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Meeting Report

4th Annual Symposium on Self Monitoring of Blood Glucose (SMBG) Applications and Beyond, May 12–14, 2011, Budapest, Hungary

Boris N. Mankovsky, M.D.

International experts in the fields of diabetes, diabetes technology, endocrinology, and pediatrics gathered for the 4th Annual Symposium on Self Monitoring of Blood Glucose (SMBG) Applications and Beyond. The aim of this meeting was to continue setting up a global network of experts in this field and provide an international platform for exchange of ideas to improve life for people with diabetes. In addition to a comprehensive program of scientific presentations, various interactive workshops, a moderated debate, and a keynote lecture were part of the meeting. All these discussions were intended to help identifying gaps and areas where further scientific work and clinical studies are needed.

How Long- and Rapid-Acting Insulin Analogs Have Changed Diabetes Care

Satish K. Garg, University of Colorado, Aurora, CO

New insights into fasting plasma glucose and glucose variability

According to Garg, there is no doubt that elevated fasting plasma glucose (FPG) is a risk factor for cancer and vascular mortality, as well as for non-cancer and non-vascular deaths. However, is this also valid for postprandial blood glucose (PPG)? Garg reminded the concept established by Monnier and co-workers, describing a larger contribution from PPG and less from FPG to lower levels of glycosylated hemoglobin (HbA1c) compared with higher levels. Implementation of these data led to an approach of primarily treating elevated PPG rather than elevated FPG, unless HbA1c is quite high, Garg explained.

At the 2010 American Diabetes Association (ADA) meeting diabetologists challenged the concept of Monnier and colleagues. They provided evidence that even at glycemic states that are close to normal, FPG is an important contributor to HbA1c. Lowering HbA1c and FPG with a long-acting insulin treatment also produces a lowering effect on PPG, Garg said. This was confirmed by an analysis of a substudy of the ORIGIN trial with insulin glargine, showing that tight glycemic control of FPG also reduced PPG.[1]

Does glucose variability influence outcomes in people with diabetes? "We still do not have a study which shows that variability is important for outcomes," Garg stated. However, there are some data that indicate an association between glucose variability and markers of oxidative stress.

In the A1c-Derived Average Glucose (ADAG) Study, there was a direct association between FPG, as well as PPG, and cardiovascular risk, as measured by a cardiovascular risk score. In addition, there was a trend indicating that higher glucose variability is associated with higher incidence of cardiovascular risk factors.[2] In the Verona Study, more than 1,400 people with type 2 diabetes mellitus (T2DM) were followed for 10 years in order to assess total and cause-specific mortality. Long-term variability of FPG turned out to be an independent predictor of mortality in people with T2DM, including cancer mortality.[3] Variability of FPG also seems to predict the development of proliferative diabetic retinopathy, independently of average glycemic indices, in a cohort of 170 people with T2DM.[4] However, Garg pointed out there has been no study with clinical end points like the Diabetes Control and Complications Trial (DCCT) yet confirming that glucose variability is in fact an independent risk factor in people with diabetes.

After about 15 years of diabetes duration, the enemy is hypoglycemia

In contrast to glucose variability, the picture appears to be much clearer for hypoglycemia. Numerous evidence exists indicating that hypoglycemia is associated with unfavorable outcomes. For example, in the Veterans Affairs Diabetes Trial (VADT), severe hypoglycemia turned out to be one of the strongest risk factors for cardiovascular mortality. In people with T2DM, the risk of hypoglycemia and unfavorable outcomes is increasing with diabetes duration. "Hypoglycemia is becoming an enemy at about 15 years of diabetes duration," Garg warned.

New insulin analogs are needed

According to Garg, it is still a challenge to achieve close to physiologically normal glycemic profiles with the currently available insulins. Rapid-acting insulin analogs have been shown to have a faster onset and a shorter duration of action compared with regular human insulin. "In most aspects, there is no difference between the available insulin analogs," Garg

Department of Diabetology, National Medical Academy for Postgraduate Education, Kiev, Ukraine.

said. In his opinion, only a slight advantage of insulin glulisine in regard to the onset of action exists. What separates this insulin analog from other rapid-acting analogs is that the insulin glulisine solution does not contain hexamer-promoting Zn, which might be helpful as it allows a more rapid absorption.

Garg presented data from the DCCT and its extension study, Epidemiology of Diabetes Interventions and Complications (EDIC), indicating that rapid-acting insulin analogs contribute to a lower risk of hypoglycemia. During the DCCT, which was finished 1993, and in the first years of EDIC, the group with intensified treatment had a significantly elevated risk of hypoglycemia. This risk decreased in the year 1996 when the first rapid-acting analog, insulin lispro, entered the market. "But until now we don't have the ideal rapid-acting insulin yet," a sentiment demonstrated by continuous glucose monitoring studies, Garg stated.

Are we expecting further improvements in the field of insulin analogs in the future? Probably yes, as some promising developments have been published recently. As an example, Garg mentioned a co-administration approach of insulin lispro and regular human insulin with recombinant human hyaluronidase (rHuPH20), which produced earlier and greater peak insulin concentrations and improved postprandial glycemic control compared with administration of lispro or regular human insulin alone.

"There is also a need for better long-acting insulin analogs that work for the full 24 hours," Garg stated. He referred to the novel ultra-long-acting insulin analog degludec, which is currently being tested in Phase III clinical trials. Insulin degludec was shown to have a durable and flat action profile. The delayed onset of action is enabled by the addition of a fatty acid, comparable to insulin detemir, causing the formation of multihexamers after injection, and thereby prolonging the duration of action. In Phase II clinical trials, degludec provided comparable glycemic control to insulin glargine at similar doses in people with type 1 diabetes mellitus and T2DM. Furthermore, people with type 1 diabetes had lower rates of hypoglycemia under degludec compared with glargine.

Garg closed his talk with some personal wishes for the future of diabetes care:

- a "real" 24-h long-acting insulin analog to be used in continuous subcutaneous insulin infusion systems
- a bolus insulin that mimics physiologic prandial insulin with onset of action in approximately 5 min, peak at approximately 30 min, and a duration of action of approximately 4 h
- making sense of, and reinforcement of, the need for SMBG
- better accuracy of SMBG with uniform connectivity with, for example, smartphones
- advanced and more proactive continuous glucose monitoring systems
- improved rapid-acting insulin analogs, and talking pens with memory
- advanced insulin infusion pumps with less catheter blockage
- closed-loop systems

All in all, according to Garg, there is still a need for smarter ways to reduce elevated glucose levels and glucose variability in people with diabetes and to allow more physiological insulin treatment.

Self-Monitoring and Educational Tools Are Means to Empower Patients and Manage Chronic Diseases

Matthias Axel Schweitzer, Roche Diabetes Care, Mannheim, Germany

The purpose of a medical device is to improve outcomes and/or the management of the disease

"We should always keep this in mind," Schweitzer stressed in his talk. He presented a selection of new structured testing (ST) concepts of SMBG and related clinical trial results through which Roche aims to evidence and implement new strategies to improve patient outcomes in diabetes.

Such concepts are the Accu-Chek® 360° View tool, the Accu-Chek Assist educational tool, and also a novel "Automated Decision Support Tool" (Roche).

A characteristic of SMBG is that it lacks a "mode of action" compared with pharmacological medication, Schweitzer said. As SMBG itself is just an act of information generation, the results of SMBG have to be transferred into a "medically meaningful treatment decision," either lifestyle modification or medication change or both.

In this light, Schweitzer gave an overview on the evolution of "glucose information generation" from random testing—for which only a trend toward more favorable outcomes was shown in clinical studies—to modern ST strategies and finally new technologies. "We start to make it better usable," he stated.

The years 2008 and 2009 marked significant milestones in this respect. In 2008, the International Diabetes Federation (IDF) Task Force on Clinical Guidelines, in conjunction with the Self-Monitoring of Blood Glucose International Working Group, convened a workshop to address the use of SMBG in people with T2DM who are not treated with insulin. In 2009, intensive or "focused" SMBG protocols for the use of pattern analysis were recommended by the newly released IDF guideline on SMBG in non–insulin-treated T2DM.[5] Furthermore, the IDF called for a new generation of clinical studies analyzing SMBG in a structured approach.

The STeP Study provided proof of concept that ST with Accu-Chek 360° View works

The randomized controlled STeP (Accu-Chek 360° View Outcome Study in the United States) trial investigated the effects of seven-point SMBG profiles over three consecutive days performed at least quarterly in non–insulin-treated people with T2DM. The main outcome of the STeP trial was that the group using ST showed a significantly greater mean HbA1c reduction over 12 months than the group using standard of care SMBG (intention to treat analysis, $\Delta = -0.3\%$; per protocol analysis [80% compliance with the protocol specifications], $\Delta = -0.5\%$).

