

Diabetes 2009

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for the Study of Diabetes ■ Vienna, Austria

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How to Screen?

Important data on diabetes presented at the 45th Annual Meeting of the European Association for the Study of Diabetes comes to you in **Diabetes 2009**, 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 2009** will be followed by a **Diabetes 2009** 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 2009 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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Diagnostic criteria for diabetes have changed over time and have become a controversial topic in the last few months. The current criteria endorsed by the ADA (American Diabetes Association) include fasting plasma glucose (FPG) ≥ 126 mg/dl, which is the preferred test, or 2-hour plasma glucose (PG) during an oral glucose tolerance test (OGTT) ≥ 200 mg/dl, which is actually rarely done in clinical practice in the US. Frank hyperglycemia (PG ≥ 200 mg/dl) in the presence of clinical symptoms also meets diagnostic criteria (Table 1). The particular cut-points for FPG and OGTT were chosen based on large cross-sectional studies which showed that the frequency of retinopathy remains low below these levels, and rises steeply thereafter (Nathan *et al.*, *Diabetes Care* 2009). However, other cross-sectional studies have not replicated this threshold effect (Wong *et al.*, *Lancet* 2008).

This summer, the International Expert Committee (IEC) recommended that HbA1c become the preferred test for the diagnosis of diabetes, with a cut-point of $\geq 6.5\%$. The three main reasons for the IEC's recommendation were: 1) HbA1c has recently become standardized globally, eliminating variability in assay performance, 2) HbA1c need not be collected in the fasting state, so it is more convenient, and 3) HbA1c has a similar relationship to retinopathy as FPG and 2-hour PG. However, it is still unclear which test, or combination of tests, is ultimately best and most cost-effective for diagnosis. The ADA and the WHO are currently deciding on whether the IEC's recommendations will be adopted.

Although the relationship between HbA1c, FPG, 2-hour PG, and retinopathy has been

explored in multiple large cross-sectional cohorts, few longitudinal studies have been done in this area. Massin *et al.* from France evaluated the predictive value of HbA1c and FPG for retinopathy in the longitudinal DESIR study (Data from the Epidemiological Study on Insulin Resistance) (abstract 55). In her presentation, Massin explained that out of over 5,000 original DESIR participants, 700 were invited to attend retinopathy evaluation 10 years after they entered the study and were included in the analysis. In the sample, there were 235 patients with diabetes, as well as age-, gender-, and center-matched 227 participants with impaired fasting glucose (IFG; ≥ 110 mg/dl in Europe), and similarly matched 238 participants with normal glucose parameters. Using established criteria for retinopathy, they found 44 cases in this cohort—19 (8.1%) among patients with diabetes, 19 (8.4%) in those with IFG, and 6 (2.5%) in subjects with normal glucose parameters. Prevalence of retinopathy was thus similar in those with diabetes and IFG. The majority of the retinopathy findings were mild, and visual impairment was not reported. Importantly, mean baseline FPG and HbA1c values were higher in those with vs. without retinopathy (130 vs. 106 mg/dl for FPG, 6.4 vs. 5.7% for HbA1c; both $p < 0.0001$). The positive predictive value of FPG and HbA1c for retinopathy were low at 17.4% and 15.9% at cut-points of 117 mg/dl and 6.5%, respectively. Although baseline retinopathy was not assessed, this study had the advantage of longitudinal follow-up. Massin's findings appear to support the diagnostic cut-point of 6.5% for HbA1c, as proposed by the IEC.

Table 1. American Diabetes Association (ADA) Diagnostic Criteria for Diabetes Over Time

	ADA Pre-1997	ADA 1997-2003	ADA 2003-2009	IEC 2009
FPG	≥ 140 mg/dl	≥ 126 mg/dl*	≥ 126 mg/dl*	≥ 126 mg/dl
2-hr PG (OGTT)	≥ 200 mg/dl	≥ 200 mg/dl	≥ 200 mg/dl	≥ 200 mg/dl
HbA1c	—	—	—	$\geq 6.5\%$ *

* Preferred test according to guideline authors.

FPG=fasting plasma glucose, IEC=International Expert Committee, OGTT=oral glucose tolerance test, PG=plasma glucose.

