonylurea, resulting in less weight gain and greater mean HbA_{1c} reduction [44]. Overall, hypoglycaemia rates were low with the addition of insulin glargine, with higher rates of hypoglycaemia when insulin was used in combination with sulphonylurea; thus demonstrating the efficacy and safety of adding insulin therapy as a second-line therapy after metformin monotherapy [44].

The BEGIN Once Long study examined the efficacy and safety of ultra-long-acting insulin degludec compared with insulin glargine in 1030 insulin-naïve people with T2DM uncontrolled by OADs [45]. People were randomized 3:1 to receive insulin degludec and insulin glargine daily with metformin. Reductions in HbA_{1c} were similar with insulin glargine and insulin degludec (1.06% *vs.* 1.19%, respectively) [45]. The study concluded that insulin degludec and insulin glargine administered once daily in combination with OADs provide good and similar glycaemic control, with lower rates of nocturnal hypoglycaemia observed with insulin degludec [45]. However, some potential CV safety concerns are associated with the use of insulin degludec [46]. Findings from a meta-analysis of phase-III trials indicate that insulin degludec may increase the risk of CV death, non-fatal MI, non-fatal stroke and unstable angina by 30% compared with study comparators [46]. As a consequence, the CV safety of insulin degludec is currently under review by the US Food and Drug Administration [46].

Meneghini et al. [47] investigated the use of insulin detemir and insulin glargine as an add-on to metformin in a randomized trial of 457 insulin-naïve patients with T2DM over 26 weeks. Mean reductions in HbA_{1c} were similar for insulin detemir and insulin glargine (0.48% and 0.74%, respectively). Thus, although glycaemic control was achieved with both insulins, the proportion of patients at the study endpoint achieving $HbA_{1c} \leq 7\%$ was higher with insulin glargine than with insulin detemir (53% *vs.* 38%, respectively) [47].

These studies all demonstrate that the use of insulin earlier in the treatment paradigm as either a first- or second-line therapy is effective and well tolerated; however, they do not indicate that clinical practice should be modified to include insulin as the first-line therapy of choice for T2DM.

5. Early transient intensive insulin therapy

A number of studies have investigated the impact of TIIT to prompt normoglycaemia in people with poorly controlled T2DM [3]. Continuous subcutaneous insulin infusion (CSII), multiple daily insulin injections (MDIs) and basal insulin monotherapy are all effective methods for TIIT in people with poorly controlled T2DM [48,49]. The impact of TIIT on glycaemic outcomes is shown in Table 2 [48–55]. The rapid acquisition of glycaemic control with TIIT has been found to enable many people to maintain normoglycaemia following cessation of insulin therapy, using lifestyle management alone for extended periods of time (Table 2). This highlights the effectiveness of TIIT, and is consistent with the ADA/EASD consensus statement suggesting that people with moderate hyperglycaemia should be started on an antihyperglycaemic agent at diagnosis [3]. A meta-analysis of studies investigating TIIT, including 839 participants from seven studies, found that 66.2% were in drug-free remission 3 months after TIIT, which decreased to 42.1% at 24 months [56]. This meta-analysis also compared the characteristics of people achieving remission with those who did not, and found that people with higher BMI or lower FPG at baseline were more likely to achieve remission [56]. Other studies have also investigated the characteristics of those who achieved drug-free remission. Xu et al. [54] found that people in remission for two years had significantly better acute insulin responses than those not in remission, and the main predictor of remission was the time between diagnosis and the two weeks of TIIT used in this trial (1.00 *vs.* 4.38 months in the remission and non-remission groups, respectively). This highlights the rapid decline of β-cell function in people with T2DM and the need for good glycaemic control early in the disease course.

5.1. Impact of early TIIT on β-cell function

The rapid acquisition of glycaemic control has been demonstrated to have a beneficial impact on β-cell function in a number of other studies, with people achieving glycaemic targets with TIIT also having improved β-cell function [49,51,54,55]; this has been confirmed by meta-analysis [56]. Li et al. [51] found that the people who experienced the greatest improvements in β-cell function were able to maintain normoglycaemia for longer with lifestyle management alone. It is likely that β-cell function would have deteriorated further in those who took longer to reach normoglycaemia and, thus, would result in a lower baseline level of β-cell function and a poorer prognosis. The impact of glycaemic control on β-cell function was also demonstrated in a study by Chen et al. [57], which compared 6 months of treatment with either insulin or OADs in 50 people with newly diagnosed T2DM and severe hyperglycaemia at diagnosis who had been treated with TIIT for 10–14 days to rapidly obtain glycaemic control. After six months, HbA_{1c} levels were significantly lower in the insulin-treated group compared with those receiving OADs (6.33% *vs.* 7.50%, respectively; $P = 0.002$) [57]. β-cell function improved from baseline in both groups; however, significantly greater improvements were seen with insulin therapy compared with OADs, most likely as a consequence of the lower HbA_{1c} levels observed with insulin throughout the study [57]. The improved β-cell function seen in these studies might be the result of β-cell rest as a result of insulin therapy, as well as reduced β-cell stress owing to reduced hyperglycaemia.

