

AHRQ's Effective Health Care Program: *Applying Existing Evidence to Diabetes Care*

Tuesday, December 14, 2010

Transcript

OPERATOR: Good day, ladies and gentlemen, and welcome to the AHRQ Effective Health Care Program—Applying Existing Evidence to Diabetes Care. If you get disconnected at any time from the Web conference, you may dial 888-632-5065 or 201-604-0318 and, when prompted, enter 25848872 followed by the pound sign. At this time, it is my pleasure to turn the floor over to Sonia Nagda. Ma'am, the floor is yours.

SONIA NAGDA, CONTRACTOR, AHRQ: Good afternoon, ladies and gentleman. Thank you for standing by. On behalf of the Agency for Healthcare Research and Quality, also known as AHRQ, welcome to today's Web conference—Applying Existing Evidence to Diabetes Care—held by AHRQ's Effective Health Care Program.

My name is Sonia Nagda. I am a contractor for AHRQ's Office of Communications and Knowledge Transfer, and I will be moderating today's event. This event is the last in a series of Web conferences we held over the last few weeks on applying Effective Health Care Program research findings to practice. If you were not able to attend past events, they will be archived on the Effective Health Care Program Web site shortly.

Before we get started, I want to review some information about the Web conference technology. If you have questions during the presentations, you may submit them electronically by entering them via the Ask Question button. The Ask Question button is located at the bottom of your screen. When you click on the button, a box will appear requesting that you enter your question. Once completed, press the Submit button. A selection of audience-submitted questions will be addressed during the moderated Q&A session at the end of the Web conference.

Also, if you are experiencing technical difficulties, there are a few options. You can click on the Click Here for Web Conference Help link and be directed to a troubleshooting Web site to do a system check, or you can open the Web conference FAQs document under the Downloadable Files button on the bottom of your screen for other troubleshooting ideas. You can also contact technical support by submitting your issue in the Ask Question box.

Under the Downloadable Files button, you will also find the slides for this event, which may be helpful for reviewing slide details. There is also a document with a speaker biosketch. Today's Web conference includes closed captioning. The captioning appears in a box on the left hand side of the screen when you enter the conference through the Windows Media Player or RealPlayer buttons on the main page. Finally, this presentation is being recorded and will be made available on the AHRQ Web site shortly.

Now we will get started with the presentation. During this Web conference, Effective Health Care investigator Dr. Rehan Qayyum and I will highlight the benefits of using patient-centered

outcomes research in clinical decisionmaking. I will kick off the conference by giving you a brief overview of AHRQ's Effective Health Care Program before I turn it over to Dr. Qayyum to share his research findings related to type 2 diabetes.

As a reminder, you can submit questions electronically by entering them via the Ask Question button at the bottom of your screen. Once you enter your question in the box, press the Submit button. You can ask either of us questions about patient-centered outcomes research, the Effective Health Care Program, and the specific findings shared today. Though we will hold most questions until the end of the event, I encourage you to ask them throughout the event as you think of them. We will do our best to address as many questions as we can during the Q&A session.

To begin, I will be discussing the AHRQ Effective Health Care Program and how you can utilize patient-centered outcomes research in your practice. Patient-centered outcomes research, also known as comparative effectiveness research, delivers unbiased, practical, evidence-based information to help you and your patients weigh different options to make the most informed health care decisions.

It compares drugs, devices, procedures, tests, and methods of health care delivery. Patient-centered outcomes research shows which treatments have been shown to work best in different clinical situations and how they compare when it comes to benefits, harms, and side effects. It also tells us what is known and what is not.

Most importantly, patient-centered outcomes research is descriptive, not prescriptive. It does not tell you how to practice medicine. It does not mandate a particular test or treatment for anyone. Nor does it prohibit any test or treatment. It gives you tools, not rules, which you and your patients can use to make the best possible decisions.

