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Diabetes Cardiovascular Outcomes Trials: What You Need to Know

**Announcer:**
Welcome to ReachMD. The following program “Diabetes Cardiovascular Outcomes Trials: What You Need to Know” is sponsored by Novo Nordisk.

To view these graphical image references, please visit www.ReachMD.com/CVOT to view the video.

**Dr. Davidson:**
Hello. My name is Dr. Michael Davidson, and I am a Preventive Cardiologist at the University of Chicago Pritzker School of Medicine in Chicago, Illinois.

You probably noticed that more and more diabetes cardiovascular outcomes trials, or CVOTs, have been completed in recent years. In fact, the number and frequency of these studies is likely to increase. While this is great for patient care, all this data can be overwhelming and may be confusing. For this reason, I am excited to present to you the following: the history and key design elements of the diabetes CVOTs, the statistical tools that are commonly used in these trials, and lastly, some guidance on how to put them into context. I hope you will find this helpful, so without any further delay, let us begin.

Why are cardiovascular outcomes trials required for diabetes medications?

In December 2008, the FDA issued draft guidance that provided recommendations on how to demonstrate that medications for the treatment of type 2 diabetes were not associated with unacceptable increase in CV risk. It is because of this guidance that all diabetes medications must demonstrate CV safety or no unacceptable increase in CV risk.

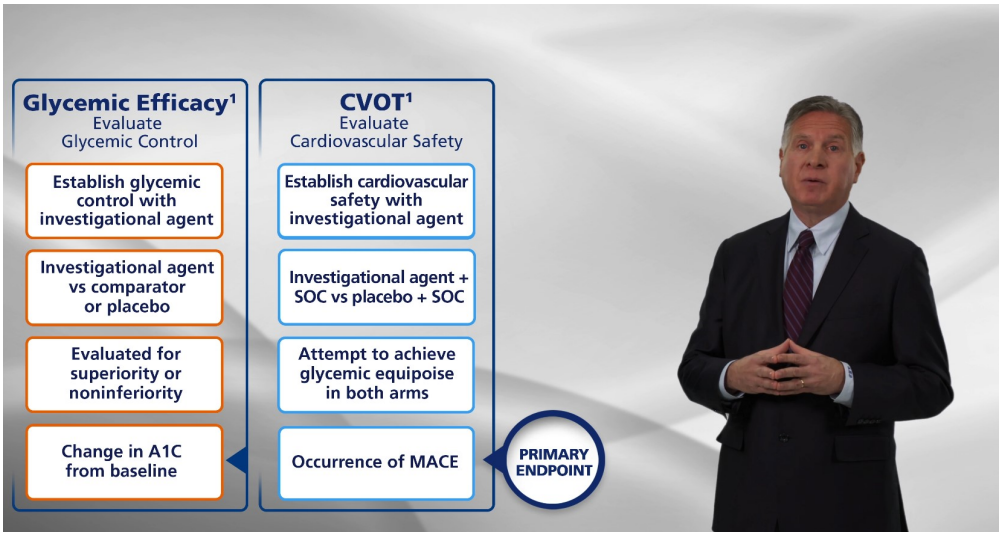
How do CVOTs assess the cardiovascular risk of a specific antihyperglycemic therapy?

Diabetes CVOTs are characteristically different from glycemic efficacy trials. First, their goals are different. Glycemic efficacy trials, as the name implies, are designed to establish glycemic control with the investigational agent. CVOTs, on the other hand, are designed with the specific goal of assessing cardiovascular safety with the investigational agent.

Next, the therapies which are compared are also different. While glycemic efficacy trials compare an investigational agent to a comparator or placebo, CVOTs typically compare the investigational agent plus standard of care, which we will describe more in a moment, to placebo plus standard of care.

Another important difference is how these two types of trials evaluate glycemic measures. In a glycemic efficacy trial, glycemic measures are evaluated for superiority or noninferiority. In a CVOT, however, glycemic equipoise, or glycemic equivalence, is attempted in both arms to control this variable so that cardiovascular safety of the specific drug being tested may be better assessed.

Lastly, glycemic efficacy trials are designed to primarily evaluate differences in glycemic control, for example A1c, whereas CVOTs primarily evaluate what is known as MACE.




What is MACE?