Patients who performed ST were able to improve their mean blood glucose levels at any time point during the day, and glucose excursions were minimized as well. Based on pattern analysis via the Accu-Chek 360° View form, the treating physicians in the ST group initiated treatment adjustments earlier and more aggressively compared with the actively controlled group. Also noteworthy is that the general

well-being of enrolled patients significantly improved in the ST group.[6]

Another study, the ACCU-CHEK 360° View Study in India, in which patients were randomized according to ST (ACCU-CHEK 360° View) or standard of care according to their specific preference, showed even stronger HbA1c reductions and a more pronounced difference between the treatment groups.

Several ongoing studies will disclose additional evidence later in 2011 and next year, in 2012 (e.g., the randomized controlled ACCU-CHEK 360° View VA US Study, the PRISMA Study in Italy, or the Compass Study in China).

Evolution of glucose information generation continues—from random testing to ST to new technologies

Next steps in the evolution of glucose information generation will be novel tools that, in addition to enabling pattern recognition by displaying the results of ST, will provide decision support and also propose treatment adjustments based on the generated information.

This "automatic decision support" has been tested in a clinical trial, the "Accu-Chek Decide Study." The trial was a virtual, online study in which 288 U.S. healthcare providers (HCPs) (internists, family practice physicians, and nurse practitioners) analyzed 30 Accu-Chek 360° View cases derived from the STeP Study. The cases depicted different blood glucose patterns, fasting hyperglycemia, preprandial hyperglycemia, bedtime hyperglycemia, hypoglycemia, postprandial excursions, and normoglycemia.

HCPs were randomized into four groups receiving:

- only the structured blood glucose monitoring data from Acu-Chek 360° View, or
- the structured blood glucose data from Accu-Chek 360° View together with printed reports from the decision support tool or
- the structured blood glucose data from Accu-Chek 360° View together with the educational DVD used in the STeP Study or
- the structured blood glucose data from Accu-Chek 360° View together with the combination of the decision support toool reports and the educational DVD

HCPs within these groups analyzed the study cases. They were asked to identify the primary glycemic abnormality and choose an appropriate therapy based on presented blood glucose information. Responses were compared with the correct answers, which derived from an endocrinologist expert panel.

Participants also completed questionnaires on the Accu-Chek 360° View form and the decision support tool report, pattern analysis training, or both. According to Schweitzer, the results of the Accu-Chek Decide Study are promising and show the additional value of both educational tools and (automated) decision support tools. They will be presented at the 2011 ADA Meeting.

In the future there will be even more options: Schweitzer proposed that one could combine ST with continuous glucose monitoring for personalized pattern analysis.

The principle of "ST" does not only apply to SMBG

At the end of his talk, Schweitzer presented a link to another indication in which patient empowerment, self-monitoring, and self-management of medication have been used successfully: in the TASMINH2 trial, telemonitoring and self-management of hypertension resulted in significant and worthwhile reductions in blood pressure that were maintained over an investigational period of 12 months compared with usual care.[7]

Management of chronic diseases, such as diabetes mellitus, moves more and more to primary care. Effective patient self-management tools and products are needed to enable patients and HCPs to meet their therapy goals. In this respect, products and concepts such as "ST" are important milestones for improved self-management of diabetes.

Evidence of Structured Testing: The PRISMA Study

Emanuele Bosi, Vita-Salute San Raffaele University, Milan, Italy

Recent findings in the field of SMBG have taught us that a successful approach to SMBG has to be structured. However, the ideal frequency and time points of SMBG measurements to generate the greatest benefits for patients still have to be determined. Bosi presented an update on the ongoing Italian PRISMA Study, which tests a different SMBG approach than the one used in the STeP Study.

There is a need to define appropriate SMBG implementation and data utilization by both patients and physicians

The debate about the usefulness of SMBG in people with T2DM who are not on insulin is still ongoing. Although several observational studies and randomized clinical trials (RCTs) have been performed on this matter, the results have been inconsistent so far. According to Bosi, this is most likely due to differences in study designs, populations, and interventions used. In his opinion, it is still a challenge for RCTs to demonstrate a potential benefit of SMBG in non–insulin-treated people with T2DM. In an RCT it is difficult to separate the contribution of SMBG from that of other components of diabetes management. Nevertheless, in view of "the high and constantly growing costs of T2DM care, it is important to determine whether resources used for SMBG are justified and effectively applied," Bosi emphasized. In his view, ST, in contrast to the classical rather randomly performed SMBG, with a clear definition of timing, frequency, and circumstances of testing, as well as its consequent translation into therapeutic decisions, represents a necessary step to promote SMBG as key to improve diabetes outcomes. The randomized controlled STeP Study was a first step toward this direction.

The PRISMA Study, if positive, will validate a new treatment approach for non–insulin-treated people with T2DM

The ongoing PRISMA Study is a prospective, open-label, randomized two-arm study with a duration of 12 months,[8] with 38 Italian centers participating. Bosi acts as head of the scientific advisory board for the PRISMA Study. The study aims to evaluate a beneficial effect of intensive SMBG management on glycemic control in 1,000 people with T2DM not on insulin. Patients randomized to the intensive SMBG management group are performing four-point SMBG profiles 3 days per week and receive additional training on how

to respond to SMBG values outside the target range, using changes in diet and exercise. In addition to blood glucose values, responsive actions as well as hypoglycemic events are captured. Based on SMBG results and the recordings, necessary changes in diabetes medications are performed at the following visits according to international and Italian guidelines.

Patients in the control group perform four-point SMBG profiles on 3 days only in the week prior to the next scheduled visit every 6 months. Indicated changes in diabetes medication will be based on HbA1c levels and reported hypoglycemic events.

All patients are educated according to a Standardized Educational Program (Accu-Chek eduCare) prior to randomization and receive recommendations about diet and exercise as well as information on postprandial glucose targets in accordance with ADA/IDF recommendations.

The PRISMA Study comprises two co-primary end points with prioritization:

- Change in HbA1c at month 12 versus baseline
- Proportion of patients meeting the risk target (Low and High Kovatchev Blood Glucose Indexes of ≤ 2.5 and ≥ 5, respectively) at month 12

So far, 1,026 eligible patients have been randomized. Mean age is 60 years, mean diabetes duration is 6 years, mean body mass index is 30–31 kg/m^2, and mean HbA1c is 7.7%. Forty percent of the subjects are women. Of the participants, 11.5% had no oral hypoglycemic agent, 40% had one, 42% had two, and 6% had three or more oral hypoglycemic agents. Enrollment is expected to close mid-July 2011.

Tools for Empowerment and Independence in Diabetes Self-Management

Debbie Hinnen, Mid-America Diabetes Associates, Wichita, KS

Various resources and educational tools are currently available to people with diabetes for many aspects of their diabetes management. The challenge for them is to access these educational tools. In the long run, consistently ensuring positive behavior change seems to be the critical issue. In her talk, Hinnen provided some guidance to the myriad of resources and educational tools for diabetes management.

Only about one-third of people with diabetes in the United States see a diabetes educator

Access to education is a significant problem for people with diabetes in the United States, Hinnen reported. Only about one-third actually see a diabetes educator,[9] although 59% reported they would learn diabetes self-management online.[10] A possible explanation for the low percentage of people with diabetes seeing an educator may be the fact that diabetes educators in North America are not plentiful because they are neither well reimbursed nor consistently trained. Thus, the obvious question is: "What happens to the rest of the patients, and who can help them to get started with an educator?"

Advice from friends or family members may not always be appropriate. Physicians simply do not have the time to adequately educate their patients: on average, a physician visit in the United States lasts 5–7 min. In this respect, Hinnen noted that manufacturers of antidiabetes drugs and diagnostic and medical devices often provide patient information material with their products. These resources might include books and starter kits, CDs or DVDs, or online interactive tools. National and international diabetes organizations may also serve as a source of advice, available in meetings or on their websites. In addition, social media on the Internet play an emerging role in providing information for certain patient groups.

Teaching the way patients want to learn is an important strategy

For Hinnen, the key to effective education in a face-to-face situation with a patient and an educator is the focus on adult learning principles: immediate feedback, use of past experiences, immediate application, and a safe environment. Furthermore, educators should take into account different "learning styles" of patients, such as observers, thinkers, and doers.

Hinnen provided an example of a patient with diabetes starting SMBG:

- An *observer* wants to see the educator perform a SMBG measurement before he or she will try it himself.
- A *thinker* will ask for the blood glucose meter manual and will then try to complete the measurements according to the written instructions.
- A *doer* will try to use the blood glucose meter intuitively without first watching someone or reading the manual.