Here at AHRQ, the investment for patient-centered outcomes research has been built around the framework displayed here. The colored boxes and ovals show the different types of work involved with patient-centered outcomes research. Underneath is the research platform that supports the work, including research infrastructure, methods development, and training of researchers.

The research process starts with scanning the horizon to identify new and emerging clinical interventions that may impact health care in the U.S. This leads to a systematic review and synthesis of current medical research to compare effectiveness. Evidence synthesis often tells us where the gaps lie between existing medical research and the needs of clinical practice. We also promote and generate new scientific evidence and analytic tools to fill those critical gaps.

All of the information gained needs to be communicated in a way that makes sense to the health care decisionmakers. This includes translating the research into plain language and making it accessible and useful to diverse audiences in order to improve health care. We also have made a commitment to reach out to stakeholders and communities for input to make sure we get the research right. If it isn't relevant and applicable, then we can't expect it to have an impact.

The Effective Health Care Program has a cradle-to-grave research agenda that focuses on the 14 priority conditions listed here. As you can see, one of the priority conditions is diabetes. Since the inception of the Effective Health Care Program, AHRQ has funded and completed dozens of patient-centered comparative effectiveness research projects. These projects include comprehensive reviews of diagnostic or treatment options for breast and prostate cancers, hypertension, osteoarthritis, depression, and many other conditions.

The Effective Health Care Program creates a variety of products that are based on these research reviews and reports. These include executive summaries, plus summary guides written for clinicians, consumers, and policymakers. We have recently added to our portfolio a number of materials to support clinician education, including continuing education modules, interactive case studies, and faculty slide sets. We'll soon be adding patient decision aids as well.

I would like to highlight our consumer guides that summarize the evidence in plain language in easy-to-read formats. These guides are paired with our clinician guides to promote shared decisionmaking. Most of our consumer guides have also been translated into Spanish. The consumer guides can be found online or are available in print. We also have audio podcasts of the guides online as well.

Currently, the Effective Health Care Program offers various decisionmaking resources about diabetes, including gestational diabetes and oral diabetes medications. Today, Dr. Qayyum will be discussing the research that he conducted leading to the Effective Health Care Program findings presented in the clinician and consumer guides related to insulin analogues. The other highlights can be found on the Effective Health Care Program Web site.

Finally, we want to encourage you to get involved in the Effective Health Care Program. Your participation is mutually beneficial. There are multiple points of involvement in our program before, during, and after the research is completed. Before, you can nominate topics for research on our Web site. If there is a diabetes-related or other topic that you feel should be addressed, we will give you instructions on how to nominate this topic at the end of the conference.

During, you can give input on draft key questions and reports. This kind of involvement helps you get the type of research that will really help answer those controversial questions, and it helps us by getting the research right.

After the research is completed, you can disseminate the information to your colleagues and patients. You can implement the findings in your clinical decisions. This helps both you and us by creating the opportunity for better, more informed decisionmaking and making an impact on the quality of health care.

So, let's start with the main presentation. We now have the pleasure of hearing from Dr. Rehan Qayyum. Dr. Qayyum is an assistant professor of medicine at the Johns Hopkins School of Medicine and an attending physician and academic hospitalist in the Division of General Internal Medicine/Hospitalist Program at Johns Hopkins Hospital in Baltimore, Maryland.

His research experience includes numerous meta-analytic studies on treatments for conditions such as type 2 diabetes, hypertension, acute coronary syndromes, and effectiveness of continuing medical education. Today, he will present his research on the Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults with Type 2 Diabetes. Dr. Qayyum.

REHAN QAYYUM, M.D., JOHNS HOPKINS: Thank you, Sonia, and thank you everyone who has joined in. So this report on the comparative effectiveness and safety and indications on insulin analogues in premixed formulations of adults with type 2 diabetes is based on research conducted here at Johns Hopkins Evidence-based Practice Center, and this was under contract from the Agency for Healthcare Research and Quality.

