**Executive Highlights**

*The diaTribe Foundation's second annual EASD event, "Solvable Problems in Diabetes," offered a sharp, realistic assessment of the many challenges and opportunities in diabetes care. Moderated by our own Kelly Close, the wide-ranging conversation featured Dr. James Gavin (Emory University, Atlanta), Prof. Ele Ferrannini (University of Pisa School of Medicine, Pisa, Italy), and Prof. Rury Holman (University of Oxford, UK) in front of 150 guests from industry, academia, and government.*

*Among other things, the panelists discussed the limitations of current guidelines (which "give you the ingredients but not the recipe"), how they would invest $500 million in the field ("guideline-changing" studies and diabetes prevention), their experience advising global governments (China, South Africa, Italy), the potential implications of EMPA-REG OUTCOME, and next-gen therapies (smart insulin, GLP-1/basal insulin, SGLT-2/GLP-1, and closed-loop).*

*Below, we have distilled what we thought were the dozen most notable quotes (it was nearly impossible to choose) and some of the most prominent themes of the evening, followed by an expanded transcript of the entire discussion. All proceeds from the event support The diaTribe Foundation and its mission of improving the lives of people with diabetes and prediabetes and advocating for action. As you can imagine, we greatly appreciate all of our sponsors and attendees for making this event a success.*

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## Solvable Problems in Diabetes

### Quotable Quotes

**On Guidelines...**

- "Right now, the status of guidelines is like a cookery book with a list of ingredients but no recipes. We don't have the evidence to make the best choice for the patient in front of you at the right time." - Prof. Holman
- "In terms of the methodologies to help doctors understand which tools to use for whom, the gaps are enormous. We treat diabetes one case at a time. There's enormous heterogeneity in this disease - both in type 1 diabetes and type 2 diabetes. It's bewildering, the degree to which one has to confront a number of questions for which we have very little insight and few tools for clinicians." - Dr. Gavin
- "On the other hand, relying on guidelines alone isn't the answer. You don't want to be a doctor that's just a robot that brings patients down a path that's telling you what to do at every fork. Because that would get rid of any exercise of clinical judgment. My younger colleagues are not enthusiastic about that. They're sitting in their offices with all these charts hanging on the walls. There are guidelines

for everything and all they have to do is to take the patient down these paths. That's true destruction of clinical judgment." - Prof. Ferrannini

**On Investing $500 Million in Diabetes...**

- "We're spoiled for choice with so many treatments, but we don't know how best to use them. Doing studies that are guideline changing, that put into context their relative merits and benefits, would be helpful. That's not the sort of money you get from industry, and governments are not keen to fund long-term outcome studies." - Prof. Holman
- "I would invest it in prevention, because it's quite clear to me that we are managing diabetes better than we have in the past." - Prof. Ferrannini
- "The Claude Bernard Lecture was timely by emphasizing that preventing diabetes is the way to go. We have a lot of people with diabetes that already need our help but it's the next generation that faces a diabetes tsunami that needs to be stopped." - Prof. Holman
- "Prevention is going to be fantastic and we'll dance in the streets. But it will be a bigger dance when clinicians don't have to worry about what to do with what and for whom." - Dr. Gavin

**On EMPA-REG OUTCOME...**

- "This is truly exciting - getting a superiority trial that is positive ... If you have diabetes, even if you optimally manage the risk factors, you can't get back to the non-diabetic cardiovascular risk level. That's extremely unfair and people with diabetes deserve better - if this drug can help, that's great." - Prof. Holman
- "I think we need to be thoughtful about what the outcomes really mean and not rush to sound bites that more often than not get us into trouble and lead to limitation of thinking, not broadening." - Dr. Gavin

**On Next-gen Therapies...**

- "I don't invest too much hope in any one drug to save us. That won't happen. And that's fine, because the complexity of diabetes will defy us. A complementarity of treatments will be required to address the pathophysiological complexity of diabetes ... But there is great hope. Grow the classes, show how they can marry and cohabitate. And there will be great outcomes and glory! And polygamy!" - Dr. Gavin
- "...we have learned so much more about use of insulin in recent years, that insulin has almost become a new drug." - Prof. Ferrannini
- "I continue to harbor the notion that the inventiveness and creativity of humankind will allow us to master technology, electronics, and gadgetry more quickly than we master biology. My optimism is that there will be strides toward development of effective closed loop systems. My pessimism is that they will be for a very narrow band of patients." - Dr. Gavin

**On a Positive Note...**

- "When I started in diabetes, a patient with type 2 diabetes had an estimated loss of life of around 15 years. Now that is probably down to about 3 to 5 years." - Prof. Holman
- "...we don't have to go all the way. We just have to do it a hell of a lot better than what we've been doing." - Dr. Gavin
- "I'm definitely more optimistic about the future of prevention, not only because we're beginning to understand the underlying disease processes, but also because society is waking up to the problem and beginning to do something about it." - Prof. Holman

## Themes

- **How would panelists invest $500 million in diabetes? Prevention and "guideline-changing" studies:**