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The diagnostic value of HbA1c was also investigated by Hu *et al.* from China in a study of 2,298 subjects from the Shanghai area who underwent all three tests—2-hour PG, FPG, and HbA1c (abstract 284). Using the 2-hour PG ≥ 200 mg/dl as the “gold standard” for the diagnosis of diabetes, they found a very high prevalence of diabetes of 34.6%. Based on the receiver operator curve (ROC) analysis, the optimal cut-point for FPG was 110 mg, which had a sensitivity of 81.5% and specificity of 80.5%, while the optimal cut-point for HbA1c was 6.1%, which had similar sensitivity and specificity (81.0%). When either test was above these cut-points, sensitivity was 96.5% and if both tests were above the cut-points, specificity was 96.3%. These cut-points are well below those proposed by the IEC and being considered by professional societies, and may reflect greater prevalence of post-prandial hyperglycemia in this ethnic group.

Certainly, there are many ways to diagnose diabetes, but does screening really matter? Zavrelova and collaborators from the Netherlands investigated whether diagnosis of diabetes by active screening vs. diagnosis in the usual practice setting is associated with a lower risk for retinopathy and chronic kidney disease (CKD) defined as estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m² (abstract 285). Using the large population-based Hoorn study (n=2,484, age 50-75 years), the investigators identified 115 subjects with newly diagnosed Type 2 diabetes by 2-hour PG (OGTT) screening, 44 of whom returned 10 years later for follow-up examination and were assessed for eye and renal complications. They compared this group to a cross-sectional population of Type 2 diabetes patients diagnosed during routine care (n=1,336), for which they estimated the incidence of complications using a regression coefficient taking into account diabetes duration. The 10-year incidence of retinopathy was 12.2% in the screened subjects

vs. 8% when estimated for the usual-care group (NS). The 10-year incidence for CKD was significantly higher at 37.8% in the screened group vs. 20% when estimated for the usual-care group. So, surprisingly, this study showed a higher incidence of retinopathy and significantly higher incidence of CKD in the screened subjects, which the investigators proposed may be due to the higher risk of asymptomatic hyperglycemia. However, other factors, such as higher blood pressure as well as higher prevalence of retinopathy at baseline in the screened group may have also contributed to the results. Certainly, this is a critically important area of study that merits further investigation, especially now that screening parameters are being reassessed.

As professional organizations put forward their recommendations for the diagnosis of diabetes, it is likely that a variety of approaches will continue to exist based on regional differences in patient characteristics, prevalence of risk factors, cost, and individual preferences.



Enhancing Incretins



Dipeptidyl peptidase-4 (DPP-4) inhibitors are a newer, but increasingly more established, class of oral anti-hyperglycemic medications. These agents, also known as the incretin enhancers, prevent the inactivation of endogenous incretin hormones, GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide). As a result, they secondarily promote glucose-dependent increases in insulin secretion from the pancreatic beta-cell and suppression of glucagon from the alpha cell. Currently, two DPP-4 inhibitors, sitagliptin and saxagliptin, are commercially available in the US. The role of these agents continues to be defined, whether used as monotherapy or in combination with other agents.

Sitagliptin was evaluated in combination with metformin as well as with the thiazolidinedione (TZD), pioglitazone. Williams-Herman and US colleagues assessed the long-term efficacy (over 2 years) of sitagliptin as monotherapy or added to metformin (abstract 754). Two pooled populations of patients with Type 2 diabetes were evaluated for HbA1c response in comparison with baseline following treatment with sitagliptin alone (n=147) and in combination with the biguanide (n=852) dosed at $\geq 1,500$ mg daily. In the monotherapy group, which importantly included only patients

Table 2. Effect of Pioglitazone ± Sitagliptin on Glycemia in Drug-Naive Type 2 Diabetes Patients

Parameter	Change from Baseline after 24 Weeks		
	Sitagliptin + Pioglitazone (n=260)	Pioglitazone monotherapy (n=260)	p-value
HbA1c	-2.4%	-1.5%	<0.001
Percent achieving HbA1c < 7%	60%	28%	<0.001
Fasting plasma glucose (mg/dl)	-63.0	-40.2	<0.001
2-hour post-prandial glucose (mg/dl)	-113.6	-68.9	<0.001

who were treatment-naive at baseline, mean baseline HbA1c was reduced from 8.5% to 6.9% at 2 years. Add-on therapy with sitagliptin decreased mean HbA1c from 8.0% to 6.9% also at the 2-year mark. These HbA1c reductions are larger than were demonstrated in the initial sitagliptin pivotal trials and may, in part, reflect study methodology. Importantly, no control groups were included in these analyses. Nonetheless, the sustained effect over 2 years is encouraging, in light of secondary drug failure rates recognized with sulfonylureas.