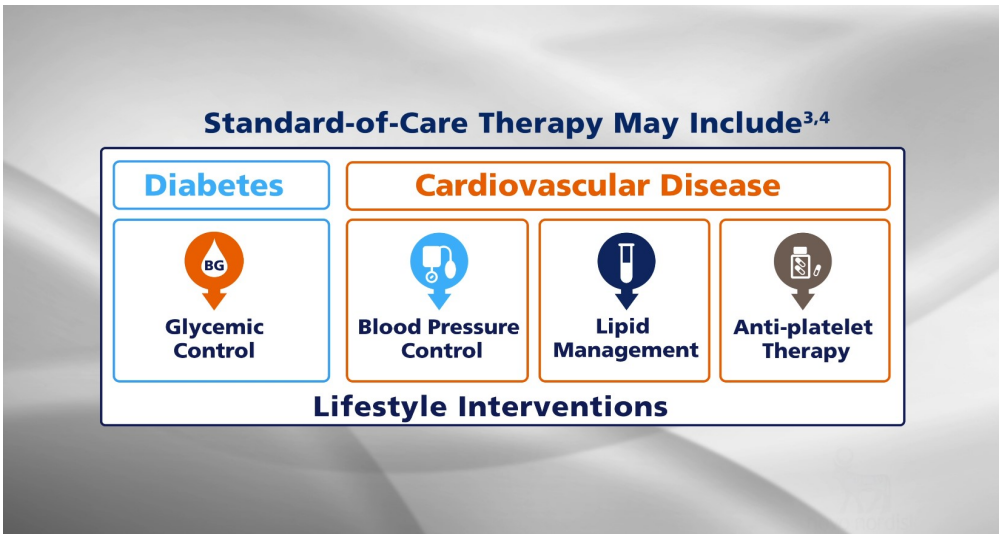
MACE stands for Major Adverse Cardiovascular Events. As the name implies, this endpoint is a composite of a number of outcomes. The FDA prefers three measures - specifically, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. That said, additional expanded composite endpoints can also be added, including hospitalization for heart failure, death from any cause, as well as the others noted here.


What is the general study design of a CVOT?

As previously noted, during a CVOT, the investigational agent being evaluated is typically compared to placebo to assess for any unacceptable increase in CV risk. To achieve the appropriate statistical power, a certain number of CV events must occur. To accumulate these events in a reasonable amount of time, these trials include patients at high risk for experiencing a MACE event. It is important to note that the FDA does not provide specific guidance on the health of the study population. As a result, baseline characteristics often vary between trials.

Remember, in a CVOT, both arms, the investigational agent and the placebo, are on a background of standard of care therapies. This is done with the intention of isolating the CV effects of the investigational agent through MACE and other secondary measures while ensuring the study is ethically sound. This standard of care therapy includes guideline-directed glycemic control, blood pressure control, lipid management, antiplatelet therapy, and finally, lifestyle interventions. How each patient is treated, however, remains dependent upon the discretion of the investigator. As such, variances can occur, making the control of these factors important pieces to consider

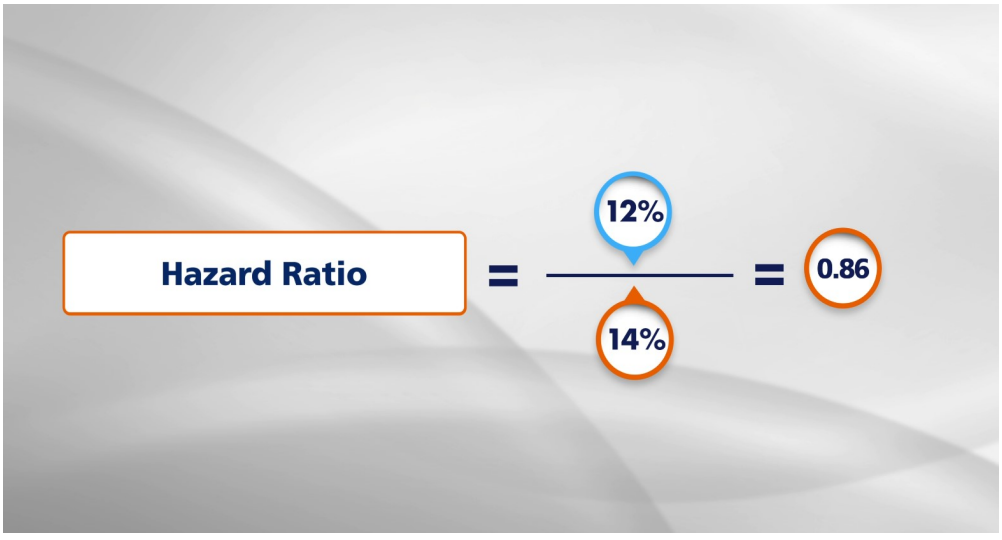
when interpreting trial results.




How are the results of diabetes CVOTs assessed?

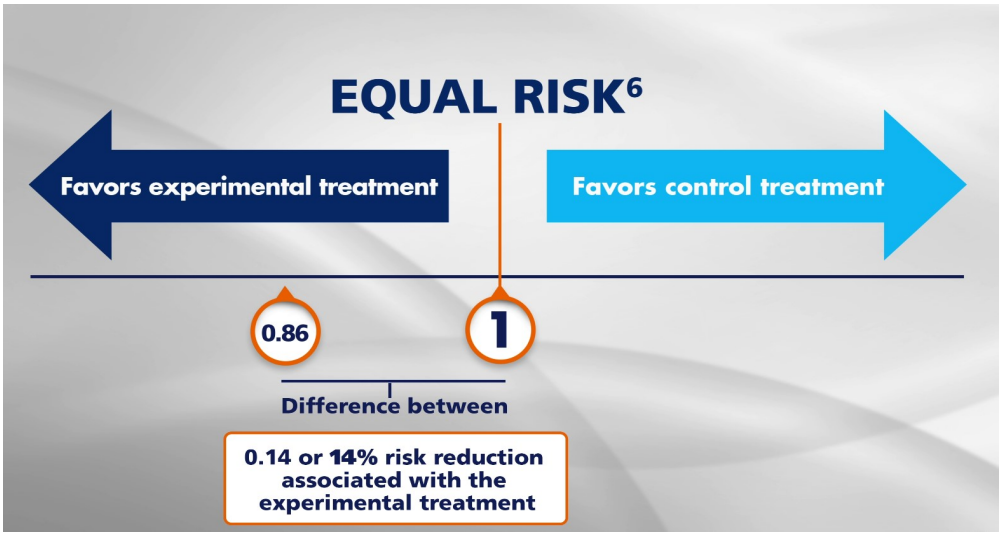
To view these graphical image references, please visit www.ReachMD.com/CVOT to view the video.