- **Speakers were unanimously negative on current treatment guidelines, citing the major lack of evidence on what to prescribe when and for whom.** The most memorable analogy came from Prof. Holman, who described guidelines as being "like a cookery book with ingredients but no recipes." Prof. Ferrannini was even more frank: "Don't believe guidelines." Panelists expressed pleas for studies that can help providers make the best treatment choice for a particular patient at a specific time - not simply yield a list of available medications in a vague order. Unfortunately, said Prof. Holman, these "guideline-changing" studies, as they call them, are unlikely to be funded by governments or industry. Indeed, he believes even the GRADE study is lacking in some respects (notable commentary, given that he was on the trial's advisory board from the start): "It was a great attempt, but it was too short and not big enough. We need to do that trial but on steroids." Prof. Ferrannini brought up an additional factor that will become increasingly important as algorithms are further developed and "get smarter" - will analytics erode clinical judgment? For example, if IBM's Watson can suggest the perfect therapy based on a patient's entire medical history and all the available literature, where does that leave doctors? An optimist would say smart analytics will augment doctors' natural abilities and free them to focus on other issues (e.g., behavior, mental health); a pessimist believes computers will largely replace doctors. The truth is probably somewhere in the middle according to the panelists, and given the current shortage of healthcare providers, what are the alternatives?
    - **Dr. Gavin captured the complicated politics of guidelines well: "**When we have even partial answers, the guidelines constantly tell us to individualize, individualize, individualize. Yet we are sort of trapped by this reductionist narrative in terms of the way the guidelines direct us. They avoid being hierarchical so they don't offend anyone. If they're not at all hierarchical, they're simply a series of options, and I don't know if that is always the most informative way to help clinicians struggling with the fundamental questions."
  - **There was clear interest in investing in diabetes prevention, and panelists highlighted and emphasized the importance of Dr. Hans-Ulrich Haring's Claude Bernard Lecture on the phenotypes of prediabetes.** As background, the Claude Bernard Lecture is a very big deal - the equivalent of the Banting Lecture at the ADA. Prof. Ferrannini stressed the need to define sub-phenotypes of prediabetes and develop new targets that can personalize prevention efforts. We found this exciting, considering that lifestyle intervention (and metformin to a lesser extent though it's not approved for this purpose in the US) is really the only mainstream approach for treating prediabetes at present. As Prof. Holman pointed out, we are finally unearthing the scientific evidence necessary to support the prediabetes rhetoric - the challenge now is translating this work into practice (therapies and technologies and behavioral approaches) and convincing payers that the benefits of "treating" prediabetes far outweigh the risks. Panelists did not mention digital interventions for prediabetes or obesity pharmacotherapy, though emerging data suggests potential for both.

- **Panelists offered tantalizing predictions of the EMPA-REG OUTCOME full results that - in retrospect - trended slightly on the optimistic side for the primary risk reduction: Dr. Gavin at 30%; Prof. Holman at 18%; and Prof. Ferrannini at 15-25%. The actual figure was a 14% risk reduction for MACE, the primary outcome; in hindsight, we should've asked the panelists their opinion on secondary outcomes.** Most in the audience concurred with the mid-teens to low-twenties predictions. Speakers agreed that a diuretic effect was a potential explanation for the benefit, though they also cautioned against over-generalizing from the results of one trial and didn't know ultimately whether the result would indicate a class effect. Dr. Gavin was particularly emphatic on this point: "I think we need to be thoughtful about what the outcomes really mean and not rush to sound bites that more often than not get us into trouble and

lead to limitation of thinking, not broadening." Despite this, panelists did demonstrate some prevailing bias toward a class effect, with both Dr. Gavin and Prof. Holman suggesting that SGLT-2 inhibitors may become the standard second-line therapy and in fact some have asked whether it should be first-line therapy in some populations. Certainly, the clinical and commercial impact of the results will be interesting to watch; unquestionably, the overall sentiment is that guidelines committees (and payers) will want to wait for results from the other SGLT-2 inhibitor trials before designating the class as the preferred second line option.

- **Dr. Gavin reflected on the need for a "complementarity of treatments" to address the pathophysiological complexity of diabetes.** This was a common refrain throughout the evening: that neither drugs nor technology alone holds the solution to diabetes care. Of course, the task of integrating care is a tall order, though all three panelists were optimistic that we are closer to multifaceted models of care than ever before. We also loved the perspective that for the many challenges in diabetes, the field currently understand what does NOT work for patients better than it ever has before. That's something to hang your hat on!
- **Panelists also debated the progress of closed-loop development, emphasizing to attendees the importance of managing sky-high expectations.** As systems near commercialization, we were reminded of the importance of considering the design elements that will maximize benefit and assure safety. Dr. Gavin stressed that artificial pancreas technology will not be appropriate for all patients when it arrives on the market - Will it only be early adopters who try it? For whom will it be financially accessible? There are big psychosocial questions that also remain that were pointed out: how large is the patient population willing to hand over complete control to a device? How much extra equipment will users need to carry? On the latter question, we believe it won't be much or any at all for current pump and CGM users; for MDI users, on the other hand, a lot of extra stuff at the start!
- **Notably, the importance of public-private partnerships in healthcare and diabetes also emerged as a key theme.** We appreciated Prof. Ferannini's reflection on the value of allowing more avenues for industry, academia, and patients to interact with each other. There was clear consensus that increasing collaboration is needed, though still a lot of uncertainty about how to get there … especially in the US. As a reminder, we received an introduction to the Accelerating Medicines Partnership (AMP) in Type 2 Diabetes at ADA 2015 that represents a step in the right direction. We'd love to see more of this kind of approach moving forward.

