Insulin as an Early Treatment for Type 2 Diabetes

ORIGIN or end of an old question?

STEFANO DEL PRATO, MD
CRISTINA BIANCHI, MD, PHD
ANGELA DARDANO, MD, PHD
ROBERTO MICCOLI, MD

The Emerging Risk Factors Collaboration (1) has recently confirmed that type 2 diabetes remains associated with substantial premature mortality. Compared with nondiabetic individuals, those with diabetes have a hazard ratio (HR) of 1.80 (95% CI 1.71–1.90) for death from any cause, 1.25 (1.19–1.31) for death from cancer, 2.32 (2.11–2.56) for death from vascular causes, and 1.73 (1.62–1.85) for death from other causes. As is apparent, the greater risk is owing to cardiovascular (CV) disease, which accounts for >60% of the years of life lost because of diabetes. Although this increase in CV risk is largely attributable to the coexistence of multiple metabolic and hemodynamic disorders, elevation of plasma glucose levels remains strongly associated with increased CV morbidity and mortality (2–4). In support of a potential direct effect of plasma glucose elevation is the association between fasting plasma glucose levels >100 mg/dL (5.6 mmol/L) and vascular death (1). Since this a near-linear association (1,5) it has been postulated that reduction of plasma glucose levels should exert a positive impact on CV morbidity and mortality.

In the UK Prospective Diabetes Study (UKPDS), improvement of glycemic control was associated with a 16% reduction in the risk of myocardial infarction without achieving statistical significance ($P < 0.052$) (6). Glycemic control in that seminal trial was, however, relatively unsuccessful. Though intensively treated patients achieved an average A1C of 7%, a progressive worsening in glycemic control occurred after the initial improvement. A more aggressive and successful approach was adopted in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (7) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) (8) trials and Veterans Affairs Diabetes Trial (VADT) (9). In all these three large studies, glycemic control was achieved (A1C 6.5–7.0%) and maintained over a substantial period of time (3.4–6.0 years). Nonetheless, no significant impact on CV outcome was observed. Only when all intervention trials were included in a meta-analysis did a 9% (HR 0.91 [95% CI 0.84–0.99]) reduction in major CV events become apparent, primarily because of a 15% risk reduction of myocardial infarction (0.85 [0.76–0.94]) with no effect on CV mortality (10).

Several hypotheses have been proposed in the attempt to account for the lack of an effect of good glycemic control on CV risk (11,12). Among these, it was claimed that the diabetic population included in these trials was not the most appropriate one because of long-standing duration of diabetes with a large percentage of the patients who already had micro- and macrovascular complications (11). Others questioned the use of some antihyperglycemic medicines used to assure good glycemic control (12). In support of these claims are the post-UKPDS results showing that in type 2 diabetic patients who were intensively treated since diagnosis, a significant reduction of both micro- and macrovascular complications was apparent 10 years after termination of the active study (13). On the other hand, attention was drawn to the potential atherogenic effect of large doses of insulin often used in these intervention trials.

These considerations have raised two main questions: *1*) Could diabetic patients with shorter diabetes duration or even with prediabetes benefit more from near-normal plasma glucose level normalization? 2) Could this be achieved with early use of insulin? To some extent, the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial (14) was design to address these questions.

ORIGIN trial

The main question addressed by the ORIGIN trial (14) was whether insulin replacement therapy targeting fasting normoglycemia (≤95 mg/dL or 5.3 mmol/L) with insulin glargine in subjects in a relatively early stage of the disease and moderate hyperglycemia as well as in subjects with impaired glucose regulation could reduce CV outcomes more than standard treatment. A total of 12,537 high–CV disease risk patients, including 1,456 individuals with prediabetes (impaired fasting glucose [IFG] or impaired glucose tolerance [IGT]) were randomized to standard care (mainly oral hypoglycemic agents) or to insulin glargine. Over a median 6.2 years of follow-up, a modest glycemic separation between groups was obtained with a 0.3% A1C difference by the end of the study, with both groups achieving A1C ≤6.5%. Inclusion in the trial of high–CV disease risk subjects resulted in an event rate (first coprimary outcome: composite of CV death, myocardial infarction, stroke, and CV death) of ~3% per year with no difference in the two treatment groups (2.94 vs. 2.85/100 person-years; HR 1.02 [95% CI 0.94–1.11]; $P = 0.63$). Similarly, no difference

