Important data on diabetes presented at the 47th Annual Meeting of the European Association for the Study of Diabetes come to you in Diabetes 2011, a newsletter CME program that is being offered to you by Yale University School of Medicine. Fax or e-mail delivery to your office of Diabetes 2011 will be followed by a Diabetes 2011 booklet (EASD and AHA newsletters) in the mail. After successfully completing the quiz and evaluation therein contained, you will qualify for up to 5.5 AMA PRA Category 1 Credits™ to be issued by Yale University School of Medicine.

Diabetes 2011 is being offered to physicians practicing in the United States. After successfully completing this program, participants will be able to:
- Describe the mechanisms of β-cell failure, the progression of diabetes, and its complications.
- Implement strategies for the early diagnosis and treatment of diabetes.
- Recognize the manifestations of the macrovascular and microvascular complications of diabetes and describe appropriate therapies.
- Understand the interrelationship between insulin resistance, hyperglycemia, and atherosclerosis in patients with Type 2 diabetes.
- Compare the mechanisms of action of diabetes therapies, their risks, benefits, and proper roles in disease management.
- Identify evolving and emerging therapeutic strategies in diabetes care.
- Describe the approach to managing dyslipidemia, hypertension, and cardiovascular risk factors in patients with diabetes.

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Diabetes Clinical Trials: Complexities and Controversies

The second day of this week's congress was led off by a major symposium entitled, "Warning Signals from Clinical Trials—All That Glitters Is Not Gold." Very clearly, over the past decade, there has been increasing attention paid to adverse effects of antihyperglycemic therapies, especially the thiazolidinediones (TZDs), which became mired in controversy during this period of time.

Dr. Robert Califf, a cardiologist and director of the Duke Clinical Research Institute, which is the largest clinical trials unit in the world, was the first speaker, delivering an address entitled, “Defining the Balance of Risk and Benefit of Commonly Used Drugs—Get the Evidence by Modern Standards or the Evidence Will Get You.”

He began by remarking on the irony of two concurrent trends. Due to scientific advances, we are now more able to approach disease in an intelligent, pathophysiology-based manner and get 'the right drugs to the right people.' However, there's simultaneously been an erosion in the public trust in the medical community's and the pharmaceutical industry's recent efforts in this regard, partly driven by several high-profile missteps in the drug approval process. Dr. Califf went on to describe what he considers a simple truth—that all drugs have risk and we as clinicians (along with industry and the regulatory authorities) must always be balancing benefit with this risk. Unfortunately, in Type 2 diabetes management, despite 11 distinct drug classes now on the US market, there is a paucity of data to inform us, with any degree of certainty, about which way this balance tips. The only exception might be metformin, widely viewed as a safe and effective agent to lower glucose. (Even with insulin, there is some evidence to suggest an association with cancer risk.) Moreover, there is a virtual absence of comparative effectiveness research to get to the real clinical outcomes differences between classes of antihyperglycemic medicines.

Table 1. Six Steps for Development of Future Diabetes Drugs

- Based on biological principles
- Standardize glucose lowering metrics
- Large Phase 3 trials (rule out major toxicity)
- Post-marketing 'mega-trials' (CV safety)
- Post-marketing pharmacoepidemiology
- Democratization of information

Dr. Califf described six steps academia and industry can take to solve this emerging crisis in diabetes care (Table 1). First, preclinical and early human studies should be founded on reproducible biological principles, i.e.,—with a cautious respect for a drug's potential off-target effects and a healthy suspicion of the value of surrogate markers for actual disease endpoints. Second, antihyperglycemic drug trials should involve standardized methods to measure the extent of glucose lowering. Third, Phase 3 trials should be large enough to rule out major toxicity. Fourth, so-called post-marketing 'mega-trials' must be conducted to ensure safety, especially from a cardiovascular (CV) standpoint. Ideally, 'mega-trials' have clinical sites in multiple countries to assess for variable effects across populations. Fifth, intelligently designed post-marketing pharmacoepidemiological surveys should be assembled. Finally, we need to develop approaches in dealing with the increasingly rapid democratization of information on a global scale—invoking public and media access to information.