### Panel Discussion

**Kelly Close: Thank you so much to all of you for being here this evening. It is so meaningful to us. We salute your families for giving you so much support in your work, as you are true visionaries for our field. Please thank them from us. To start - this is very exciting. What has struck you the most at EASD 2015? What has moved you here in Stockholm?**

Prof. Ele Ferrannini: I heard the Claude Bernard Lecture, and I thought Dr. Hans-Ulrich Häring did a superb job. He's taken the knowledge of the science from the cellular to the genetic and all the way to the phenotypes. He's begun to identify specific changes in physiology in muscle and brain tissue - he only left out the gut, likely because of time. He's begun to put this into the scientific terms towards what we are all taking about: individualization. This is what we try to do with our clinical judgment every day.

Dr. Rury Holman: I would say, even preceding the Bernard Lecture, was the address by Andrew Boulton which I thought was amazing and detailed the achievements of the EASD which is just over 50 years old. Andrew demonstrated the power of a group of academics who first met in the small town of Montecatini in 1965 but had the ambition that together they should start a diabetes group. It was slow progress, but what's come out of it is extraordinary. Now, with the availability of European Foundation for the Study of Diabetes funding we have the power to do research in an academically driven way with the help of industry. The Claude Bernard Lecture was timely by emphasizing that preventing diabetes is the way to go. We have a lot of people with diabetes that already need our help but it's the next generation that faces a diabetes tsunami that needs to be stopped. I thought what was really interesting was data that goes all the way back to the womb -

detecting changes in utero induced by elevated glucose levels. We should be worried at how early these changes are occurring and Dr. Haring now has the science to underpin this process with his scientific expertise.

Dr. James Gavin: Solving the problems of diabetes is no small task. I was in the exhibit hall for a bit today and I was so happy to have time to go in and look around. For example, I went to a session on newer insulins. Some of what I learned there I was already exposed to, such as the research on super rapid-acting insulin and the degree they're likely to make a difference in patients' lives. So we can hopefully ultimately approximate what you hope to accomplish with the artificial pancreas. I am absolutely struck and impressed by what I've seen in terms of development and capabilities that will allow us not to chase blood sugars but to treat what glucose levels are coming and to avoid them. The coming of new technologies will allow us to engage patients, so people won't have to be reminded that they have a disease hour by hour, day by day. These technologies will allow people to live their lives and come back occasionally for therapeutic treatment.

**Ms. Close: Thank you. I love hearing what's most exciting to you. And now I'd like to move the conversation in a high-level direction. We saw in the US that the Robert Wood Johnson Foundation gave $500 million to fight childhood obesity - that's adding on to another $500 million for childhood obesity several years ago. The influence of Dr. Gavin played a major role here. If the three of you could work with any foundation who was set to give $500 million to diabetes, in what area would you advise them to work?**

Prof. Holman: I'm biased as a trialist. The issue is we're spoiled for choice with so many treatments available, but we don't know how best to use them. Doing studies that are "guideline changing", that put into context their relative merits and benefits, would be helpful. That's not the sort of money you get from industry, and governments are not keen to fund long-term outcome studies. I'm not talking about cardiovascular outcomes. I'm talking about which treatment works best for which people, when we should we start, who should use what and in what order. If I were blessed with that money, I would look at guideline-changing trials.

**Ms. Close: That's so interesting, Professor Holman - before we move on to the others, as a quick follow-up, could we ask how you feel about the GRADE study?**

Prof. Holman: I must declare a conflict of interest. I was on the original study design team. I think it was a great attempt, but it is too short and not big enough. We need to do that trial but on steroids.

Prof. Ferrannini: I have difficulty in even fantasizing about this kind of money to invest in diabetes. You know, if that became true, I cannot even tell you what I would do with that money [laughter]. Ultimately, I would invest it in prevention, because it's quite clear to me that we are managing diabetes better than we have in the past. We heard from Dr. Andrew Boulton earlier today that diabetes is no longer the primary cause of blindness; we've seen in the *New England Journal of Medicine* recently (Gregg et al., 2014) that complications have fallen to 50% of what they were; and clearly, the survival and the quality of life for patients have improved. However, we just cannot cope with the number of new cases. For that, we can only use prevention. And for prevention, we have to refine our tools to ensure that the people getting treatment are the ones who need it.

Dr. Gavin: I have had the gratifying experience of knowing that such a fantasy could happen since I spent 12 years on the Robert Wood Johnson Foundation. Seeing us get that funding, I think this can actually happen. Now, I would hope that we would be able to split the $500 million into at least two parts. I think prevention is absolutely one of those frontiers that we need to continue to push forward on. Also, I think we're getting closer to the point where we can differentiate the different forms and stages of diabetes in ways so that we can use our tools most appropriately. Prevention is going to be fantastic and we'll dance in the streets. But it will be a bigger dance when clinicians don't have to worry about what to do with what and for whom. It's a great conundrum.

