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Antithrombotic Treatment of Patients With ST-elevation Myocardial Infarction (STEMI)

A Panel Discussion with James J. Ferguson, MD, James Hoekstra, MD, and David A. Morrow, MD, MPH

[Transcript]

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Dr Ferguson

Hi, I'm Terry Ferguson. I'm the associate director of cardiology research at the Texas Heart Institute. And I'm here today with 2 esteemed colleagues, Dr David Morrow from Brigham and Women's Hospital and Harvard Medical School, and Dr Jim Hoekstra from Wake Forest University.

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We are here to discuss clinical trials in ST-segment elevation myocardial infarction. One of the challenges we face in medicine today is the continuing accumulation of information. We are constantly bombarded with new clinical trials, and the challenge we face is how to take this information and apply it in the real world of clinical practice.

No clinical trial answers all the questions that we have. There are always questions that remain, there are always issues that come up about all the clinical trials, and no clinical trial is absolutely perfect, and what we have to deal with is the totality of evidence.

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There are 2 important clinical trials that I would like to discuss today — the ExTRACT-TIMI 25 [Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis in Myocardial Infarction] trial and the OASIS-6 [Organization for the Assessment of Strategies for Ischemic Syndromes] trial. Both of these were presented at the American College of Cardiology meetings this past spring, and both of them have been recently published, and we've had the opportunity to look at the data. But the

question arises, now that we have the data, what do we do with this? And Jim and David can help me sort of work our way through the implications that these trials have in the real world of clinical practice, what the data mean, what they mean to our practice, and what they may mean to the future guidelines.

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I'd like to start with the ExTRACT-TIMI 25 trial. ExTRACT-TIMI 25, as you know, was a trial in patients with ST-segment elevation myocardial infarction who were lytic eligible, 20,000 patients with ST-segment elevation myocardial infarction who were treated with a variety of different lytic agents, the lytic choice was up to the physicians, and were randomized very simply to either receive unfractionated heparin as per standard dosing regimens, or low-molecular-weight heparin in the form of enoxaparin.

Something that was different about this trial was the dosing scheme that was used in elderly patients. In patients less than 75 years of age, they received the standard 30-mg IV bolus and 1 mg/kg subcutaneously. If patients were greater than 75 years of age, this was adjusted to no bolus and 0.75 mg/kg.

The patients were then followed in-hospital, and the primary end point of the trial was death or myocardial infarction at 30 days. The primary safety end point was TIMI major hemorrhage.

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I don't need to recapitulate the data in exquisite detail for all of you, but simply stated, as one looks at the outcomes at 30 days, the primary end point of death or myocardial infarction, there was a significant reduction at 30 days in the enoxaparin-treated group. And I think that this has profound implications as one looks at the outcome end points. From the standpoint of bleeding, there was also an increase in major bleeding in the enoxaparin group, so there is a price that one pays in terms of better outcomes but maybe more bleeding.

And the question I pose to you, Jim, first of all, is from the standpoint of the emergency department, what implications does this trial have for your practice now, in terms of the patients that now present with acute myocardial infarction to Wake Forest?

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Dr Hoekstra

Well, I think we have to take the trial in context of it is a fibrinolytic trial, and many emergency departments, like my own, don't use fibrinolytics. We are a PCI [percutaneous coronary intervention] center, so if a patient comes in with ST-elevation MI [myocardial infarction], they go to the cath lab.

As a result, the implications of this trial for me personally are relatively small, but the majority of hospitals that ST-elevation MI patients present to are not cath lab hospitals, do not have the ability to provide timely primary PCI, and they have to give fibrinolytics. This trial for those hospitals is very applicable, the results are very applicable, and the treatment that is prescribed based on this trial, the use of enoxaparin instead of heparin, actually makes it easier to give.

I can see this being, shall we say, a very big changer of practice in those non-cath lab hospitals.

Dr Ferguson

So, right now, pretty much everybody who comes to Wake Forest with an acute myocardial infarction will wind up going for primary PCI.

Dr Hoekstra

That's correct, 24 hours a day, and a lot of tertiary care hospitals, that is indeed the case, but referral hospitals…

Dr Ferguson

So you also have a feeder system as well, too, of outside hospitals who may treat people initially and then send them to you as well, too. These would be the hospitals that would be more likely to use fibrinolytic therapy, do you think?