From the Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy.
Corresponding author: Stefano Del Prato, stefano.delprato@med.unipi.it.
This publication is based on the presentations from the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Ethicon Endo-Surgery, Janssen, Medtronic, Novo Nordisk, Sanofi, and Takeda.
DOI: 10.2337/dcS13-2019

was apparent with respect to second coprimary end points (composite of revascularization procedures or hospitalization for heart failure, 5.52 vs. 5.28/100 person-years; HR 1.04 [0.97–1.11]; $P = 0.27$). Insulin glargine treatment was associated with a rate of severe hypoglycemia of 1.00/100 person-years compared with 0.31/100 person-years with standard care. Moreover, in the insulin glargine group, body weight increased by 1.6 kg compared with −0.5 kg decrease in patients randomized to standard care. Finally, 3 months after therapy was stopped, new diabetes, as diagnosed by oral glucose tolerance test [OGTT], was found in 30 vs. 35% of the subjects with prediabetes at baseline (odds ratio [OR] 0.80 [95% CI 0.64–1.00]; $P = 0.05$). Cancer events were also monitored and adjudicated throughout the study. There was no association between use of insulin glargine and risk of any form of cancer (HR 1.00 [95% CI 0.88–1.13]; $P = 0.97$)

The results of this study are far from being clear-cut, as they can be read in different ways. Overall, the impression is that we have, once again, a classic half-full, half-empty glass. Therefore, some consideration is worthy with respect to the rationale of the study, the population that has been included, and the implications of the treatments adopted.

Study rationale

In the meta-analysis of 20 studies performed by Coutinho et al. (5) including 95.783 subjects with a median follow-up of 12.4 years and a total of 3.707 CV events, a positive association was found between fasting plasma glucose and CV events. As confirmed in recent analysis (1), this association was also present for nondiabetic fasting hyperglycemia. Compared with a reference fasting plasma glucose of 75 mg/dL (4.2 mmol/L), a plasma glucose level of 100 mg/dL (5.6 mmol/L) was associated with a 33% increase of CV risk (5). Therefore, fasting plasma glucose can be seen as a sound therapeutic target, as it has been in the ORIGIN trial (15). The authors, however, must be very well aware of epidemiologic data suggesting that post-OGTT and, therefore, postprandial glucose may be a better predictor of CV morbidity and mortality. In the meta-analysis by Coutinho et al. (5), CV risk increased to 58% for a 2-h OGTT of 140 mg/dL (7.8 mmol/L). This finding is corroborated by the results of the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study (16) including data from 13 European prospective surveys. The study showed a 20% increase in risk of all-cause mortality in IFG individuals compared with 50% increase in those with IGT. An association between all-cause mortality and fasting plasma glucose was apparent only for 2-h plasma glucose ≤140 mg/dL (7.8 mmol/L), whereas the latter remained an independent predictor even after adjustment for fasting plasma glucose. When CV disease was considered (17), fasting plasma glucose had less predictive power (HR 1.20 [95% CI 0.88–1.64] for mortality from CV disease and 1.09 [0.71–1.67] from coronary heart disease) compared with 2-h plasma glucose (1.40 [1.02–1.92] and 1.56 [1.03–2.36], respectively) (Fig. 1).

Therefore, tackling fasting rather than postprandial glucose may have reduced the possibility of affecting CV outcomes. Though increased basal plasma glucose levels may sustain vessel damage (18,19), a large literature body supports a more deleterious effect of postprandial hyperglycemia (20–22).

In line with this possibility are the results of the Study to Prevent Non–Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial showing that acarbose, possibly through diminution of oxidative stress induced by postprandial glycemic excursion, was associated with a 49% risk reduction of CV events (23). In a subgroup of subjects, acarbose treatment was accompanied by a 50% decrease in the progression of intima-media thickness of carotid arteries (24). Finally, a meta-analysis of seven major studies showed that the use of acarbose in type 2 diabetes was associated with a 35% risk reduction of CV disease (25). The other study carried out in prediabetic patients for which postprandial glucose ideally was the main treatment target is the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial (26). The study was largely negative, as the use of nateglinide in prediabetic individuals was not associated with significant reduction in the development of type 2 diabetes and CV events. However, in the NAVIGATOR trial, mean 2-h OGTT glucose levels in the annual tests were higher in the nateglinide group than in the placebo group. Finally, A1C data were not presented, other than in the subgroup that progressed to diabetes, to assess whether a significant overall improvement in glycemic control was obtained.