**Ms. Close: Thank you for these fascinating impressions. On a bit of a different front, Jim, you alluded to different therapies and technology. How much are these helping doctors and nurses? Is that a frontier we're moving toward? Helping health professionals better understand what therapeutic tools patients need when?**

Dr. Gavin: In terms of the methodologies to help doctors understand which tools to use for whom, the gaps are enormous. We treat diabetes one case at a time. There's enormous heterogeneity in this disease - both in type 1 diabetes or type 2 diabetes. It's bewildering, the degree to which one has to confront a number of questions for which we have very little insight and few tools for clinicians. When we have even partial answers, the guidelines constantly tell us to individualize, individualize, individualize. Yet we are sort of trapped by this reductionist narrative in terms of the way the guidelines direct us. They avoid being hierarchical so they don't offend anyone. If they're not at all hierarchical, they're simply a series of options, and I don't know if that is always the most informative way to help clinicians struggling with the fundamental questions.

**Ms. Close: That's so well said. I want our doctors and nurses to feel more successful themselves. Along those lines, can I ask broadly about how you all define success in your own careers? This is so important for all generations here to hear, especially the youngest.**

Dr. Gavin: In childhood obesity, defining success has been fairly easy. At the end of the day, we want to see the trend reverse and to see a new level set for the prevalence of childhood obesity. This is about diabetes prevention. This strategy hits multiple touch points - it touches childcare, it touches the messages kids are getting, etc. And all those touch points affect not just kids, but their families. And all those things affect diabetes.

**Ms. Close: That goes back to the Claude Bernard Lecture from this morning about how work with children doesn't start at zero, it really starts nine months earlier right after conception. Thank you, Dr. Gavin. What would you say, Professor Holman?**

Prof. Holman: I think defining success is actually making a difference. I have had the extraordinary opportunity to work with people in so many different countries to try to get definitive answers. It goes back to what Jim was saying about guidelines. I don't think people are afraid to make comments, but it remains an area of ignorance without the evidence base needed. Right now, I'm striving to move from simple outcome studies to trials that can inform the relative impact of treatment strategies on the person, the payer, and the physician. Meanwhile, we need to pull together all the information in our rich toolbox, including digital tools and computers, to make it more accessible to people with diabetes. It'd be great to have a physician with unlimited time who can make wise choices for them, but sadly for many people are lucky if they are able to see a physician. We need something that can help support diabetes management at the patient level - and something that means they don't have to obsess about managing their diabetes every minute of the day.

**Ms. Close: I think it's great we're getting help from friends who are in technology. If you look at the innovation over the last couple of decades, that's absolutely where it's been. What about you, Professor Ferrannini?**

Prof. Ferrannini: I may be less ambitious than you guys. [Laughter] As a researcher, success is when a paper gets accepted. [More laughter] Which doesn't happen all the time. As a physician, success with a diabetic patient is when I can find the time - not the eight to ten minutes the healthcare system allows. Success is the first time I can spend the time necessary to explain the disease. Patients have probably been on the web, they have all sorts of information, and you can explain what diabetes is about. It shouldn't be frightening, but you should explain the risks and complications. That initial imprint on the patient and on the family is the time when you are doing all that is possible to put in the most promising premise for future management suggestions. It's a bit like what you do with infectious disease. You don't say, "Take some of this antibiotic and then come back in three days." You treat it aggressively immediately, and I think that's what needs to be done in diabetes. I think that's what's needed to gain adherence, and I feel success when I have that time and he comes back with better control. If he's obese, my success is if he loses weight because we know obesity is a major risk factor for diabetes and diabetes is the daughter - though not the only daughter - of obesity.

**Ms. Close: I'd like to talk about governments around the globe. I'm really curious since you're all advising them. Who is doing the best job? Who are you most impressed by? What can the EU learn? What can the US learn? Tell us some stories about interacting with policymakers and the biggest payers.**

Dr. Gavin: I recently came back from an interesting tour of South Africa and had a chance to speak at length with payers and policymakers about diabetes in particular. At the end of those eight or nine days, I came back home with the conclusion that our doctors are doing a wonderful, fantastic job in the US. I stopped complaining so much because there was resistance from payers to novel therapies in South Africa, the likes of which I hadn't encountered in a long time. I can't speak for many governments or payers, but the largest of payers in South Africa have enormous resistance to novel therapies, seeing no benefit in those offerings beyond traditional therapies. Therefore, there's no chance of achieving the necessary level of patient engagement in diabetes. It's just not going to be done. It also reminds me that the information and awareness needed to change diabetes is lacking. I think that's one extreme.

Now I'll contrast that with a fascinating conversation I had with Dr. Griffin Rogers, the head of the NIDDK. I was just so thrilled to hear about one example of government-industry partnerships, and some of the partners involved are on this board. They're looking at ways in which to take the burgeoning field of proteomics, genomics, metabolomics and to make big data available in a place that's accessible. And they want to make it accessible to anybody that needs it for advancing work to continue to move forward on issues like differentiation of diabetes, appropriate phenotyping, staging, and the designation of who needs what. To see what's happening here, it's not with the goal of a proprietary outcome but making available all this data that's already here but organizing it in such a way and presenting it in a way that the public, and I mean the public globally, can access it. That is the kind of thinking and action I'd like to see characterize governments everywhere.

