Table 1: Unadjusted Incidence Rate per 1,000 Person-Years.

Index HbA1c (%)	AMI	CABG	Stroke	AMI/ CABG/ Stroke
<6	16.5	4.4	63.3	76.5
6-7	18.2	6.0	65.0	80.5
7-9	21.6	6.9	63.8	81.7
≥9	20.6	6.9	48.1	65.2
Overall	19.4	6.1	60.0	76.0

After adjusting for baseline characteristics (gender, age, baseline hypertension, AMI, congestive heart failure, peripheral vascular disease, and cardiovascular disease), hazard ratios for survival and AMI increased with worsening glycemic control (HR=1.57 for HbA1c ≥9%, p<0.001) when compared with the baseline <6% HbA1c group. The same pattern persisted for survival and CABG (HR=1.19 for index HbA1c 6-7, HR=1.56 for index HbA1c 7-9, HR=1.38 for index HbA1c ≥9). With adjusted survival and stroke, however, differences were not significant.

Dr. Thomas concluded, "Elevated index HbA1c is a significant risk factor for AMI, CABG and poorer survival. Glycemic control is associated with real-world, long-term macrovascular outcomes." The data suggest, he added, that "early intervention with intensive diabetes treatment may reduce macrovascular risks." Finally, he noted that ongoing trials (ORIGIN, ACCORD, VADT) are addressing the potential benefits of insulin therapy in patients with cardiovascular disease.

Limitations of this study include the fact that it was an observational study with short follow-up and that because the data were taken from the IHCIS managed care employee database, the population was likely to have been healthier and younger than the usual diabetes database.

Diabetic Peripheral Neuropathy: More Effective Treatments Needed

In a pooled analysis of 1,510 patients enrolled in seven randomized controlled trials, pregabalin (150-600 mg/day) provided significant improvements in pain, sleep interference due to pain, and global health, said Roy Freeman, MD, Harvard Medical School, Boston, Massachusetts, United States. Improvements in pain were dose-related; a clinically meaningful (≥30%) improvement in pain was noted by 43- 62%, though 37% of placebo patients also reported this level of improvement.

"There was a dose-related rapid onset of durable pain relief," Dr. Freeman reported. While pregabalin was well tolerated overall, there was also a dose-related increase in weight gain of approximately 2 kg. For 4% of the 600 mg group, the weight gain was a clinically meaningful increase of at least 7% of body weight. Peripheral edema occurred in 10% (300 mg) to 16% (600 mg). "Clearly the 600 mg dose was more effective, though there were more side-effects," Dr. Freeman said.

Results of another international study, the NATHAN 1 Study, showed that antioxidant treatment with α-lipoic acid improved some neuropathic deficits and symptoms in mild to moderate diabetic neuropathy, but did not affect nerve conduction, based on a composite neurological assessment. The randomized study included 454 subjects given α-lipoic acid 600 mg/day. After 4 years of treatment, the difference between the treatments based on the changes of the composite score including clinical signs (neuropathic deficits) and nerve conduction was only 0.7 points, but the neuropathic deficits did improve in the α-lipoic acid-treated group compared to placebo administration. Dan Ziegler, MD, German Diabetes Center, Dusseldorf, Germany, noted that the "marginal progression" of neuropathy in the placebo arm made it difficult to show a treatment effect. "The designs of future trials must assume a long-term stable neuropathic condition," he said.

Perspective

MD Conference Express asked Nicolaas C. Schaper, MD, PhD, Professor of Endocrinology and Diabetes at University Hospital, Maastricht, the Netherlands, and session moderator, to comment on the studies reported at the Novel Therapies for Peripheral Neuropathy session.

He first noted that there are problems with clinical trials of agents. "You see a huge placebo effect in many studies, as in this study with pregabalin, and many are too short to be clinically relevant," he pointed out. Another problem is the inconsistency between epidemiologic data and clinical trial data, he said. Epidemiologic data suggest there is a steady deterioration in nerve function over time however, a study reported at this EASD showed very little deterioration among trial subjects. "Clinical trials, therefore, may not reflect our clinical practice with this complication," he said.

In studies reported at the EASD α-lipoic acid and aldose reductase inhibitors were found to be either problematic or with relative small effects. "While there may be short-term efficacy in reducing pain with pregablin, there were some relevant side-effects, including edema and weight gain. If these appear by 13 weeks, as shown in this study, then what happens after treatment for 10 years? We need to think carefully about this issue," he continued. "Although we currently have treatments such as tricyclic antidepressants (eg, amitriptyline) and anticonvulsants

(eg, pregabalin and gabapentin) that can result in pain relief, pharmacologic pain treatment is still ineffective in too many patients and we urgently need more effective therapies."