Similar results were achieved when this DPP-4 inhibitor was added to pioglitazone in

drug-naive patients. In a randomized, controlled trial of patients with Type 2 diabetes, Yoon and international co-investigators compared sitagliptin 100 mg and pioglitazone 30 mg daily to monotherapy with pioglitazone, also 30 mg daily (abstract 747). The primary endpoints were measures of glycemic control at baseline and at 24 weeks. The combination regimen produced a more favorable response (Table 2) in glucose as well as in two markers of beta-cell function, insulinogenic index and the post-prandial proinsulin/insulin ratio ($p \leq 0.001$). Patients in either group tolerated the regimens well, experiencing similar rates of hypoglycemia, gastrointestinal adverse effects, and edema.

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In a related study, the investigational DPP-4 inhibitor alogliptin (12.5 mg and 25 mg daily) in combination with pioglitazone (30 mg daily) was compared with either agent alone. Fleck and co-investigators from the US and Germany conducted this randomized, double-blind trial in 655 patients with Type 2 diabetes inadequately controlled by diet and exercise (abstract 749). The 25 mg dose of alogliptin in combination with pioglitazone demonstrated the greatest impact on HbA1c as measured by change from baseline (-1.71%) versus monotherapy with alogliptin (-0.96%) or pioglitazone (-1.15%) ($p < 0.001$). The lower dose combination regimen demonstrated a significant decrease in HbA1c when compared to pioglitazone alone (-1.56% versus -1.15%, respectively, $p < 0.001$). Statistical significance with respect to HbA1c was achieved at 4 weeks in both combination regimens (vs. monotherapy) and was maintained for the entire 26-week study. Other measures (e.g., percentages achieving HbA1c $\leq 7\%$ and mean fasting plasma glucose change from baseline) favored combination therapy, but did not reach statistical significance. Weight gain was greatest with the combination regimens; for unclear reasons, edema was associated only with pioglitazone monotherapy; and hypoglycemia was rare in all four groups. From this data, the investigators suggested the

potential future use of combination TZD/DPP-4 inhibitor as initial oral therapy in Type 2 diabetes. Currently, of course, metformin is widely considered the optimal first-line agent.

In a longer-term trial (102 weeks), the recently approved saxagliptin when added to metformin was evaluated for safety and efficacy in comparison with metformin alone. DeFronzo and international colleagues randomized four groups of patients to receive either saxagliptin 2.5 mg, 5 mg, 10 mg once daily or placebo with metformin (1,500-2,500 mg daily) for 24 weeks (abstract 132). Patients who did not achieve glycemic control criteria received open-label pioglitazone (15-45 mg daily) for an additional 42 months in a long-term extension trial. At 102 weeks, placebo-subtracted HbA1c values for the three dosing groups were similar at -0.62 (95% CI, -0.84, -0.40), -0.72 (-0.94, -0.50), and -0.52 (-0.74, -0.30), respectively. Rates and severity of hypoglycemia were low and numerically comparable between groups, as was a small decrease in body weight.

Lastly, vildagliptin 50 mg twice daily, available only overseas, was assessed for its utility when added to basal insulin in patients with suboptimal control (HbA1c $> 8.0\%$). A total of 14 patients with Type 2 diabetes receiving ≥ 25 units of insulin glargine and at least 1 gram per day of metformin were evaluated by Brooks and UK colleagues (abstract 750). Patients underwent 48 hours of continuous subcutaneous glucose monitoring

prior to and 2 days after the initiation of vildagliptin. Changes from baseline following 8 weeks of vildagliptin in these patients were as follows: mean HbA1c decreased from 8.4 to 7.3%; fasting glucose and post-prandial glucose decreased by 11% and 29%, respectively. Body weight was stable. The total number of hypoglycemic events was similar during the 8 weeks before initiation of vildagliptin ($n=6$) and after 8 weeks of therapy ($n=7$). These data are somewhat surprising in these patients with longstanding disease, as the main mechanism of action of the DPP-4 inhibitors is to augment insulin secretion. This may suggest a predominate benefit on glucagon in these patients or the maintenance of some residual insulin secretory capacity despite their requirements for exogenous insulin therapy.

In general, the DPP-4 inhibitors offer a treatment option to improve glycemic control in patients with Type 2 diabetes, particularly in those earlier on in the disease course before insulin secretion has deteriorated too much. They have not been associated with common side effects of other agents such as hypoglycemia and weight gain. A recent FDA safety alert (September 25, 2009) identified a potential association between sitagliptin and acute pancreatitis, but a direct causal relationship has not been determined. We advise the cautious use of all drugs for diabetes, taking into account their risks, benefits, and costs, as well as the importance of individualizing treatment targets.