Before we get into a more in-depth statistical discussion of CVOT results, let us quickly touch on how the data are presented. According to the FDA guidance, the primary endpoint must be reported as a risk ratio. For the purpose of this discussion, we will focus on what is known as a hazard ratio. A hazard ratio is a ratio of the hazard rate or the probability of an event occurring over a defined period of time in the experimental group versus the control group. Assume the hazard rate of the experimental arm is 12% and the hazard rate of the control arm is 14%. The hazard ratio would simply be 12% divided by 14% or 0.86.



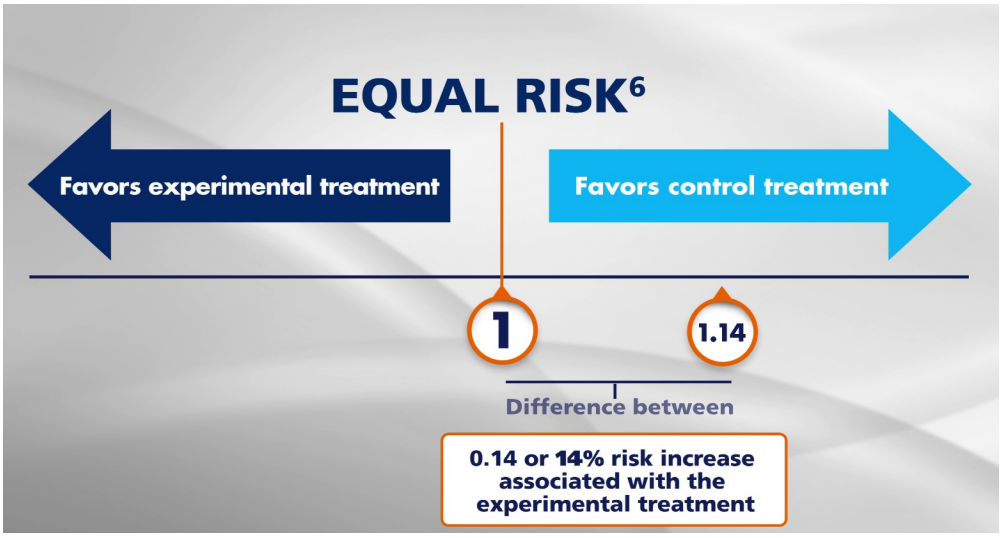

What does this mean?

This is easiest to understand when we look at this figure here.




One, which is the middle, represents an equal risk. To the right or above 1 means an increased risk relative to the control, and to the left or below 1 is a decreased risk relative to the control. If we place 0.86 on this graph, we can see that the risk is decreased relative to the control and that the difference between the two numbers, that is 1 and 0.86, is 0.14 or 14%. This means that there is a 14% reduction in risk with experimental treatment relative to the control.

Alternatively, if the hazard ratio were 1.14, there would be 14% greater risk of experiencing an event with the experimental treatment relative to the control.

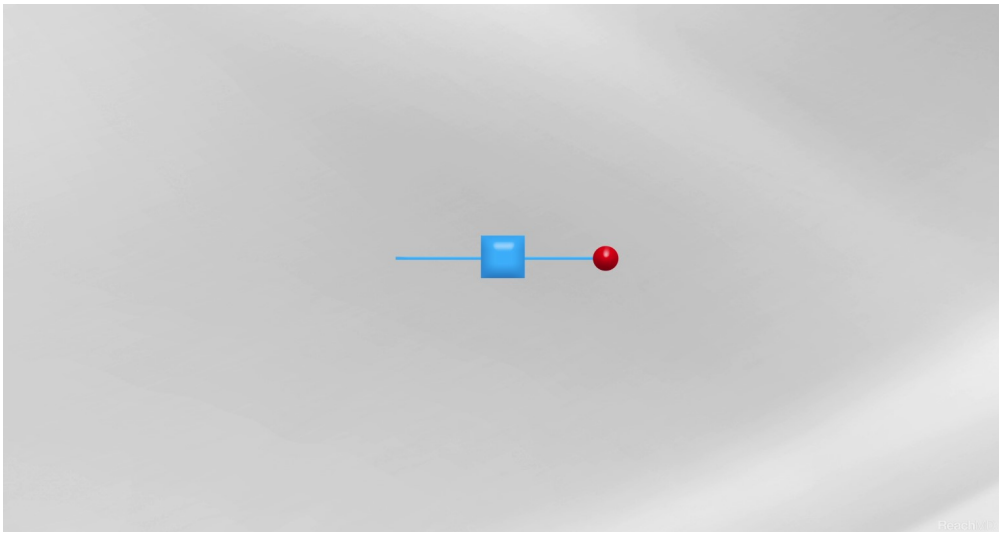



Hazard ratios, such as these, are frequently used to estimate the treatment effect for time-to-event endpoints, such as MACE.