In summary, whether fasting or postprandial plasma glucose may be a better target in the attempt to reduce CV events in subjects with diabetes or at risk for diabetes remains to be determined. However, while there was no significant reduction in CV with insulin glargine in the ORIGIN trial, the use of acarbose was associated with better outcomes. Obviously, the two trials are not readily comparable. In the ORIGIN trial, insulin glargine treatment was compared with standard care (14,15), while in the STOP-NIDDM study acarbose was compared with placebo (23). Major differences also exist with respect to study populations

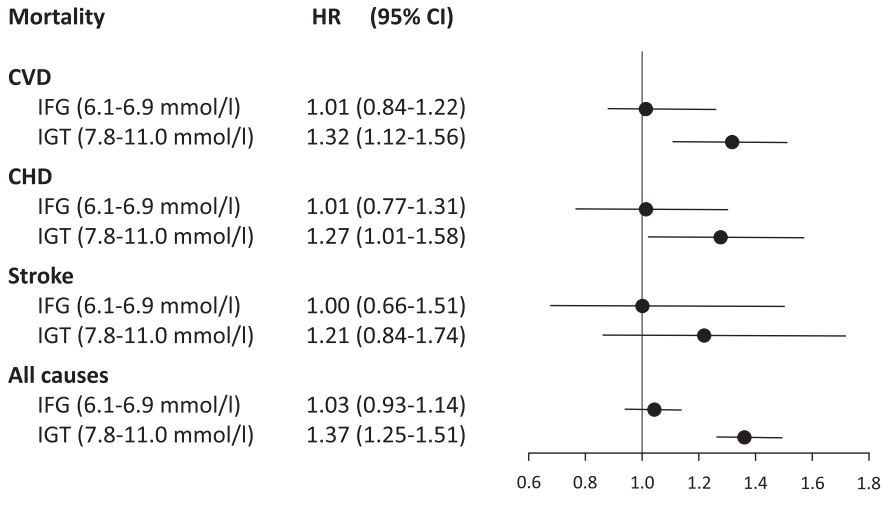

Figure 1—*Multivariate-adjusted HRs (95% CI) for deaths from CV disease (CVD), coronary heart disease (CHD), stroke, and all-cause mortality according to fasting and 2-h OGTT plasma glucose in the DECODE Study. Adapted from ref. 17.*

with high–CV risk diabetic and prediabetic subjects recruited in the ORIGIN trial versus prediabetic subjects with no predefined CV risk who participated in the STOP-NIDDM study. A more direct comparison may be made between ORIGIN and the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) (27) study. Patients with longer duration of diseases (~9 vs. 5.5 years in ORIGIN) entered the trial within 18 days after an acute myocardial infarction to be randomized to prandial or basal insulin. In spite of lower fasting plasma glucose concentration with basal insulin and smoother glucose fluctuations throughout the day with prandial insulin, no difference in CV event rates became apparent (HR 0.98 [95% CI 0.8–1.21).

Study population

As already mentioned, high–CV risk subjects were recruited in the ORIGIN trial in order to assure a sufficient number of CV events. Besides this common feature, the study population was, however, heterogeneous including 82% of subjects with known diabetes (average duration 5.4 years) of whom 23% were not taking any diabetes drug, 6% had newly diagnosed type 2 diabetes, and 12% had IFG/IGT.

To which extent this population may reflect the overall population of diabetic and prediabetic individuals is hard to say. By and large, these subjects had good glycemic control to start with as indicated by a median A1C level of 6.4% in both the insulin glargine and standard care groups. Nonetheless, ~60% of them had a prior CV event and 35% had a prior myocardial infarction. No information is available on baseline microvascular complications except for in 15% of the study population with some form of albuminuria. Whether this is a mere CV risk factor (a strong possibility in this kind of population) or the sign of diabetic glomerular involvement is not clear. Nonetheless, the annual rate of CV events appears to be the highest among the intervention trials performed in diabetic patients. As recently pointed out by Pieber in his commentary on the ORIGIN trial at the 48th Annual Meeting of the European Association for the Study of Diabetes (28), the annual mortality rate was 2.57% per year, i.e., almost twice that recorded in other intervention trials (Fig. 2) and greater than the that in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) where 100% of the enrolled patients had some form of prior CV disease (29). The reason for this exceedingly high event/mortality rate is not readily apparent, since age, BMI, smoking, and prevalence of hypertension were not different among trials. However, it should be kept in mind that many of the patients in the ORIGIN trial were recruited from cardiology practices with many having their diabetes diagnosed after an acute CV event. Therefore, these patients can be expected to have higher CV risk than that in the general diabetes population. Nonetheless, the generalizability of the results obtained in the ORIGIN trial to the usual population of people with diabetes or prediabetes remains highly questionable.