So entering analogues after forms of human insulin with minor structural changes. These structural changes do not affect the glycemic effect of these molecules, but at the same time these structural changes impart certain pharmacokinetic properties that allow better control of the onset and duration of insulin-like activity.

So, the certain changes in insulin molecule can result in a more rapid but shorter onset of insulin analogues usually known as rapid-acting insulin analogues. Other types of structural changes in insulin molecule can result in a more sustained effect over a longer period of time. And these are generally called long-acting insulin analogues. Almost all of these insulin analogues are produced using recombinant DNA technology.

This figure shows a simplified diagram of two rapid-acting insulin analogues, and I'm showing these two molecules as these are the ones that are included in premixed insulin analogue preparations available. In the upper half of the figure is the structure of insulin as part in which proline add position 28 of B chain insulin molecule is replaced by aspartic acid.

In the lower half of the figure is structure of insulin lispro. In this analogue, the positions of two adjacent amino acids on B chain are switched. And the lysine amino acid at position 29 is replaced by proline, and proline at position 28 is replaced by lysine.

Now, while these rapid-acting insulin analogues are available in market and are used with meals, these analogues need to be given with every meal. In addition, some form of basal insulin is also prescribed when these rapid-acting insulin analogues are prescribed, so that an average patient will need to take about four insulin injections in one day.

Of course, it's easy to imagine that this limits the utility of these analogues and those patients who want better control but would not like to take so many injections every day. To address the needs of such patients, pharmaceutical companies have developed mixtures of rapid-acting insulin analogues and intermediate-acting insulin analogues.

As these are preformulation preparations, these are generally called premixed insulin analogues. The immediate-acting insulin compound is prepared by mixing rapid-acting insulin analogue with the protamine sulfate, creating crystals under appropriate conditions, and then these crystals are suspended in the respective insulin analogue solutions.

So, the study commissioned questions to us by the Agency for Healthcare Research and Quality are listed on this and next slide. And we were asked to review the available literature and assess effectiveness, safety, adverse effect, and adherence of premixed insulin analogues as compared to other antibiotic agents.

We were also asked to examine the comparative effectiveness and safety in certain subpopulations and individuals on oral antibiotic agents; individuals who had the different blood glucose patterns or individuals with different types of glucose control.

This slide continues with the key questions. As you can see, these key questions are quite comprehensive, and we were asked to review the literature comprehensively and, based on the evidence, answer these questions.

To answer these questions, we performed an extensive literature search as recommended by the latest draft at that time of comparative effectiveness of your guide. This guide was being prepared at that time by experts in the field of comparative effectiveness research and was funded by AHRQ.

We performed an extensive literature search as recommended by Comparative Effectiveness Review Guide draft. We searched MEDLINE®, EMBASE®, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cumulative Index to Nursing & Allied Health Literature (CINAHL) from inception to February 2008. We also reviewed reference lists of included articles, recent issues of 13 medical journals, the Food and Drug Administration and European Medicines Agency Web sites for the premixed insulin analogues, unpublished data from premixed insulin analogue manufacturers, and Web sites of public registries of clinical trials.

In other words, we did an extensive search to identify evidence on which we can base our recommendations. We included studies that compared one of the premixed insulin analogue preparations as of February 2008 to any other drug for adults with type 2 diabetes and evaluated either clinical outcomes such as mortality or what we called intermediate outcomes such as hemoglobin A1C or fasting glucose or postprandial glucose. Or also we evaluated adverse events such as hypoglycemia.

And, to be comprehensive, we included all type of trials. We included randomized control trials; non-randomized but controlled clinical trials; observational studies that had a control group for comparison, and we included studies regardless what was the duration or sample size. And we went to the standard of process of evaluating such a literature in which of two of us reviewed titles, abstracts, full articles for inclusion and abstracted data.

So, we abstracted on all outcomes I mentioned earlier. And for those outcomes that are either progressive or irreversible such as nephropathy or myocardial infarction, we excluded crossover studies, but for other outcomes, we did include crossover studies.