Now that we have covered hazard ratios, we need to discuss how to interpret them in the context of a CVOT.

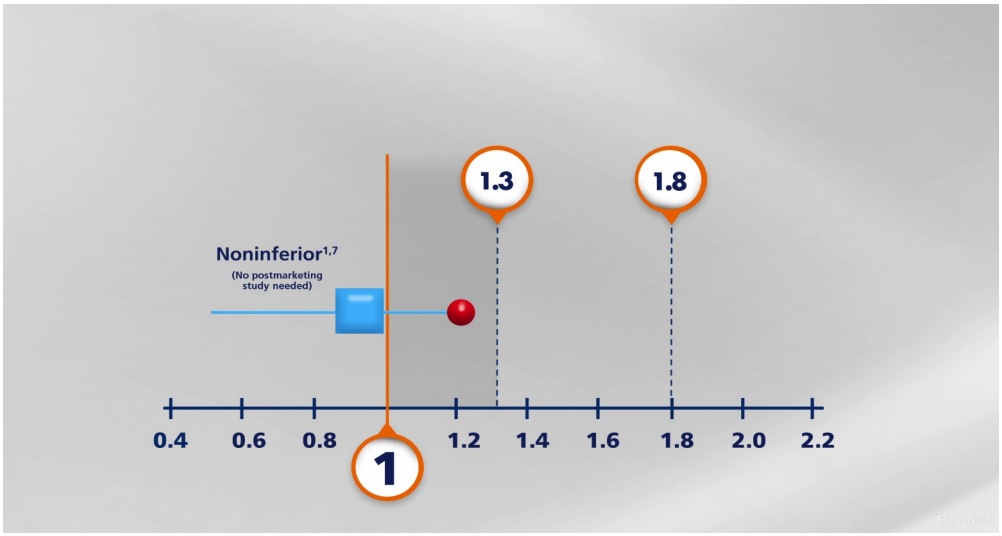
According to the 2008 FDA guidance, this is explained through the evaluation of the upper bound of the 95% confidence interval of the hazard ratio. That is less complicated than it sounds, so let me explain.

First, let us take a look at an example hazard ratio. Here we can see the point estimate and the 95% confidence interval.

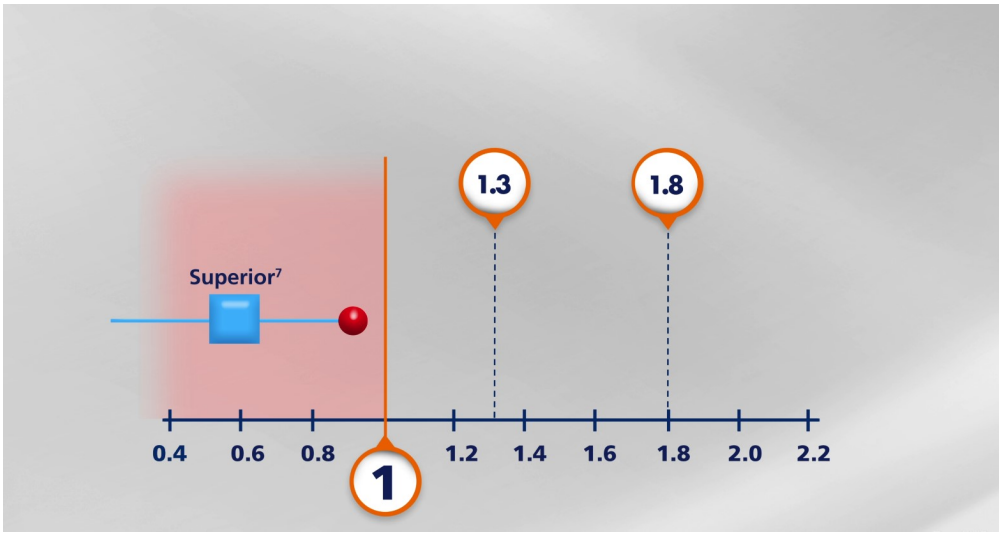


This point on the right side of the line is what is known as the upper bound of the confidence interval. Remember this because we will be coming back to it.