What can I eat?

In the course of her talk, Hinnen referred to one of the most prominent questions from her work with people with diabetes: "What can I eat?" In this respect, it is important to match the answer to this question to the medication the patient takes. If a patient is on oral hypoglycemic agents, for example, the answer to this question should relate to portion control, whereas for a patient on insulin, matching the amount of carbohydrates/calories to an appropriate insulin dose is the challenge. For this purpose, online as well as hands-on calculation tools and food databases are needed.

Numeracy is a major problem for many people with diabetes. Patients tend to give up on carbohydrate counting or just estimate, which consequently leads to deterioration of their glycemic control. To address this problem, bolus calculators are useful tools, whether they are built into blood glucose meters or just paper tools. At present, there are several applications for smartphones available that support insulin dose calculations, as well as systems of insulin pumps and blood glucose sensors that communicate to assess and determine bolus calculations and consequent insulin doses. Nevertheless, the patient still has to enter the amount of carbohydrate taken.

Another common question in diabetes education is: "What do these numbers mean?" Hinnen pointed out that it is the job of HCPs and educators to assist patients who comply with SMBG recommendations to determine how to use the captured blood glucose data. For this purpose, pattern recognition tools like the Accu-Chek 360° View form, downloaded meter software, and continuous glucose monitoring systems can be of help.

As an example, Hinnen described the pattern management process used with the Accu-Chek 360° View tool:

- Step 1: Identify the predominant glycemic abnormality ("What is the problem?"); priority 1 is hypoglycemia, priority 2 is fasting hyperglycemia, and priority 3 is postprandial hyperglycemia
- Step 2: Determine timing and frequency of occurrence ("Is it a pattern?")
- Step 3: Investigate potential causes ("Look at diet, exercise, and medication")
- Step 4: Take action

In conclusion, Hinnen reiterated that various resources and tools for obtaining diabetes information are available today. However, there is no easy and consistent way for patients to find them. Finally, she called for additional tools to ensure behavior change and persistency. These tools could be reminder programs for testing blood glucose, taking medication, or refilling prescriptions. Support groups like Weight Watchers, as well as refresher courses for follow-up and behavior change goal evaluation, are further examples.

Telemedicine in Chronic Metabolic Disease: Recent Perspectives and Experience

Steven B. Leichter, Columbus Research Foundation, Columbus, GA

Management of chronic metabolic diseases offers many opportunities to assess telemedicine as a model. These opportunities relate to a wide variety of possible applications, multiple and objective end points for assessment of a model, and the fact that patient self-care is an essential component of the care process. On the other hand, many questions remain: What is the appropriate application? How can efficacy be documented? And how should reimbursement be organized? Leichter presented the results of a new study with the Accu-Chek 360° View form demonstrating that patients can be partially managed via remote care, thereby reducing the usual costs associated with visits to clinicians.

Telemedicine is especially attractive in regions where patients have to travel long distances to reach their doctor

Today, data transfer is no longer a problem as there are numerous options available: computers, telephones, cell phones, or even smartphones. Telemedicine models have already been successfully studied in different chronic metabolic diseases, including hypertension, diabetes, hyperlipidemia, and cardiovascular diseases. Many policy makers in the United States advocate telemedicine as an integral part of the healthcare system.

Evidence for a beneficial effect of telemedicine in hypertension and diabetes is less robust than desired

Leichter presented the results of a meta-analysis of 15 blood pressure telemedicine studies in people with essential hypertension that revealed a reduction in systolic/diastolic blood pressure of 3.9–13/2.0–8.0 mm Hg achieved by using telemedical management.[11] The authors of this meta-analysis claimed that these reductions are comparable to the ones achieved with antihypertensive medications in clinical trials. However, when the existing evidence is comprehensively analyzed for a potential beneficial effect of telemedicine on hypertension, it must be concluded that the outcomes are inconsistent and that the committed personnel time varies widely, depending on the model applied.

A similar picture can be observed when looking at the effect of telemedicine on diabetes treatment. In these cases the major challenge turned out to be the prevention of patients from losing interest and motivation over time. An analysis of 21 studies evaluating the effect of remote telemonitoring and five studies evaluating the effect of telephone support in diabetes showed that telemonitoring lowered HbA1c slightly, yet significantly, compared with usual care; in contrast, telephone support had no beneficial effect on HbA1c levels.[12] According to Leichter, these results indicate that the application of personnel time alone, as was performed in the telephone support approach, does not lead to an improvement of glycemic control in these patients; therefore, these results indicate the use of telemonitoring.

It appears to be a common trend in all these studies that telemedicine can support chronic care of people with metabolic disorders. However, patient outcomes vary in relation to the application of personnel time. Additionally, there are still few up-to-date data on the economic benefits of these applications of telemedicine.

Conducting two office visits per year by computer would save 30% of usual visit costs

The Accu-Chek 360° View Trial of the Columbus Research Foundation involved chronic management of diabetes, hypertension, and hyperlipidemia via a common software pathway. The trial was designed to show non-inferiority of a telemedicine approach by remotely conducting two out of the four annual visits via computer compared with the standard approach with four usual face-to-face visits per year.

One hundred people with diabetes were enrolled; 14% were Accu-Chek Spirit pump users. Changes in HbA1c were identical over 1 year for both groups (+0.4%). Therefore, non-inferiority for the telemedicine arm was shown.

Leichter stated it was noteworthy that remote visits were well accepted in terms of convenience and clinical reliability. According to his calculations, conducting two remote visits via computer per year that would be reimbursed (as proposed by insurance providers) would save 30% of the usual costs associated with visits. As the working time per remote patient visit was much shorter, specialists could leverage patient volume and increase their revenues despite lower reimbursement per patient contact. The results of the study will be presented at the 2011 ADA Meeting.[13]

Leichter concluded that in order to expand the role of telemedicine in the future, it is necessary to define standard clinical situations in which its application is clearly compelling. Efficacy will have to be clearly documented, cost savings will have to be modeled, and public and professional support will have to be garnered. Finally, in nations in which telemedicine is of relevance, as it is in the United States, there should be a wider support for adequate reimbursement policies.

Why Is It so Difficult to Change Behavior?

Latchezar Traykov, Medical University, Sofia, Bulgaria

The presence of the so-called metabolic syndrome exerts detrimental effects on memory and executive functioning.

These effects can be found in subjects without a history of strokes or dementia. Consequently, such patients struggle to organize and monitor their behavior properly, resulting in either passivity or chaotic, impulsive behavior, Traykov explained.

There is a strong correlation between diabetes and cognitive decline

Diabetes is especially associated with vascular dementia, Traykov stated. Macrovascular disease can lead to brain infarcts; microvascular disease promotes insidious white matter lesions and microinfarcts. Additionally, glucose toxicity and insulin can influence brain function. The domains of executive functioning and memory are most often affected.[14,15]

Executive functioning describes cognitive processes that are necessary to organize goal-directed behavior: to plan actions, make decisions, re-evaluate, and change decisions. Executive functioning is impaired if there is damage to the prefrontal cortex, damage to the subcortical structures, or interruption of connections between frontal and non-frontal areas.[16,17]

Men are more affected than women, particularly if they have high levels of inflammatory markers

There is growing evidence that small-vessel diseases play an important role in vascular dementia. Today the term vascular cognitive impairment, or subcortical vascular cognitive impairment, encompasses all forms of cognitive impairment due to cerebrovascular disease.

For the management of vascular cognitive impairment, Traykov recommends interventions targeting cerebrovascular risk factors, especially hypertension, hyperlipidemia, and elevated blood glucose levels. Both the metabolic syndrome and diabetes have a strong association with cognitive dysfunction caused by silent brain lesions. Characteristic features in these patients also include high levels of inflammation markers.

Studies indicate that microstructural white matter alterations occur primarily in the frontal lobe. However, the mechanism of this white matter damage in people with metabolic syndrome is not yet clear.[18]

Interventions should concentrate on improving executive functioning in daily life

According to Traykov, further studies are necessary to determine if improving the hallmarks of the metabolic syndrome, including high blood pressure, high blood lipid levels, insulin resistance, and a high body mass index, also has the potential to prevent cognitive decline in patients. A better understanding of the nature of the relationship between the metabolic syndrome/diabetes and brain damage/dementia will be a key step in the development of preventive measures.

Current management of these patients should focus on activities of daily life, Traykov proposed. Generalization of strategies and skills, as well as the use of external aids, could help improve executive functioning in daily life.