The statistical matters in detail are given in the complete report that is available on the AHRQ Web site. Briefly, for intermediate outcomes and adverse effects, we used a pretty standard model, we used random effects model.

For clinical outcomes, our limitation was fewer studies that reported outcomes. And the number of reported events were also few. So we decided to include all studies that reported any information about clinical events.

Our analysis followed intention to intent-to-treat principle and 95 percent confidence intervals were calculated using fixed-effect models for clinical outcomes. And then we did sensitivity analysis.

Now, this slide presents results of our literature search, which found 50 articles that reported 45 studies and included at least one of our intermediate clinical outcomes our adverse events. Other than two, all were randomized control trials, so, you know, the studies were better quality.

In one of these two studies that were not randomized, in one, patients were enrolled consecutively and followed prospectively while other study data were obtained from the medical record database of a large employer. Of these randomized control trials, 23 were parallel arm, and 20 were crossover. Immediate duration of followup in these trials was 16 weeks but duration of followup ranged from 1 day to 2 years.

Now, this slide shows pooled results of comparative effect of premixed insulin analogues on fasting glucose. Moving downward, this figure is divided into three parts, with each part providing a comparison. Horizontally, the middle section is a pictorial representation of the pooled results.

The back squares represent mean values, and black lines on each side of the square represent 95 percent confidence intervals. The vertical line in the center represents no change in fasting glucose. There is no statistically significant difference if the lines, of 95 percent confidence interval, cross this vertical line.

On the right-hand side, the same results that are depicted pictorially in the center are presented in numbers. The most extreme column on the right hand presents the number of studies that we found for each comparison and the total number of subjects enrolled in these studies.

OK, so now let's look at the actual results. First comparison is between long-acting insulin analogues and all premixed insulin analogues pooled together. The long-acting insulin analogues appear clearly better than premixed insulin analogues in lowering fasting glucose. And this is a priority (ph) of long-acting insulin analogues is also seen when we look at premixed insulin analogues individually.

In comparison to premixed human insulin interpretations, there is an indication that perhaps premixed human insulin analogues are better. Sorry—that—yes, premixed human insulins are better as compared to analogues, you know, but this small difference was not statistically significant except for insulin lispro 50/50. On the other hand, premixed insulin analogues

together or separately, like when looked at individually, were better than non-insulin antidiabetic agents in controlling fasting glucose.

In summary long-acting insulin analogues and premixed insulin analogues were better than premixed insulin analogues in lowering fasting glucose, although the effect did not reach statistical significance for premixed insulin analogues. Premixed insulin analogues were better than noninsulin antidiabetic agents in lowering fasting glucose.

Now, moving on to the comparative effect of premixed insulin analogues on postprandial glucose, the organization of this figure is similar to the previous one. This slide shows clearly a superiority of premixed insulin analogues over the other three groups, which is kind of different than what was in the previous slide.

At an average, premixed insulin analogues decreased postprandial glucose an additional 28 milligrams per deciliter in comparison to long-acting insulin analogues, an additional 19 milligrams per deciliter in comparison to premixed human insulin preparations, and 37 milligrams per deciliter at an average in comparison to noninsulin antidiabetic agents.

In words, the message from this slide is that if you watched your target postprandial hyperglycemia, premixed insulin analogues offer a better choice in comparison to these three groups. This is different than previous slide, which showed the long-acting insulin analogues are better for fasting glycemic control.

Now, moving on to hemoglobin A1C, which is probably the most important clinical parameter on which we, you know, focused on as clinicians. And which actually incorporates both fasting and postprandial glycemic control. And this figure is quite, you know, as far as organization is concerned quite similar to previous two figures.

When compared to long-acting insulin analogues, premixed insulin analogues were better and were able to decrease A1C by an additional 0.4 percent. On the other hand, there was no difference when premixed human insulin was—when premixed human insulins were compared with premixed insulin analogues. And both groups were quite similar in their effect on decreasing hemoglobin A1C.