**Ms. Close: We look really forward to hearing more about that. On a different front, it is also so instructive in diabetes to look at what's happening in other therapeutic areas. Interestingly, when other areas are having breakthroughs like hepatitis C for example, it is effectively hurting diabetes because payers are stressed about investing in their most significant ROIs - the ROI for diabetes spending effectively goes down when there are breakthroughs in other areas. So I love the point about presenting things more compellingly in diabetes, and ideally with more focus on systems and behavior change, we can see more of that.**

Dr. Gavin: One of the things I would emphasize is on public-private partnerships. Because when I think about the amount of data we're getting in, it's too big. Someone other than the government is going to have to take the lead in gathering that information and making sure everyone's interests are appropriately tamed - so that people do not feel they are giving in to someone else - for the greater good. It's up to someone other than government to take the lead in that.

Prof. Ferrannini: I would have a word of caution with that. Big data can be used for different purposes and should be for the benefit of the people. And there are already striking examples of that. On one hand, it's good to pull data and to have some way of accessing and analyzing it. But I believe that this is a process that should be controlled. Perhaps by the government, but even better by a synergy with all different stakeholders, including industry, academics, payers, patient reps, and insurance companies. I've had a brief experience thinking about this shared risk approach to developing new drugs because industry takes a lot of risks. Perhaps stakeholders should be part of this process very early on. Reps of patients, for example, would say that this injectable would not go far. The biology is interesting and the data can be promising and a therapy can lower A1c. But patients may not take it up as people would think. So I think big data should be controlled.

Dr. Gavin: I share your caution. My point on the government taking the lead is very different from the government taking control. I think the trouble is when there isn't appropriate input, we need appropriate input from all stakeholders. Big data needs to be seen as a potentially enormously valuable resource and it needs to be harvested. But as with every resource, there is potential for great good and for great harm. We need to learn from the lessons of being burned badly.

**Ms. Close: It's interesting to think about how to bring people into government. Many leaders in tech in the private sector who've done very well are being asked by President Obama to come work on technology in the government - this was true for example of the great Megan Smith at Google who is now the White House's Chief Technology Officer and basically "on loan" to the government if I understand it right. It is a great example of service that high tech**

**is giving the US government. There was a piece in Wired about this that was quite a compelling model for healthcare although our sector just doesn't yet have the health that high tech does; yet and still, with all the incredible commitment and mission-driven approach by young leaders today, I think there's a lot of really good models we can think about with government on people moving to work for even a short time in the public sector on healthcare.**

Prof. Holman: Back on systems, there are many examples I could give you from different countries, but I'll talk about China. We've worked there for nearly eight years, and in that time while we're concerned about the diabetes epidemic in US, they're racing ahead. It's interesting to see how they choose to deal with it. It intrigued me that they understand that type 2 diabetes is a societal problem, not just a medical one. They have perhaps a more balanced view, which some may feel is less empathic, but is realistic with concerns for potential problems for both the health and the wealth of the country. In a one-parent family society, the impact of diabetes can be greater if the only child has to take time off work to care for a parent. Diabetes management may have to be driven more by economics than some would like but that's the reality.

The conversations we're tiptoeing around in the UK at present are about whether we should pay more for cancer drugs that give a slightly extended period of life for very sick people, or to invest more in other disease areas. This is becoming a stark choice in China where over 35% of people are diabetic or have pre-diabetes and there are few primary care physicians. The Chinese government is now taking a robust approach, driven by the metrics, to come up with a three or five year plan to address the diabetes issue.

**Ms. Close: That's amazing to hear. In China, what will we see on that three to five year trajectory? What's different there about the approach?**

Prof. Holman: I think the perspective over there is realistic. They have the data and they see the problem. You know, there was a publication in the *NEJM* a few years back (Yang et al., 2010) that was a bit of a wakeup call with regard to the prevalence of diabetes. Instead of just worrying about it, they repeated the study (Xu et al., *JAMA* 2013) and found that the number of people at risk had gone up! Managing the emerging number of people with diabetes poses a major problem given that healthcare is provided mainly through hospitals. In the face of their diabetes epidemic, China is exploring alternative strategies with a greater emphasis on more locally provided care - something that is being trialed by the Beijing Diabetes Community Study which I help support.

**Ms. Close: Thank you so much for that. Now, I want to move to thinking about EMPA-REG. I wonder what you think of the potential impact of therapies that are cardioprotective and renoprotective. When I saw the original press release a few weeks ago about empagliflozin and cardioprotection, I started to weep because I thought about what this could actually mean and what the impact could be. *All* of these therapies will be generic one day (at least the orals, presumably) and we won't have to be worried about access and patients could do significantly better globally. Can the three of you speak to these results? What are major things you'll be looking for? Are these class effects? Will these therapies be disruptive? And specifically, on Thursday, what kind of risk reduction are you looking for? [Note - it wasn't specified but "primary risk reduction" was understood.]**

Dr. Ferrannini: I think that the press release has already made a big splash, so one can only be disappointed [joking]. And I have no idea because it's two doses so we'll just have to wait to see whether it's just the higher dose, if it's due to a subgroup, or whether it's because of effect size. And I presume that most people would think that the results would be applied to the class rather than a single agent. And clearly, they're going to make a lot of noise about it. This is the first CVOT that has shown protection. One must say that there was biological plausibility, which was probably better than the other single drugs that have been tested. The intrinsic changes with weight loss and blood pressure are major players and they're convincing.