Dr. Califf concluded by describing his vision for clinical investigations of the future. Trials and surveys will pick up early signals of previously unrecognized toxicities of medications by using data available in huge electronic medical records repositories. Sanctioned 'data portals', combined with advanced information systems, will assess the safety of recently available therapies in...
potentially hundreds of thousands of patients throughout the world. If this technology had been available over the last few years, recent drug debates may have been avoided.

The second speaker of the session was Dr. Rury Holman, Professor of Diabetic Medicine at Oxford, director of the Diabetes Trial Unit at that institution, and one of the developers of the famous UKPDS study. Dr. Holman echoed Dr. Califf’s calls for a focus on the randomized, controlled trial (RCT) as the gold standard to evaluate new diabetes therapies. He reviewed many examples where clinical observations, pathophysiological studies, and retrospective investigations have led us down the wrong path. A classic example is the use of estrogen replacement therapy for CV disease prevention in post-menopausal women, since observational trials had indicated a benefit. Later, well-designed clinical trials exposed the potential increased risk of CV events from estrogen administration. Observational trials may have allowed bias by enrolling women who were more health conscious in seeking estrogen therapy for its reported benefits.

RCTs for diabetes drugs in the future need to be large enough to detect a benefit on top of existing therapies, to assess for previously undisclosed risk, and conducted with patients representing multiple ethnicities to provide a full picture of risk vs. benefit. Trials may need to include multiple interventions (ideally in a head-to-head design) to enhance efficiency and to assess for comparative effectiveness. He briefly reviewed the upcoming GRADE trial, which will be NIH-funded and compare 5 initial therapies for diabetes after metformin—inulin, sulfonylureas, TZDs, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like-peptide-1 (GLP-1) receptor agonists. This 7,500 patient study will also explore the potential benefits of beginning with 2 drugs simultaneously.

From the large crowd who gathered to listen to Drs. Califf and Holman, it is clear that there is intense interest in the future of diabetes drug development. The cardinal question is how do we efficiently get improved, safer medicines to our patients in order to achieve better glycemic control and prevent the devastating long-term complications of their diseases?

Many different formulations of insulin exist, from rapid-acting analogues, which attempt to mimic normal prandial insulin secretory dynamics, to basal insulins, which aim to provide stable control of blood glucose in between meals and overnight. Modest improvements in post-prandial glucose with the former and in hypoglycemia rates with the latter have been demonstrated in clinical trials. Never insulin formulations with even better efficacy and side effect profiles continue to be sought.

One investigational insulin product garnering some attention at international diabetes meetings is insulin degludec, whose duration of action exceeds that of the current longest-acting insulin, namely glargine. This insulin forms soluble multihexamers upon subcutaneous injection, and their slow dissolution translates to an ultra long-acting and peakless pharmacokinetic (PK) profile. Two convincing PK/pharmacodynamic studies of degludec were presented by Heise (abstract 1046) and Novec (abstract 1055) and Danish collaborators this week. In the Novec study, three doses of degludec were used with extremely and equally flat activity levels demonstrated (Figure 1).

Several presentations this week went beyond pharmacology, exploring more clinically relevant aspects of this emerging basal insulin. Atkin and international collaborators studied 459 patients with Type 2 diabetes suboptimally controlled on oral agents, who were randomized to once daily injections of either degludec or glargine over 26 weeks, using a ‘treat-to-target’ titration strategy (abstract 112). In this trial, patients assigned to degludec were asked to purposefully alter the timing of their injection, in order to assess its consistency of effect over variable dosing intervals, ranging from 8 up to 40 hours. Mean baseline characteristics were equivalent between the degludec and glargine groups, including age (56.2 vs. 56.7 years, respectively), HbA1c (8.5 vs. 8.4%), fasting plasma glucose (FPG) (162 mg/dl in both), diabetes duration (10.8 vs. 10.8 years), and BMI (29.3 vs. 30.0 kg/m2). At 26 weeks, both groups required a similar insulin dose and experienced a reduction in HbA1c of ~1.3%. Because the upper bound of the treatment difference confidence interval was <0.4% (treatment difference 0.04%, 95% CI: 0.12, 0.20), ‘non-inferiority’ was confirmed for degludec.

