Diabetes Ther (2023) 14:1–10
https://doi.org/10.1007/s13300-022-01331-y

COMMENTARY

Diabetes Therapy Podcast: Real-World Data for Glucose Sensing Technologies in Type 1 Diabetes

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Received: August 10, 2022 / Accepted: October 25, 2022 / Published online: November 25, 2022

ABSTRACT

For people living with type 1 diabetes (T1D), home glucose monitoring has evolved from occasional qualitative urine tests to frequently sampled continuous data providing hundreds of data points per day to inform optimal self-management. Continuous glucose monitoring technologies have a robust evidence base derived from randomized controlled trials (RCTs) over the last 20 years, and are now implemented in routine clinical practice, reflecting their clinical and cost effectiveness. However, while randomized studies are the gold standard, they can be slow to set-up, unrepresentative and do not provide data for efficacy in large, unselected populations. Real-world data can be responsive to rapid product cycles in technologies, provide a large, representative population, and have a lower regulatory burden. In this podcast we discuss the advantages and pitfalls of using real-world data to assess the efficacy of continuous glucose sensing technologies in people with T1D, with reference to examples of real-world data for real-time and intermittently scanned continuous glucose monitoring. Large datasets confirm the RCT data for real-time technologies and additionally provide data for work absenteeism and hospital admissions, as well as showing the impact of advanced technology features that can be difficult to assess in randomized studies. Real-world data for intermittently scanned monitoring also confirm the randomized controlled trial data, provide additional insights not shown in controlled study environments and highlight the importance of health equality. A mature real-world dataset for automated insulin delivery systems is now available and the future of glucose sensing is also discussed.

Keywords: Clinical trials; Continuous glucose monitoring; Intermittently scanned continuous glucose monitoring; Real-time continuous glucose monitoring; Real-world data; Type 1 diabetes

DIGITAL FEATURES

This article is published with digital features including a podcast audio file to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.21379776.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-022-01331-y.

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INTRODUCTION

L.A.: Hi everyone and welcome to the Adis Rapid + podcast series. Joining us today is Professor Nick Oliver from the Imperial College London. Today we will be discussing the topic of real-world data for glucose sensing technologies in type 1 diabetes (T1D). So Nick, thank you so much for taking the time to join us on this podcast where we will be talking about the advancements of home glucose monitoring, and its application in this field via real-world data. We will touch upon the advantages and pitfalls of using real-world data, discuss key examples of these datasets, and how real-world data might shape the future of glucose sensing. So, first things first, how far has glucose monitoring come Nick? I am really interested to know a bit more about the history of this technology and how it first came about.

THE HISTORY OF GLUCOSE SENSING TECHNOLOGY

N.O.: Thanks very much for inviting me to do this. So glucose monitoring has been the cornerstone of self-management of diabetes, and in particular T1D, really dating back well into the 1980s and even before. Before the 1980s, it was mostly focused on urine testing, so people would measure urine at home with the complicated bit of home chemistry, and they would do that intermittently, looking at whether or not they had fasting glycosuria. The 1980s changed that with the ability to start measuring glucose on capillary blood samples, initially in the clinic and then that transferred fairly quickly to the home. These were fairly big devices that relied on colorimetric technologies and used reasonable volumes of blood and took up to 10 min or even longer to give a result. But over time, as always happens, things became smaller, required a much smaller volume of blood and provided more accurate results more quickly, and certainly since the 1990s, we have had standard care of self-monitoring of blood glucose in T1D, as well as in insulin-treated type 2 diabetes (T2D) and for anyone with T2D at high risk of hypoglycemia. Since 1999, we have had continuous glucose monitoring (CGM) technologies available to us. These started off as being wired devices that recorded glucose over 3 days and then had to be downloaded, but again, over time have become smaller, more accurate, the sensors last longer, and they now provide real-time continuous glucose information to the user, which can be looked at by healthcare professionals or carers.

L.A.: Wow so it really has come a long way then; I suppose with technology in general. So, as there are so many options available for patients, could you maybe talk us through the key ones that are in circulation right now?