5.2. Impact of early TIIT on low-grade inflammation and endothelial function

The effect of TIIT on the vasculature has also been explored, with a number of mechanistic studies describing beneficial effects on the vasculature. Chen et al. [53] investigated whether TIIT affected serum tumour necrosis factor (TNF)-α, which causes an inflammatory response and is related to insulin resistance. Their study of 138 people with newly diagnosed T2DM found that TNF-α levels were significantly increased by T2DM, and that TIIT reduced FPG as well as increased β-cell function

Table 2
Effects of intensive insulin therapy (IIT) at time of diagnosis on glycaemic control (GC).

	Treatment	*n*	Baseline HbA_{1c} (%)	HbA_{1c} after IIT (%)	Baseline FPG (mmol/L)	FPG after IIT (mmol/L)	Baseline PPG (mmol/L)	PPG after IIT	Days to achieve GC	Duration of IIT	% in GC (duration in months)[a]
Ilkova et al. (1997) [50]	CSII	13	11.0 ± 0.7	6.1 ± 0.5	12.1 ± 1.1	6.6 ± 0.4	16.9 ± 1.8	7.4 ± 0.4	1.9 ± 0.8	2 weeks	69 (26)[b]
Li et al. (2004) [51]	CSII	126	10.0 ± 2.2	8.7 ± 1.9	13.3 ± 4.4	6.3 ± 1.3	18.7 ± 6.1	8.6 ± 2.3	6.3 ± 3.9	2 weeks	42.3 (24)
Ryan et al. (2004) [52]	MDI	16	11.8 ± 0.3	N/A	13.3 ± 0.7	7.0 ± 0.4	N/A	N/A	N/A	2–3 weeks	44 (12)
Chen et al. (2007) [53]	CSII	138	11.9 ± 2.0	N/A	14.62 ± 1.68	6.62 ± 0.54	24.67 ± 8.03	N/A	3.15 ± 1.99	N/A	N/A
Weng et al. (2008) [49]	CSII	133	9.8 ± 2.3	8.0 ± 1.5	11.3 ± 3.3	6.6 ± 1.5	16.1 ± 5.5	7.5 ± 2.2	4.0 ± 2.5	N/A	51.1 (12)
	MDI	118	9.7 ± 2.3	8.0 ± 1.6	11.5 ± 3.2	6.8 ± 1.6	17.5 ± 5.5	8.1 ± 2.9	5.6 ± 3.8	N/A	44.9 (12)
Xu et al. (2009) [54]	CSII	84	9.91 ± 2.16	8.69 ± 1.78	13.73 ± 4.57	6.26 ± 1.16	19.36 ± 5.77	8.86 ± 2.49	N/A	2 weeks	50 (24)
Chon et al. (2010) [55]	MDI	61	10.7 ± 1.8	6.2 ± 1.1	11.8 ± 3.1	N/A	21.5 ± 4.1	N/A	2.6 months	N/A	8.7 (48)
Zeng et al. (2012) [48]	CSII	32	10.93 ± 2.23	10.03 ± 1.91	12.47 ± 3.70	5.89 ± 1.22	N/A	6.2 ± 0.9	3.8 ± 1.9	2 weeks	N/A
	BIM	27	10.78 ± 2.57	9.91 ± 1.95	13.27 ± 3.80	5.66 ± 1.09	N/A	10.2 ± 2.7	5.4 ± 1.4	2 weeks	N/A

GC: normoglycaemia without use of antiglycaemic therapy; FPG: fasting plasma glucose; PPG: postprandial glucose; CSII: continuous subcutaneous insulin infusion; MDI: multiple daily insulin injection; BIM: basal insulin monotherapy.

[a] Glycaemic remission is defined by normoglycaemia without use of antiglycaemic therapies.

[b] Median.

and decreased TNF-α levels [53]. The authors suggest that the decrease in the TNF-α inflammatory marker might be related to improved β-cell function [53]. Li et al. [58] compared the effect of either TIIT (prandial insulin thrice daily and intermediate-acting insulin before bedtime, targeting FPG 4.0–6.1 mmol/L and 2-h PPG 5.0–7.8 mmol/L) or conventional insulin treatment (premixed insulin twice daily, targeting FPG 6.0–8.0 mmol/L and 2-h PPG 9.0–11.1 mmol/L) on serum adiponectin and endothelial function in 42 people newly diagnosed with T2DM; treatment was maintained for two weeks after glycaemic targets had been achieved. Intensive insulin therapy was observed to increase serum adiponectin and nitric oxide concentrations, and to improve endothelial function to a greater extent than conventional insulin therapy [58]. Tian et al. [59] compared the effect of treatment with either OADs plus antihypertensive and lipid-lowering medication or TIIT for two weeks on endothelial injury/dysfunction in 116 people with newly diagnosed T2DM. They found that, compared with the multiple treatment, TIIT significantly improved endothelial injury/dysfunction [59]. These studies demonstrate that rapidly controlling hyperglycaemia has beneficial effects on the vasculature. Such effects and the impact of TIIT on β-cell function might explain the beneficial long-term outcomes seen in clinical trials of early insulin use, including the improved microvascular and macrovascular outcomes observed in the UKPDS [4,5].