Meters & Monitors



Reports this week add to a building reassessment of the importance of routine self-monitoring of blood glucose (SMBG; 'fingersticks') in stable patients with Type 2 diabetes.

SMBG has been shown to improve glycemic control in patients using insulin, but not in Type 2 diabetes patients taking oral agents. Effects on health related quality of life have been reported as either neutral or negative (i.e., more depressive symptoms). It was in this context that Logtenberg and colleagues from the Netherlands conducted a study in which they randomized 40 Type 2 diabetes patients who had persistent moderately controlled glycemia (median diabetes duration 6.0 years, mean age 59 years, HbA1c 7.6%, BMI 31 kg/m²) to either SMBG added to usual care vs. usual care without glucose monitoring (abstract 85). All were using a stable regimen of 1-2 different oral anti-hyperglycemic drugs during the preceding 3 months, and had not used any SMBG in the pre-

ceding 6 months. Treatment was intensified when HbA1c reached or exceeded 8.5%. At the end of the 1-year study, there were no significant changes between groups on four different, standardized tests of health-related quality of life and treatment satisfaction. The investigators argued that SMBG should be reconsidered in patients being treated solely with oral anti-hyperglycemic agents.

Where Does CGM Fit In?

Newer monitoring technologies continued to receive significant attention at this week's EASD meeting.

Raccach and French colleagues randomized 132 adults and children with Type 1 diabetes, insufficiently treated with multiple daily insulin injections (MDI) (HbA1c $\geq 8\%$) to treatment with 6 months of insulin pump integrated with subcutaneous interstitial continuous glucose monitor-

ing (CGM, Paradigm[®] REAL Time System) or to continuous subcutaneous insulin infusion (CSII) with standard SMBG (abstract 89). HbA1c decreased in both study arms after treatment was changed from MDI (CGM, $n=55$, $-0.81\% \pm 1.09$; CSII, $n=60$, $-0.57\% \pm 0.94$; $p=0.087$), but in a per-protocol analysis of 91 patients who wore sensors more than 70% of the time (as required by study protocol), HbA1c improved significantly more in the CGM group (Figure 1). CGM hyperglycemia parameters decreased in line with HbA1c, without any increased hypoglycemia.

Beginnings of the 'Artificial Pancreas'?

Hermanides and European coworkers conducted the first study in which treatment utilizing a CGM sensor-augmented insulin pump (SAP) (Paradigm[®] REAL-Time) or standard care with MDI were compared in a randomized, multicenter,

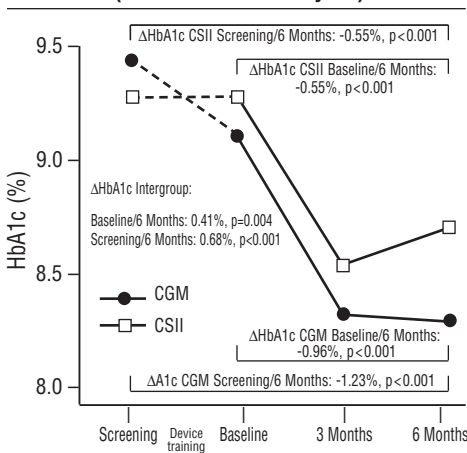
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prospective manner (abstract 90). SAP involves the sensor advising a certain meal-time bolus in part dependent on recent interstitial glucose reading. The study population was comprised of 83 Type 1 diabetes patients who were matched between the randomization groups (age 39 ± 12 and 37 ± 11 years; diabetes duration 17 ± 11 and 21 ± 9 years, 50% and 46% female, respectively);

Figure 1. Reduction in HbA1c With CGM or CSII in Compliant Patients (Per-Protocol Analysis)



CGM=continuous glucose monitoring.
CSII=continuous subcutaneous insulin infusion.