CONTINUOUS GLUCOSE SENSORS TODAY

N.O.: Yes, sure. There are broadly three categories of continuous glucose sensors that we have available to us for care of all diabetes, but in particular T1D. These are real-time CGM (RT-CGM), which gives the user a real-time glucose value along with the rate and direction of change of glucose and the preceding few hours of glucose trend, and that is available either on a receiver or a smartphone device and gives the user that real-time information whenever they wish to see it. Real-time devices also give alerts and alarms for either impending or established hypo- and hyperglycemia or if glucose is very rapidly changing. The second implementation of continuous glucose data is flash glucose monitoring or what is sometimes called intermittently scanned CGM, and that does not give real-time values but instead relies on the user swiping their device, so that is either the receiver or the smartphone over the sensor to give them the information, and the alerts and alarms are either not present at all with intermittently scanned CGM, or they are qualitative alarms, and what that means is rather than giving you the immediate alarm and the information around the alarm, it tells you that something has happened that requires a swipe to look at what the alarm status is. And then finally, there is blinded CGM, where the user cannot see any of the values and at the end of the sensor session, the data is downloaded for review. That is

used far less frequently in clinical practice but can be a very useful research tool. So continuous glucose monitors do not measure blood, they measure interstitial fluid glucose so the glucose in the fluid underneath the skin and they report frequently sampled glucose values between every 1 min to every 15 min or so. Most of them are around the 5 min mark so that gives you 288 glucose values per day, and they enable you to make clinically meaningful changes to your self-management on a reasonably regular basis.

L.A.: Well that is fantastic. It seems there really are so many options available to us. It must be quite difficult to work out which one might be best. As we know these have developed so much in the past 20 years because of technological advancements, but also because of randomized controlled trials (RCTs), which have been crucial in building up the robust evidence base. So, could you actually talk us through some of the key evidence that has come out of these clinical trials?

THE EVIDENCE BASE FROM RANDOMIZED CONTROLLED TRIALS

N.O.: Yes, absolutely. As you say, making the choice about which technology is most appropriate in a clinical scenario is really important, and that choice should be an informed choice between the clinician and the person who is going to be using the device. So if we think about those three categories, I will park blinded GCM because it is really not frequently used as I said in clinical practice, so there is not a great evidence base for that recently. But if we think about real-time continuous glucose monitoring, there is a fantastic evidence base, particularly over the last 10 years or so, which tells us that RT-CGM can significantly reduce glycated hemoglobin (HbA1c) [1, 2] in young people, older adults, and adults living with T1D [3–5], and importantly RT-CGM can do that irrespective of whether you use an insulin pump or a multiple dose injection regimen. Along with the reduced HbA1C, real-time monitoring reduces exposure to hypoglycemia at all thresholds [1]. The International Hypoglycemia Study Group suggested that everyone should use a threshold of less than 3.0 mmol/L or 54 mg/dL as the threshold for important hypoglycemia, and CGM certainly reduces exposure to all thresholds including that one. And really importantly, for people at highest risk of severe hypoglycemia requiring the assistance of a third party for active treatment, RT-CGM can reduce the incidence of those severe episodes [6], and that is really important because they can be incredibly disabling and they are associated with morbidity and mortality. CGM also reduces glucose variability [1, 2], and these changes to glucose, these improvements to overall glucose and glucose below target happen during the day and during the night [1, 2]. The concept study showed that RT-CGM used by pregnant women living with T1D can reduce adverse maternal–fetal outcomes [7], and that included neonatal intensive care admissions for the newborn, neonatal hypoglycemia, and the length of stay for the baby. In terms of how people live with T1D and the psychosocial outcomes or the patient-reported outcomes, RT-CGM can reduce hypoglycemia fear [2], and in particular the worry aspect of the hypoglycemia fear score and can increase treatment satisfaction [1]. Flash glucose monitoring has a slightly smaller evidence base, but can reduce exposure to hypoglycemia below 3.9 mmol/L or 70 mg/dL [8], again can increase treatment satisfaction [8], and until recently, flash glucose monitoring did not have an evidence base for a reduction in HbA1c compared with self-monitoring blood glucose. The IMPACT Study, which was the main RCT in T1D, did not show a change in HbA1c [8, 9], but the FLASH-UK study [10], which has just been published in the *New England Journal of Medicine*, showed that the FreeStyle Libre 2 device, which is an intermittently scanned CGM device with qualitative alarms, can reduce HbA1c compared with self-monitored blood glucose. As I said at the start, it is really important to be able to make an informed choice about which monitoring technology is most appropriate, and there are three studies that have pitched both flash glucose monitoring and RT-GCM in a head-to-head study. One of these, the I HART CGM study [11, 12], did

that in very high-risk people, so people with impaired awareness of hypoglycemia or previous severe hypoglycemia, and then there was the CORRIDA study [13] and the ALERTT1 [14] study, which were larger and less selective populations and really interestingly, all three showed exactly the same thing, which is that RT-CGM had a significantly greater beneficial impact on glucose outcomes than flash glucose monitoring, so it is really down to informed choice, personal preference, and what you are trying to achieve with your CGM technology.