To which extent these unknown risk features may have affected clinical outcome also is something to consider. A main conclusion of the paper is that insulin glargine had a neutral effect on CV outcomes. Though they may sound reassuring, we should agree that these results do not support the ORIGINal question as to whether insulin therapy in subjects with early diabetes and high–CV risk could reduce CV risk. Moreover, inspection of the Forest plot presented as Fig. 2 in the online Supplementary Appendix of the ORIGIN paper (14) shows that subjects without prior CV events allocated to insulin glargine treatment had a 17% increase in the risk of first coprimary outcome (HR 1.17 [95% CI 1.00–1.37]) compared with an HR of 0.97 (95% CI 0.87–1.07) (P = 0.05 for interaction of prior CV disease by treatment). For patients with no prior CV events, these figures translate to an incidence of 2.21/100 person-years among insulin glargine–treated subjects compared with 1.89/100 person-years in subjects on standard care. Of note, these rates are much higher than expected for asymptomatic diabetic patients. In the Detection of Ischemia in Asymptomatic Patients with diabetes (DIAD) study, including 1,123 type 2 diabetic patients with no symptoms of coronary artery disease, the cumulative cardiac event rate was 2.9% over a mean follow-up of 4.8 years for an average of 0.6% per year (30) (Fig. 2).

In summary, the ORIGIN trials have included a very selected population characterized by high CV morbidity and mortality in spite of mild hyperglycemia making extrapolation of the results to common forms of type 2 diabetes or prediabetes highly questionable. Moreover, though no difference in CV outcome was detected in the two treatment arms when the whole population was considered, insulin glargine was associated with increased risk of CV outcome in subjects with no prior CV disease. This subgroup analysis casts some doubt about safety of insulin treatment and prevents drawing of general conclusions on early insulin therapy and CV risk.

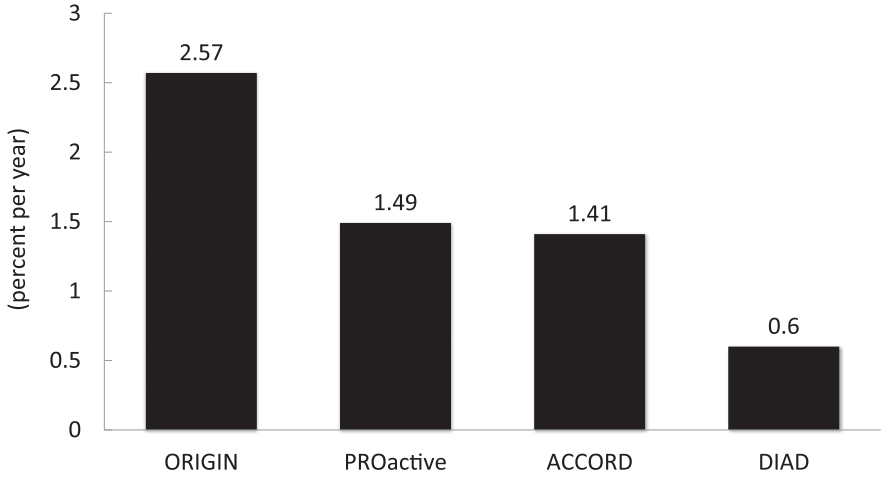

Figure 2—*Annual mortality rate in the ORIGIN, ACCORD, PROactive, and DIAD studies. The ACCORD trial was prematurely interrupted because of an excess of mortality in the intensively-treated arm (ref. 7). The PROactive trial included patients with some evidence of prior CV disease (ref. 28). The DIAD study reported annual mortality in asymptomatic patients (ref. 29).*

Treatment strategy

In the ORIGIN trial, treatment with insulin glargine was compared with standard care (mainly oral hypoglycemic agents). The rationale for using basal

insulin replacement has previously been discussed by the ORIGIN investigators (15). This was largely based on the concept that inappropriate plasma insulin concentration relative to tissue insulin resistance results in mobilization of free fatty acids (FFAs) from adipose tissue and reduction of HDL (15)—two important CV risk factors. Unfortunately, in the study no information is given on insulin sensitivity, plasma insulin concentration, or plasma FFA levels, so it is not possible to ascertain whether any difference occurred with the two treatments on any of these variables, all of which are independent CV risk factors. On the contrary, serum HDL cholesterol levels are available showing no changes with insulin glargine (from 46 ± 12 to 45 ± 13 mg/dL by the end of study) or standard care (from 46 ± 12 to 46 ± 13 mg/dL), though the 1 mg/dL difference by the end of the study was statistically different ($P < 0.001$).