Dr Hoekstra

Yes, and all hospitals are under specific guidelines for time to treatment. You know, we have a 90-minute window of getting a patient from the door to having a balloon cross their artery for PCI. If you present to an outside hospital without cath lab capabilities, the ability to get that patient from the outside hospital to the tertiary care hospital to get PCI performed within 90 minutes, it's very, very difficult, even in the best of streamlined systems.

So most outside hospitals or referring hospitals are treating with thrombolytics, treating with fibrinolytics, and then transferring the patient, and those hospitals, the results of this trial are very applicable.

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Dr Ferguson

And what about the bleeding? I mean, there is a significant increase in TIMI major bleeding, 1.4% versus 1.0%. Is that a problem, from your perspective?

Dr Hoekstra

Well, you have to look at what type of bleeding it is and you have to look at the bleeding in context with other outcomes. First of all, what type of bleeding? If this was intracranial bleeding, where you have a high percentage of patients who either die from it or have significant disability, that would be worrisome, but it's not.

Intracranial bleeding is the same, whether it's unfractionated heparin or enoxaparin.

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Secondly, look at the amount of bleeding versus the other end points, and you know, we are looking at this concept called net clinical benefit, which is death, MI, revascularization, versus bleeding, bleeding being the downside.

If you look at the results of ExTRACT, the results in terms of reduction of death and MI and urgent intervention, significantly outweigh the bleeding problems. So without the intracranial hemorrhage difference, and an overall net clinical benefit, you still see the results of this trial pointing toward enoxaparin being a better drug with fibrinolytics.

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Dr Ferguson

Okay, David, what about from the standpoint of the cardiologists that have to then deal with the patients once they've worked their way through the emergency system? What are the implications of this trial for your practice at Brigham and Women's Hospital?

Dr Morrow

I think that the main area that we have to grapple with is that in those patients who are treated initially with a pharmacologic reperfusion strategy, that there is still a substantial proportion who end up going to the cath lab at some stage in their management. So that's one important domain.

And how do these patients fare with respect to efficacy and safety? And we'll have more information that will be forthcoming soon, but already we can say that the same general observations that we saw in the overall cohort are the same in the PCI population.

Dr Ferguson

So, we're still waiting for that piece of the data?

Dr Morrow

That's correct.

Dr Ferguson

We knew from the original presentation and the publication, at least generally, that the patients who underwent elective coronary intervention, or did that also include rescue coronary intervention?

Dr Morrow

Yes, it includes rescue as well. So there are roughly 2100 patients or so who ended up undergoing intervention in the first 48 hours, and just under a quarter of patients ended up undergoing PCI at some point during the first 30 days.

Dr Ferguson

And at least from what we know right now, before the more detailed analysis came out, that what we saw in the overall population was generally what we saw in the PCI population as well.

Dr Morrow

That's correct, and I think that's encouraging for cath lab-based hospitals that may be receiving these patients as well. I think the other important observation that was made both in OASIS-6, which we'll be talking about in a while, and also ExTRACT-TIMI 25, is that both of these trials evaluated a strategy of antithrombin therapy. And that the experimental arm, in this case, enoxaparin, was continued throughout the index hospitalization, the qualifying hospitalization, up until a maximum of 8 days, and that there appeared to be a benefit of including in that strategy the sustained antithrombin therapy.

And I think that's something that we still look to tease out more, but that's an important aspect of our care for these patients.

Dr Ferguson

And I think that that becomes a very important change in what has gone before, heretofore with unfractionated heparin, just the simple logistics of managing intravenous unfractionated heparin made it really impractical to continue unfractionated heparin for more than about 48 hours in these patients.

Now, the data from ExTRACT, which strongly suggest that there is benefit to a strategy that includes anticoagulation up to the time of hospital discharge. And I think that may have profound implications for how we continue to manage these patients in the hospital as well, too. And you mention one of the very interesting subgroups that we're going to be looking more closely at, which is the PCI subgroup.

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What about the subgroup of the elderly? Now the elderly had their dose adjusted. This was the first time in any clinical trial that we have had the benefit of recognizing the increased bleeding risk in the elderly, and adjusting their dosing. Do we have any information on the elderly in this population?

Dr Morrow

I think that also we very much look forward to presenting those data in detail as well soon. I think we can say overall we saw the overall rates of bleeding in ExTRACT-TIMI 25 were lower than previous experience, and that, just as a global assessment, speaks to the fact that the dosing regimen may in part be responsible for the lower rates of bleeding.