L.A.: That is so interesting that they all have such similar results. It is clear that these clinical trials have given us a lot of information, which has been crucial in informing clinical practice, but it cannot really be ignored that there must be some blind spots from these clinical trials just because they are in such a controlled environment. So what do these clinical trials actually not tell us about these technologies? What are these gaps?

THE LIMITATIONS OF RANDOMIZED CONTROLLED TRIAL DATA

N.O.: Absolutely. Doing clinical trials is great, we have a really controlled environment, and we can very carefully and closely look at outcomes, but inevitably the people that we recruit as participants to RCTs may not entirely be reflective of the population that live with T1D. If we think about the selection bias of RCTs, it can sometimes be difficult to get a diverse representative population, and by diverse I mean in terms of age groups, in terms of ethnicity, and in terms of socioeconomic deprivation particularly. Obviously these are really important, we know that people who live in an environment where there is deprivation are at higher risk of adverse outcomes living with diabetes, so it is crucial that we recruit these people if possible so that we can see the benefits, or not, in that group. Inevitably, we always do clinical trials in academic centers, so centers that have both clinics and also people who do clinical research, and that means we can have a slightly skewed population and we are not always great in RCTs at looking at outcomes that are important to people living with diabetes. I just listed a load of glucose outcomes and only a couple of patient-reported outcomes, but of course if you live with T1D for decades, it is really important how you live with that and your experience of living with it. It is very useful to look at clinical and cost-effectiveness from RCTs but it does not tell you the lived experience of the technology and it does not tell you what the real-world change might be for someone who is less selective and the impacts for someone who has less education and less support at the outset.

REAL-WORLD DATA

L.A.: They are really important points, which I suppose now brings in our key theme of the podcast today, which is real-world data. Could these data help fill these gaps? Why is real-world data so important?

N.O.: I think real-world data is incredibly powerful. I think sometimes there is a temptation to have an argument about whether it should be RCTs or real-world data. I think it is really important to take the two together; they are adjuncts to each other. Clinical trials will tell you about efficacy, while real-word data will tell you about effectiveness. If you take the example of RT-CGM, we know that there is significant efficacy from the RCTs, but there is lovely real-world data confirming real-world effectiveness too, so they are an adjunct to each other. You might see different effect sizes and that is very important as well. In RCTs, we sometimes bring people up to the clinical research facility once a month or with a similar frequency and that does not reflect usual clinical care, so you can get the skewing of the influence of observation. In real-word trials, you can have a much larger population without that skew from being observed in a RCT that you have consented to, so you can have this large diverse representative population. Though it is then challenging because you may not be able to collect quite as much data, but you can certainly have an accurate cost-effectiveness analysis from a large population that tells you much more about how something would work if you

rolled it out across the whole population in a country, for example. So they are really important to look at in context; they need to be adjuncts to the clinical trial data, but they can really enrich the story for a technology.

L.A.: Definitely. I think you have already touched upon some pretty prominent advantages there, but are there any others that you think are valuable to share?

The Advantages of Real-World Data

N.O.: RCTs can be very expensive to undertake; they need lots of monitoring, they need lots of people to deliver the studies, so they can be very expensive and that is not necessarily a bad thing. They remain important to do and it remains an important investment for clinical science, but real-world data can give you much better value for money because they are much lighter touch and can often be undertaken remotely, so you can enroll a large population at a reasonably lower cost with a representative cohort, and you can include a really long-term follow up. Clinical trials will have an end date, they will have a primary outcome date and sometimes that is 3, 6, or 12 months, so in the lifespan of someone living with diabetes, that is a really short time, but if you collect real-world data over 5–10 years, that can tell you much more about the evolution of things like complications or glucose self-management. There is this regulatory structure in real-world studies, so they can be simpler or more rapid to set up, and the technology uses is reflective of what happens in the real world. In a clinical trial, you have to write a protocol that includes the education that you will deliver at the start of a technology use, but if you take real-world data, particularly for things such as glucose sensors, these are off-the-shelf devices. People can go on a website and buy a continuous glucose monitor and just start using it, and it is really interesting to see if that has a differential in terms of how effective it is. You do not get the confounding of that frequent contact with study teams and you can do things such as linkage to larger electronic data collections and a lovely example of that would be the National Diabetes Audit data that we have in England and Wales that tells us huge amounts about things such as the progression of complications and how many people have care processes that are required as part of diabetes care. You can have massive advantages by tapping in to the real-world data, and as I said, really enriching that story about how a technology works at a population level.