Prof. Holman: This is truly exciting - getting a superiority trial that is positive. Until we see the data, it is difficult to generalize about the results. Presumably the effect size is going to be larger than the usual 15%. We have seen UKPDS data before for metformin that demonstrated cardiovascular positivity. We did see in the PROactive study that their secondary endpoint suggested a cardiovascular benefit. When we simulated their

results using the UKPDS Outcomes Model, the cardiovascular benefit was fully explained the pioglitazone induced changes in multiple risk factors. We need to understand how an SGLT-2 inhibitor can have a beneficial cardiovascular effect and whether, as is most likely, it is a class effect. Improving glucose control has led to a massive reduction in microvascular disease - triggered by DCCT and UKPDS. Retinopathy is no longer a major cause of blindness. Optimising glucose control goes a long way to stopping microvascular complications but there is only a modest impact on macrovascular complications. The EMPA-REG data are exciting because people with diabetes remain at twice the risk for macrovascular disease even when treated to target with current therapies. If an SGLT-2 inhibitor can help even up these odds, that's great.

Dr. Gavin: I have very little to add. I'm obviously as excited as anyone about the data, and I hope that whatever they are, they don't diminish the importance of us continuing other conversations in diabetes. This in no way implies that we don't continue to push as hard as we can on the prevention front. The fact is that the need for individualization of therapy will remain. Everybody affected by this disease has higher risk, and they're not all appropriate candidates for this class. Many other therapies with potential will continue to develop data on their contributions to outcomes. I think we need to be thoughtful about what the outcomes really mean and not rush to sound bites that more often than not get us into trouble and lead to limitation of thinking, not broadening.

Ms. Close: I can't wait for Thursday and to hear the results across the board. Thank you for these comments. We are going to start the "Lightning Round" (quick answers to quick questions) now, while all of you in the audience think about your next questions to our experts.

### Lightning Round

**Ms. Close: How would you rank your enthusiasm for the artificial pancreas on a scale from 1 to 10?**

Dr. Gavin: 5.

Prof. Ferrannini: 5.5.

Prof. Holman: 6.

**Ms. Close: What is most likely to become the standard second line therapy?**

Dr. Gavin: SGLT-2 inhibitors.

Prof. Ferrannini: GLP-1 agonists.

Prof. Holman: I think GLP-1s are in a favored position. You did mention the Intarcia implantable device earlier. With that being by design a 100% compliant therapy, their data there could be become persuasive especially if the ongoing GLP-1 outcome studies are positive.

**Ms. Close: For combination therapy, which combination are you more excited about? Basal + GLP-1? Or GLP-1 + SGLT-2?**

Dr. Gavin: GLP-1.

Prof. Holman: Depends on the stage of disease. If it's in the middle or end stage of the disease, I think *both* combinations have great promise.

Prof. Ferrannini: I agree.

**Ms. Close: What risk reduction percentage is most likely in the EMPA-REG Outcome Study?**

Dr. Gavin: 30%.

Prof. Holman: 18%.

Prof. Ferrannini: In the range between 15%-25%.

**Ms. Close: What do you think is the right first injectable for patients who are not at target? Basal insulin and GLP-1 combined? Once weekly, injectable, or basal only?**

Dr. Gavin: I say incretins before insulin. This is all based on where you get the patient and at what stage. You lose none of the subsequent options, but incretins before insulin.

Prof. Holman: For a patient with reasonable beta cell function, use an incretin first. If they don't have that, then insulin.

Prof. Ferrannini: I think that starting with a combo early would be promising, if the data shows they need it.

**Ms. Close: Would you say that you are more or less pessimistic about strides that could be made on the prevention front relative to five years ago?**

Dr. Gavin: I'm more optimistic. I guess that makes me less pessimistic [laughter].

Prof. Holman: I'm definitely more optimistic, not only because we're beginning to understand the underlying disease processes, but also because society is waking up to the problem and beginning to do something about it.

Prof. Ferrannini: And I agree!

**Ms. Close: Let's go back to the closed loop that we spoke about briefly at the start of the Lightning Round. How optimistic should we be about automating insulin delivery and the future of the closed loop?**

Prof. Ferrannini: Well the idea of closed loop has been around for very long. I think there are some fundamental problems with it, so I don't have the highest levels of optimism. There's the difficulty of monitoring for long periods of time and accurately, but also because one way or the other, you're going to be providing insulin in the peripheral circulation and that is not the physiological route. There is very little that can be done with other transplantations. So I'm moderately optimistic.

Prof. Holman: So it's been a battle for years. We worked on it and other people worked on it. Insulin is one of the drugs with the narrowest therapeutic window. It's got to be ultra-safe 24/7, 365 days a year. I think we're some way off from doing it. I don't think it's impossible, but the current technology is not robust enough - maybe five to ten years down the line.

**Ms. Close: Well, we're going to have to go back and talk to technology companies about what they can do.**

Dr. Gavin: I continue to harbor the notion that the inventiveness and creativity of humankind will allow us to master technology, electronics, and gadgetry more quickly than we master biology. My optimism is that there will be strides toward development of effective closed loop systems. My pessimism is that they will be for a very narrow band of patients.