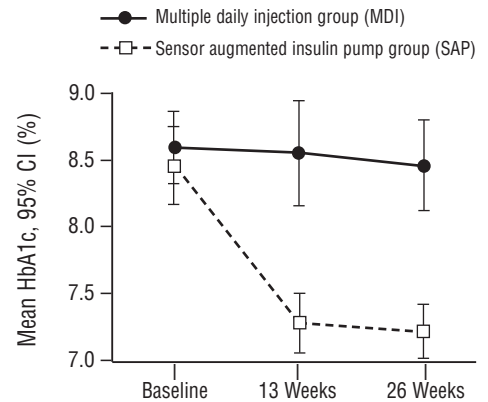
the majority (98%, 43/44; 90%, 35/39) of patients completed the 26-week trial. SAP effectively lowered HbA1c in these poorly regulated patients (Figure 2). The magnitude of the difference in HbA1c change between the treatment groups was -1.10% (95% CI, -1.41 to -0.71, $p < 0.001$). The proportion of patients reaching HbA1c target of $< 7.0\%$ was 34.1% with SAP and 0% with MDI, $p < 0.001$. There was no between-group difference in number of severe hypoglycemia episodes (4 in the SAP group versus 1 in the MDI group, $p = 0.22$) or change in sensor mean area-under-the-curve (AUC) for hypoglycemia. An insulin pump augmented with CGM and mealtime insulin dose advisor is the first step towards a so-called "closed-loop" system.

Into the Future...

Even more novel approaches to glucose monitoring were introduced this week. Herbrechtsmeier *et al.* from Germany reported preliminary results from studying a new optical method for blood glucose assessment in 11 patients with Type 1 diabetes (abstract 934). A small hydrogel chip with a chemical sensor was inserted below the conjunctiva in a minimally invasive procedure. Glucose concentration was measured optically by a small, handheld photometer.

Gal and investigators from Israel and the US reported on *Glucotrack™*, a non-invasive device that uses a weighted average glucose from 3 independent non-invasive methods (ultra-

Figure 2. Mean HbA1c for MDI vs. Sensor-Augmented Insulin Pump



MDI=multiple daily injections.

sound, electromagnetic, and thermal) to provide a more accurate, real-time (prospective) assessment of glucose (abstract 935).

So, the messages on glucose monitoring were mixed in this week's meeting. Routine glucose monitoring may be less important than previously thought in Type 2 diabetes, whereas the emerging consensus is that, in properly selected patients with Type 1 diabetes, even more refined techniques, such as CGM, may provide substantial benefits. The emerging technologies are interesting, but we await more data.



Renally Speaking



In diabetes, hypertension and albuminuria are major risk factors for both cardiovascular (CV) and renal complications. They may be successfully addressed by the pharmacological inhibition of the renin-angiotensin system (RAS). Several presentations this week addressed these important and related issues.

Risk Factors for CKD

The incidence of end-stage renal disease (ESRD) is 10-fold higher in diabetes patients than in normal subjects. Svensson presented data, on behalf of her Swedish colleagues, regarding 3,677 patients with Type 2 diabetes (aged 30-74 years) and no renal dysfunction at baseline (no albuminuria and $eGFR > 60$ ml/min/1.73m²). They were followed for 5 years to determine clinical risk factors associated with development of renal dysfunction (abstract 45). The onset of albuminuria and renal impairment was each independently associated

with high systolic blood pressure (BP) (each $p < 0.02$), increased age ($p < 0.001$), increased triglycerides ($p < 0.02$), as well as higher BMI. (The later was determined when renal impairment was defined by $eGFR$ based on the MDRD (Modified Diet in Renal Disease) equation but not by creatinine clearance based on the Cockcroft-Gault formula, which includes body weight in the calculation). Additional independent risk factors for albuminuria were: increased HbA1c ($p < 0.001$), smoking ($p < 0.001$), HDL-cholesterol ($p < 0.05$) and male gender ($p < 0.001$); and for renal impairment, elevated plasma creatinine at baseline, and female gender (both $p < 0.001$). The adverse effects of BMI on HbA1c, BP, and lipids accounted for ~50% and ~40% of the increased risks for albuminuria and renal impairment, respectively.

The authors proposed that, since not all risk factors for albuminuria and for renal impairment were shared, these may not be entirely linked

conditions in Type 2 diabetes. Moreover, these data suggest that albuminuria screening may not be sufficient and that other markers, such as $eGFR$ (by MDRD), may be needed to better monitor renal function prospectively in diabetes patients.