Premixed insulin analogues were also superior to noninsulin antidiabetic agents. And we found that they were able to reduce hemoglobin A1C by an additional half a percentage point. So, now you know just a little bit deeper into these numbers the message here appears that premixed insulin analogues are superior to long-acting insulin analogues.

There were several methodological issues that are not apparent in these results. But perhaps the most important one is that the amount of total daily insulin that a study participant received was generally lower in long-acting insulin analogue arm as compared to in the premixed human insulin analogue arm.

Also, in quite a few studies that compared noninsulin antidiabetic agents, the dose of noninsulin antidiabetic agent was kept fixed throughout the study while premixed insulin analogue dose was

titrated up. A more detailed discussion of these points can be seen—can be read in the full report that is available on AHRQ Web site.

Moving on to the most common adverse event of insulin therapy, hypoglycemia, now this slide is slightly different because here instead of having individual premixed insulin analogues listed, hypoglycemia is further categorized. So this is a slight difference on this slide.

So, overall long-acting insulin analogues appear safer than premixed insulin analogues. This is true for hyperglycemia without a specified severity and for symptom-only hyperglycemia. The trend of course is towards less hyperglycemia with long-acting insulin analogues. But the overall events were much lower. And therefore these confidence intervals are overlapping the midline.

Now, with premixed human insulin preparations versus premixed insulin analogues, the overall hypoglycemic events were relatively quite similar, although for hyperglycemia that is listed here, severity was not specified. It appears that premixed human insulin is probably better. It's generally the overall trend was really not in any particular direction for one agent or the other. There were no data reported for symptoms, only hyperglycemia.

So premixed human insulin analogues appear somewhat less effective in decreasing hyperglycemia, or there were more events—hyperglycemic events—when comparison was with noninsulin antidiabetic agents.

Now, here these definitions in articles of serious hyperglycemia, mild hyperglycemia, and symptom-only hyperglycemia were pretty consistent. Serious hyperglycemia was considered a type of hyperglycemia when some sort of intervention by a third party was needed, which means either a patient needed to be taken to hospital, or EMT needed to be called, or some that sort of activity happened.

Mild hyperglycemia, on the other hand, was in which it's documented hyperglycemia, and something was done, but the third-party intervention was not needed. And symptom-only hyperglycemia was when there was no documentation of glucose level and a third-party intervention was not needed. So definitions were kind of more or less pretty consistent across studies. So pulling all this together was considered safe.

Now, moving on to weight change with insulin therapies, there's always a concern that patients generally gain weight while they are taking insulin. So there was not really much data on weight change when we looked at literature. And whatever we found is more or less presented here. So what we found was that long-acting insulin analogues and noninsulin antidiabetic agents were better than premixed insulin analogues.

But, as I stated in one of the—in discussing one of the previous slides that this could be simply because the dose of insulin that was used was higher in premixed insulin analogues generally in studies quite often. And that may be a reason why just a higher dose could have increased weight more as compared to long-acting insulin analogues.

And it's possible, although it's just a hypothesis, and we did not find it in literature that we studied that the equal amount of insulin, long-acting or premixed insulin analogue dose, was given. You know, there may be no weight change. Similarly for noninsulin antidiabetic agents, quite often metformin was one of the drugs that was used, and that is known to actually reduce weight.

Only two studies comparing insulin aspart 70/30 with premixed human insulin reported weight change, but the results were statistically significant in one study. And the second study did not report a statistical significance

Now there are, of course, other antidiabetic treatments; however, we did not find much evidence to draw any conclusions from any of those comparisons. In fact, for many of these comparisons, there were no studies. And further comparisons, one or two studies, for example, we found only two studies that compared premixed insulin analogue with a rapid-acting insulin analogue. We found two studies that compared a premixed insulin analogue with a combination regimen of a long-acting and a rapid-acting insulin acting also known as Basal Bolus Regimen.