Rates of confirmed hypoglycemia (blood glucose <56 mg/dl) or severe hypoglycemia (ADA definition: ‘needing assistance of another’) were similar (3.6 vs. 3.5 episodes/patient-year for degludec and glargine, respectively), as were rates of confirmed nocturnal hypoglycemia (0.6 vs. 0.8 episodes/patient-year).

The investigators concluded that despite extreme dosing intervals, degludec appeared to be as effective and as safe as glargine and suggested that the new insulin could be flexibly dosed (i.e., at different time periods from day to day) without compromising glucose control or increasing hypoglycemia risk. A better study design might have been to allow flexible dosing intervals with glargine as well—although, understandably, this may have raised safety concerns at the level of the investigational review board(s) supervising the study’s conduct.

In a related abstract, Hollander and US colleagues compared degludec with glargine in a more advanced ‘basal-bolus’ strategy in 992 Type 2 diabetes patients (mean age 58.9 years, diabetes duration 13.5 years, FPG 166 mg/dl) with HbA1c 7-10% (mean baseline HbA1c 8.3%) after at least 3 months on any insulin regimen with or without oral antihyperglycemic drugs (abstract 1035). The study was conducted over 1 year and randomization was 3:1 in favor of the newer insulin; the design was open-label, using a treat-to-target algorithm. Both insulins were administered in conjunction with insulin aspart as the rapid analogue, ± metformin, and ± pioglitazone. At one year, both insulins reduced HbA1c to the
same degree (degludec-1.2%, glargine-1.3%), with roughly half of patients in both groups achieving a value <7%. FPG fell by 43 and 38 mg/dl in the two groups, respectively (p=NS). Total daily doses of all insulins was ~1.4 units/kg/day, with an approximate 50/50 ratio between basal and prandial insulins.

In contrast to the Atkinson study, the rates of overall confirmed hypoglycemia (defined as an episode associated with a blood glucose <56 mg/dl or severe by ADA definition) were significantly lower with degludec (11.1 vs. 13.6 episodes/patient-year; estimated rate ratio [ERR] degludec/glargine: 0.82 [95% CI: 0.69; 0.99], p=0.0359). Similarly, the rate of confirmed nocturnal hypoglycemia was reduced by 25% in the degludec group (1.4 vs. 1.8 episodes/patient-year; ERR: 0.75 [95% CI: 0.58; 0.99], p=0.0399).

The investigator’s impression was that insulin degludec as part of a basal-bolus program in Type 2 diabetes improves long-term glucose control similarly, but with slight reductions in hypoglycemia risk as compared to insulin glargine.

One potential advantage of degludec is its ability to be premixed with rapid-acting insulin analogues without any alteration in PKs. In this light, Vaag et al., a European consortium, evaluated the efficacy and safety of IDegAsp, a formulation consisting of 70% degludec and 30% aspart (abstract 1040). It should be noted that other currently available basal insulins (glargine, detemir) cannot be mixed with any other type of insulin because of altered PK. The new formulation was compared to aspart 70/30 (a widely available mixture of 70% intermediate insulin [protamine aspart] + 30% aspart) in 125 insulin-naïve Type 2 diabetes patients inadequately controlled on oral agents.

Hypoglycemia and the Heart

Svetlova and Russian collaborators have studied the effects of autonomic neuropathy on electrical cardiac conductance (abstract 1144). They noted that patients with Type 1 diabetes and cardiovascular autonomic neuropathy (CAN) have a poor sympathetic response to hypoglycemia, QTc prolongation, exercise intolerance, and are at increased risk of sudden death. In their laboratory, 80 patients with Type 1 diabetes (mean age 35.7 years) underwent 72-hour continuous glucose monitoring (CGM), ECG with QTc measurement, and comprehensive CAN testing before and after treadmill exercise. The patients were divided into three groups based on their CGM findings: (1) those with symptomatic hypoglycemia (42.5%), (2) those with 1-2 episodes of hypoglycemia unawareness (35%), and (3) those with 3+ such episodes (22.5%). Impressively, 73 of 80 patients (91%) had some evidence of CAN, but the degree was greater in groups 2 and 3 than in group 1. The investigators also found multiple levels of association between CAN and hypoglycemia unawareness (r=0.76, p<0.001), between CAN and QTc (r=0.73, p<0.01), and between QTc and hypoglycemia unawareness (r=0.71, p<0.001). QTc was increased only in group 3 (447.1±2.3 ms). Evidence of CAN was greater after treadmill exercise in each group (p<0.01). The investigators concluded that there were significant relationships between hypoglycemic unawareness, CAN, and ventricular depolarization that are deserving of further exploration.

