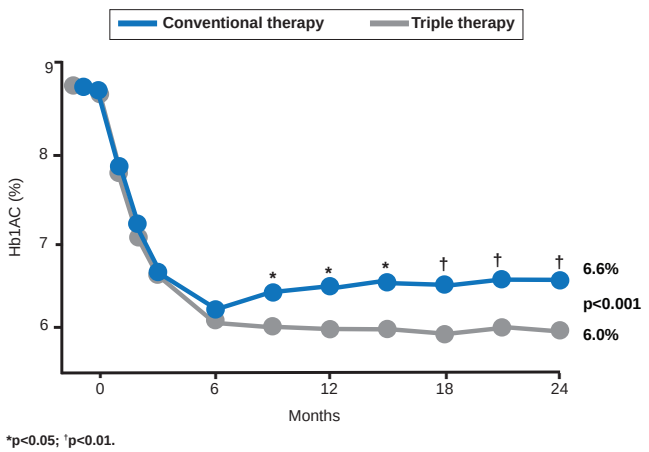
Participants were ~47 years of age, with duration of diabetes of ~5 months, and an initial mean HbA1C of 8.6% (range, 6.6% to 14.0%). HbA1C decreased sharply in both treatment groups by the 6-month time point. HbA1C remained below 6.5% for the triple-therapy arm from 6 to 24 months, but it gradually increased to 6.6% at 24 months in the conventional-therapy arm (Figure 1).

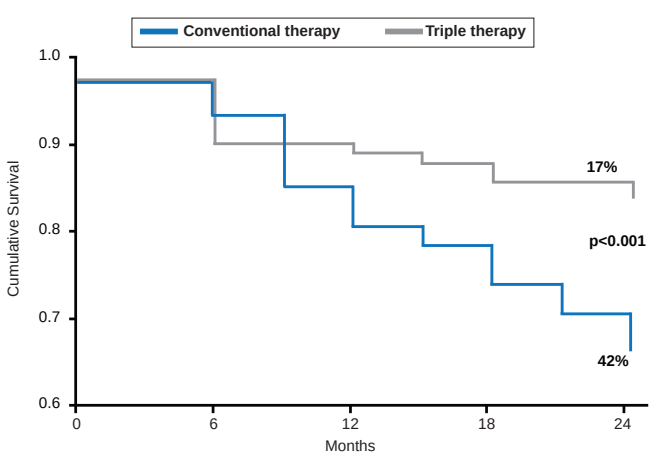
Figure 1. Change in HbA1C Over Time



Reproduced with permission from M Abdul-Ghani, MD, PhD.

Additional analyses indicated that 60% of patients in the triple-therapy group achieved an HbA1C <6.0% versus 27% in the conventional-therapy group (p<0.001). At 24 months, significantly fewer patients in the triple-therapy group (17%) were considered treatment failures compared with the conventional-therapy group (42%; p<0.001; Figure 2).

Figure 2. Time to Treatment Failure



Reproduced with permission from M Abdul-Ghani, MD, PhD.

Patients in the triple-therapy group lost a mean of 1.2 kg whereas those in the conventional-therapy group gained a mean of 4.1 kg at 24 months (p<0.001). Significantly fewer hypoglycemic events occurred in the triple-therapy group (15%, 0.27 events per patient-year) versus the conventional-therapy group (46%, 2.1 events per patient-year; p<0.0001).

Dr. Abdul-Ghani concluded that initiating triple therapy with metformin/pioglitazone/exenatide at diagnosis achieves a greater and more durable reduction in HbA1C with less risk of hypoglycemia compared with the stepwise add-on conventional therapy.

Insulin Dose Not Linked to Cardiovascular Mortality in the ACCORD Trial

Written by Muriel Cunningham

Previously published results from the Action to Control Cardiovascular Risk in Diabetes study [ACCORD; ACCORD Study Group. *N Engl J Med* 2008] showed an increased risk of all-cause and cardiovascular (CV) mortality in the intensive control group (HbA1C target, <6.0%) compared with the less intensive group (HbA1C target, 7.0% to 7.9%). "This brought a huge puzzle to the diabetes community, to figure out why we were seeing this result," said Elias S. Siraj, MD, Temple University School of Medicine, Philadelphia, Pennsylvania, USA. Several post hoc analyses have been conducted to date to determine what factors may have influenced this outcome [ACCORD Study Group. *N Engl J Med* 2008; Bonds DE et al. *BMJ* 2010; Riddle MC et al. *Diabetes Care* 2010; Seaquist ER et al. *Diabetes Care* 2012]. These analyses did not find a conclusive link between the ACCORD results and factors such as hypoglycemia, low HbA1C, the rapid decline in HbA1C during the first year of the study, weight gain, and specific medication use.

To better understand the findings of this study, ACCORD investigators hypothesized that higher doses of exogenous insulin may be associated with the CV mortality results from the ACCORD trial. To investigate this idea, data for insulin exposure and CV mortality from 10,163 patients were analyzed. HRs and 95% CIs were calculated, and multivariable Cox regression performed to choose the most appropriate baseline covariates and models.

The updated average total, basal, and bolus insulin doses were significantly higher in the intensive-control arm (all p<0.0001). In addition, there was a significant linear association between the updated average HbA1C level and updated average insulin dose in both groups (both p<0.0001). Four different Cox proportional hazards models were employed to determine HRs for CV mortality. The first model controlled for the following 14 baseline covariates: age, history of CV disease, heart failure, QT-index, baseline HbA1C value, high-density lipoprotein, amputation, presence of peripheral neuropathy, serum

creatinine, urinary ratio of albumin to creatinine, use of angiotensin receptor blockers, educational status, presence of integrated health plan, and presence of certified diabetes educator on staff at randomization. Model 2 added assignment to blood pressure or lipid trial, treatment assignment within these, severe hypoglycemia, and weight change. Model 3 added the updated average HbA1C, and Model 4 added the glycemic treatment arm assignment. Results from all 4 models by total, basal, and bolus insulin are presented in Table 1.