How Should We Promote Behavioral Change in Diabetes?

Mirjana Pibernik-Okanović, Merkur University Hospital, Zagreb, Croatia

Many patients fail to integrate self-management behaviors into their lives

Sharing responsibility for health between patients and HCPs is considered crucial but difficult to achieve. In her talk, Pibernik-Okanović proposed integration of behavior/psychosocial interventions into regular office visits. Her practical approach is to find the patient where he or she is, understand his or her needs and thoughts, and offer help without controlling him or her.

Successful behavior change depends on the use of specific counseling techniques at specific stages

Pibernik-Okanović introduced the transtheoretical model of behavior change, which was proposed by Prochaska and DiClemente[19] in 1989. This model assumes behavior change to be a process, rather than a single event. The five steps of the transtheoretical model are:

- *Precontemplation*: patients are not prepared to take action and are generally unaware of their unfavorable behavior.
- *Contemplation*: patients start recognizing that their behavior may be problematic, and they begin to look at the pros and cons of actions.
- *Preparation*: patients are intending to take action and may start with small changes.
- *Action*: patients modify their lifestyle, positive changes occur.
- *Maintenance*: in this stage the main task is to prevent relapse.

In practice, patients do not progress through these steps in a linear fashion, but rather move back and forth between steps, Pibernik-Okanović said. Successful behavior change depends on the use of specific counseling techniques at respective stages. For example, if a patient is currently at the step of precontemplation, the planning of behavior change would probably not be appropriate. Instead, addressing and trying to help the patient by resolving his or her ambivalence might be an adequate approach. For patients who are currently at the step of preparation, the determination of individually achievable goals for behavior change would be an appropriate response.

The self-regulation theory, also called the common sense model, hypothesizes that when people become ill, they create a kind of mental representation of their illness.[20] This process of illness representation is critical to make sense of the problem and to actually manage it. The personal model of diabetes according to the self-regulation model is distinguished by three stages:

- *Information*: in the process of creating a mental representation of their illness, patients usually gain information by social communications, opinions and attitudes of others, and their current experiences with diabetes, such as symptoms or somatic information.
- *Cognition*: patients usually try to characterize what has caused their disease, which consequences it will have, which symptoms they will probably have to experience,

how long it will last, whether or not it is curable, and to which degree it is under their control.
- *Interpretation*: patients' individual interpretation of information and cognition determines potential behavioral responses in terms of adopting established diabetes regimens and emotional responses regarding emotional and psychological well-being.

Another model, the social cognitive theory, extends beyond individual factors in diabetes care by incorporating social and environmental factors.[21] In keeping with this model, it was shown that educational programs accompanied by sessions of diabetes-specific coping skills had positive long-term effects on patients' self-efficacy and diabetes-related outcomes,[22] Pibernik-Okanović reported.

People with chronic conditions are their principal caregivers

Pibernik-Okanović also addressed the empowerment model by Anderson;[23] this model is based on the fact that at least 95% of health-related decisions that people with diabetes have to make daily are made without an HCP's knowledge of the decision. These so-called informed autonomous decisions led to the emergence of a new paradigm: "People with chronic conditions are their principal caregivers, and health care professionals should be consultants supporting them in this role."[24]

In a variety of prospective studies, behavioral interventions were shown to promote improvements in glycemic control, self-efficacy, and psychological variables, Pibernik-Okanović reported. Psychological interventions additionally improved depression and anxiety symptoms, as well as distress.[25]

Pibernik-Okanović concluded that three major imperatives must be followed in order to successfully translate the presented research into clinical practice:

- Take patient ambivalence to change into account
- Strengthen patient self-efficacy
- Support patient informed autonomous decisions

How can behavior/psychosocial interventions be integrated into a 15-min routine visit?

Even time-limited consultations may allow simple problem- and emotion-focused interventions that could facilitate active roles in self-management of diabetes, Pibernik-Okanović stated. In this respect, she referred to a step-by-step approach based on research in this area that recommends taking the following steps into account:[26]

1. Problem-focused interventions:

- Start with the patient's problem
- Specify problem
- Negotiate appropriate goal
- Identify barriers to achieve goal
- Contract for change
- Track outcome
- Provide ongoing support

2. Emotion-focused interventions:

- Identify diabetes distress
- Alleviate diabetes distress
- Identify depression
- Treat disorder or refer for treatment

Internet-Based Behavioral Change Tools

Sebastian La Bastide, Roche Diabetes Care, South San Francisco, California

What will diabetes management look like in 10 years?

This was the crucial question in the talk of La Bastide. In his opinion, trends in diabetes treatment are increasingly meeting trends in technology adoption. Many companies are currently working on technology facilitating behavioral change, but promising business models still have to be established. An environment in which diabetes management is aligned along all stakeholders and which is utilizing technology could potentially provide a promising holistic approach.

La Bastide drew the audience's attention to the dramatically increasing economic burden of the diabetes epidemic of the 21st century. Unfortunately, as the number of diagnosed people with diabetes is strongly rising, the number of active HCPs is not increasing proportionately. Hence, the time for individual care of people with diabetes will inevitably decline.

The IDF estimates that T2DM is preventable by adoption of healthy diets and increasing physical activity in 80% of cases. Lifestyle interventions have been proven to be effective in the prevention of diabetes and diabetes-related end points in various RCTs.

Can we use technology to deliver behavioral change?

The current clinical practice, which basically comprises a relationship between the patient with diabetes and his HCPs, does not effectively facilitate lifestyle and behavioral changes. We have learned from RCTs that introducing lifestyle coaching by a third party, such as a dietitian, diabetes educator, or psychologist, has the potential to improve metabolic control in obese people with diabetes. However, this approach is not easily scalable. Adding virtual coaching technology based on best practice in behavioral change to this setting would provide a scalable solution and could leverage further improvements in achieving metabolic targets.

La Bastide presented some results of an analysis that was performed in the United States. Accordingly, approximately 1,800 "eHealth" companies have been identified, of which 500 focus on diabetes/obesity by developing "modules" with behavioral change support. These "modules" include diet, exercise, reminders, and rewards. Nevertheless, certain potential obstacles still have to be addressed: people with diabetes and HCPs do not use the technology, there is no proof yet that these "modules" in fact improve long-term outcome, and currently no viable business models exist for them.

Physicians are rapidly embracing mobile devices

"More and more people go online and use the Internet for health questions," La Bastide reported. In the so-called "boomer" generation, characterizing people 47–56 (younger boomer) and 57–65 (older boomer) years old, 81% and 76%, respectively, use the internet.

Physicians in the United States are rapidly adapting new mobile devices: in 2012, it is estimated that more than 80% will use smartphones, and more than 60% will have touchscreen

tablet PCs like the iPad® (Apple, Cupertino, CA). Furthermore, a strong growth in mobile health apps and especially in paid apps has been observed. Not surprisingly, the number of companies that are active in technology development aiming to support behavioral change has increased exponentially over the last 15 years.

La Bastide envisions a holistic approach for the management of diabetes, which he calls "solution ecosystem." This "solution ecosystem" would ideally integrate professional support by HCPs, diabetes educators, and dietitians, personal support by friends, family, and community, and support by institutions (such as payers and hospitals) as well as communication technologies such as the Internet, monitoring devices, and smartphones. Its main objectives would be to empower the adoption and maintenance of healthy behaviors, to connect and align stakeholders, and to monitor lifestyle and health-related outcomes of people with diabetes. According to La Bastide, implementation of research findings from behavioral science as well as best practices in diabetes care, a user experience design, and tailored community support are critical issues in determining the success of such a proposed "solution ecosystem."

La Bastide concluded his talk by recapping the remaining challenges of web-based interventions to induce behavior change in people with diabetes. These include the ability to ensure sustainability of results and maintain patients' engagement. Furthermore, the adoption of technology by the elderly is still limited, and healthy, elderly patients are more likely to use technology than unhealthy ones. Therefore, technology has to be kept simple while perceived benefit, training, and ongoing support are essential, he emphasized.

Controversy Session: The Future of Diabetes Management—Where Can We Achieve the Most?

Boris N. Mankovsky, Department of Diabetology, National Medical Academy for Postgraduate Education, Kiev, Ukraine; and William H. Polonsky, Diabetes Institute, University of California, San Diego, California

To tell it right away: this session turned out not to be that controversial. Both speakers agreed that further improvements in pharmacological treatment are needed in coping with the diabetes epidemic, but it is important as well to ensure that patients take their medications appropriately.