In summary, based on the available data it is not possible to ascertain whether the lack of positive effects on CV outcomes with insulin glargine may be due to inability, on top of modest improvement of glycemic control, to assure concomitant amelioration of insulin sensitivity, plasma FFA, or lipid profile. Alternatively, one could argue that the beneficial effect generated by the modest glycemic improvement could be offset by potential atherogenic impact of chronic hyperinsulinemia (Fig. 3) (31). Experimental data have shown that modest elevation of plasma insulin levels, mimicking fasting hyperinsulinemia of insulin-resistant states, abrogates endothelium-dependent vasodilation in large conduit arteries, probably by increasing oxidative stress (32). Moreover, in the presence of insulin resistance, hyperinsulinemia, at least in the in vitro setting, can overstimulate the intracellular mitogen (mitogen-activated protein kinase dependent) signaling pathway in endothelial cells, which, together with impaired phosphatidylinositol 3-kinase activation of nitric oxide synthase, could yield an atherogenic state (33).

Given the speculative nature of the above considerations, the fact remains that insulin glargine treatment in this high–CV risk population was not associated with any specific advantage. Moreover, risk-to-benefit ratio of early insulin intervention must be carefully assessed. Though rate of hypoglycemia was claimed to be low, this was three times higher compared with standard care (severe hypoglycemia 1.0 vs. 0.3 6/100 person-years, confirmed nonsevere symptomatic hypoglycemia 9.83 vs. 2.68 6/100 person-years, and nonsevere symptomatic hypoglycemia 16.72 vs. 5.16/100 person-years; all $P < 0.001$ [Table 1]), accounting for a larger dropout (8.2 vs. 4.1%) among insulin-treated subjects. The impact of these events is difficult to extrapolate, but hypoglycemia has been associated with increased risk of CV complications (34), impaired quality of life (35), defensive eating, and body weight gain (36), as it occurred in the insulin glargine–treated subjects in the ORIGIN trial (median changes from baseline 1.6 vs. −0.5 kg). Finally, hypoglycemia remains a major cause of drug-related hospitalization (37), which, together with the intrinsic costs of injectable insulin and need for blood glucose monitoring, contributes to the excess cost of diabetes (38).

From this analysis, it may sound difficult to claim that insulin glargine treatment may offer much of an advantage in high–CV risk subjects with mild hyperglycemia or dysglycemia compared with standard care apart from a modest improvement in glycemic control. Moreover, insulin treatment seems unlikely to provide any more durable effect compared with standard care. Analysis of data presented at the 72nd Scientific Sessions of the American Diabetes Association (39) shows that after the initial year when best glycemic control was attained, A1C slightly but progressively increased over the years at a similar rate in the two intervention arms (insulin glargine 0.061 vs. 0.050% per year [Fig. 4]). What is remarkable, however, is that with both treatments excellent and sustained control was maintained over the 7-year follow-up with an average A1C level that remained <6.5%. Though this may be sounder when basal insulin therapy is considered, it is surprising when the effect of standard care is taken into consideration. The rate of deterioration observed in the control group, which was mainly treated with oral agents, is quite different from the "progressive nature" of type 2 diabetes as described in the UKPDS (6). In that seminal trial, after the initial 7 years of treatment average A1C was >7.5% with a progressive and steady increase after initial improvement in glycemic control. The reasons for these differences between the two trials are not readily apparent and may include evolution of the clinical approach and management over the years as well as distinctive features of the two study populations.