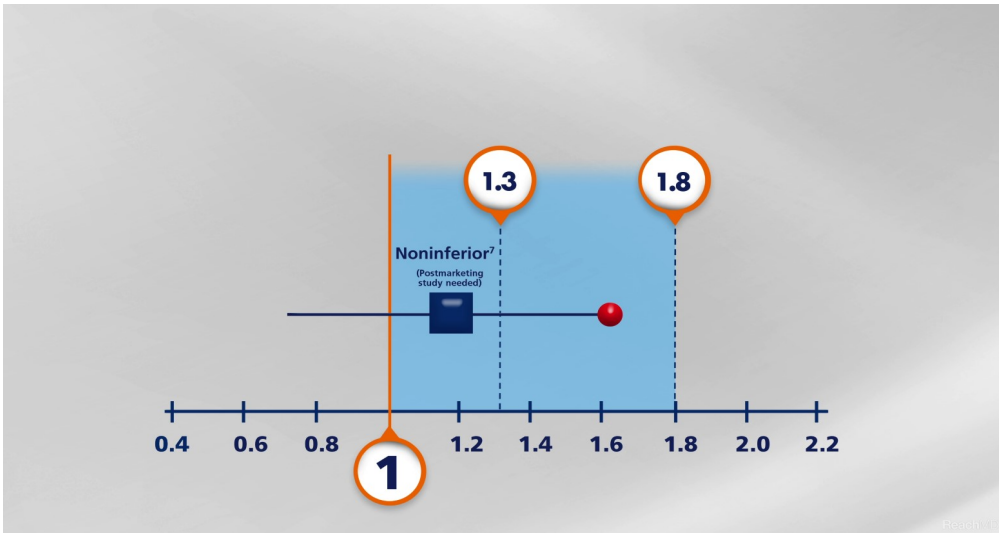
For the FDA guidance, there are two upper bound thresholds that we must be mindful of, 1.3 and 1.8. Because 1.3 is closer to 1 or unity with the comparator, it represents the more difficult goal to reach for any experimental treatment. In other words, achieving such a result as illustrated in this example means that in the eyes of the FDA, the treatment is not associated with unacceptable CV risk. It also means, assuming this was a premarketing trial, that the agent is approvable and that a postmarketing trial may not be required.




If the upper bound of the 95% confidence interval is not only less than 1.3 but also less than 1.0, the agent may be considered superior to the comparator in terms of the cardiovascular outcome. Not being below the 1.3 threshold does not mean that an investigational agent is unapprovable, however.



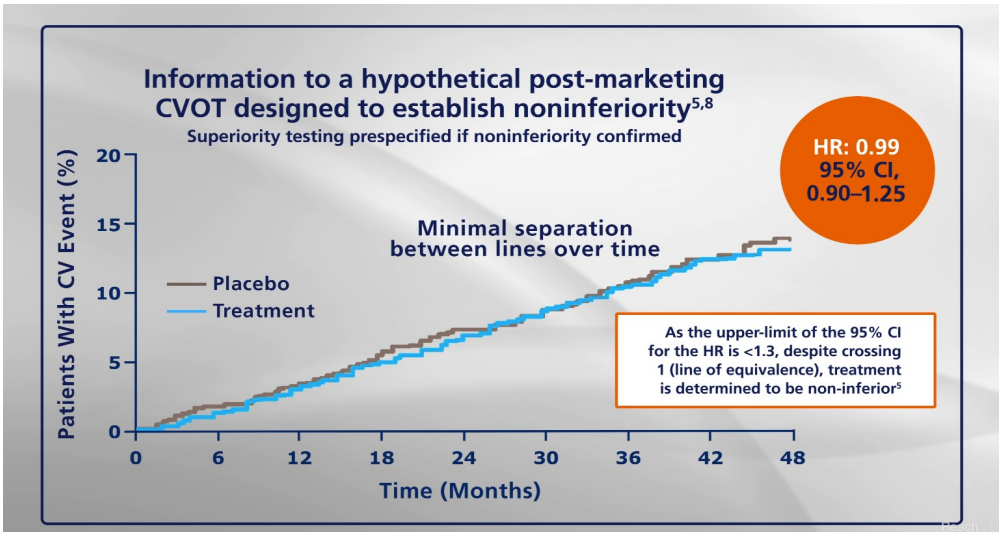

According to the FDA, as long as the agent is below the 1.8 threshold, it can still be approved, but a postmarketing study must now be completed. That study will need to result in the primary endpoint being below the 1.3 threshold.




It is exceedingly important to consider the methodology of the study you are reviewing to see which of these two thresholds, 1.3 or 1.8, the study was hoping to achieve as this determines the context.