L.A.: It certainly seems that there are a lot of positives to using real-world data, so I am sure it will be applied more often. But I suppose, as with anything, there must be a flip side. Are there any problems which you think need to be highlighted?

The Limitations of Real-World Data

N.O.: Yes, nothing is perfect is it? Real-world data have huge power but they must be taken in context and you need to be slightly careful about interpreting them. They are limited by what people feel is routine care, so what I do in my clinic might be different from what somebody does even a few miles down the road, so there is a limitation that routine care is not standardized. One of the big problems that we have seen with glucose sensing real-world data is that we sometimes do not have reliable baseline data. There are some lovely data that show things change once you start a technology but do not necessarily tell you what the absolute baseline for that population is, so it is very difficult to know what the change has been over time. People are lost to follow-up in real-world studies because you have not enrolled them and do not necessarily have all of their details. There is inevitable attrition of data collection down the line and because your outcomes are not time bound, so for example, in a clinical study you might say we are going to collect an HbA1c outcome at 3 months, but we do not have the opportunity to do that rigidly in a real-world dataset, so the outcomes might be a little bit less clearly defined in terms of the time-bound way. There is the risk of some clinician bias in how we manage people, so if we know that we are collecting data for a real-word study, we might slightly change how we manage things, and in terms of how the data are looked at, if you take

real-world data to NICE for example, they may feel that they are of lower quality and sit below RCT data in how they are prioritized for access to technologies or medications, so it can be difficult to use real-world data to really change practice. The other thing that is hard to do is you cannot do things such as head-to-head studies, so I told you three studies that were head-to-head studies of flash and RT glucose monitoring; it is really difficult to do that from real-world data because it is very hard to match a population and see what the differences are in terms of effectiveness. So there are some limitations, and as I said, I think the important thing is you take real-world and RCT data and you use them together to tell a story.

REAL-WORLD DATA FOR GLUCOSE SENSING TECHNOLOGIES

L.A.: Yes, everything does have its limitations, and if we do combine them that would be really beneficial. We discussed earlier the evidence base that existed for these clinical trials. How about this real-word data? What evidence base is here for glucose sensoring technologies?

N.O .: There are a few. If we think again about RT-CGM, there is the RESCUE study [15], which was very detailed and confirmed the RCT data for the glucose signals of improved overall control and reduced exposure to hypoglycemia, but because it was real-world data, it was also able to tell us about work absenteeism and hospital admissions, and these are not things that are always routinely collected in RCT data and showed very nicely that RT-CGM means that people are able to work more often and have fewer hospital admissions. These are really important not just for the individual, but they have really large impacts on cost effectiveness, so work absenteeism and productivity are really important, particularly for people who are self-employed, and obviously hospital admissions are critically important to the person living with diabetes, but also really important to the healthcare system because you can reduce bed use and that reduces costs and burden on a healthcare system. The COMISAIR study [16], as I said earlier, one of the benefits of real-word data is that you can do it for longer, and the COMISAIR study is a RT-CGM long-term follow up study over 3 years, which is significantly longer than any of the RCT data. Then we have manufacturer data, so often with devices, the manufacturer themselves collect lots of data and are able to collate that and publish it. The data for the Dexcom G6 device shows that the Urgent Low Soon alert, which is the only urgent predictive hypoglycemia alert, shows that there is a real impact in the real world of using that in reducing exposure to hypoglycemia [17, 18], so that tells us not just about the device itself, but about the feature use. All of these devices have these features that you can turn on and off and it is really nice to see a well-conducted, real-world study that tell us that those advanced features can be really helpful. In terms of real-world studies of flash glucose monitoring, there is the FUTURE study [19], which is a national registry and showed a stable HbA1c, as with the RCT data, but again, importantly, reduced work absenteeism and reduced severe hypoglycemia, so those are really important outcomes for people living with diabetes. In the UK, we have the ABCD [20], the Association of British Clinical Diabetologists, which collected real-world data for flash use, and this is an example where there was really high attrition of follow-ups, so it started off with a large number of people and that was slowly whittled down over time, which means that the real-world data that are published at the endpoint are at risk of selection bias and that is one of the disadvantages of real-world data. The Swedish registry [21] on the other hand, is another national registry that showed a small HbA1c reduction in people who were above target who used flash glucose monitoring, and again, a signal of reduced severe hypoglycemia. Severe hypoglycemia is a really important outcome for the person, but it is also really important from a clinical study point of view because it is a relatively rare event it is really hard to power a randomized controlled study to show a reduction in severe hypoglycemia, so being able to look at it robustly in a national registry for real-world data is really impactful. Similarly, the Scottish data [22], again, another national registry, showed a reduction in HbA1c and diabetic ketoacidosis,