Table 1 offers a summary of the ORIGIN results. It is apparent that insulin treatment besides a modest improvement

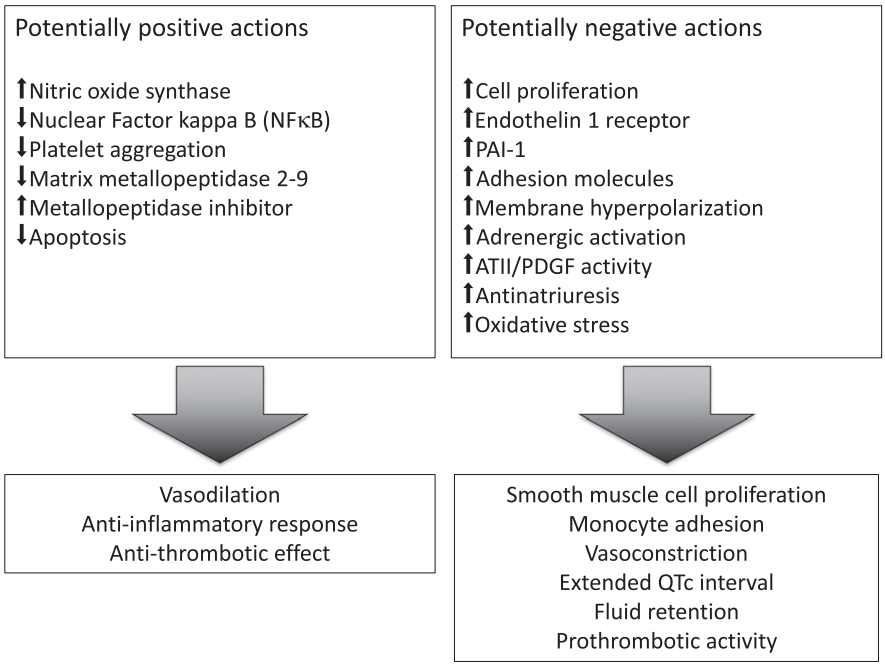

Figure 3—*Synopsis of potentially positive and potentially negative effects of insulin with respect to CV risk (adapted from ref. 30).*

Table 1—*Summary of the main results of the ORIGIN trial*

	Insulin glargine	Standard care	*P*
A1C (%)*			
Baseline	6.4	6.4	NS
End of study	6.2	6.5	NS
Primary outcome (100 person-years)	2.94	2.85	NS
Secondary outcome (100 person-years)	5.52	5.28	NS
Hypoglycemia (100 person-years)			
Severe	1.0	0.31	<0.001
Confirmed nonsevere symptomatic	9.83	2.68	<0.001
Any nonsevere symptomatic	16.72	5.16	<0.001
Body weight changes from baseline (kg)*	1.6	−0.5	—
Cancer (100 person-years)			
Any cancer	1.32	1.32	NS
Death from cancer	0.51	0.54	NS

*Median values.

of glycemic control does not provide any CV protection at its best while increasing the risk of hypoglycemia and body weight gain. Should we than conclude that no benefit can be expected from early use of insulin in type 2 diabetes?

Does early insulin treatment provide any significant benefit?

Two more results were reported from the ORIGIN trial (14). The first is that there was no significant difference in cancer events during the 6-year follow-up (HR 1.0 [95% CI 0.88–1.13]; $P = 0.97$). This is good news, which, together with no adverse effect on CV outcomes, should provide sufficient confidence to physicians and patients with respect to use of insulin glargine.

The second "positive" result is the significant reduction in the number of subjects with new diabetes diagnosed 3 months after therapy withdrawal (30 vs. 35% of 1,456 participants without diabetes at baseline; OR 0.80 [95% CI 0.64–1.00]; $P = 0.05$). Though this may be seen as a potential advantage of early use of insulin in people with prediabetes, its risk-to-benefit ratio must be fully appreciated. Benefit has to be evaluated with respect to the potential efficacy, which appears to be less than the one observed with lifestyle modification (HR 0.51 [95% CI 0.44–0.60]) (40) or other pharmacologic agents. In a recent meta-analysis (41), the use of oral antidiabetes drugs in prediabetic patients was shown to double the odds of achieving normoglycemia compared with control subjects (OR 2.03 [95% CI 1.54–2.67]). When individual classes of oral antidiabetes drugs were evaluated, use of thiazolidinediones (2.33 [1.93–2.81] and α-glucosidase inhibitors (2.02 [1.26–3.24]) was associated with significantly increased odds. With insulin glargine, 15 patients (number needed to treat) have to be treated for 6 years to prevent 1 new case of type 2 diabetes. This figure has to be confronted with 25 patients treated to incur an event of severe hypoglycemia (number needed to harm). This could be judged acceptable assuming that prevention is persistent and that only subjects who will develop diabetes will experience severe hypoglycemia. It would be more questionable if subjects naturally reverting to normal glucose tolerance were exposed to just one of these severe events.