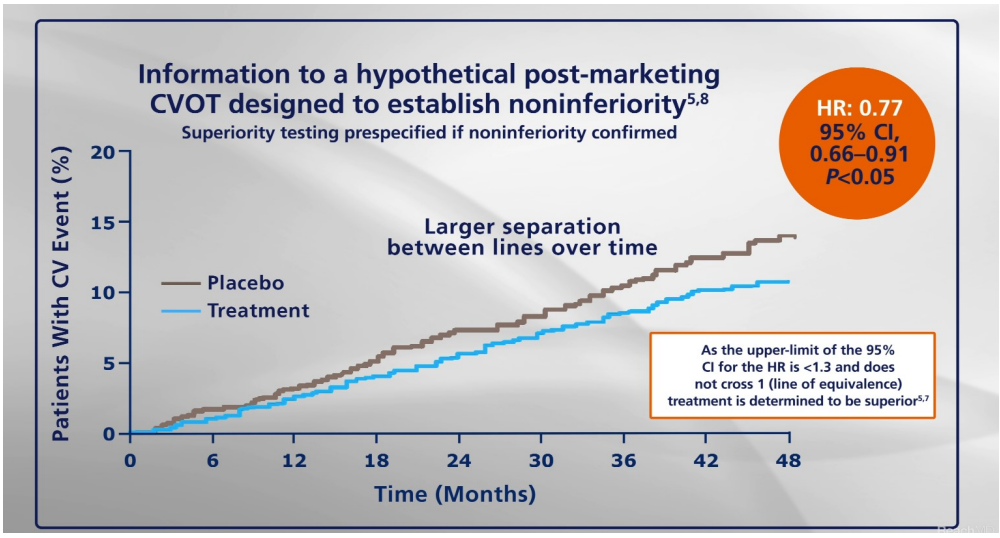
We just reviewed the two statistical thresholds a treatment must meet as defined by the FDA. Let us apply this information to a hypothetical postmarketing CVOT designed to establish noninferiority for cardiovascular outcomes. Remember, because this is a postmarketing CVOT, noninferiority needs to be established by ensuring the upper bound of the 95% confidence interval is less than 1.3.

Shown here is a Kaplan-Meier (KM) curve.




It shows the accumulation of events over the course of the trial, in this case, patients with a major adverse cardiovascular event or MACE. At the end of these lines are the statistical results aligned to these data. As we can see, the hazard ratio is nearly 1, and the 95% confidence interval is 0.90 to 1.25. In this context, the upper bound of the 95% confidence interval is 1.25. Since this number is less than 1.3, which was what the trial was designed to evaluate, we can conclude that the noninferiority of the investigational agent is confirmed, and the medication is not associated with an unacceptable increase in CV risk compared to standard of care alone.

Here we have another example of a KM curve.




Same hypothetical context as the CVOT before, meaning that the upper bound of the 95% confidence interval must be less than 1.3 to confirm noninferiority. In this instance, not only is the upper bound less than 1.3, it is also less than 1.

As we discussed before, this means that this particular treatment is superior to placebo when assessing the risk of experiencing a CV event.

We just discussed hazard ratios and how they can give us not only a sense of the reduced or increased risk that an experimental treatment group might have experienced, but also a sense of the importance of the upper bound of the 95% confidence interval for this ratio for interpreting the trial itself.

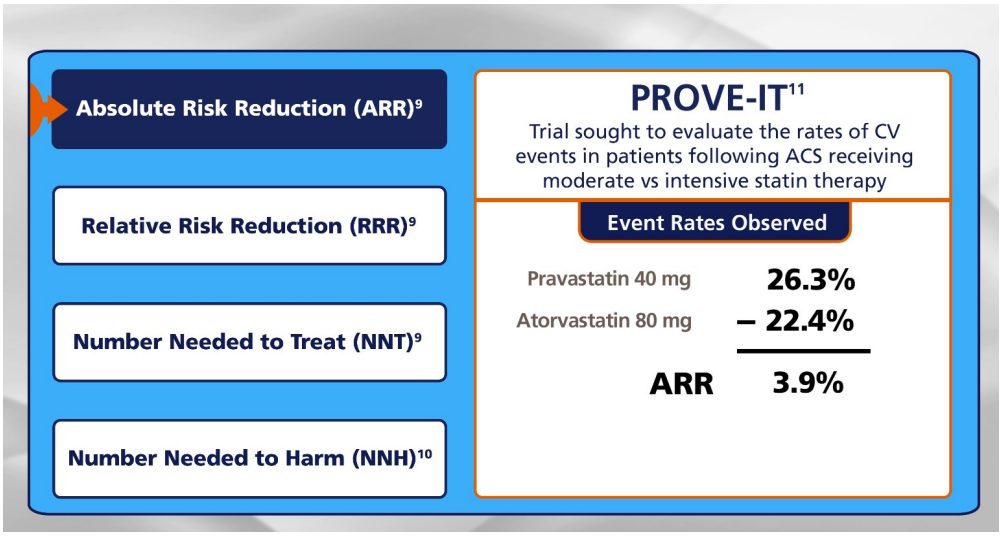
Now let us take a look at a few other ways in which CVOT data may be presented.

Let us start with absolute risk reduction. To explain this, we are going to use a real-life example. In this case, the PROVE-IT trial, which

evaluated intensive versus moderate lipid-lowering therapy with statins following acute coronary syndromes.