Cardiac Benefits of ARIs?

Kajiwara et al. from Japan were interested in the influence of aldose reductase inhibitors (ARIs), which reduce intracellular sorbitol concentrations, on cardiac outcomes (abstract 1241). This class of drugs has been studied for years as a remedy for neuropathic hyperglycemic damage, with mixed results. Epalrestat, an ARI only available in Japan, has been used in that country for diabetic polyneuropathy since the early 1990s. It has been proposed to have anti-oxidant effects. As a result there is some interest in its possible protective role in atherosclerosis as well as in reducing ischemic damage to the heart.

The group conducted a retrospective analysis of patients treated with epalrestat for at least 5 years, comparing their outcomes to matched patients never treated with the ARI. CV outcomes between the two groups were then compared. All patients had diabetic neuropathy as defined by criteria of the Diabetic Neuropathy Study Group in Japan. This involved the presence of two of the three following criteria: (1) classical sensory symptoms, (2) bilaterally decreased or absent ankle reflex, and/or (3) decreased vibratory sensation in bilateral medial malleoli (in the setting of no other obvious cause). 111 patients comprised the epalrestat group (150 mg QD) and 64, the non-epalrestat group. The prevalence of
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neuropathy, retinopathy, and nephropathy was 100% vs. 100% (p=NS), 57.7% vs. 59.4% (p=NS), and 49.5% vs. 82.8% (p<0.01) in the two groups, respectively. There were significant differences in proportion of patients using oral antihyperglycemic drugs (98.2% vs. 56.3%, p<0.01) and antihypertensive drugs (60.4% vs. 31.3%, p<0.01) but no differences in the frequency of insulin therapy (55.0% vs. 56.3%) or use of lipid-lowering drugs (45.9% vs. 31.3%) between the epalrestat and the non-epalrestat cohorts.

The incidence of myocardial infarction (MI) was 3.5 per 1000 person-years in the epalrestat patients and 12.8 per 1000 person-years in non-epalrestat patients. There was no difference, however, in the incidence of stroke between the two groups (8.9 vs. 9.3). Kaplan-Meier analysis demonstrated a significant difference in the incidence of MI (log-rank test, p=0.01) between the cohorts (Figure 2). The investigators suggested that epalrestat may have a protective effect against MI in patients with Type 2 diabetes and neuropathy. These conclusions are premature given the differences in renal disease and in drug therapy between the groups, but deserve of further study in a randomized, placebo-controlled trial.

Figure 2. Kaplan-Meier Analysis of MI

Glucose & Heart Failure

Increasing in frequency among our aging diabetic and hypertensive population, heart failure is emerging as a major cause of morbidity and mortality in patients with diabetes. Lind and Swedish researchers investigated the Swedish national health registries and found 83,021 patients with Type 2 diabetes between 1998 and 2003 (mean age 65.8 years) who were initially without heart failure and followed through 2009 (abstract 50). During a median follow-up of 7.2 years, 10,969 patients (13.2%) were hospitalized with a diagnosis (primary or secondary) of heart failure. There was a clear relationship between the quality of glycemic control and heart failure risk in these patients, with the unadjusted incidence rates per 1,000 person-years being 13.8% (95% CI: 12.9-14.8) for patients with HbA1c <6.0%, but up to 25.8% (23.5-28.4) for patients with HbA1c ≥10.0%. Cox regression was performed adjusting for age, gender, diabetes duration, smoking, BMI, systolic and diastolic blood pressures, history of MI or other evidence of ischemic heart disease, atrial fibrillation, valve surgery, use of beta blockers, ACE-inhibitors and angiotensin receptor blockers (ARBs). The adjusted hazard ratio was 2.01 (95% CI: 1.79-2.27) for patients with an updated mean HbA1c >10.0% compared to patients <6.0%. Heart failure risk increased by 16% for each 1% increase in HbA1c.

