EASD Diabetes Technology Meeting: Medical Associations Are on Track

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EASD Diabetes Technology Meeting: Medical Associations Are on Track

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Abstract

The first diabetes technology meeting organized by the European Diabetes Association covers the range from regulatory aspects, patient safety, about registries to clinical studies. After an intensive discussion about the evidence required for registration and reimbursement on new medical devices and in vitro diagnostics it becomes clear that more and better clinical trials will be required in the future. This was also highlighted by representatives of the American Diabetes Association. The 2 associations will be active in this field of research by a joint committee. This meeting is intended not to become a large-scale meeting focused on education but to provide a platform for an open discussion of experts involved in all areas that are relevant to achieve a meaningful usage of diabetes technology.

Keywords

diabetes technology, regulations, insulin pumps, artificial pancreas, blood glucose meters, continuous glucose monitoring

On February 26-27, 2014, the European Association for the Study of Diabetes (EASD) hosted their first official Diabetes Technology meeting in Düsseldorf. This medical Association (which interacts intensively with the American Diabetes Association) intends to establish this meeting as a high-profile exchange of views on aspects that are relevant for scientific progress in the field of diabetes technology (DT). Subsequently the conversations and the exchange of views during the breaks were important to discuss the presented content. The meeting is a top-level forum for general open questions and discussions of new study results by leading experts. The main topics are herewith presented shortly.

Changes in the Approval of Medical Devices in Europe

It has been clear for years that there is a need for updating the CE marking system for medical devices in the European Union (EU). EASD sees a clear need to step up the process significantly, as the statement of the EASD president, Andrew JM Boulton, made clear in his introduction of the meeting: "This system has been established in the last century, and there it also belongs." The European Commission adopted proposals for Regulations on in vitro diagnostic (IVD) medical devices and medical devices (MD) which were subsequently sent to the European Parliament and Council (EU member states). Parliament and Council have to agree and adopt the final text of both Regulations. However, until now only a few things have actually changed, which is also a reflection of the complexity of the legislative process in the EU. The changes that were introduced as immediate measures (eg, better control of the Notified Bodies, unannounced inspections, better monitoring and tracking of products after admission, more transparency in the system, etc) are expected to tighten the oversight of MD and IVDs considerably particularly for the quality management system. There are also a number of other measures with regards to postmarket surveillance which member states need to put in place well before the end of the transition period for the new regulation. This includes a considerable update to European Databank on Medical Devices (EUDAMED) for traceability requirements such as the unique device identification (UDI) code. In October 2013 the EU Parliament agreed on its position in first reading, which was confirmed early April this year—just ahead of the EU elections (May 2014). Now all 3 institutions (Council, European Commission, and the EU Parliament) have to agree on the final text in so-called trilogue negotiations. It will have to be seen if the intensively discussed major changes and tightening will become accepted. If not, this process will be delayed by at least 1 year, that is, into 2015. Combined with an expected transition period of 3 (MD) to 3 to 5 years (IVD) for manufacturers to change adapt their processes accordingly, this means that if the EU Parliament finally accept these changes, they will not be enforced for some years!

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In the first session of the EASD-DT meeting, various aspects in this context were discussed, in particular the complex EU rules and the bureaucratic system; it is a challenge to get all different EU member states, the "Notified Bodies" and other interested groups together into an agreement.

Does Reimbursement Represent the Real New "Approval"?

In recent years, not only the evaluation of new drugs, but also of diagnostic products, by the German Institute for Quality and Efficiency in Health Care (IQWiG) and the Federal Joint Committee (G-BA) represents a barrier for (new) products in Germany because of their careful evaluation of the evidence for the benefit/cost ratio with respect to reimbursement. As other countries in the EU have similar systems established, a CE mark for a new medical device does not mean that reimbursement by the health care insurance companies is granted. The representative of the IQWiG argued in his presentation that access to the market for medical devices in Europe is still relatively simple compared to the US. He suggested that medical products should be treated exactly like drugs (Devices = Pharma), that is, all medical products should be investigated in properly designed and performed randomized controlled studies (RCTs). The need for documenting the benefits of their products by RCTs is still a new and challenging requirement for many manufacturers. Therefore, it was not a surprise that the representative of the European Association of Manufacturers of Medical Devices (EUCOMED) disagreed with the position of the IQWiG. He argued that it does not make scientific or ethical sense to mandatorily run RCTs for all the different types of products on the market, which are also quite costly and time consuming. RCTs require the use of a placebo/comparator which in the case of medical devices is not always appropriate, for example, carrying out a placebo hip implant. Until now RCTs were not the "gold standard" in the medical devices sector and therefore, industry believes that the legislation should not automatically refer to or limit trial designs to RCTs or other designs types but should simply indicate them as examples of possible designs. Presumably, there is need for further dialog and common understanding.

Who Should Be Involved in the Approval Process and to What Extent?