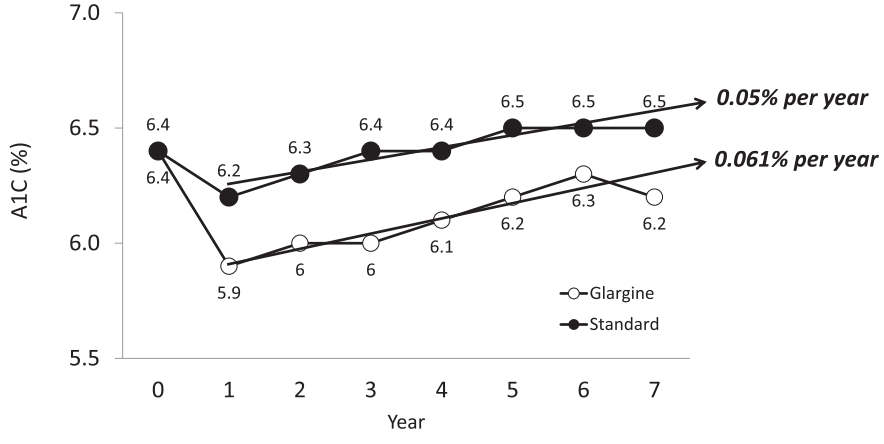

Figure 4—*Annual rate of A1C changes in the insulin glargine–treated subjects and in subjects on standard treatment after the initial year of treatment (years 1–7).*

Conclusions

In summary, the ORIGIN trial could not document CV benefits from early insulin treatment in high-risk patients with recent-onset diabetes while it increases severe and nonsevere hypoglycemia (Table 1). On the other hand, one could read the trial's results to conclude that insulin treatment in high-risk CV patients is not associated with increased CV or neoplastic event rate. Given prior concern associated with insulin use, this may be seen as a reassuring finding.

Insulin glargine also slowed progression from prediabetes to diabetes, but cost-effectiveness doubts remain. Therefore, it is unlikely that ORIGIN strategy will significantly impact current management of diabetes. Moreover, the results of the ORIGIN trial are not going to put a final word on the long-debated question about the best time to initiate insulin treatment and whether maintenance of good glycemic control may convey any CV advantage. Rather, the trial is likely to ORIGINate more questions.

Though it sounds possible to conclude that insulin glargine treatment can be deemed safe, the choice of an insulin treatment as initial therapy in type 2 diabetes may not be the most convenient one unless specific indications exist. Guidelines (42,43) suggest that insulin treatment should be considered in all newly diagnosed type 2 diabetic patients with elevated A1C levels, particularly if they are symptomatic. This approach, irrespective of unproven CV benefits, still may provide, per se, some advantages. When initiated in a symptomatic newly diagnosed patient, insulin treatment will result in rapid improvement of glycemic control and the patient's well-being. Whether this approach could provide

some β-cell preservation as suggested in some studies (44) is a question requiring further investigation. Nonetheless, insulin treatment can be stopped as soon as stable improvement is achieved to start the patient on alternative forms of treatment. The person with diabetes will appreciate that insulin treatment is not necessarily a forever therapy, and it will make it easier to restart insulin treatment when and if that will be needed later in the natural history of diabetes. In conclusion, no specific benefits are likely to be obtained with early insulin therapy, once again suggesting that what matters is to provide our patients with good glycemic control before they develop high CV risk and definitely before they experience a CV event.

Acknowledgments—S.D.P. has received advisory/consultancy/speakers bureau/lecture honoraria and research support from sanofi-aventis, Novo Nordisk, and Eli Lilly. No other potential conflicts of interest relevant to this article were reported.