But in particular in the elderly population, the same pattern was seen in that the net clinical benefit was preserved with the same numbers needed to treat, and that's driven by a higher risk in the elderly population, and with similar outcomes in terms of both efficacy and bleeding.

Dr Ferguson

So that what we seem to be seeing here is consistency, so that there appears to be consistency in the PCI subgroup, there appears to be consistency in the elderly group, at least in the big picture views right now, and I think that that may give us a little more confidence in terms of something that may be more broadly applicable.

You mentioned the bleeding issue. Jim didn't seem all that concerned about the bleeding issue. What about you? I mean, from the standpoint of you're the one who the patient is

going to come complain to about a bleeding episode, hopefully they are still around to complain about it. How do you feel about the increase in bleeding?

Dr Morrow

Yes. I look at the things the same way as Jim, and that we recognize that in this trial, enoxaparin, as it was dosed, that there was a 0.7% higher absolute rate in TIMI major bleeding, but that that was offset by the advantages with respect to ischemia and recurrent myocardial infarction. So that the net clinical benefit from a variety of prespecified end points was still 14% to 18% reduction in an overall composite of clinical events for these patients.

So again, thinking about taking care of the patient as a whole, the enoxaparin strategy was superior to our current guidelines-based regimen using unfractionated heparin.

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Dr Ferguson

And catastrophic bleeding, intracranial hemorrhage, was not significantly increased, as Jim mentioned. I think it's also important to remember that the anticoagulation strategy that we talked about, we're talking about coagulation throughout the hospitalization as opposed to 48 hours' worth of anticoagulation.

To my mind, it sort of intuitively makes sense that if you're going to anticoagulate people for a longer period of time, you might have a higher risk of, somewhat higher risk of bleeding complications as well, too, and that may just be the price you pay for a prolonged anticoagulation strategy.

Dr Morrow

Yes, I think that that accounts for some of it. We do already see some separation in bleeding at 48 hours as well, even when there is a head-to-head comparison. But both of those factors are at play, a more potent antithrombin agent risk strategy, and also the extent of duration of anticoagulation.

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Dr Ferguson

From the standpoint of guidelines, is this going to impact on emergency guidelines?

Dr Hoekstra

Yes. I think if you look at the present ACC/AHA [American College of Cardiology/American Heart Association] guidelines for ST-elevation MI, the recommendation for enoxaparin is, you know, downplayed compared to heparin, and also there is a warning for not using it in elderly patients. I think there's enough safety data from this regarding the elderly that we may see that disappear, and there's enough efficacy data in terms of the 20,000 plus patients involved, that we may actually see enoxaparin changed to a, for instance, class 1. I can't predict, but I would assume that that's probably the direction things may go.

Moreover, from a standpoint of what happens in real practice, aside from the guidelines, clinicians understand a 20,000-patient trial with results as compelling as these provides pretty substantial evidence for the therapy that they choose.

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Dr Ferguson

There's a little bit of a disconnect, though, because at least, as was used in this study in the patients less than 75 years of age, there's a 30-mg IV bolus. That doesn't happen to currently be in the labeling for enoxaparin right now, but I think it's going to be important for people to recognize that at least with enoxaparin in patients less than 75 years of age, probably an IV bolus is going to be worthwhile. Would you recommend that to the cardiology community as well, too?

Dr Morrow

I think if we're going to take this and extrapolate to evidence-based medicine for studying patients with STEMI receiving fibrinolytic, that these data would advocate inclusion of the 30-mg IV bolus.

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Dr Ferguson

So in addition to the PCI subset, and the elderly subset that are going to be discussed in more detail, are there any other things that we should be looking for importantly to come forward from the trial as well, too?

Dr Morrow

Well, I think there will be other important subgroups that have, where there have been questions regarding the risks and benefits of fibrinolytic or pharmacologic reperfusion therapy. All of our women who present with ST-elevation myocardial infarction, we know they are at higher risk for complications, and sometimes complications of therapy, so I think that will be another important group.

Also, in terms of background pharmacologic therapy, while the ExTRACT-TIMI 25 trial was ongoing, the CLARITY [Clopidogrel as Adjunctive Reperfusion Therapy]-TIMI 28 and the COMMIT [Clopidogrel and Metoprolol in Myocardial Infarction Trial] trials were completed, and those, both of those studies provide strong evidence for the use of clopidogrel in patients with ST-elevation MI. And I think we'll look for more information about these 2 drugs being used in combination as well.