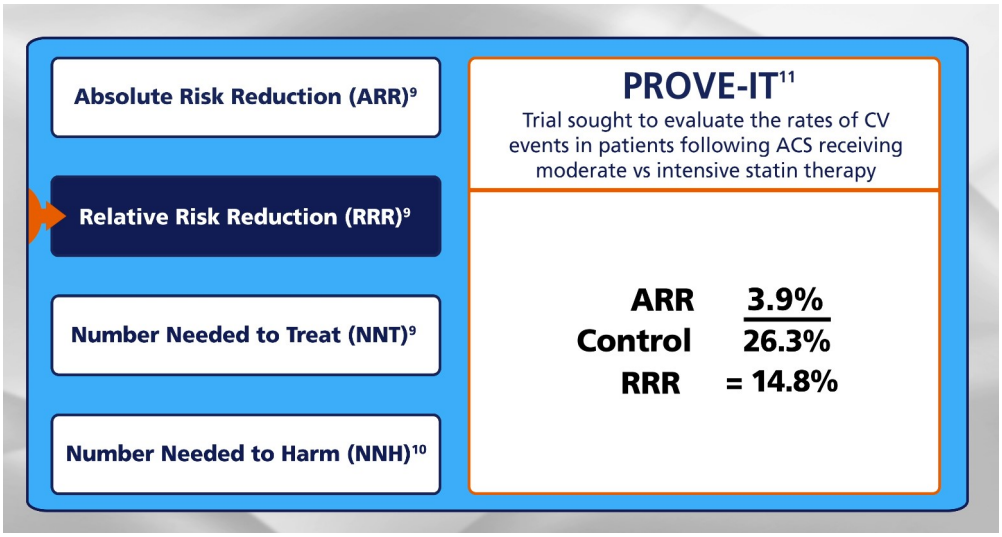
Moderate therapy served as the control arm and was represented by 40 mg of pravastatin daily while intensive therapy is represented by 80 mg of atorvastatin daily.

In this trial, the event rate of the primary endpoint was 26.3% for the moderate therapy arm and 22.4% for the intensive therapy arm. The absolute risk reduction in this case, which is the difference between the risk of an event in the experimental group versus the control group, was 3.9%.



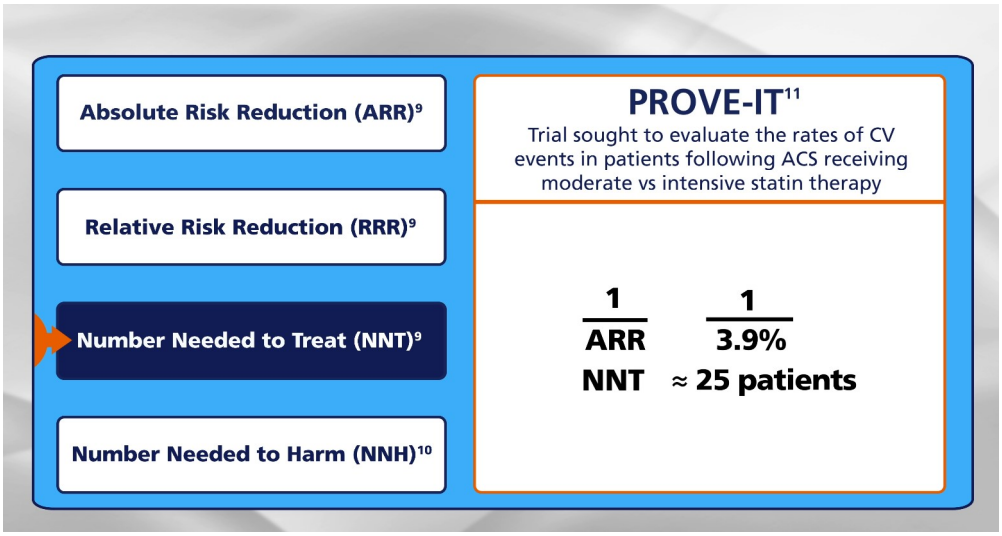

Another way to express this difference is by calculating the relative risk reduction, which is the difference in outcomes being assessed in the experimental group relative to the control group.

To determine this, we divide the absolute risk reduction or 3.9% by the event rate for the moderate therapy group, which was 26.3%. Doing so means that the intensive therapy group achieved a relative risk reduction of 14.8%.




Next, we will review the number needed to treat and number needed to harm, again using the PROVE-IT trial as our example. The number needed to treat is the number of patients that need to be treated to prevent the occurrence of one event over a given period of time. This is calculated by dividing 1 by the absolute risk reduction.

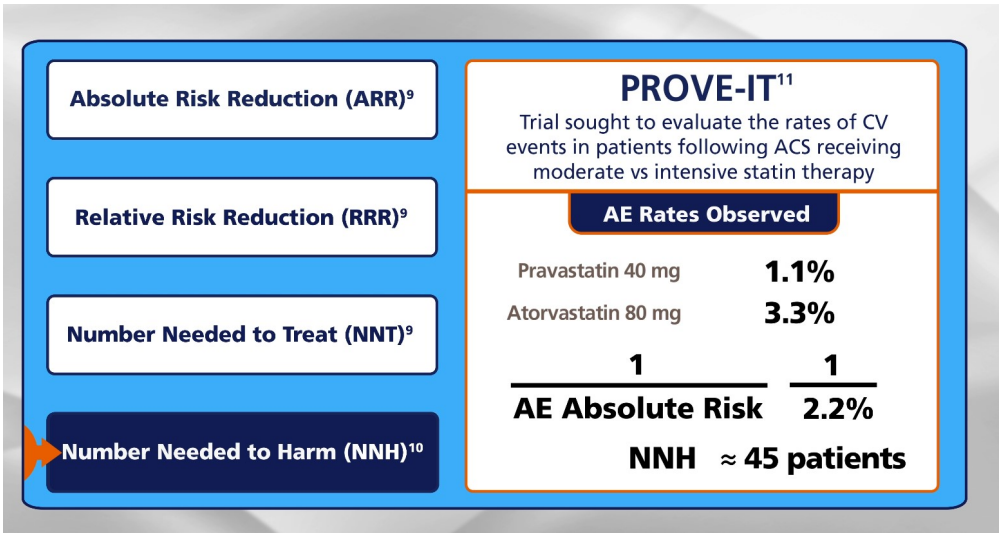
As we just discussed, the absolute risk reduction was 3.9% for the intensive therapy arm in the PROVE-IT trial. When we divide 1 by 3.9%, we get 25, which means that to avoid one event, approximately 25 patients need to be treated with atorvastatin 80 mg as compared with those treated with pravastatin 40 mg.