S.D.P. and R.M. wrote the manuscript. C.B. and A.D. performed the literature search and contributed to critical discussion and manuscript review. S.D.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Seshasai SR, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–841
2. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800–811
3. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004; 141:421–431
4. Sarwar N, Aspelund T, Eiriksdottir G, et al. Markers of dysglycaemia and risk of coronary heart disease in people without diabetes: Reykjavik prospective study and systematic review. PLoS Med 2010;7: e1000278
5. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22: 233–240
6. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352: 837–853
7. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
8. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;24:739–743
9. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360: 129–139
10. Control Group, Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52: 2288–2298
11. Del Prato S. Megatrials in type 2 diabetes. From excitement to frustration? Diabetologia 2009;52:1219–1226
12. Schernthaner G. Diabetes and cardiovascular disease: is intensive glucose control beneficial or deadly? Lessons from ACCORD, ADVANCE, VADT, UKPDS, PROactive, and NICE-SUGAR. Wien Med Wochenschr 2010;160:8–19
13. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
14. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367: 319–328
15. Origin Trial Investigators. Rationale, design, and baseline characteristics for a large international trial of cardiovascular disease prevention in people with dysglycemia: the ORIGIN Trial (Outcome Reduction with an Initial Glargine Intervention). Am Heart J 2008;155:26–32
16. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. Lancet 1999;354:617–621
17. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001; 161:397–405
18. Yan SF, Yan SD, Herold K, Ramsamy R, Schmidt AM. Receptor for advanced glycation end products and the cardiovascular complications of diabetes and beyond: lessons from AGEing. Endocrinol Metab Clin North Am 2006;35:511–524, viii
19. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813–820
20. Ceriello A. Cardiovascular effects of acute hyperglycaemia: pathophysiological underpinnings. Diab Vasc Dis Res 2008;5: 260–268
21. Node K, Inoue T. Postprandial hyperglycemia as an etiological factor in vascular failure. Cardiovasc Diabetol 2009;8:23
22. Del Prato S, Tiengo A. The importance of first-phase insulin secretion: implications for the therapy of type 2 diabetes mellitus. Diabetes Metab Res Rev 2001;17:164–174
23. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA 2003;290:486–494
24. Hanefeld M, Chiasson JL, Koehler C, Henkel E, Schaper F, Temelkova-Kurktschiev T. Acarbose slows progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance. Stroke 2004;35:1073–1078
25. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. Eur Heart J 2004;25:10–16
26. Holman RR, Haffner SM, McMurray JJ, et al.; NAVIGATOR Study Group. Effect of nateglinide on the incidence of diabetes and cardiovascular events. N Engl J Med 2010;362:1463–1476
27. Raz I, Wilson PW, Strojek K, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. Diabetes Care 2009;32:381–386
28. EASD 2012 meeting [video online], 2012. Available from www.easdvirtualmeeting.org/resources/2830. Accessed 17 October 2012
29. Dormandy JA, Charbonnel B, Eckland DJ, et al.; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–1289
30. Young LH, Wackers FJ, Chyun DA, et al. DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA 2009;15:1547–1555
31. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. Lancet 2012;380:601–610
32. Arcaro G, Cretti A, Balzano S, et al. Insulin causes endothelial dysfunction in humans:

sites and mechanisms. Circulation 2002; 105:576–582
33. Rensing KL, Reuwer AQ, Arsenault BJ, et al. Reducing cardiovascular disease risk in patients with type 2 diabetes and concomitant macrovascular disease: can insulin be too much of a good thing? Diabetes Obes Metab 2011;13:1073–1087
34. Barnett AH. Avoiding hypoglycaemia while achieving good glycaemic control in type 2 diabetes through optimal use of oral agent therapy. Curr Med Res Opin 2010;26:1333–1342
35. McEwan P, Evans M, Kan H, Bergenheim K. Understanding the inter-relationship between improved glycaemic control, hypoglycaemia and weight change within a long-term economic model. Diabetes Obes Metab 2010;12:431–436
36. Foley JE, Jordan J. Weight neutrality with the DPP-4 inhibitor, vildagliptin: mechanistic basis and clinical experience. Vasc Health Risk Manag 2010;6:541–548
37. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 2011;365:2002–2012
38. Jönsson L, Bolinder B, Lundkvist J. Cost of hypoglycemia in patients with Type 2 diabetes in Sweden. Value Health 2006;9: 193–198
39. Trial results: insulin glargine [article online], 2012. Available from http://origintrial.org/trial-results/insulin-glargine#nogo. Accessed 3 October 2012
40. Gillies CL, Abrams KR, Lambert PC, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007;334:299
41. Phung OJ, Baker WL, Tongbram V, Bhardwaj A, Coleman CI. Oral antidiabetic drugs and regression from prediabetes to normoglycemia: a meta-analysis. Ann Pharmacother 2012;46:469–476
42. Handelsman Y, Mechanick JI, Blonde L, et al.; AACE Task Force for Developing a Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. Endocr Pract 2011;17:287–302
43. Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2008;32(Suppl. 1): S53–S61
44. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008;371:1753–1760