The investigators concluded that poor glycemic control is a strong and independent predictor of heart failure hospitalization. We note, however, that no study has been able to demonstrate that lowering glucose actually reduces the incidence of heart failure. One drug class, the TZDs, actually increase the risk of heart failure—although this is clearly related to renal sodium retention and has little to do with these drugs’ glucose-lowering effect.

SU vs. Metformin: Which is Heart-Friendly?

The influence of antihyperglycemic therapy on CV sequelae of diabetes continues to be a question of great interest. Using the GE Centricity database (2003-2007), Fu and American colleagues conducted a retrospective cohort study to examine the association between initial monotherapy with either a sulfonylurea or metformin and subsequent CVD events in elderly patients with Type 2 diabetes (abstract 156). Upon enrollment, all patients were over 65 years old, without prescriptions for any antihyperglycemic drug, no history of CVD within 1 year of the index date, and at least 2 years of subsequent follow-up in the database. Cox regression models estimated the time to first CVD event in those patients treated with either category of drug. Using propensity score matching, the investigators attempted to control for differences in baseline characteristics.

There were 4,251 patients per group, with a mean age of 75 years, and even distribution between the genders. After 2 years of follow-up, patients who initiated antihyperglycemic therapy with a sulfonylurea had a significantly higher incidence of CVD events (12.4% vs. 10.4%, p<0.001) compared to those who began metformin. This difference was mainly driven by an increased incidence of ischemic heart disease with sulfonylureas compared to metformin (7.2% vs. 5.5%, respectively; p=0.002). With the regression models, the likelihood of having a CVD event was 23% higher in patients initiated with a sulfonylurea (OR [95% CI] =1.23 [1.08, 1.41]; p=0.002). Sensitivity analyses with 1 or 3 years of follow-up resulted in similar findings.

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The investigators summarized that in their older cohort of diabetic patients, sulfonylurea therapy appears to be associated with an increased CVD event rate versus metformin. Whether this relationship is cause and effect is less clear. Despite propensity matching, other baseline characteristics may be serving as confounders. Nonetheless, in the UKPDS, a randomized trial, CVD outcomes were indeed better in metformin-treated patients, while those in sulfonylurea patients were not significantly different from diet-treated patients, despite a ~1% better HbA1c. It should be noted that sulfonylureas may not actually increase CVD risk. More likely, metformin may have CV advantages.

We remind our readers that, with a paucity of data showing any conclusive benefit of tight glycemic control on CVD outcomes in at-risk diabetic patients, we should also be focusing our efforts on blood pressure and lipid management to optimize their chances of avoiding serious cardiac complications.

Hypoglycemia remains the ‘rate-limiting step’ in the management of many patients with diabetes, especially those on insulin therapy. With the recent ACCORD findings showing increased CV mortality in more intensively treated Type 2 diabetes patients at high CV risk, there is increasing interest in the potential deleterious sequelae of hypoglycemia, especially in those of advanced age. We found two studies this week that shed further light on this important issue.

Shzali and British collaborators conducted a retrospective analysis of patients admitted to a medical hospital ward during a 6-month period in 2008 (abstract 652). Ninety-four patients with documented hypoglycemia were found, 25 of whom had diabetes. The investigators then identified 91 age-gender matched controls with normoglycemia, 11 of whom had diabetes. Post-discharge, over a median follow-up period of just 1.1 years, 54 deaths were recorded, comprising 44.6% in those with hypoglycemia vs. 13.2% in those without hypoglycemia (p<0.0001). Crude mortality rates were 62.6 deaths per 100 person-years in the hypoglycemic group and 11.7 deaths per 100 person-years in the controls. In multivariate models, age, hypoglycemia (HR: 4.86 [95% CI: 2.39-9.86]), and BUN (HR: 1.05 [1.02-1.08]) independently predicted mortality in these acutely ill patients. It was concluded in-hospital hypoglycemia is an important risk factor for mortality. Of course, these data do not prove a cause-and-effect relationship. Indeed, previous studies from both the inpatient and outpatient settings appear to suggest that hypoglycemia may simply serve as a risk marker for the sickest patients. The odd proportion of non-diabetics with hypoglycemia in this study suggests that multiple other severe comorbidities were in fact driving the mortality statistics.