In a related study, another group from Sweden (Möllsten *et al.*) assessed the impact of age at onset and gender on the risk of young, Type 1 diabetic patients developing ESRD (abstract 46). 6,788 patients from the Swedish Childhood Diabetes Register (incident Type 1 diabetes cases in ages 0-14 years recorded) and 4,847 patients from the Diabetes Incidence Study (incident Type 1 diabetes cases in ages 15-34 years recorded) were followed for a median of 21.2 and 18.9 years (range 13-30 years), respectively. Of these, 125 patients developed ESRD due to diabetic nephropathy. The cumulative incidence of ESRD 25 years after a Type 1 diabetes diagnosis was low in the study cohort: 3.0% in men and

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1.9% in women. In female patients, the risk of ESRD was increased when diabetes was diagnosed during puberty, and was lower when diabetes occurred either before or after puberty. In contrast, male patients had a continuing increase in ESRD risk with older age at diabetes diagnosis. Developing Type 1 diabetes after 15 years of age doubled the risk for male as compared with female patients (HR=2.4). The investigators suggested a role for pubertal status, perhaps related to gonadal steroid modulation, in the development of renal complications. In response to a concern raised by a session attendee, Dr. Möllsten agreed that a more robust analysis would evaluate interactions between age and gender in Cox proportional hazard models. It should be noted that the rates of ESRD are remarkably lower than reported in the past, a reflection of the dramatic improvement in insulin therapy in the past two decades.

HTN in the Elderly: Surprising Findings

Blood pressure is positively correlated with adverse outcomes in the general population irrespective of age. Moreover, anti-hypertensive therapy has been shown to reduce CV outcomes and mortality in both younger and older patients. There is less data across the spectrum of age in diabetic patients, however. Van Hateren and co-workers from The Netherlands investigated the relationship between BP measures over time and all-cause and CV mortality in 881 elderly (≥ 60 years) patients with Type 2 diabetes (abstract 43). The variables used as potential confounders in a Cox proportional hazard model included gender, smoking status, BMI, duration of diabetes, serum creatinine, total cholesterol:HDL ratio, presence of macrovascular complications, albuminuria, use of lipid-lowering and antihypertensive drugs, and age. Over a median follow-up period of 5.7 years, all of the BP measures were *inversely* related to all-cause mortality in the group >75 years of age. *Increases* of 10 mm Hg in systolic, diastolic, and pulse pressures were associated with 19%, 27%, and 19% *decreases* in mortality risk, respectively. Similarly, an *increase* in systolic and pulse pressure resulted in 12% and 14% *decrease* in CV mortality risk, respectively. In the group between 60 to 75 years, the associations between BP and mortality were not significant. Van Hateren concluded that the BP level at which hypertension treatment should be initiated in elderly diabetic patients may not be the same as that for younger individuals. During the Q&A session, Dr. van Hateren admitted that

other confounders may have contributed to their findings (e.g., heart failure) and acknowledged the need for a meta-analysis or a targeted randomized trial.

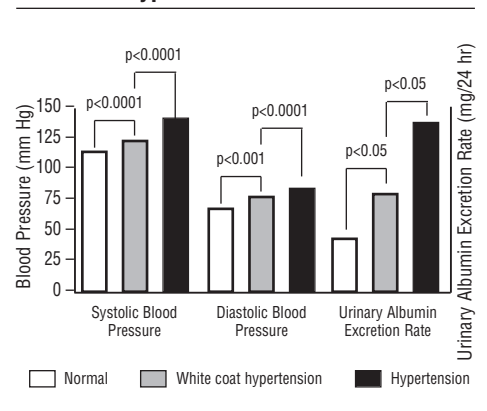
Dual RAS Blockade

Modulation of the RAS has been shown to be renoprotective in patients with diabetes, with most of the data involving ACE inhibitors and angiotensin-II receptor blockers (ARBs). In a study of 599 patients enrolled in a multinational, randomized, double-blind study, Parving and associates of Denmark and the US assessed the impact of baseline renal function on the effect of adding aliskiren, a direct renin inhibitor, to the ARB losartan (abstract 48). Patients (aged 18-85 years) with diabetes, hypertension being treated with optimal antihypertensive therapy, and eGFR ≥ 30 ml/min/1.73m² were administered open-label losartan for 3 months and then randomized to 6 months of add-on treatment with placebo or aliskiren (150 mg daily for 3 months followed by forced titration to 300 mg daily for 3 months). The baseline characteristics of the two groups were similar across eGFR (by MDRD) subgroups (i.e., <60 , ≥ 60 - <90 , and ≥ 90 ml/min/1.73 m²) included in *post hoc* analyses of the study data. The investigators reported that treatment with aliskiren/losartan, as compared with placebo/losartan, reduced the mean urinary albumin-to-creatinine ratio (mean of 3 samples) by 20% ($p<0.001$) in the total study population, with the anti-albuminuric effects consistent across eGFR subgroups (-19%, -22%, and -18%, respectively). Similarly, there was a more favorable effect with dual renin blockade on eGFR—both overall (-2.4 vs. -3.8 ml/min/1.73 m², $p=0.07$) and in each subgroup—as well as in the incidence of patients developing renal dysfunction, defined as serum creatinine >2 mg/dl (16.4% vs. 30.1%, $p=0.02$). The incidence of hyperkalemia (>5.5 mEq/l) was more common in aliskiren-treated patients with eGFR <60 (22.5% vs. 13.6%), but equal in the other eGFR categories.