The focus should be on intensifying pharmacological treatment

In his introduction, Mankovsky reviewed progress in the pharmacological treatment of diabetes, especially through the availability of insulin. The discovery of insulin and the first treatment with the hormone were acknowledged with the Nobel Prize. With the introduction of better treatments, such as intensive insulin treatment after the DCCT or the introduction of the first insulin analog (lispro), glycemic control in people with diabetes was significantly optimized.

In other fields of medicine the progress made by new medicines was similar. For instance, in blood pressure treatment new antihypertensive drugs significantly reduced the risk of stroke. Statins helped save many lives by avoiding coronary events. The best effects, especially in people with diabetes who typically have multiple risk factors, can be achieved with a multifactorial intervention as demonstrated in the Steno-2 Study.

Mankovsky was confident that continued advancements in drug development will be able to improve glycemic control in people with T2DM. New fixed combinations ("polypills") and better insulin analogs will help optimize the management of these patients in the future. "Further improvements in pharmacological treatment are the only promising options to cope with the diabetes epidemic," Mankovsky stated.

The focus should be to improve behavioral change

Polonsky led the discussion on the adherence problem: the best medications cannot help if the patient does not take them. Data from many studies demonstrate that the average patient may miss approximately 25% of prescribed antidiabetes drugs. With insulin the situation is not better: overall use is estimated at 58–65%.[27] Consequences of poor medication adherence include a decline in self-reported health, poorer glycemic control, increased healthcare costs, more frequent hospitalizations/emergency unit visits, and higher rates of all-cause mortality.

Polonsky addressed the question of how better medication adherence could be guaranteed through behavior changes of the patients. In his opinion, the big obstacles to adherence are the costs of medications, complexity of treatment, depression, and—most importantly—beliefs about medication and diabetes as well as the patient–physician relationship.

"The main reason why people do not take their medicines as prescribed is not because of failings in patients, doctors or systems, but because of concerns about the medicines themselves," Polonsky quoted from a publication by Pound et al.[28] There is considerable reluctance to take medicine and a preference to minimize medicine intake. Perceived "costs" such as concerns about adverse effects and long-term effects and the thought that taking the drugs represents "sickness" are often weighted higher than perceived benefits. These benefits are seldom apparent because HCPs often focus on long-term benefits with few immediate rewards for patients who take prescribed medicine.

Another important aspect is the physician–patient relationship. Polonsky described a study with patients who were asked 4 days after a physician's office visit if they thought the physician understood why they came in and if they agreed with the physician about the problem or needs.[29] Patient compliance was much better if there was agreement with the treating physician.

Diabetes and Cardiovascular Risk—Results from the "Silent Diabetes" Study

Rolf Doerr, Praxisklinik Herz und Gefaesse, Dresden, Germany

Diabetes and coronary heart disease are just two sides of the same coin

The analogy of diabetes as a risk equivalent to coronary heart disease (CHD) reaches back to data presented in the late 1990s; at that time, Haffner et al.[30] concluded from their research that people with diabetes without prior myocardial infarction have the same risk of myocardial infarction and death from cardiovascular causes as people without diabetes but with prior myocardial infarction. These observations have

been recently confirmed by the Cardiovascular Health Study, a longitudinal study of 5,784 men and women ≥65 years of age.[31]

A significant percentage of patients with CHD also have impaired glucose tolerance (IGT) or diabetes. The Euro Heart Survey revealed that 33% of patients with acute myocardial infarction also had diabetes, another 34% displayed IGT, and only 33% had normal glucose tolerance (NGT) when an oral glucose tolerance test (OGTT) was performed in these patients at hospital discharge. In other words, 67% of these acute myocardial infarction patients had abnormal glucose tolerance. During 4 years of follow-up, people with abnormal glucose tolerance had a significantly higher risk for recurrent major cardiovascular events.[32]

In people with diabetes, cardiovascular disease often presents in a diffuse form

Doerr presented the results of the "Silent Diabetes Study." The primary aim of this study was to compare the percentage of patients newly diagnosed with diabetes while undergoing angiography because of coronary artery disease by using either HbA1c or OGTT for diagnosis. A secondary aim was to investigate the correlation between the extent of CHD and the glycemic status of the patients.

For this purpose, 1,015 patients with suspected CHD consecutively admitted for catheterization at the Clinic Weisser Hirsch, Dresden, Germany, between June 2007 and June 2009 were included in the study. People with known diabetes mellitus were excluded. An OGTT was performed according to the World Health Organization recommendations in all patients on the day after coronary angiography. Diagnosis of diabetes by means of HbA1c testing was made according to the recommendations of the International Expert Committee Report.[33]

Mean age of patients was 68 years, 31% were women, mean body mass index was 27.4 kg/m^2, and nearly half of patients were smokers. According to the OGTT approach, 14.1% of study participants were newly diagnosed with diabetes, in 34.4% IGT was detected, and only 50.5% showed NGT. In people with diabetes and/or IGT, CHD was found to be more progressed, and these patients had more frequent multivessel disease. Results of the OGTT significantly correlated with the severity of CHD. "These findings underline that not only diabetes but IGT already is a cardiovascular risk equivalent," Doerr pointed out.

With HbA1c testing alone you may miss a substantial proportion of people with silent diabetes!

Remarkably, by the HbA1c testing approach only 4.1% of the study participants were newly diagnosed with diabetes. In 37.9% IGT was detected, and 57.9% showed NGT. No correlation was found between HbA1c and the severity of CHD.[34]

As a consequence of these results, Doerr recommends performing OGTT routinely in all CHD patients undergoing coronary angiography. After the presentation there was a short discussion about the best eligible time point for OGTT in patients undergoing coronary angiography. Accuracy of OGTT after catheterization, as was done in the Silent Diabetes Study, may be challenged by stress-induced elevation of blood glucose. Doerr admitted that if there is sufficient time left (e.g., in elective interventions), it would always be better to perform OGTT prior to the intervention.

Lipids and Cardiovascular Risk in Diabetic vs. Non-Diabetic Patients

Arnold von Eckardstein, University of Zurich, Zurich, Switzerland

According to von Eckardstein, statins reduce cardiovascular risk in people with and without diabetes by lowering low-density lipoprotein (LDL) cholesterol (LDL-C) levels. In people with T2DM, low high-density lipoprotein (HDL) cholesterol (HDL-C) levels and hypertriglyceridemia are caused by insulin resistance through both direct and indirect pathways and mark important independent cardiovascular risk factors. Protective functions of HDL on the endothelium are lost in these patients. HDL may be a dual therapeutic target in people with diabetes: first for prevention of cardiovascular events, and second for the prevention of new-onset diabetes.

Prevalence of dyslipidemias in people with and without diabetes differ

According to data from the PROCAM Study, people with diabetes display significantly lower HDL-C levels accompanied by significantly higher levels of triglycerides and total cholesterol compared with people without diabetes. However, there is no difference between the two groups in regard to the total amount of LDL-C.[35] In patients without diabetes, high levels of triglycerides as well as low levels of HDL-C significantly increase the risk of developing diabetes, whereas high levels of LDL-C do not increase this risk. Although high levels of LDL-C and low levels of HDL-C were associated with a higher incidence of cardiovascular events in people with and without diabetes, the difference between these patient groups was that the absolute incidences of cardiovascular events at the same levels of LDL-C and HDL-C were higher in people with diabetes compared with people without diabetes.

Unmet medical needs in the prevention and treatment of cardiovascular diseases remain

Currently, efficacy of LDL-C lowering by statins in people with or without diabetes mellitus has been established as a part of standard of care treatment for patients at risk. A recent meta-analysis of 26 RCTs with 170,000 patients and a median follow-up of 4.8 years revealed that lowering LDL-C by 2–3 mmol/L reduces the incidence of heart attack, revascularization, and ischemic stroke by 40–50%.[36] Although this seems quite impressive, it reveals that 50–60% of cardiovascular events cannot be prevented by statin therapy alone.

Although classical risk factors like smoking, high blood pressure, and elevated LDL-C levels can be targeted effectively by interventions today, several novel or untreated cardiovascular risk factors like elevated triglycerides, low HDL-C, a high level of inflammation, and a hypercoagulatory state remain untreated and still contribute to an elevated cardiovascular risk.

10–15% of people with diabetes can benefit from fenofibrate treatment

Fibrates and nicotinic acid effectively reduce triglyceride levels and increase HDL-C. The ACCORD-Lipid Trial analyzed whether the addition of fenofibrate to statin therapy would reduce the incidence of cardiovascular events. Although mean HDL-C levels were significantly higher and mean triglyceride levels were significantly lower in the fenofibrate group at study end, there was no difference between the groups regarding the occurrence of cardiovascular events.[37] It is noteworthy that subgroup analysis revealed that people with high triglyceride levels (≥ 204 mg/dL) and low HDL-C levels (≤ 34 mg/dL) at baseline had a 31% relative risk reduction compared with the group receiving the placebo. According to von Eckardstein, approximately 10–15% of people with diabetes have atherogenic dyslipidemia, which is characterized by high triglycerides and low HDL-C, and hence might benefit from treatment with fibrates.