One of the measures proposed in the changes in the CE mark process in the EU is the involvement of a specialized Advisory Committee on medical aspects. The crucial questions are, at which point in time will this committee be involved in the approval process, and what impact will it have? In the EU, some medical associations, like the European Society of Cardiology, have issued guidelines and standards for the development of new medical devices in their field. The idea of involving patient representatives in the approval process, that is, the involvement of nonprofessionals, can complicate the process further but bring important other aspects into the process at an earlier stage. Diabetes differs in this respect from many other diseases as the patients have to use the devices themselves 24/7.

Position of the American Diabetes Association (ADA)

The chief scientific officer of ADA, Robert Ratner, at first states the interest of this medical association in becoming more active in the field of diabetes technology. He also stressed the need for good clinical trials with medical devices. It is clear that performance of RCTs to show the efficacy of their devices (and also safety) represents a hurdle for smaller manufacturers and innovative start-ups which want to bring new products to market; however, patient safety is of very high value. In the clinical recommendations ADA publishes annually, which are based on available evidence, it becomes obvious which devices have gaps in their evidence for usage. While self-monitoring of blood glucose has an evidence category of B (with A as the highest category), continuous glucose monitoring (CGM) until now was in category E (expert consensus or clinical experience) when it comes to evidence for usage in patients with severe hypoglycemia or frequent episodes of hypoglycemic events. The ASPIRE study was not taken into account for the recent guideline. He urged the representatives present from the academic world and industry to work together toward answering clinically relevant questions.

Joint Committee of ADA/EASD Diabetes Technology (AEDTC)

In October 2013, EASD and ADA established a joint committee to support these professional societies by writing recommendations for medical devices used in diabetes therapy. The first paper concerns insulin pumps and will be published later in the year simultaneously in Diabetes Care and Diabetologia. The members of this committee presented the aspects to be addressed in this paper: evidence prior to approval, clinical trials, registries, and monitoring of pumps after their approval. The goal of the paper is to increase awareness of the issue of the safety of insulin pumps in everyday life, to provide clear advice for evaluating them and thereby to obtain more robust data for approval and reimbursement of pumps. An analysis of the thousands of Medical Event Reports (500 new sets are entered per week!) stored in the publicly accessible FDA database in which all medical reports about insulin pumps are collected, provided surprising results. More than 80% of the adverse reaction reports in 2013 concerned an insulin pump with a small market share. The data from the 2 previous year's show similar

results. It is not clear what the reason for this massive attention bias is. It can be due to differences in the respective company's policy with regard to the reporting of adverse reactions. It seems that most side effects are user induced and are not due to a malfunction of the device. However, it is clear that such a database does not provide reliable data about the safety of insulin pumps. The statements to be presented by the AEDTC—there should be statements about any medical product used in DT—should support all parties involved: patients, diabetologists, manufacturers, regulatory agencies and health policy makers. Three colleagues from the United States (Richard Bergenstal, Alexander Fleming, and Anne Peters,) represent ADA and 3 from Europe (Lutz Heinemann, Reinhard Holl, and John Petrie) represent EASD on the joint committee (AEDTC).

Improvement in the Safety of Insulin Pumps From the Manufacturer Perspective

An expert for regulatory affairs from the largest pump manufacturer explained how work is being done on further improving the safety of their insulin pumps:

- Improving the user interface device (in the United States this development is strongly driven by the Human Factor initiative of the FDA)
- Earlier involvement of patients in the design and development process (see above)
- Improving communication with patients in general
- New concept of product design
- Better understanding of the risks associated with the growing automation of insulin administration

Therefore, the preparation of risk analyzes will be improved; more reliable testing of the pumps under real operational conditions and—above all—an active survey of users was initiated with the most recent pump generation in the United States. Overall, the goal is "making the use of pumps easier."

In the past, companies tended to believe that they knew what the patients wanted and accordingly developed and built the pumps without too much patient involvement before they brought it to the market. An example for this approach is the frequent alarms provided by insulin pumps or CGM systems. Quite often patients do not respond adequately to them ("alarm fatigue").

Diabetes Registry in Sweden

Sweden has established an impressive National Diabetes Register. An analysis of data on 350 000 patients in this database—representing >85% of all known people with diabetes in Sweden—shows that the mean HbA1c is 8.0% in patients with type 1 diabetes and 7.8% for those with type 2 diabetes who are cared for in hospitals and 7.1% in those who are cared for in private practice. Of all patients with type 1 diabetes, 19% use insulin pumps, with clear differences in the prevalence in the different age groups. The costs of insulin pumps are fully reimbursed for all patients. With the support of EASD, more parameters will be recorded in the registry in the future; diabetologists will also document the pump manufacturer, the serial number, the start date of pump usage, complications, and the termination of use.