but highlights socioeconomic inequality and access of flash, but not outcomes. It showed that people from more deprived areas were less likely to access flash glucose monitoring, certainly at the start, but were exactly able to achieve the same outcomes as people from lower deprivation areas, so what we should really be trying to do here is address health inequalities and it is these sort of findings that you would not be able to get from RCTs. Finally, there is the European analysis of data [23], and this is a huge dataset but no baseline data, so we can only look at associations over time. So there is loads of data there, they all have slight weaknesses, but taken as a whole on top of the RCT data, really confirms what we have found, and tell us where the benefits lie for each of the technologies.

L.A.: Yes, absolutely and I think it is really important that you did highlight that there are still some limitations, but I think the overarching theme is that we are really seeing the evidence base grow and become established in the real-world data setting. So what comes next? What is next in the real-world data space?

The Future of Real-World Data in Continuous Glucose Monitoring Technology

N.O.: So certainly in T1D, one of the things we are starting to see, which is fantastic, is the real-world studies of automated insulin delivery, so hybrid closed-loop systems that use a continuous glucose sensor connected to an insulin pump to automatically adjust insulin delivery and certainly basal insulin delivery. There are some very large studies of highly advanced technologies [24–26], and these measure in the thousands of patient years, which is hugely impactful and something that would be so difficult and expensive to do in a RCT environment. These confirm exactly what we expect from the RCT data of automated insulin delivery—that overall glucose, and particularly exposure to higher glucose above target, is significantly improved by automated insulin delivery. The other thing about real-world data and what comes next is that unlike drugs to a certain extent, there is a very rapid turnover of technologies, so product cycles are much more akin to mobile phone and iPhone product cycles than they are with drugs, so we tend to have a new CGM technology every year or two, whereas we get a new class of drugs much less frequently than that. Real-world data can jump onto a new device very quickly and can give us a much more rapid turnover of an evidence base that builds on previous data. I think the next thing that we will see is embedding CGM and continuous glucose technologies into routine data reporting for rapid dissemination. A lovely example of where that happened, albeit outside of continuous glucose sensing data, is in the National Diabetes Audit COVID data [27, 28], which managed to very rapidly publish data for people living with diabetes who developed COVID both in and out of hospital and showed morbidity and mortality from that. That is such an important way to use real-world data to really populate a national evidence base in a really highly impactful way.

L.A.: That is such a fantastic example of how it has actually been used in the real world to make real change. Thanks so much Nick, this has really been a valuable discussion and I am sure that there will be far more to discuss about this in the coming years as this technology develops and more and more data comes out. I just wondered if you had any final words on the matter that you would like to discuss?

SUMMARY

N.O.: I think the summary is that real-world data can be hugely powerful and impactful, they are an adjunct to clinical trial data, which needs to tell us about effectiveness before we can build on efficacy, but they are hugely impactful. They enrich and tell the story beautifully sometimes and particularly when done well. I think there is a temptation with real-world data to just collect what we have, but just like a good clinical study, good real-world data needs to be carefully designed and collated but it can be incredibly powerful. I think what we are going to see over the coming years is

increasing use of glucose sensing data in the real world, with linkage to real-world outcomes for people living with diabetes, and we will start to get a really carefully drawn picture of the impact of continuous glucose sensing technologies as they become standard of care for everyone living with T1D and for the majority of people living with T2D, certainly those people who are insulin treated.

L.A.: That is a fantastic summary. Thank you so much Nick and I really look forward to seeing these barriers to patients lowered so everyone can access these technologies, which I am sure we will see as years go on. Thank you so much again for being here. It has been such an interesting topic, I really value your time and I hope everyone joins again for future podcasts.

N.O.: Thank you very much.

L.A.: Thanks Nick.

ACKNOWLEDGEMENTS

Funding. No funding was received for the creation or publication of this podcast.

Authorship. The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, takes responsibility for the integrity of the work as a whole, and has given their approval for this version to be published.

Author Contribution. Nick Oliver conceived and wrote the invited manuscript.

Disclosures. Nick Oliver has received research funding from Medtronic Diabetes, Roche Diabetes and Dexcom, and has received honoraria for advisory board attendance and speaking from Medtronic Diabetes, Dexcom and Roche Diabetes.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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