Epidemiological data suggest that a correction of low HDL-C levels might be a promising strategy for cardiovascular risk reduction in those people with low baseline levels; however, increasing HDL-C levels in people with normal baseline levels will most probably not result in a risk reduction. "It is the low HDL-C that increases cardiovascular risk; it is not the high HDL-C that protects from cardiovascular events," von Eckardstein emphasized.

It is important to keep in mind that the multiple pleiotropic functions (e.g., antioxidation, anti-inflammation, effects on homeostasis, endothelial function, cholesterol homeostasis, insulin secretion, and β-cell function) of HDL do not merely depend on quantity but also on quality of HDL because it consists of more than 10 subclasses, over 80 proteins, and hundreds of lipids.

In people with diabetes, HDL-C is not only quantitatively diminished but also dysfunctional

Von Eckardstein presented recent results from in vitro and animal experiments analyzing endothelial-protective effects of HDL from people with and without diabetes. HDL from people with diabetes had substantially impaired endothelial-protective effects compared with HDL from healthy subjects. When people with diabetes were treated with extended release nicotinic acid for 3 months, endothelial-protective functions were markedly improved.[38] "We urgently need functional biomarkers to assess and monitor the cardiovascular risk of disturbed HDL metabolism," he stated.

In addition to being risk factors for cardiovascular disease, lipoproteins display treatable risk factors for the manifestation of diabetes

Insulin resistance leads to hypertriglyceridemia, low HDL-C levels, and an increase in small dense LDL. This so-called "lipid triad" further aggravates insulin resistance and is accompanied by continuous loss of β-cell function in patients. When experimentally infused in people with T2DM, HDL (recombinant HDL; 80 mg/kg over a 4-h period) significantly improved β-cell function as measured via the homeostasis model assessment β-cell index and activating AMP-activated protein kinase in skeletal muscle compared with patients receiving the placebo.[39] Also, data from in vitro experiments and genetic animal models suggest that HDL improve both the survival and the function of β-cells.[40]

At the end of his talk, von Eckardstein concluded that HDL may be a promising dual therapeutic target for the prevention of cardiovascular events, for the treatment of clinical sequelae of dyslipidemia in people with low baseline HDL-C levels, and for the prevention of new-onset diabetes mellitus in patients at risk.

CRP, Inflammation, and Risk for Diabetes and Cardiovascular Disease

Aruna D. Pradhan, Harvard Medical School, Boston, MA

The American College of Cardiology/American Heart Association 2010 guidelines for assessment of cardiovascular risk in asymptomatic patients recommend the ascertainment of a global risk score and the elucidation of a family history of atherosclerotic cardiovascular disease as an initial step. These Class I recommendations are simple and inexpensive means to determine subsequent strategies to undertake. In her talk, Pradhan discussed the role of the C-reactive protein (CRP) and inflammation on the risk of experiencing cardiovascular events and developing diabetes.

CRP has been one of the most frequently investigated inflammatory biomarkers

Conventional risk factors like age, high blood pressure, diabetes, smoking, total cholesterol, and HDL-C levels have been established by the Framingham Study. However, more than 20 years later, it has been shown that approximately 60% of patients with CHD display either none or only one of the classical risk factors mentioned above,[41] Pradhan reported. Refinement of the Framingham Risk Score resulted in the Reynolds Risk Score. In its simplified form, the Reynolds Risk Score includes high-sensitivity CRP (hsCRP) and parental history of myocardial infarction with the traditional risk factors of the Framingham Risk Score.

In recent years, evidence of the role of inflammation in atherosclerosis has increased. Among other inflammatory biomarkers prospectively investigated in epidemiological studies of CHD, CRP has been one of the most frequently studied proteins. Data of several studies have demonstrated that elevated levels of hsCRP are consistently associated with future cardiovascular events, independently of the level of LDL-C. Furthermore, CRP does not exhibit any significant diurnal variation or dependence on fasting status and adds to other risk factors in terms of global cardiovascular risk prediction.

hsCRP adds prognostic information beyond traditional risk factors in all major cohorts evaluated

Statins were not merely shown to reduce cardiovascular risk by their LDL-C-lowering effect, but also to reduce hsCRP by LDL-independent mechanisms. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) Study[42] revealed that in people without hyperlipidemia, but with elevated hsCRP levels, rosuvastatin reduced the incidence of cardiovascular

events by 44% with an estimated number needed to treat of 25 over 5 years. As the observed benefit was more than twice as high as the predicted figure based on absolute LDL-C reduction, the additive effect is probably due to the reduction of both risk factors: LDL-C and hsCRP. Hence, people with normal LDL-C levels but elevated hsCRP levels may benefit from a statin-mediated reduction of hsCRP levels.[42]

Pradhan referred to the 2009 Canadian Guideline for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in the Adult, which recommends determining hsCRP levels in patients who have been stratified to a moderate risk according to classical risk factors and global risk scores. In addition, an hsCRP level of <2 mg/L is recommended as a secondary treatment target.

Are we treating the right surrogate end point in diabetes?

Inflammation, obesity, and T2DM frequently go hand in hand. Adipose tissue in obese patients is characterized by macrophage infiltration. These macrophages represent an important source of chronic inflammation, which is now thought to play a crucial role in the development of insulin resistance.

When the LANtus for CRP Reduction in Early Type 2 Diabetes (LANCET) Study was designed, it was uncertain whether commonly used antidiabetes treatments have the potential to reduce inflammation in addition to their glucose-lowering effects in people with diabetes. In the LANCET Study, Pradhan et al.[43] demonstrated that despite substantially improving glucose control, neither insulin nor metformin improved inflammatory status as measured by hsCRP beyond diet and exercise alone among people with T2DM initiating antidiabetes treatment. Future studies using hsCRP as a surrogate end point may elucidate whether other therapies in T2DM may beneficially modulate inflammation both in the prevention of cardiovascular disease and also for improved glycemic control.

As one such example, Pradhan presented the Targeting Inflammation using SALsalate in Type 2 Diabetes (TINSAL-T2D) Study, which intended to analyze the effect of the non-steroidal anti-inflammatory drug salsalate in people with T2DM.[44] Salsalate lowered HbA1c levels and improved other markers of glycemic control as well as adiponectin, a marker for insulin resistance. These results indicate that an anti-inflammatory therapy might indeed be a promising approach for the treatment of T2DM in the future.

Pradhan summarized that chronic inflammation is involved in the development of atherosclerosis as well as T2DM. CRP is a potent indicator of this inflammatory process, a reliable marker of subclinical inflammation, and a strong marker predicting development of diabetes. It further predicts the development of future vascular disease and contributes to the global risk prediction beyond traditional risk factors. Anti-inflammatory therapies with hsCRP as a target may hold potential for the treatment of hyperglycemia in T2DM. Efforts to determine whether anti-inflammatory therapies may be beneficial for the prevention of macrovascular complications in these patients are highly valued.

New Biomarkers to Assess Risk for Diabetes and Cardiovascular Disease

Veikko Salomaa, THL-National Institute for Health and Welfare, Helsinki, Finland

A considerable proportion of cardiovascular events occur among subjects at only low or intermediate risk, according to traditional risk scoring. Combinations of novel biomarkers and genetic markers could help to further stratify their risks. Salomaa suggested a simple score of three biomarkers (hsCRP, N-terminal pro-B-type natriuretic peptide, troponin I) that has the potential to improve prediction of potential cardiovascular events and a score of four biomarkers (adiponectin, apolipoprotein B, hsCRP, and ferritin) that might help to predict the risk for developing T2DM.

Recent research has shown that the onset of T2DM can be prevented or postponed, and there is every reason to believe that macrovascular complications of T2DM are preventable as well, Salomaa stated. However, this requires early identification of patients at high risk. In this respect, obesity is a very simple and strong marker of diabetes risk, but there are other biomarkers that can improve the risk assessment even after accounting for obesity.