**Ms. Close: I'm curious if you say that meaning narrow for those that can benefit or narrow for those that can access it? We'll come back to you on this! Professor Ferrannini?**

Prof. Ferrannini: There are also some promising developments in dual hormone control because the major problem with insulin is obviously hypoglycemia. And also the fact that a lot of patients with type 2 diabetes don't need insulin - they've got plenty of it. They just can't put it out in a timely fashion.

**Ms. Close: I remember when CGM was just in its nascent days. I saw JDRF really encourage companies to work together. That was when technology was so much worse than it is today. A lot of things had to go right to make improvements happen. Sensors were not accurate; algorithms were not good enough; and insulin was too slow. Now, we've got better sensors and smarter algorithms, but the speed of insulin has not changed. How do you feel about smart insulin, technically speaking? Of course, we know access is always a big issue.**

Dr. Gavin: Part of the session I was in today had presentations about smart insulin. I think it will align well with the technology and newer algorithms that we're trying to implement without the serious limitations on the effectiveness of other developments.

Prof. Holman: Smart insulin is a closed loop system in a syringe. In people with type 2 diabetes the insulin dose is less critical, any insulin is better than none, but the challenge is in type 1 diabetes - you need to have the dose precisely right at all times. Smart insulins are probably also going to struggle with rapid responses to meals. I think we're always going to be in a situation where type 1 diabetes will have different challenges.

**Ms. Close: What technology will be the biggest game-changer in the next ten years in developing countries?**

Prof. Ferrannini: Making management more accessible. There are large areas in Africa where the situation is completely different from China. I don't know much about China other than that I don't like their food. [Laughter] But in Africa, I'm told that the major problem is access to treatment, even just basic treatment like insulin or any oral. I think technology would be like eating dessert before dinner.

Prof. Holman: Access to treatment is a much greater issue than technology. In some parts of Africa if you do a consult on a patient for insulin, often the choice is not what regimen is preferred but what if any insulin there is in the pharmacy that week. We're not even at the stage of discussing technology, it's having people and resources to provide what is in fact a lifesaving drug.

Ms. Close. Thank you, such fantastic insights. We'll now open up the floor for Q&A.

### Audience Q&A

**Q: I want to return to the closed-loop discussion. Could you elaborate? Do you think algorithms will overrun the need for glucagon? How do you see insulin evolving? How do you see the technology developing in this space?**

Prof. Ferrannini: The basic algorithms have been there for quite a long time. We can account for every drop of glucose in the blood. What we can't do is change the way we deliver insulin and the onset and offset time of insulin. Remember, it takes time not only for insulin to be absorbed but to exert its primary effects at the cellular level. Even If you reduce the dose, it takes time for the insulin at the receptor to stop working. It has to do with complicated cellular kinetics. That's why, I think, having glucagon available is a sound idea. Whether it's workable, I'm not sure.

Prof. Holman: The delivery of insulin is always a tricky problem. The best insulin will never be perfect. People do strange things and they can outwit the algorithm. Having glucagon as backup helps in those life or death situations. I think it's really important to have that back-up system but do understand that it does add complexity and cost. If you have insulin in the right place with instantaneous algorithms, that could be perfect but for now we continue to give insulin peripherally. There is also a medical and legal issue - if things go wrong with an automated delivery system, who gets sued? The software engineer, the physician prescriber or the educator? It's a difficult area.

Prof. Ferrannini: I also think that we have learned so much more about use of insulin in recent years, that insulin has almost become a new drug. The contrast between long-acting and short-acting insulin, and not to speak of the possibility of smart insulins - that would be transformative.

Dr. Gavin: The partnering of insulin with other molecules has enormous potential.

**Dr. Robert Vigersky (Medtronic, Los Angeles, CA): The title of this was "Solvable Problems," and I'm heartened by the optimism of the panel. But are we going to solve it before it bankrupts the economy?**

Ms. Close: I'm going to defend our title. We were going to call it addressable problems, but it doesn't quite have the same ring to it as solvable problems! [Laughter] Listening to you talk about cardioprotection, that's such an exciting approach and could be lifechanging - but we'll always hear complaints about expensive drugs or technology as if those are the major problem areas. It's the heart attacks and strokes and patients being in and out of the hospital driving the cost curve up!

Prof. Ferrannini: The problems are solvable to the extent that we understand the potential for the solvable better than we did years ago. The research efforts ongoing in -omics that you mentioned are very helpful. Whether it's actually solved depends on money. We had heated discussions in Italy where the healthcare

system is public and regional. The discussion was if you had a monoclonal antibody that cured hepatitis C, every citizen will raise their hand and say I demand to be cured, and that would run the system bankrupt. Another example is cancer. Cancer drugs are extremely expensive and on top of what the old drugs do, any new drug only guarantees an extra week of life. What if it rains that week? [Laughter] This is in contrast to the notion and the data we're accruing that we can actually prolong the survival and quality of life in diabetes but we have to wait 20 years. The metrics to allocate resources here or there are not there. You can't compare the metrics of a cancer drug with a statin, the benefit of which will be seen 20 years down the line. It becomes a societal problem, an economic problem.