We found two studies that compared a premixed insulin analogue to intermediate-acting insulin and one study that compared a premixed insulin analogue with a combination of rapid-acting insulin analogue with an intermediate-acting human insulin. So, as I just stated, due to the sparseness of data, we were unable to draw any formal conclusions from these studies about these comparisons.

Now, moving on to actually hard clinical outcomes, to our surprise we found only 16 studies that evaluated on reported clinical outcomes. No statistically significant differences were found between premixed insulin analogues and their comparators in terms of all-cause mortality, cardiovascular mortality, or cardiovascular morbidity.

It's here you can see that there seems to be some trend in one or the other direction. But this needs to be taken with some caution. Although there's a suggestion of harm in pooled odds ratios for all-cause mortality, for cardiovascular mortality, and the combined outcome of cardiovascular morbidity and mortality when premixed insulin analogues were compared to other antidiabetic medications.

These point estimates were based on few absolute events in only a few studies in which clinical outcomes were not the primary endpoint. And so really it's very difficult to say that one is safer than the other one. And here you see that we have put all comparators in one category and compared against combining all premixed insulin analogues in another group.

And comparing both, this was done simply because—this was done because there were actually not enough events to look at this separately. And even when we, you know, pulled all this together, you can see here that for all of these, 95 percent confidence interval does cross midline.

There was insufficient or no evidence with regard to microvascular events such as retinopathy or nephropathy, although we specifically looked for those. As you can see, this is a big gap in literature. Where you know other symptoms, these hard outcomes are also quite important both

for clinicians as well as for patient. And we really don't know much about comparative effectiveness of these agents as—of premixed insulin analogues as compared to others.

So, we were also asked to look at quality of life. And that also there were—there was not much good-quality data. Eight studies evaluated this outcome, but only four studies used a validated scale. In one of these four studies, only one of the six quality-of-life outcome measures, which was psychological distress, showed a statistically significant difference in favor of premixed insulin analogues over oral antidiabetic agents.

So, really, overall either there was no difference but because studies are so few, so no formed conclusions can be drawn regarding quality-of-life outcomes for any of the comparisons because of other reasons and because differences were in outcome definitions, minor techniques in population studies, and comparators between studies. So that—this is another field that has not been studied well.

And we also looked at premixed insulin analogues in combination with oral antidiabetic agents versus premixed insulin analogues alone. Very few studies compared this combined treatment with oral antidiabetic agents and premixed insulin analogues with premixed insulin analogues alone.

When premixed analogues with oral antidiabetic agents were compared with the premixed insulin analogue alone, we didn't find any difference in fasting and postprandial glucose and incidents of hypoglycemia and weight change or in clinical outcomes.

However, it appeared that combination was better in lowering hemoglobin A1C as compared to when premixed analogues are given alone. So, adding an oral agent to premixed insulin analogue or adding premixed insulin analogue to an oral agent appears to help in lowering hemoglobin A1C.

As I stated earlier while talking about the key questions, we were also asked to comment on other things as well. But our literature research did not find any evidence on adherence to treatment regimen or effectiveness and safety of premixed insulin analogues in subpopulations of interest as outlined in key questions.

And individuals with different intensity of glucose control and in targeting fasting versus postprandial glucose so, you know, as such, no particular study was focusing on one particular type of either fasting or postprandial glucose control.

So this is basically in a nutshell of results of our—this comparative effectiveness, a systematic review and that I just presented. To highlight what we found, just these couple of case studies that I'm going to be presenting really very simplified, you know. So this first one is a 50-year-old obese diabetic male who comes in for his regular clinical visit.

And you see that he has a hemoglobin A1C of 8.7. His fasting glucose is 160 to 190. He is taking glipizide 10 milligrams twice daily and metformin, long-acting 1,000 milligrams twice daily. So you know at this stage you have several options, but if you know he is agreeable to using insulin,

perhaps in his case because his fasting glucose is elevated and hemoglobin A1C of course way out of target range.