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Dr Ferguson

Okay, so I think that we've still got some things to look forward to, to keep us interested. The next trial that I would like to turn to is the OASIS-6 trial. OASIS-6 is also a trial in patients with ST-segment elevation myocardial infarction, but it's looking at a different

drug — it's looking at fondaparinux, which is pentasaccharide, which is a direct Xa inhibitor.

Low-molecular-weight heparins, like enoxaparin, have both Xa and IIa effects, with maybe more Xa than IIa. Fondaparinux has a pure Xa drug, and in the OASIS-6 trial, it looked at patients, also, with ST-segment elevation myocardial infarction, but it looked at things a little bit differently. ExTRACT-TIMI 25 was fibrinolytic-treated patients. OASIS-6 was patients eligible for reperfusion, and it stratified patients on the basis of whether unfractionated heparin was going to be indicated or not.

And on the basis of whether unfractionated heparin was indicated or not, they developed 2 strata, 1 where it's not indicated, where there is a placebo control, and the stratum 2, where heparin was indicated, where there is an active control with unfractionated heparin. So the trial becomes a little bit more complicated to sort through when you have patients where the control arm is placebo and patients where the control arm is unfractionated heparin.

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The primary end point of this trial was death or reinfarction at 30 days. It also looked at bleeding end points as well, too. And I think that as one looks at the top-line results from OASIS-6, it shows something very similar to what was shown in ExTRACT, and that is a significant reduction in death or myocardial infarction at 30 days. Then the analysis gets a little bit more complicated as you try and tease out the results in terms of bleeding.

Overall, there was really not a difference in bleeding results, and we can perhaps talk about some of the different strata, but at least from a big-picture standpoint, again from the emergency department perspective, what implications does this have for Wake Forest or US practice in general?

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Dr Hoekstra

This is a little bit more difficult a trial to apply than ExTRACT-TIMI 25, and the reason it's difficult is because, as you mentioned, there are so many different treatment strategies employed. And when you look at patients who are treated with fibrinolytics or even patients who are not treated with fibrinolytics, and patients treated with primary PCI, the way this trial was designed was to look at fondaparinux as an option for an overall, you can treat anybody with this drug, strategy. But when we try to apply that to our practice, we have to say, well, wait a minute, how do we treat patients in this country and in my setting, and what part of OASIS-6 is actually applicable to what I do?

Now, in this country, patients who are treated, for instance, in an outside hospital with fibrinolytics and then are transferred to a tertiary hospital, typically get a catheterization within 24, 48, maybe 72 hours, so we have a very invasive strategy-oriented approach to ST-elevation MI here. In a cath lab hospital you get primary PCI, in a non-cath lab hospital you get fibrinolytics and then they are sent to a hospital where they get PCI.

So you have to look at OASIS-6 and say what part of OASIS-6 fits that strategy? Well that would be the patients treated either with primary PCI or the patients treated with fibrinolytics, followed by PCI, and it doesn't look, in those patients, as if fondaparinux is advantageous. There are complications in the cath lab, clot on the wire in the cath lab, increased bleeding in the cath lab, that make me think, this may not be the right drug for the pattern of care that we provide here.

Add to that the fact that there is almost no experience with this drug in ACS [acute coronary syndromes] or ST-elevation MI in this country, and it becomes very difficult to say, this is going to change practice. I think there's going to be a problem with that.

Now, that being said, in settings where streptokinase is used, in settings where fibrinolytics are used without PCI, there may be some advantages to this drug, for instance, in Europe, or in more rural settings or in less invasive settings in this country. But for the majority of the practice at least that I'm seeing, I'm having a tough time applying the results of this trial.

Dr Ferguson

I think it's very interesting that for both of these trials, you know, the immediate point of reference that you go to is the catheterization laboratory. Cardiologists do get important from time to time with respect of the emergency room guys.

Dr Hoekstra

Again, it's an overall strategy, and in this country, the overall strategy typically ends in the cath lab, and what you do up front can either make that easy or make it hard. And let's face it, we want to make this a smooth, smooth strategy across the board, from the start in the emergency department to the finish in the cath lab and discharge.

Dr Ferguson

So, all roads lead to Rome or the cath lab or something…

Dr Hoekstra

Yes. I don't know if I'd go that far, but yes, you're right.

Dr Ferguson

I think that the point I'm making is that particularly in things like acute myocardial infarction, the strategies that one is developing are strategies that fit in with the overall pattern of care. You don't want things that are going to disrupt the potential options that are available to the patients, and nowadays the cath lab becomes such an important part of that management picture. Maybe not everybody is going to the cath lab, but it's such an important part of the picture that you want strategies that are going to fit well with the catheterization laboratory.