Prof. Holman: It's a very real problem. There is a limited size cake and different countries cut it differently. We have NICE in the UK, and some people feel we weigh cancer vs. diabetes patients somewhat unfairly. However, I'm optimistic because all this effort means we're developing new drugs that will be cheaper over time. The onus is on us to weigh outcomes appropriately. When I started in diabetes, a patient with type 2 diabetes had an estimated loss of life of around 15 years. Now that is probably down to about 3 to 5 years. We need to find a way to give a fair share of the funding for the facilities and strategies that work. There is never enough money for everybody, but this is about getting the playing field level. For people with diabetes, it has not been as favorable as it should be.

Prof. Ferrannini: The only thing is that we have to be careful of the economists because they're very good at predicting things past. I haven't seen many reasonable cost analyses. If that 15% reduction in cardiovascular outcomes were calculated, what would the cost savings of that be?

Prof. Holman: We have the UKPDS Outcomes Model that was developed with the help of health economists. What the model does is predict reasonably well what complications will occur in which people over time. If we did have a drug that reduces heart attacks or strokes, then you could simulate its impact over a longer time to estimate the cost reductions that might accrue. Governments, however, don't like to think about five to ten years down the line because they'll be out of office; so short-term thinking remains a big problem. If you think in the longer term, you can ultimately save money or not spend as much.

**Ms. Close: One thing on that point: Let's get the data. It's much easier to get that data today. Being able to show how people with diabetes are really doing is so important.**

Dr. Gavin: It's a critical question, and I do have optimism that we can bring some solvability and some solution to these problems before they bankrupt us. Because we don't have to go all the way. We just have to do it a hell of a lot better than what we've been doing. We need more pressure, and we need to get rid of the drain these problems are causing us. If we can achieve cardioprotection, stroke protection, delay of dialysis or transplantation … that's something that is possible with our tools and with algorithms appropriately used. Something like that would go an enormous way in terms of the economic stress. And in many of those instances, we can get there.

Prof. Holman: Don't lose faith, the problems are solvable. The strides being made are phenomenal. For instance, it's been two years since I have sent a patient to a renal unit. Things have gotten better but also more complicated. There are more battles to fight and we do need more money. I think collaboration is the word for me - we need industry, academia and clinicians to work collectively to solve the problems.

**Q: We talked about microvascular complications, and we've made great progress. Is NASH a disease that should be adopted by the diabetes community as a non-paradigmatic diabetes complication and a problem of endocrinologists and diabetologists?**

Prof. Holman: I'll declare an interest because the last person we appointed to our Unit is a NAFLD expert. I think the concern about with NASH moving to hepatic cirrhosis may have been overstated but for the diabetes community we heard this morning that ectopic fat in the wrong place can create havoc. I suspect it generates more problems in the metabolic sphere than a few cases of cancer downstream. It's enormously important.

Prof. Ferrannini: I think steatosis is relatively speaking no problem because it's a consequence of insulin resistance in many cases. There are polymorphisms of some genes that produce accumulation of fat in the liver without insulin resistance, but it's a very small fraction of the general population. It's what causes the

next step, fibrosis, that's interesting. As I was discussing this afternoon, it's crucial for research to understand the cases where you have fibrosis without steatosis. That will point in the direction of the second hit that will transform steatosis into NASH, which is at risk of progressing to cirrhosis and in a few cases cancer.

Dr. Gavin: And that brings us back to the question of the resources necessary to do that.

Prof. Ferrannini: The imaging tools we have are not good enough for fibrosis. They can tell us how much fat there is in the liver, but not how much fibrosis there is.

Prof. Holman: In our Unit, we are exploring a urinary proteomic test that will screen and stage NAFLD more effectively. It's a new technology that does not require a biopsy.

**Ms. Close: My last question is if you had just one single biggest advice for all of our amazing supporters, what would that be?**

Prof. Ferrannini: Don't believe guidelines. [Laughter] You know, I have a problem with guidelines because like it was said earlier, they give you the ingredients but not the recipes. And those recipes can't be given because the evidence isn't there. But they give a lot of info on the ingredients. You don't want to be a doctor that's just a robot that brings patients down a path that's telling you what to do at every fork. Because that would get rid of any decisions of clinical judgment. My younger colleagues are not enthusiastic about that. They're sitting in their offices with all these charts hanging on the walls. There are guidelines for everything and all they have to do is to take the patient down these paths. That's true destruction of clinical judgment.

Dr. Gavin: I've developed an enormous respect for those working in diabetes. I don't invest too much hope in any one drug to save us. That won't happen. And that's fine, because the complexity of diabetes will defy us. A complementarity of treatments will be required to address the pathophysiological complexity of diabetes. We're now developing a pathway for a conundrum. But there is great hope. Grow the classes, show how they can marry and cohabitate. And there will be great outcomes and glory! And polygamy! [Laughter]

**Ms. Close: What an amazing way to end this intriguing and very rich discussion. Thank you so much, Dr. Gavin and Professors Holman and Ferrannini - your thoughts on all of these complex subjects have been remarkably valuable. And thank you so very much to all of our supporters for tonight and to our teams - this would not have been possible without you.**

*-- by Varun Iyengar, Melissa An, Helen Gao, Emily Regier, Adam Brown, and Kelly Close*