Lastly, we have the number needed to harm, which represents how many patients need to be treated for one additional patient to experience a given adverse event or AE.

The number needed to harm is calculated by dividing 1 by the absolute risk of the adverse event you are evaluating. Since statins are known to raise liver enzymes, let us look at that AE.

In this instance, alanine aminotransferase (ALT) was greater than three times the upper limit of normal in 1.1% of patients treated with pravastatin versus 3.3% treated with atorvastatin ($p<0.001$). For every 45 patients treated with atorvastatin, we will see one additional occurrence of this AE as compared to those treated with pravastatin. These two numbers, the number needed to treat and the number needed to harm are often used to establish the benefit and risk profile of a given drug.




We discussed a lot of information on how to interpret an individual CVOT, but it is important to remember not to be tempted to compare CVOTs to one another. While the FDA guidance does provide a framework, it does not dictate how these trials must be designed. As a result, CVOTs can vary quite significantly. They often have different inclusion criteria and evaluate different study populations in primary and secondary endpoints. Just as importantly, the statistical context the studies are designed to incorporate, the 1.3 and 1.8 thresholds we reviewed earlier are different, so be sure to keep that in mind. In short, while many trials share the CVOT designation, there are often significant differences between their designs.

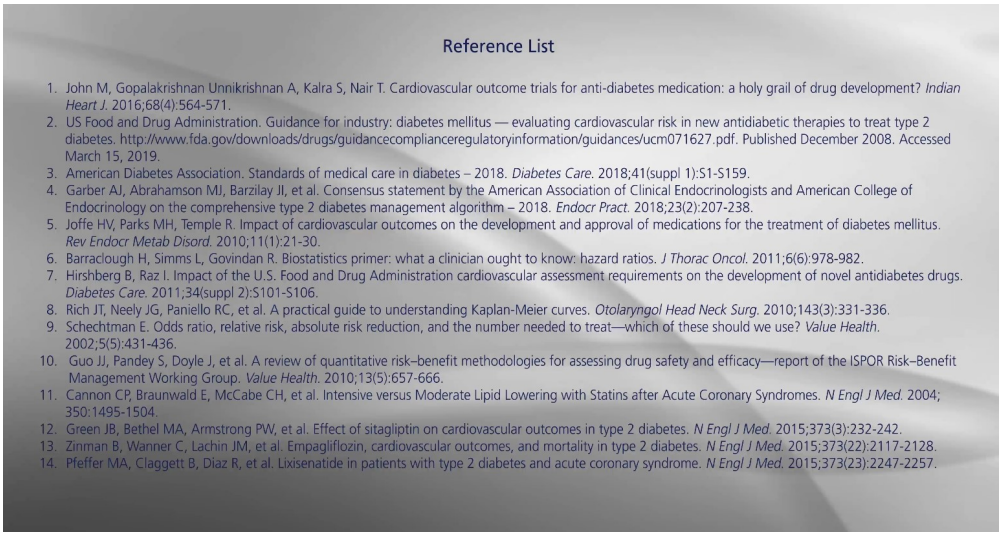
Let us briefly recap what we have discussed. Diabetes CVOTs are different from glycemic control trials because the primary endpoint evaluates a composite endpoint known as MACE. They are conducted on the background of glycemic and cardiovascular standard of

care typically on a population at increased risk for cardiovascular events.

According to the FDA guidance, CVOTs must evaluate their treatment groups based on a risk ratio much like the hazard ratio we reviewed. It is important to keep in mind what the upper bound of the 95% confidence interval for the hazard ratio of the CVOT was designed for as this contextualizes the results of the trial. Be mindful of the differences in absolute and relative risk reduction as well as the differences in the number needed to treat and number needed to harm as these statistics are often used to convey CVOT results data.

Finally, it is important to remember that not all CVOTs are designed in the same way, so they cannot be compared. Baseline characteristics, such as duration of diabetes, patient age, cardiovascular risk or history, as well as how statistics are prespecified can all be very different. Even how MACE is defined can differ.

I truly hope that this has been informative and has provided you with a solid knowledge base for reviewing the next CVOT or helped refresh key concepts about these trials. On behalf of Novo Nordisk and myself, I thank you for your time.



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**Announcer:**

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