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if anyone in your clinic is diagnosed before 6 months, he or she doesn't have type 1 diabetes, but rather what I would term neonatal diabetes."

Further research showed that mutations in the insulin gene that are responsible for permanent neonatal diabetes replace or introduce cysteine residues or alter cysteine's structure, substituting serine for glycine at B8 (Støy J et al. *Proc Nat Acad Sci USA* 2007). "We are beginning to understand the biology," Prof. Hattersley said. "So we can begin to think of exciting ways in which we can continue the normal allele and downregulate the mutant allele, which should result in the patients being able to keep their β-cells if we can do it early enough."

The aforementioned patient above had the Kir6.2 mutation, the most common cause of neonatal diabetes. With that mutation, ATP does not close the K_{ATP} channel and the membrane becomes hyperpolarized, with the result that there is no calcium influx and no insulin secretion. The Kir6.2 channel is also expressed in the muscles, nerves, and the brain. The most severe cases, about 5% of those with the Kir6.2 mutation, have the DEND (Developmental delay, Epilepsy and Neonatal Diabetes) syndrome that is characterized by severe developmental delay, epilepsy <12 months, and permanent neonatal diabetes; another 16% has what can be referred to as intermediate DEND in which there is mild developmental delay, no epilepsy, and permanent neonatal diabetes.

While mutational analysis helps predict onset and relapse of diabetes, Prof. Hattersley said, what is of preeminent interest to patients and the mother of the neonatal diabetes child is whether it can help with treatment. The ATP channel that does not close with the Kir6.2 mutation is acted upon by sulfonylureas, but by a different route — a non-ATP-dependent route. The question became, "Could sulfonylureas close the ATP channel and result in insulin secretion?"

A chance event helped answer this question. A man included in the first study, who had been diagnosed with diabetes 46 years earlier at the age of 3 months, had come from a rural family that, not being able to afford insulin, begged that he be allowed to take tablets. As a result, he had been treated with sulfonylureas all along and turned out to have the best glycemic control of all the patients in the series. Subsequent studies in Kir6.2 children showed better (Pearson ER et al. *New Engl J Med* 2006) and more stable (Zung A et al. *J Clin Endocrinol Metab* 2004) glycemic control with sulfonylureas (HbA1c 6.4%) than with insulin (HbA1c 8.1%). Clinical experience showed, unfortunately, that neurological features were not helped by sulfonylureas. However, a child with an insulin pump unable to pull himself up at nearly 2 years of age began walking 3 weeks after starting sulfonylurea treatment. Another child's school reported immediate changes in concentration and speech (he had been unable to speak at age 5). Every single case since has demonstrated improvement with sulfonylurea treatment in function and in diabetes, Prof. Hattersley said.

"We have shown that knowing the cause of people's diabetes can lead to very unexpected treatments. Also, the finding of new genes really gives the possibility that we may start to individualize treatment" Prof. Hattersley closed, urging that patients diagnosed with diabetes before 6 months should definitely be sequenced for Kir6.2 (and SUR1). "It's crucial because their lives can change."

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Improving Risk Calculations Through Genotyping

Traditional calculations of cardiovascular risk, such as the Framingham Risk Score, only accurately predict events only in a minority of subjects. Investigators from the United Kingdom evaluated whether a set of common variants in genes previously found related to coronary heart disease risk might enhance the utility of such algorithms. In a multivariate analysis, they found that several genes significantly ($p<0.001$) improved the predictive utility of such algorithms, including those related to uncoupling protein 2, apolipoprotein E, lipoprotein lipase, and apolipoprotein A4, as well as several genes showing interaction with smoking, interleukin-6 and platelet/endothelial cell adhesion molecule genotypes. In the future, risk estimates may include not only conventional risk factors but also a panel of selected genotypes concluded Philippa Talmud, PhD, University College London, United Kingdom.

Severe Mental Illness and Type 2 Diabetes

The prevalence of diabetes among patients with severe mental illness is 2-3 times higher than that for the general population. While this disproportionate risk has largely been attributed to treatment with atypical antipsychotic agents, Stephen Gough, MD, University of Birmingham, UK, said, "I think the link goes well beyond this."