Dave, from a cardiology perspective, you know, is OASIS-6 and fondaparinux going to have application in your practice?

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Dr Morrow

Yes, I'd start by saying overall it was a very important result in that it adds to the overall evidence base that we have, that have actually established the importance of administering an antithrombin at all in patients with ST-elevation MI, which has still been an area of debate over time. And it adds to recent trials like CREATE [Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation] that have established a clear benefit over placebo when you consider the participants in stratum 1.

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For my practice, though, again, I practice in a tertiary care center where the vast majority of my patients are going to go to the cath lab, either up front as part of their reperfusion strategy, or down the road. And so the implications for patients going to the cath lab where there was a 14% to up to 25% hazard across the efficacy end points with the fondaparinux at least gives me some pause as to how I might apply it.

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For, taking a step back and thinking about all my colleagues who are practicing in hospitals in the surrounding area where they administer fibrinolysis, that the overall amount of data, the number of patients who were treated with a fibrinolytic and then randomized to unfractionated heparin or fondaparinux in the trial was just a little over 1000 patients out of the entire population. And so in terms of the number of patients treated in the way we practice, generally, in the United States, the experience is not as large as the overall trial population would reflect.

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Dr Ferguson

What about the point that was made very emphatically in this trial, there also happens to be a significant mortality difference. It's hard to find a harder end point than mortality, and as you look from the intention-to-treat overall standpoint of the trial, you showed benefit in death and myocardial infarction, and you showed benefit in mortality.

Personally, I was a little bit surprised that a pure Xa strategy did so well, but it emerges as an option that at least needs to be considered. Did the results surprise you at all, the mortality difference?

Dr Morrow

Yes. I think coming back again to my first point that I think in terms of the utility of antithrombin therapy for patients with ST-elevation MI as an adjunct particular to pharmacologic reperfusion strategy, these results are great for our patients, and they showed that with a strategy that inhibits higher up in the coagulation cascade, that there is a potential for reduction in mortality.

We also might add to it the lower risk of bleeding that was seen, or at least no excess of bleeding, in particular, with fondaparinux compared to the control population in the trial, which included some patients treated with unfractionated heparin and some with placebo. And I think it is, it brings our attention around to the importance of bleeding in our patients who are being treated with pharmacologic therapy, and may also speak to the dosing that we may be using over antithrombin therapy in conjunction with fibrinolysis.

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Dr Ferguson

I think another message that actually parallels the message that came forward from ExTRACT has to do with the duration of therapy as well, too, because in OASIS-6, the fondaparinux arm was treated for a longer, extended period of time as well, too. And I think that it's causing a lot of us to sort of rethink what we do for in-hospital anticoagulation in our MI patients.

Now, this may become somewhat moot once they've been revascularized and made their trip to the catheterization laboratory, but I think that that is one thing that is probably going to substantially change in terms of how people are thinking about anticoagulating. Go ahead.

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Dr Hoekstra

What's interesting is that a significant part of the death/MI benefit is in stratum 1, where the placebo is the comparator. If nothing else, what we learn from this trial is that treating ST-elevation MI without some sort of anticoagulation, and maybe even with a longer period of time of anticoagulation, is not a good idea.

And that may be a bit of a home run for fondaparinux in that there was significant benefit over what's happening in the standard of care right now, not necessarily in this country, but certainly in Europe, for those patients with ST-elevation MI, that are not treated with a cath-lab strategy.

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Dr Ferguson

Now, we had talked about some of the subgroups in ExTRACT that were important, the PCI group and the elderly group and things like that. OASIS-6 is, you know, the way it is set up, it is sort of carved into subgroups as well, too. And the difficulty that I face is, at what point do you look at the totality and at what point do you look at the subgroups and how do you tease that out? What for you are the important subgroups in OASIS-6?

Dr Hoekstra

Well, the ones that I'd be most interested in are the ones that again apply to what I do, the primary PCI group, for instance. I mean, I do primary PCI in my hospital. I would like to see that the patients placed in these different subgroups, the PCI group, the thrombolytic group, the stratum 1, are not necessarily placed there by, for instance, a randomization strategy.