So, in this case, perhaps adding a long-acting insulin will be better. And just remember for fasting hyperglycemia, long-acting appears to do better than premixed insulin analogues. And so in this—for this particular person, you know, one option could be choosing a long-acting insulin analogue.

And this is a second patient, a 56-year-old diabetic female who comes in for her regular clinic visit. Her hemoglobin A1C is 7.4. Her fasting glucose is 120 over—120 to 140, which is not bad. Her postprandial glucose is somewhat elevated, 180 to 220. She is on a combination of glyburide and metformin. And she's also taking sitagliptin.

So, in her situation, it appears that she has a close target, but she has not yet achieved her hemoglobin A1C target. She is controlling her fasting glucose, but she seemed to have some postprandial hyperglycemia.

So, in her case, you know, one of the options could be adding premixed insulin analogues. The other option could be just adding a rapid-acting insulin analogue that she can take with meals. And so now this slide—this next slide basically summarizes what our, you know, I have presented so far.

It seems somewhat quite busy but it's—let me explain it just a little bit. So, arrow moving upwards means that particular variable goes up using premixed insulin analogue when compared to whichever this column is. So, for example, this third column for long-acting insulin analogue, the first one is insulin aspart 70/30. So this is a horizontal arrow.

There is really—both seem to do as well but 75/25 and 50/50, in both cases fasting blood glucose is higher when we use premixed insulin analogue as compared to the long-acting insulin analogue. On the other hand, for postprandial blood glucose, whether it's aspart 70/30 or lispro 75/25 or lispro 50/50, blood glucose goes down with the premixed insulin analogues as compared to long-acting insulin analogues.

And the same with A1C hyperglycemia rate change. So this is basically what this summary sort of summarizes that evidence. This figure is taken from the actual report, which is available on the AHRQ Web site.

Thank you for listening. Sonia, back to you.

SONIA NAGDA: Thank you, Dr. Qayyum. We all appreciate your making the information and research we are sharing today salient to the clinician audience. Now, we would like to start the Q&A session. If you have not already submitted a question, please type your question into the Ask Question box at the bottom of your screen.

So, to get started, we have a couple of questions. The first question is about newer agents that have recently become available for the treatment of type 2 diabetes. Do we know which one is better?

DR. QAYYUM: Sure, as I stated earlier that we looked at all the literature that was available, we also contacted pharmaceutical companies. We looked at the FDA Web site. We also looked at the Agency's Web site as well. We basically did a comprehensive search of literature to identify studies.

We did find, you know, studies comparing insulin with—premixed insulin analogues with long-acting insulin or with premixed human insulin with noninsulin antidiabetic agents mostly. But, really, for newer agents that have just been introduced in the market over the last few years, we did not find any study except one study with exenatide.

And that we have included in analyzing results in noninsulin antidiabetic agents part, and, if you see there, there are—there were—the results). And that is excluding exenatide, and other results were including study with exenatide.

So there's very little data available at this time. And it's very difficult to say that, in comparison to premixed insulin analogues, how do these newer agents do. So, this is definitely one gap in evidence that needs to be filled for clinicians to decide which one is more effective and for what.

SONIA NAGDA: OK, great, actually we've gotten our next question in. The question is: Is there a comparison between premixed versus long-acting plus nutritional?

DR. QAYYUM: So many of these studies, actually most of these studies that compared a long-acting insulin analogue with premixed insulin analogue did—had some complement of patient education or nutritional education. But, really, as such when comparing long-acting insulin with nutrition versus premixed insulin analogue alone, there was no study.

However, I think that a nutritional component or nutritional education complement is important; that regardless of whether someone is on premixed insulin analogue or taking long-acting insulin analogue, this should be addressed with every patient. But then, you know, this is my opinion, but evidence we did not find a study studying this comparison.