Artificial Pancreas, Blood Glucose Systems, CGM Systems, and Others

In other sessions, approval aspects of artificial pancreas (AP) systems were discussed and how much Juvenile Diabetes Research Foundation (JDRF) was involved in the preparation of the respective guideline by the FDA. Europe is far behind in this respect.

Experts from the United States and the EU made it clear that the new requirements of the FDA for the accuracy of blood glucose systems (glucose meter in combination with test strips) which are used in a professional environment are so high that none (!) of the currently available devices can fulfill them. It remains to be seen how the FDA reacts in response to complaints by the manufacturer. These high requirements also leaves no room for imprecision of the reference method used, all of which have some in reality. The much higher relevance of a precise reference method has ignored somewhat until now.

A review of the available evidence for CGM usage (including the most recent studies) showed an improvement in HbA1c by about 0.5% and in severe hypoglycemia; however, there is weaker evidence regarding the latter. Also in pregnancies there is a limited number of RCTs with conflicting outcome. JDRF has initiated a large international study on the benefits of CGM before and during pregnancy to clarify this question. With respect to cost–benefit calculations, there are also only a few publications. A factor, important for the cost analysis, is usually not adequately taken into account: patients use the sensors of the CGM systems for longer periods of time than specified by the manufacturers; such calculations are usually made with an intention-to-treat approach, as is usually done with drugs as there is no way to verify if the patient has taken the medicine or not. However, with CGM this is different because it is relatively easy to check whether the device was used or not. Therefore, a per-protocol analysis is justified. In summary, the technology and the evidence for the use of CGM have improved significantly in recent years.

Politicians With Diabetes Become Active!

In a more unusual presentation, a member of the British Parliament with type 1 diabetes presented his initiative to

bring together all parliamentarians with type 1 diabetes. He also tries to involve members of local parliaments and those outside the United Kingdom to be active in the European Policy Action Network on Diabetes (Expand). The idea is that this initiative provides presentations, information, and so on to such parliamentarians to fight against diabetes. On the occasion of the IDF conference at the end of 2013, the Melbourne Forum was founded to tackle this global challenge; more than 50 parliaments are represented in this forum.

Summary

The clear message of the presentations and discussions was that there is a need for better quality data, that is, there are needs not simply for more studies, but for studies with a better study design, and so on. The data available to date are not sufficient in most cases to meet the demands of a Health Technology Assessments (HTAs). There is not so much need for "product" studies to be used for marketing purposes, but for "class" studies answering more general questions. The questions to be addressed in such studies are these:

What are the most appropriate patient groups and how should they be treated?
What are the true clinical risks associated with the use of a given device?
What are the relevant endpoints, either those that are reported by patients or hard endpoints?
What is the cost–benefit ratio?

These questions cannot be answered by postmarketing evaluations. A critical question in this context is who pays for such investigations. Studies for the approval of a given device have to be paid by the manufacturer; however, already such studies should be performed in a manner that enables "coverage with evidence determination." To a certain extent, also regulatory structures should be willing to support studies that answer clinically relevant questions; they may give conditional approval to a defined number of patients using a given device. Then data obtained after a predefined period of time should be analyzed and a decision made regarding reimbursement in the future.

This nonprofit conference is not intended to become a large teaching and training event for diabetologists interested in learning more about the most recent studies and devices, but it should rather enable an open and critical exchange of views on the pending issues in this area of research. This approach defined this meeting, which while having no industry exhibition but only a small poster session, clearly differed from other DT meetings. Representatives of regulatory authorities and institutions such as IQWiG cannot officially participate in events that are not hosted by medical societies. In summary, this kind of more specialized meeting has an important role in providing a high level platform for the exchange of thoughts of all stakeholders in diabetes technology. The scientific discussions about specific questions should not only stimulate the performance of adequate studies but should also end in specific statements and recommendations. For example, when we think about the approval process for AP systems and their practical usage, the following questions arise:

- What will happen first—nocturnal or 24 hours closed loop?
- Will it be control to target or control to range?
- Which evidence is needed in the process of approval and for reimbursement?
- How about legal/liability barriers?

All presentations from the meeting are available on the EASD website.

Abbreviations

ADA, American Diabetes Association; AEDTC, Joint Committee of ADA/EASD diabetes technology; AP, artificial pancreas; CGM, continuous glucose monitoring; DT, diabetes technology; EASD, European Association for the Study of Diabetes; EU, European Union; EUCOMED, European Association of Manufacturers of Medical Devices; EUDAMED, European Databank on Medical Devices; Expand, European Policy Action Network on Diabetes; G-BA, Federal Joint Committee; HTA, Health Technology Assessments; IQWiG, Institute for Quality and Efficiency in Health Care; IVD, in vitro diagnostic; JDRF, Juvenile Diabetes Research Foundation; MD, medical device; RCTs, randomized controlled studies; UDI, unique device identification.

Declaration of Conflicting Interests

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