Kalopita et al. from Greece (abstract 252) were interested in the relationship between hypoglycemia and cardiac electrical conduction, given the proposed relationship between hypoglycemia and sudden cardiac death. They studied 26 patients (14 males) with Type 2 diabetes (mean age 60.3±10.9 years, HbA1c 6.73±0.73%, diabetes duration 6.9±5.0 years), of whom 7 were being treated with insulin and 19 with insulin secretagogues. Continuous glucose and ECG monitoring were performed over a 24-hour period. Hypoglycemia was defined as an episode of <70 mg/dl for more than 5 minutes; hyperglycemia was defined as >200 mg/dl for the same duration. The mean QTc by ECG during these episodes was compared to that during euglycemic periods (70-120 mg/dl). A total of 26 non-severe hypoglycemic episodes in 13 patients (5 insulin-treated, 8 secretagogue-treated) patients were discovered. Mean blood glucose (BG) during hypoglycemia was 59.2 (95% CI: 56.4-62.0) mg/dl, while BG during normoglycemia was 98.7 (90.4-107.0) mg/dl. Mean QTc during hypoglycemic episodes was significantly higher than during normoglycemia (431.4 [416.6-446.2] vs. 416.6 [397.6-435.5] msec, p=0.015). No changes were seen in more intensively treated Type 2 diabetes patients, while those in sulfonylurea patients were not significantly different from diet-treated patients, despite a ~1% better HbA1c. It should be noted that sulfonylureas may not actually increase CVD risk. More likely, metformin may have CV advantages.

We remind our readers that, with a paucity of data showing any conclusive benefit of tight glycemic control on CVD outcomes in at-risk diabetic patients, we should also be focusing our efforts on blood pressure and lipid management to optimize their chances of avoiding serious cardiac complications.

Feeling Low

So Many Posters, So Little Time....

Drink Up!

Given the previously disclosed independent association between plasma copeptin, a surrogate marker for vasopressin secretion, and the risk of diabetes, Roussel et al. from France evaluated the relationship between water intake (which suppresses vasopressin) and subsequent risk for developing hyperglycemia (abstract 274). 3,615 study participants (aged 30-65 years, normal baseline FPG) in the 9-year follow-up DESIR study (Data from an Epidemiological Study on Insulin Resistance Syndrome) were asked to complete a self-administered questionnaire, including reports of mean daily intake of water, wine, beer-cider, and sweet beverages, every 3 years. During follow-up, there were 565 incident cases of hyperglycemia (defined by FPG ≥110 mg/dl or diabetes treatment). After adjustments for confounding factors (gender, baseline age, BMI, FPG, physical activity, smoking status, triglycerides, HOMA-IR, total cholesterol, GGT, and familial history of diabetes), risk of incident hyperglycemia was inversely related to self-reported daily water intake (Figure 3). The ORs were similar when stratified by various characteristics, including gender and alcohol consumption. Further studies

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will be needed to confirm this interesting observation and to determine whether copeptin/vasopressin secretion may be the mediator. Confounders to consider are stress hormones that may be provoked by dehydration, as well as healthier lifestyle habits in those who consciously keep ‘well hydrated.’

**Insulin Therapy at Discharge**

A group of US investigators used data from multi-institutional electronic health records (01/2004 to 04/2010) to evaluate outcomes in two groups of patients who had used insulin during a hospitalization based on whether or not they subsequently continued it after discharge (abstracts 1028 and 1029).

Of 732 adult patients with Type 2 diabetes who were newly initiated on insulin during a hospitalization with a last recorded HbA1c ≥8% within 3 months of the hospital stay, 182 patients continued and 550 discontinued insulin upon discharge. The baseline HbA1c levels in the two groups were 11.1% vs. 9.5%, respectively (abstract 1028). During the 12-months post-discharge, patients who continued insulin had greater HbA1c reduction (3.4% vs. 1.5%, p<0.01), higher HbA1c goal achievement (41% vs. 31%, p=0.02), and comparable hyperglycemia rates (8% vs. 5%, p=0.25) vs. those who discontinued insulin. The same between-group patterns were observed in the sub-group of patients with HbA1c ≥9%.