SONIA NAGDA: OK, great. And the next question we have is related to hemoglobin A1C. Would you suggest that we use premixed insulin analogues to bring A1C down?

DR. QAYYUM: So with A1C it's quite interesting because it includes both—it includes basically at an average what is glycemic control over the past approximately three months or so. And, you know, as I presented that for fasting glucose, premixed does not appear to do as well, but for postprandial, premixed insulin analogues do pretty well.

There seems to be from our study, from our examination of the evidence, there appears that asking for the long-acting insulin analogues, premixed insulin analogues are probably better. And as compared to noninsulin antidiabetic agents, also premixed insulin analogues are probably

better. But, like I stated, that, you know, our concern was which we actually alluded in our report as well was that the dose of insulin was not similar in two arms.

This could be simply because with long-acting insulin analogue there's only so much you—high you can go before you start having hyperglycemic events prior to meals. And so that may be a limitation. But A1C—lowering A1C premixed insulin analogues seem to do better than long-acting insulin analogues.

But then here there's a little—what A1C generally—or very high A1Cs or high A1Cs are usually associated with fasting—with fasting hyperglycemia. And those elevated A1Cs that are closer to target A1C quite often are due to postprandial hyperglycemia, with a somewhat adequate fasting glucose control. So, you know, it's better to see overall glucose control pattern of an individual patient before deciding what actual agent will be useful for that individual patient. So, you know, whether it's for fasting glucose, postprandial glucose, or it's for hemoglobin A1C for all of these; these are general outlines, these are general comparisons, and so these results are average of patients.

But, then, if a situation is different for each individual patient and so treatment choice should depend on looking at each individual patient and what is perfectly fine for one patient may not be a good choice for another one.

SONIA NAGDA: OK. And our next question is, if patients are currently not on premixed insulin, would you suggest changing their insulin medication, and is evidence for this conclusive?

DR. QAYYUM: You know, so there is no evidence as such that a look at two arms, so, yes, an ideal study in this situation would be a study that two arms and one arm, you know, one is continued on the same previous insulin regime and another arm that previous insulin regime is switched to a premixed human insulin analogue. And then, you know, to have more conclusive evidence this needs to be the case, that the comparator should be different in one study than another study.

So there is actually no evidence that switching from one particular insulin preparation on which a patient has adequate control, adequate glycemic control, has achieved a target A1C to a premixed human insulin analogue will do any better. It may be that the choice, you know, may be based on other factors other than fasting postprandial A1C, which may be patient convenience or other reasons for switching to one preparation.

But, as far as evidence is concerned, that we looked at, there was no study that specifically looked at this comparison.

SONIA NAGDA: Thank you, Dr. Qayyum. Our time is almost up. If we did not get to your question today, please e-mail us at ehc_clinicians@ahrq.hhs.gov. To access all other resources mentioned today and print them out, you can find them on the Effective Health Care Program Web site listed here, or you can order them en masse for free through the AHRQ Publications

Clearinghouse. The various reviews and reports on prescription medications can be easily accessed as well as many related educational materials.

Also on the Web site, you can become involved in the topic nomination and refinement that I described as well as comment on draft reviews and reports. All of these features, in addition to signing up for e-mail updates, can be easily navigated in the panel on the left hand side of the Effective Health Care Program Web site.

I would like to thank Dr. Qayyum for sharing his research findings with us today. It was very informative. I would also like to thank our many participants for joining us today. We hope that the information presented here informed you about how you can implement patient-centered outcomes research into everyday practice and how the Effective Health Care Program resources are available to assist you and your patients with decisionmaking.

As we conclude this Web conference, let me remind you that this event will be archived and available shortly on the Effective Health Care Program Web site. Finally, as you leave the event, please answer the one feedback question posed. Your feedback is very important to us as we develop more resources and plan similar events. Have a nice day.

END