In Contrast...

Zaytseva and fellow Russian researchers reported on the incidence of and risk factors for contrast-induced nephropathy (defined as increase in serum creatinine of at least 25% or 0.5 mg/dl over baseline within 48 hours) in patients with Type 2 diabetes who underwent coronary angiography (abstract 1056). The diabetic patients (n=151) had similar baseline serum creatinine to those without diabetes (n=50). Not surprisingly, the incidence of contrast-induced nephropathy

Figure 3. Effect of 'White Coat' Hypertension on Albuminuria



was significantly higher in the diabetic group (40% vs. 16%, $p<0.01$). Risk factors for post-contrast nephropathy in diabetes included contrast volume administered (odds ratio [OR] 2.0 per 100 ml), anemia (OR 2.2), diuretic use (OR 2.6), multivessel coronary disease (OR 3.0), low ($<40\%$) ejection fraction (OR 3.3), and clinical heart failure (NYHA functional classification III or IV) (OR 4.7). In Kaplan-Meier survival analyses, contrast-induced nephropathy was a significant predictor of death, heart failure (new onset or hospitalization), myocardial infarction, stroke, doubling of serum creatinine, and coronary artery bypass surgery within 24 months of follow-up ($p<0.0001$). The investigators recommended intensified control of risk factors, as identified in their study, to potentially protect diabetic patients from such adverse events following contrast administration.

'White Coat' Syndrome

Garcia *et al.* from France followed 412 Type 2 diabetes patients (mean age 58.4 years) who received no CV treatment over a mean observation period of 10.6 years (abstract 1103). They divided the study population into three groups based on their clinic BP and mean diurnal BP, as measured by ambulatory monitoring: (1) normal (clinic $<140/90$ and diurnal $<135/85$ mmHg, n=225), (2) 'white-coat' hypertension (clinic $>140/90$ and diurnal $<135/85$, n=76), and (3) hypertension (clinic $>140/90$ and diurnal $>135/85$, n=111). There were no differences among the groups based on age, duration of diabetes, BMI, or estimated creatinine clearance. There were significant between-group differences (i.e., normal BP vs. 'white-coat' hypertension vs. hypertension) for systolic and diastolic BP, as well as in urinary albumin excretion rates (Figure 3). For the entire population, urinary albumin excretion was weakly associated with the difference between clinic and

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diurnal BP ($r=0.188$, $p=0.002$ with systolic BP; $r=0.145$, $p=0.003$ with diastolic BP). The researchers concluded that 'white-coat' hypertension may not be a benign condition as it may, over time, lead to renal injury. One might therefore argue that

affected patients should still be candidates for BP lowering (and renoprotective) therapy.

In summary, hypertension and albuminuria are important risk factors associated with both CV and renal complications in diabetes. Comprehensive management of patients at risk for diabetic nephropathy should include recognition of related

risk factors, careful monitoring of both urinary and serum markers of renal integrity, and optimization of BP control, including the use of a RAS-modifying agent. Clinicians caring for diabetic patients should also recognize their significantly increased risk of contrast-induced nephropathy and perhaps be less forgiving of isolated in-office elevated BP readings.



So Many Posters, So Little Time....



LADA v. T1DM

Lukic and Serbian colleagues assessed the similarities and differences between patients diagnosed with Latent Autoimmune Diabetes in Adults (LADA) and patients recently diagnosed with Type 1 diabetes (abstract 487). LADA is a slowly developing form of Type 1 diabetes in adult patients. Differentiating clinical, immunological, and metabolic traits have not been fully characterized. The incidence of positive antibodies to glutamic acid decarboxylase (GAD) and tyrosine phosphatase (IA2) was lower in patients with LADA as compared to Type 1 diabetes, regardless of age (<20 years, 20 to 25 years, and ≥ 26 years) ($p<0.001$). Incidence of single positivity to GAD was greater ($p<0.001$) and single positivity to IA2 was lower ($p<0.001$ for ages <25 years; NS for ≥ 26 years) in the LADA group. With respect to clinical course, patients with LADA had longer symptom duration ($p<0.01$), a lower frequency of ketosis ($p<0.01$), less weight loss ($p<0.05$), and a lower incidence of clinical remission ($p<0.05$) in comparison to those with Type 1 diabetes, regardless of age. More preserved insulin secretory capacity favored the LADA group, with higher basal and C-peptide levels ($p<0.01$). The researchers concluded that patients diagnosed with LADA demonstrate more favorable characteristics relative to autoantibody response, clinical course, and metabolic parameters when compared with adult, recent-onset Type 1 diabetes, independent of the age of onset.