Re-analysis after multivariate adjustments were generally consistent with the unadjusted findings for both HbA1c subgroups—HbA1c reduction: adjusted absolute difference, 1.67% and 1.53%, respectively, both p<0.01; HbA1c goal achievement, OR 1.66 and 2.15, p=0.06 and p=0.03, respectively; hyperglycemia, OR 1.02 and 0.91, p=0.97 and 0.90, respectively). Notably, among the HbA1c ≥9% subgroup, insulin continuation was associated with lower risks of all-cause hospitalizations (HR 0.58, p<0.05) and diabetes-related hospitalizations (HR 0.46, p<0.05).

In a related presentation, of 2,160 adult diabetic patients who used insulin within 30 days before and during a hospital stay, 851 patients continued insulin over the first 60 days post-discharge and 1,309 patients did not (abstract 1029). Compared with the patients who interrupted their insulin at discharge, those who continued it were slightly younger (63 vs. 65 years, p<0.01), had more frequent baseline ophthalmic complications (36% vs. 29%, p=0.01), and higher blood glucose on admission (211 mg/dl vs. 187 mg/dl, p<0.01). Kaplan-Meier analysis showed that patients who continued insulin had significantly lower risks of all-cause hospital re-admissions (HR 0.88; 95% CI: 0.77, 0.99) and ER visits (HR 0.88; 95% CI: 0.78, 0.99). Furthermore, multivariate analysis showed that patients who continued insulin had a significantly higher HbA1c reduction, both in the overall population (diff=0.31%, p<0.01) and in those patients with HbA1c ≥7% before discharge (diff=0.29%, p<0.05).

Taken together, these findings indicate more favorable metabolic control and reduced risk of re-hospitalizations among Type 2 diabetes patients who were treated with insulin during a hospitalization and then continued it after discharge, irrespective of whether the patients were treated with insulin prior to the hospitalization. Of course, possible confounders that were not adjusted for in these studies include the overall quality of medical care post-discharge in the two groups or greater frequency of medical follow-up visits in insulin-treated patients—which might easily explain some of the readmission results reported.

**Cognitive Dysfunction in Elderly Type 2 Diabetes Patients**

Type 2 diabetes is associated with a high risk of dementia. Milrad and coworkers from Argentina analyzed the association between glycomic control and cognitive dysfunction in 427 elderly patients with Type 2 diabetes and without a prior diagnosis of Alzheimer’s or other dementing illness (55% female, age 71.8±5.6 years, diabetes duration 11.8±9.2 years, HbA1c 7.2±2.7%, BMI 29.7±5.7 kg/m2) (abstract 1288). Other patient attributes included: smoking 7%, dyslipidemia 87%, hypertension 88%, peripheral arterial disease 9%, CAD 20%, and carotid disease 13.1%. Cognitive dysfunction (defined as ≤27 points on Mini-Mental State Examination [MMSE]) was observed in over half of patients (52.7%), and depression was noted in 18.5%. Predictors of cognitive dysfunction, determined by Forward Stepwise Logistic regression, were HbA1c >7% (OR=0.52; 95% CI: 0.28-0.94; p<0.02), depression (OR=1.80; 95% CI: 1.03-3.15; p<0.03), low income (<300 Euro per month) (OR=2.37; 95% CI = 1.26, 3.41; p<0.002), and lower education level (≤7 years) (OR=3.71; 95% CI: 2.35-5.86; p<0.001). Living alone (OR: 0.50; 95% CI: 0.28-0.94; p<0.03) and obesity (OR: 0.62; 95% CI:0.40-0.96; p<0.03), for unclear reason, appeared to be protective. These data reaffirm the high prevalence of cognitive dysfunction in older diabetic individuals and identify several risk factors (poor glycemic control, low education level, low income, depression), which—if confirmed—might be used to identify at-risk patients for screening.

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