Troponin I, N-terminal pro-B-type natriuretic peptide, and hsCRP contribute to a better estimation of risk for cardiovascular disease

The multinational MONICA, Risk, Genetics, Archiving, and Monograph (MORGAM) project was initially established to develop cardiovascular risk scores based on classic risk factors and to determine whether genetic variability or biomarker assessment could improve the ability to predict this risk. Salomaa reported that he and his colleagues evaluated 30 novel biomarkers for cardiovascular risk in men and women of the FINRISK97 Study cohort with cardiovascular events at 10 years and developed a biomarker score, which was then validated in men of the Belfast Prospective Epidemiological Study of Myocardial Infarction (PRIME) cohort. The main outcome of this approach was that elevations in levels of troponin I, N-terminal pro-B-type natriuretic peptide, and hsCRP were significantly associated with an increased risk for incident cardiovascular events. A biomarker score including these three novel biomarkers might therefore be useful for the risk estimation for cardiovascular events in addition to conventional risk scoring.[45]

Adiponectin, apolipoprotein B, CRP, and ferritin improve the assessment of risk for incident diabetes

Salomaa and his co-workers also evaluated 31 novel biomarkers in the hope of predicting the risk of incident diabetes in the same population cohort. Again, obesity was the strongest single predictor of diabetes risk in middle-aged individuals. After classic risk factors like body mass index, blood glucose, and others were accounted for, the results of this study identified adiponectin, apolipoprotein B, CRP, interleukin-1 receptor antagonist, and ferritin as the strongest predictors of incident diabetes.[46] Adiponectin increases insulin sensitivity, improves glucose tolerance, and inhibits inflammation but seems to be associated with increased cardiovascular and total mortality risk. Adiponectin was significantly associated with a reduced risk for incident diabetes. Ferritin, a

ubiquitous intracellular protein that stores iron and releases it in a controlled fashion, was associated with increased risk of diabetes; the association was particularly evident among men. Interleukin-1 receptor antagonist is an anti-inflammatory cytokine, but its elevation may be compensatory to the increased production of pro-inflammatory interleukin-1β in the pancreas, which is known to induce β-cell apoptosis and impair insulin secretion. A combined score consisting of adiponectin, apolipoprotein B, CRP, and ferritin improves the assessment of diabetes risk, Salomaa concluded.

Theoretical considerations and animal experiments suggest a causal link between B-type natriuretic peptide and diabetes risk

Another interesting finding was that natriuretic peptides, including mid-regional pro-A-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide, and B-type natriuretic peptide, were significantly associated with a reduced risk of developing diabetes. The N-terminal pro-B-type natriuretic peptide phenotype is a significant predictor for an increased risk of future cardiovascular disease events but is inversely associated with the risk of incident diabetes. A T-381C polymorphism in the promoter area of the *B-type natriuretic peptide* gene is modestly protective against T2DM.

Based on the currently available data, Salomaa concluded that a combined score of N-terminal pro-B-type natriuretic peptide, CRP, and troponin I modestly improves the assessment of cardiovascular disease risk and that a combined score consisting of adiponectin, apolipoprotein B, CRP, and ferritin improves the assessment of diabetes risk. Genetic determinations are of great scientific interest but are not clinically useful at present. Studies are needed to evaluate whether the improved risk assessment leads to improved prevention and treatment in practice and to perform cost–benefit analyses. Upcoming studies are needed to evaluate whether the advanced risk assessment leads to more effective prevention and treatment in clinical practice. Cost–benefit analyses of new biomarkers and genetic risk scores are also required.

New Therapeutic Approaches to Address Cardiovascular Residual Risk in Diabetes

Richard Hobbs, University of Oxford, Oxford, UK

Diabetes is one of the leading causes of premature death worldwide. People with diabetes have a significantly elevated risk for experiencing cardiovascular events. A large percentage of the evidence available on cardiovascular risk reduction by lipid modification has focused on LDL-C lowering. In brief, a reduction of LDL-C by 1 mmol/L leads to a reduction of the risk of cardiovascular events by approximately 25%. However, a substantial residual cardiovascular risk remains. Rising HDL-C in people with low levels of HDL-C may be the strongest and most promising approach to address this residual cardiovascular risk of patients at risk, Hobbs stated.

Is diabetes a cardiovascular risk equivalent?

Since Haffner et al.[30] published their epidemiological data suggesting that people with diabetes but without signs of cardiovascular disease have the same risk for experiencing myocardial infarction as patients without diabetes having experienced myocardial infarction, there has been a significant amount of controversy in regard to diabetes as a CHD equivalent. Not all published data have confirmed this hypothesis, although all showed a high cardiovascular risk in people with diabetes combined with a very poor prognosis when they had previously experienced a cardiovascular event. The observed discrepancies are most likely due to the fact that the incidence of cardiovascular events varies with the number of prevalent risk factors in people with diabetes, as well as with their duration of diabetes.

When people with diabetes experience a cardiovascular event, it is frequently more serious than in patients without diabetes. Despite significant advances in cardiac care, people with diabetes have a doubled risk for early myocardial infarction mortality compared with the total group of patients.

Taken together, available evidence reinforces the urgent need to address the elevated risk for cardiovascular events of people with diabetes, regardless of whether or not diabetes is a CHD risk equivalent, Hobbs emphasized. Which interventions are appropriate to treat patients at risk? For example, quitting smoking is effective, as well as lowering elevated blood pressure and LDL-C levels.

In large statin and blood pressure trials at least two-thirds of events could not be avoided

Despite optimal care of hyperlipidemia, a significant cardiovascular risk remains. Some of the risk factors for cardiovascular events may not be modifiable, Hobbs stated. Age and diabetes duration are two examples for these kinds of risk factors. In addition, onset of risk prevention by medical interventions might frequently be delayed in patients at risk, and the cardiovascular risk is influenced by multiple factors besides LDL-C.

"Is there a need to go beyond LDL-C in lipid modification?" Hobbs asked. The Framingham Study demonstrated that both LDL-C and HDL-C predict the CHD risk, and according to the INTERHEART Study, nine potentially modifiable risk factors are associated with 90% of myocardial infarction in men and 94% of myocardial infarction in women.[47] In addition, in the United Kingdom Prospective Diabetes Study, baseline HDL-C was revealed as the second most important marker after LDL-C for predicting CHD in people with T2DM.[48] Evidence from epidemiological studies compels us to investigate beyond LDL-C and consider low HDL-C as a candidate target, Hobbs concluded.

Are clinical outcomes linked to lipid changes beyond LDL-C?

Statins have a limited effect on HDL-C levels. In contrast, fibrates raise HDL-C moderately as well as lowering triglycerides. Nicotinic acid offers the most pronounced effect on HDL-C, but to date no well-conducted studies have demonstrated an effect of nicotinic acid on "hard" clinical end points, Hobbs commented. The ARBITER 2 Trial showed a beneficial effect of nicotinic acid on slowing down the progression of coronary intima media thickness.[49] Hobbs expressed his hope that statins and HDL-C-raising drugs like nicotinic acid—and in future also cholesteryl ester transfer protein (CETP) inhibitors—will show beneficial effects in the prevention of cardiovascular events. The AIM-HIGH Trial and the Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-THRIVE) Trial are ongoing RCTs testing the efficacy of

combined lowering LDL-C/triglycerides and raising HDL-C by nicotinic acid in combination with statin therapy versus statin therapy alone in the prevention of "hard" clinical end points in people at risk. [Editor's note: immediately following the 4th Annual Symposium on Self Monitoring of Blood Glucose (SMBG) Applications and Beyond, the AIM-HIGH Study was prematurely terminated because of failure to show any benefit of niacin.]

Hobbs offered the following conclusions:

- Although efficacy of LDL-C lowering by statins is beyond dispute today, a significant residual cardiovascular risk remains for patients at risk.
- Residual risk may be partly due to non-modifiable factors, insufficient or delayed risk reduction interventions, or additional risk factors.
- A new promising target in this respect may be decreased levels of HDL-C. This is supported by major epidemiological evidence, by consistent observational therapeutic benefits, and additionally by data from small RCTs. Results of ongoing RCTs analyzing "hard" outcomes are anticipated.

Cholesteryl Ester Transfer Protein (CETP) Modulation as a Therapeutic Approach

Wolfgang Koenig, University of Ulm, Ulm, Germany

CETP plays an important role in cholesterol homeostasis

Inhibition of CETP raises HDL-C levels and so may reduce the progression of atherosclerosis. As of now, there have been clinical studies with three small-molecule CETP inhibitors: dalcetrapib, torcetrapib, and anacetrapib. The study program with torcetrapib has been discontinued because of its adverse off-target effects on the renin–angiotensin–aldosterone system. Preclinical and clinical evidence suggest that dalcetrapib and anacetrapib lack these adverse effects. Therefore, according to Koenig, CETP inhibition as a therapeutic strategy remains a valid option to be tested.