The Low Down

Concern about the potential relationship between hypoglycemia and adverse CV outcomes has been heightened since publication of the results of several recent intensive glucose control trials. Miller and US researchers conducted case control studies to determine the potential risk for myocardial infarction (MI) in patients with diabetes experiencing hypoglycemia (abstract 138). Utilizing a US Veterans Health Administration (VA) database, patients with diabetes were identified

during the years 2000 to 2004. They were further divided into no history of MI and cases with first MI. Controls were randomly matched in a 12:1 ratio and were assigned an index date (hospital admission date for MI). Several analyses were conducted including assessment of hypoglycemic events the year prior to MI and estimation of MI risk controlling for confounding variables (e.g., CV risk factors, diabetes complications, concomitant medications). Cases were also stratified by insulin use. The incidence of hypoglycemic events prior to the index date (i.e., first MI) was greater in patients with diabetes (9.6%) versus controls (4.2%). The highest incidence of events occurred during the 2 weeks prior to first MI: 1.60 (1.41 to 1.81) for non-insulin users; 1.53 (1.33 to 1.75) for insulin users, and 1.94 (1.28 to 2.94) for new insulin users. In insulin users, there was not an increased MI risk if the hypoglycemic event(s) occurred more than 6 months prior. The investigators noted that hypoglycemia occurred more often than expected before MI in patients with diabetes. Further research is needed to determine if hypoglycemia is merely a marker for CV risk or if it might directly relate to these events on a pathophysiological basis. Given the recognized counter-regulatory hormonal response to hypoglycemia, the latter is certainly a tenable hypothesis.

"D"-fense!

The results of 2 trials presented this week add to the growing evidence of an association between vitamin D deficiency and Type 2 diabetes. Laboratory experiments have suggested that vitamin D may affect several aspects of glucose metabolism, including pancreatic β -cell function and peripheral insulin sensitivity. In a large cohort study ($n=3,290$) of patients referred for coronary angiography, Pilz and coworkers from Austria and Germany measured 25-hydroxyvitamin D (25[OH]D) levels and found medians of 16.8 ng/ml in patients with normal glucose metabolism ($n=1,415$), 16.4 ng/ml

in those with impaired glucose metabolism (impaired fasting glucose and/or impaired glucose tolerance) ($n=827$), 14.9 ng/ml in newly diagnosed diabetic patients ($n=476$), and 12.7 ng/ml in patients with established diabetes ($n=572$) (p for trend <0.001 , ANCOVA adjusted for age, gender, BMI, and season of blood draw) (abstract 309). In a linear regression analysis, with insulin sensitivity (assessed by homeostasis model [HOMA-IR]) as the dependent variable and age, gender, BMI, season of blood draw, and 25(OH)D as independent variables, there was a significant inverse association between 25(OH)D concentration and insulin resistance (β -coefficient = -0.070 ; $p<0.001$).

Dobnig, Pilz, and others from Austria and Germany determined the impact of low vitamin D levels on all-cause mortality in a mixed population (1,036 patients with and 2,221 patients without diabetes) over a median 7.7-year follow-up period (abstract 316). Mean levels were lower in those with diabetes (15.3 vs. 18.2 ng/ml, $p<0.001$). The investigators observed an inverse relationship between vitamin D status and all-cause mortality, more prominent in those without diabetes. A statistically significant increase in all-cause mortality became evident with 25(OH)D levels below the 70th percentile in non-diabetic patients, and below the 20th percentile in diabetic patients, as compared to the referent group (> the 90th percentile.) In Cox proportional hazards models (adjustments for age, gender, physical activity, smoking status, systolic and diastolic BP, use of statins, ACE inhibitors and beta blockers as potential confounders), the risk of all-cause mortality was increased by ~5-fold and ~3-fold in non-diabetic and diabetic patients, respectively. 20% of patients with diabetes had 25(OH)D levels associated with a 2- to 3-fold increase in mortality, as compared to those with the highest levels.

These data lend support to optimizing our patients' vitamin D status.