Table 1. HRs for CV Mortality of Insulin Dose (per 1 unit/kg) From Cox Proportional Hazards Model

Insulin Categories	Unadjusted HR (95% CI)*	Model 1*	Model 2*	Model 3*	Model 4*
Total insulin	1.83 (1.45–2.31) p<0.0001	1.21 (0.92–1.6) p=0.1726	1.21 (0.91–1.61) p=0.1912	1.12 (0.84–1.49) p=0.4540	0.99 (0.74–1.34) p=0.9693
Basal insulin	2.29 (1.62–3.23) p<0.0001	1.3 (0.87–1.94) p=0.2073	1.29 (0.85–1.95) p=0.2272	1.13 (0.74–1.72) p=0.5636	0.94 (0.61–1.46) p=0.7955
Bolus insulin	3.36 (2.0–5.66) p<0.0001	1.65 (0.88–3.11) p=0.1172	1.63 (0.85–3.12) p=0.1399	1.48 (0.77–2.84) p=0.2365	1.23 (0.63–2.4) p=0.5478

*For the unadjusted model, and Models 1 to 4, only a single insulin exposure was entered into the model at a time. Thus, each cell represents the results for that insulin variable being the only one within the model.

Based on the unadjusted HRs, a daily insulin dose increase by 1 unit/kg of body weight was associated with a 1.83- (total insulin), 2.29- (basal insulin) and 3.36-fold increase in risk of CV mortality (all p<0.0001). However, results from the four models did not confirm these findings. After adjustment for baseline covariates in Model 1, the HRs became nonsignificant indicating no association of insulin dose with CV mortality. Additionally, no association between insulin dose and CV mortality emerged after adjustments were made for on-treatment factors.

Dr. Siraj concluded that these results do not support the idea that insulin dose is an independent risk factor for CV mortality in the ACCORD population.

Canagliflozin Reduces HbA1C in Patients With Stage 3 CKD, With the Change Greater in Patients With Higher eGFR

Written by **Wayne Kuznar**

The sodium glucose cotransporter-2 inhibitor canagliflozin reduces HbA1C level in patients with type 2 diabetes mellitus (T2DM) and stage 3 chronic kidney disease (CKD), an effect that is more pronounced with higher levels of estimated glomerular filtration rate (eGFR), according to the results of a pooled analysis. Gary Meininger, MD, Janssen Research and Development LLC, Raritan, New Jersey, USA, presented the results of this pooled analysis of four randomized, double-blind, placebo-controlled Phase 3 trials that compared canagliflozin with placebo in patients with inadequately controlled T2DM and stage 3 CKD.

Options for glycemic control in patients with T2DM and impaired renal function are limited, said Dr. Meininger. Canagliflozin has been approved in the United States as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. However, its approved dosage is limited to 100 mg QD in patients with moderate renal impairment with an eGFR ≥45 and <60 mL/min/1.73 m^2, and it is not indicated in patients with an eGFR <45 mL/min/1.73 m^2.

The present pooled analysis included 1085 patients with T2DM and stage 3 CKD (eGFR ≥30 and <60 mL/min/1.73 m^2) who were randomized to canagliflozin 100 or 300 mg, or placebo for 18 to 26 weeks.

In the overall study population, the mean change from baseline to efficacy assessment in HbA1C was –0.52% in the canagliflozin 100-mg group; –0.62% in the canagliflozin 300-mg group; and –0.14% in the placebo group (p<0.001 for both canagliflozin groups vs placebo). When assessed by baseline eGFR, a greater reduction in HbA1C with canagliflozin was observed in patients with eGFR ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2 than in those with eGFR ≥30 and <45 mL/min/1.73 m^2.

In the 88.2% of all participants who were on background insulin or a sulfonylurea, the rates of documented episodes of hypoglycemia were greater with canagliflozin 100 mg and 300 mg (41.9% and 43.8%, respectively) than with placebo (29.2%).

Weight loss was also greater in the canagliflozin groups than in the placebo groups, and the effect was greater in patients with eGFR ≥45 mL/min/1.73 m^2 than in those with eGFR ≥30 and <45 mL/min/1.73 m^2.

Systolic blood pressure decreased more in the overall study population in the canagliflozin groups versus the placebo group. In the subgroup with eGFR ≥30 and <45 mL/min/1.73 m^2, systolic blood pressure increased by 0.8 mm Hg in each canagliflozin group and by 5.7 mm Hg in the placebo group.

The incidence of overall adverse events (AEs) was higher with canagliflozin (74.0% with 100 mg and 75.3% with 300 mg) than with placebo (70.4%). Intravascular volume-related adverse events were also more common with canagliflozin (5.0% and 8.5% in the 100- and 300-mg groups, respectively) than with placebo (2.6%). The percentage of these events in the canagliflozin groups was greater in patients with eGFR ≥30 and <45 mL/min/1.73 m^2 (6.6% and 11.1% in the 100- and 300-mg groups, respectively) relative to placebo (1.7%) than in those with eGFR ≥45 mL/min/1.73 m^2 (4.2% and 7.1% with 100-mg and 300-mg