5.3. *Early TIIT in clinical practice*

Studies of TIIT suggest that a more proactive approach to the management of early dysglycaemia can lead to long-term benefits. A treatment pathway involving initial TIIT to rapidly obtain glycaemic control, followed by withdrawal of insulin and initiation of OADs according to a patient-centred treatment approach, is likely to provide improved outcomes in people with T2DM. However, it should be noted that intensive glycaemic control is not suitable for everyone with T2DM, and such care needs to be personalized. For example, in frail people with poor glycaemic control, less intensive HbA_{1c} control should be applied, as this will reduce the risk of hypoglycaemic episodes, which can have catastrophic consequences in such a population [3].

6. Conclusion

Long-term prospective studies investigating the effect of intensive glycaemic control on CV outcomes have produced contradictory results. However, meta-analyses including these trials suggest that intensive glycaemic control reduces the risk of CV outcomes without increasing the risk of mortality. Sub-analyses of these long-term prospective studies suggest that intensive control is beneficial only for some people, which has led to clinical guidance recommending personalized care for patients with T2DM. This means that glycaemic targets, as well as the therapies used, should be chosen based on the characteristics of the given individual, with elderly and frail people having less stringent glycaemic targets. The ORIGIN study demonstrated that insulin therapy does not increase the risk of complications in people with T2DM and CV risk factors compared with standard care; thus confirming that it is safe to use in this population. Moreover, in the ORIGIN study, early insulin therapy targeting $HbA_{1c} < 6.5\%$ reduced the risk of people with IGT progressing to T2DM, with a low risk of hypoglycaemia, only moderate weight gain and doses of insulin glargine consistent with those typically required during phase-III studies of T2DM. There is now a mass of evidence from clinical trials and long-term outcome studies that early introduction of basal insulin is effective at keeping glucose levels within the target range with doses < 0.4 U/kg, which are associated with a low risk of severe hypoglycaemia and only moderate, if any, weight gain [8,31,39]. In contrast, late basal insulin introduction requires a high dose of insulin glargine with excessive weight gain observed as an adverse effect [60]. The same applies for the introduction of basal insulin after maximum-dose sulphonylurea, and dual and triple oral combinations with sulphonylurea and/or dipeptidyl peptidase (DPP)-IV inhibitors [61]. The best evidence supports early insulin use in combination with metformin as an antihyperglycaemic drug and other recently introduced combinations with glucagon-like peptide (GLP)-1 analogues and sodium–glucose cotransporter (SGLT)-2 inhibitors [62–64]. In addition, the ORIGIN–GRACE substudy demonstrated a decrease in the progression of CIMT with insulin glargine therapy that might explain the CV benefits seen in some of the earlier trials; however, long-term follow-up is needed to confirm whether this effect produces clinically relevant differences between groups.

While the use of insulin as a long-term therapy has not been shown to provide clinical benefits beyond glycaemic control, early TIIT has been found effective for rapidly achieving glycaemic targets and enabling long-term maintenance of normoglycaemia with lifestyle management alone in about 50% of people with newly diagnosed T2DM and hyperglycaemia. TIIT also preserves β-cell function possibly by reducing glucotoxicity and lipotoxicity through strict glycaemic control, which enables recovery of residual β-cell function. This preserves glucose homoeostasis, reducing the need for complex treatment regimens and lowering the risk of long-term complications even if control deteriorates, possibly through metabolic memory. Thus, people newly diagnosed with T2DM and $HbA_{1c} > 9\%$ should be given TIIT to rapidly obtain normoglycaemia before moving them onto standard care, with different glycaemic targets based on their given clinical characteristics. In addition, the earlier use of insulin in the treatment paradigm as second-line therapy is recommended, as this reduces the risk of hypoglycaemia following the addition of insulin compared with the later addition of insulin, as well as enabling further β-cell rest, which preserves β-cell function for the longest possible time.

Disclosure of interest

Markolf Hanefeld has received speaker honoraria from Roche, Bayer, Lilly, Takeda, GlaxoSmithKline and Sanofi-Aventis, and advisory board honoraria from Takeda, Bristol-Myers Squibb, Sanofi-Aventis and GlaxoSmithKline.

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Author contribution: the contents of this article and opinions expressed within are those of the author, and it was the decision of the author to submit the manuscript for publication. The author conceived and critically reviewed the manuscript, including input into every stage of the development of the manuscript, and approved the final version for submission.

Appendix A. Supplementary data

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