The inverse correlation of HDL-C and the risk for cardiovascular events is well known today. Epidemiological studies such as the Framingham Heart Study consistently show low HDL-C levels to be a predictor of cardiovascular events, independent of LDL-C levels. HDL-C is involved in reverse cholesterol transport and has many properties that appear to be beneficial in terms of prevention of atherosclerosis, including antithrombotic, anti-inflammatory, anti-apoptotic, and antioxidative effects. It modulates endothelial function and repair. As a result of these properties, HDL-C exhibits protective effects on the vessel wall.

CETP is a hydrophobic glycoprotein secreted mainly from the liver. It circulates in plasma bound primarily to HDL-C. It acts as a kind of "shuttle," Koenig explained: it transfers cholesteryl esters from HDL-C to very LDL-C (VLDL-C), intermediate-density lipoprotein cholesterol, and LDL-C in exchange for triglycerides. This lipid transfer activity contributes to the remodeling of HDL-C. CETP participates in the indirect pathway of reverse cholesterol transport by transferring cholesteryl ester to apolipoprotein B-containing lipoproteins for delivery to the liver. Combined actions of CETP and hepatic lipase promote reduction in HDL-C size and formation of lipid-poor, pre-β-HDL-C particles. By transferring cholesteryl ester to LDL-C and VLDL-C, CETP also reintroduces cholesterol to the endogenous lipid pathway.

CETP activity is inversely correlated with plasma concentrations of HDL-C

Human CETP deficiency is usually associated with marked increases in HDL-C, and CETP activity is inversely correlated with plasma HDL-C. In animal models, decreasing CETP activity has consistently inhibited atherosclerosis, Koenig pointed out. Consequently, CETP inhibition has been identified as a potential therapeutic target for prevention/treatment of atherosclerosis in humans. CETP inhibition may exert its anti-atherogenic effects by increasing HDL-C concentration, HDL particle size, and apolipoprotein A-I levels, he reported. A reduction in LDL-C concentration, an increase in LDL-C particle size, and a reduction in cholesterol content of chylomicrons and VLDL-C have also been observed.

Three small-molecule CETP inhibitors have been or are currently being investigated in Phase III clinical studies: dalcetrapib, torcetrapib, and anacetrapib. Each CETP inhibitor has demonstrated potential beneficial effects on the atherogenic lipid profile of treated patients. However, there are differences in molecular structure, physicochemical properties, mode of action, and adverse effects. In one of the Phase III trials, torcetrapib showed an excess mortality, and thus the further development of this drug had to be discontinued.

Dalcetrapib shows significant inhibition of CETP and increases in HDL-C and was generally well tolerated

The newer CETP inhibitor dalcetrapib differs from torcetrapib in its mode of action of decreasing CETP activity. Dalcetrapib induces a conformational change to CETP that inhibits lipid transfer from HDL-C to LDL-C and VLDL-C, but it does not inhibit CETP-induced HDL-C remodeling like torcetrapib does. Dalcetrapib (300, 600, and 900 mg) has been evaluated in six double-blind, randomized placebo-controlled Phase II trials. In these studies, dalcetrapib alone, or in combination with statins, showed significant inhibition of CETP activity, significant increases in HDL-C (>30% with 600 and 900 mg), and no significant effects on LDL-C levels. It is important that dalcetrapib was generally well tolerated, Koenig reported. The incidence of adverse events and changes in blood pressure were similar to those with placebo. Most common adverse events were headache, nausea, diarrhea, and pharyngitis.[50] Similar results were obtained with the CETP inhibitor anacetrapib in a trial with 1,500 patients on statin therapy and LDL-C levels of <100 mg/dL. Anacetrapib showed robust effects on HDL-C, LDL-C, non-HDL-C, and lipoprotein(a) over 18 months with an acceptable side effect profile, with no significant effects on blood pressure, electrolytes, or aldosterone.[51] Long-term safety and efficacy of both anacetrapib and dalcetrapib will now be tested in large clinical trials. The dal-HEART Program encompasses four ongoing trials that are investigating the potential beneficial effects of raising HDL with dalcetrapib on clinical outcomes, atherosclerosis, and vascular function[52–54] in people with CHD or CHD risk equivalents.

At the end of his talk, Koenig summarized some challenges of CETP inhibition as a future therapeutic approach:

- Some analyses of cardiovascular risk in people with certain CETP genetic variants and higher than average HDL-C levels have revealed, paradoxically, an increased cardiovascular risk.
- Some epidemiological studies have failed to support the concept that low levels of CETP are associated with a reduced cardiovascular risk.
- Clinical studies with torcetrapib failed to demonstrate any beneficial effects of CETP inhibition on atherosclerosis or clinical outcomes.

Nevertheless, Koenig emphasized that preclinical and clinical evidence to date suggests that dalcetrapib lacks the off-target adverse effects on the renin–angiotensin–aldosterone system associated with torcetrapib. The lipid profile generated as a result of CETP inhibition varies between the tested CETP inhibitors; clinical relevance of these differences remains to be determined. In his opinion, CETP inhibition with CETP inhibitors that do not share torcetrapib's off-target effects remains a promising option to be tested.

Keynote Lecture—How Cognition and Motivation Can Make Us Fat or Slim: Insights from Consumer Neuroscience

Hilke Plassmann, INSEAD The Business School for the World, Fontainebleau, France

Food marketing shapes consumers' perception and helps them to categorize food as "good" or "bad" with respect to different consumption goals such as health and taste. This "good" or "bad" signal also changes the neuropsychology underlying food decisions: a "good" food signal (here "good" = high quality) triggers the brain's motivational system and increases "wanting." Plassmann further explained that the "wanting" system is connected to the "liking" system associated with increased pleasure experience, higher consumption, and other positive attributes.

Food marketing can "make people fat" but also may help us to design foods that "make us slim"

Obesity has become a worldwide epidemic: two-thirds of Americans are overweight, of whom one-third are obese. Obese subjects have higher morbidity and mortality rates, and obesity increases healthcare costs, Plassmann stated. She is analyzing the role of food marketing from a neuropsychological perspective: how do food perceptions shape motivational factors underlying food decisions?

Food is judged as either "good" or "bad," she explained. Independent of the total calories or amount of food, a diet without "bad" salt is perceived as better than a diet with minimal traces of salt. This can cause a systematic calorie underestimation: food labeled "low fat" is perceived to have fewer calories, and so is consumed more.

The negative calorie illusion of adding something "good" is remarkable: on average, people estimate that one hamburger alone has 761 calories, and they estimate that one salad has 67 calories—but both together result in an estimation of only 583 calories.

Labels like "low fat" lead to a "license-to-sin" effect, Plassmann explained. People think, "I'm allowed to eat more!" People firmly believe they can eat more and do eat more when marketing leads to perception of food as "good." The signal "good" also impacts the "wanting system."

A signal on how "good" the food is may be the price, for example, the price of a bottle of wine. A high price builds up a high expected value. Plassmann talked about a study in which participants first took an energy drink and then had to solve a puzzle. Two groups were told different prices of the drinks. If the participants were told higher prices, they performed better in the puzzle test.

High reward prediction modulated the release of dopamine in the striatum

The current consensus is that the striatum is the anticipated pleasure (reward prediction) center of the brain; the greater the reward prediction, the greater the release of dopamine in the striatum. This affects the "juice" that is put in the task (e.g., solving the puzzle), Plassmann explained. The results will be confirmed in an ongoing study in which test subjects receive a pill of either a dopamine antagonist or a placebo. The antagonist group then should remain unaffected by the prices of the energy drink.

In another study, the Wine (fMRI) Study, participants had to consume red wine. They were told different prices of the wine, but actually all participants received the same wine and taste perception as well as neurohumoral activity by magnetic resonance imaging was measured.[55] If participants believed they were testing a more expensive wine, the activity in the prefrontal cortex turned out to be higher. This means that prices affect not only self-reports but valuation in the brain; people not only think they like wine more, they feel they like this particular wine more.

The wanting system sensitizes the liking system to an impending experience such that the greater the anticipated reward, the greater the sensitization of the liking system and the greater the actual liking, Plassmann explained. As a consequence, the experience will be skewed toward the positive (unless there is a really bad experience). The brain becomes more forgiving of small negatives.

This is good for marketing purposes: the sensitization of the liking system through the wanting system must not be related to the consumption experience. The rewards can derive from different sources. Plassmann reported another example: if someone is playing at a slot machine, and you serve him a wine—the higher the awards with the slot machine, the better the perceived taste of the wine.

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Address correspondence to:
Boris N. Mankovsky, M.D.
Department of Diabetology
National Medical Academy for Postgraduate Education
Dorogogizkaya Street, 9
Kiev, 04112, Ukraine

E-mail: mankovsky1964@yahoo.com