These patients are essentially different, so you have to look at each group and risk adjust each group to really get a clean analysis of the effect of a drug or the effect of a strategy in that group. But the primary PCI group I'd be very interested in, the fibrin-specific

thrombolytic group, especially compared to heparin like in stratum 2, I'd be very interested in.

I think those are probably the 2 biggest, whether there's rescue PCI and will there be complications with that, again, in a risk-adjusted population, would be interesting to see as well. Those are the ones, because they're applicable to what I do, that I'd really like to see.

Dr Ferguson

And again, it becomes just sort of mind-boggling to me that the view of the emergency department has now expanded considerably beyond what is happening to the patient in the emergency department, to encompass the rest of the care within the hospital. What about from your standpoint, David, about the subgroups that are most important in OASIS-6?

Dr Morrow

Yes, I think actually my interests mirror Jim's, in that again I'm thinking principally about the way I treat patients and the way my colleagues treat patients in the United States, and so that's either with a fibrinolytic-based reperfusion strategy that's usually going to be fibrin specific, or with primary angioplasty and PCI.

And so those really are the core groups that are going to give me the most information about what I might do for my patients. I think just to add other groups that may be interesting, actually, from both trials are patients with renal dysfunction, where both of these drugs are cleared in part renally, and so I think we'll look for more information around those patients from both studies. And perhaps as well additional information about the elderly being treated in OASIS-6.

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Dr Ferguson

So, we've spent some time on ExTRACT, we've spent some time on OASIS. How does one now take a step back and look at the totality of the information here right now, because both of these trials are sort of yes, but…. And the point with ExTRACT-TIMI 25 is that you have better outcomes, but, you have more bleeding. The point in OASIS-6 is that you have better outcomes, but, there appears to be some heterogeneity in the population, and there are subgroups that may benefit and subgroups that may not benefit.

How does one put all of that together in a big-picture standpoint to sort of decide? The one consistent message for me is, we can do better than 48 hours' worth of unfractionated heparin. But then it becomes a matter of finding things that fit with our institutions and our practice and the options that we have available. Again, one size doesn't fit all. David, from a big-picture standpoint, what are the messages that we learn from both of these trials?

Dr Morrow

I think again we come back to a point that we've made but that is worth reiterating, which is that both of these trials reiterate the value and importance of antithrombin therapy in patients with ST-elevation MI and have a huge impact for the worldwide care spanning from those who are being treated without any pharmacologic or mechanical reperfusion therapy, including those who are being treated with nonfibrin-specific agents through to those who are going to the cath lab. So there is a lot of information that comes from these 2 studies and for those who are being treated pharmacologically, the importance of an antithrombin.

Dr Ferguson

So, antithrombin therapy matters. It's not just one size fits all, it doesn't really matter what you use, there in fact are capabilities of improving the care by adjusting your antithrombin regimen. So that's an important message.

Dr Morrow

I'd echo your thought as well, that I think that both of these show that a strategy in which we're able to continue that antithrombin therapy for a longer period of time, that's how it

was tested in both of these studies, and it's certainly plausible that it contributed to some of the benefit that we see, compared to our current standard of care with guidelines-based administration of unfractionated heparin. So I agree, I'd take that away as an important message as well.

Dr Ferguson

Okay. Jim?

Dr Hoekstra

And again, as we talked about before, you know, what pieces of these studies will impact what we do in our day-to-day care of these patients? What pieces, what substudies, what findings are going to change what we do and change our therapy?

I agree completely, the antithrombin is an important part across the board, whether it's a medical therapy, whether it's PCI therapy, it's important to have an antithrombin on board. Your choice of which one you want to use, whether it's unfractionated heparin, enoxaparin, fondaparinux, is going to depend on where you are and where you treat your patients and what your typical treatment patterns are. And different pieces of this are going to be applicable in different areas of the country, different countries, and different hospitals depending on their capabilities. Take the pieces that are applicable to you and use them in your care.

Dr Ferguson

I think that we have had a lot of lively discussion today, and a couple of messages seem to have come forward. An important message that David articulated is that antithrombin therapy does matter. Yes, we've got wonderful new tools, primary PCI has changed what we do with acute myocardial infarction in many tertiary institutions. But in a lot of other institutions using fibrinolytic therapy, the antithrombin strategy you use may impact on the outcome of your patients, and we have ways of improving on 48 hours' worth of unfractionated heparin. I think that's an important message.

We have different alternatives that have been tested in ExTRACT-TIMI 25 with enoxaparin, and OASIS-6 with fondaparinux. Both of these trials have good news and bad news, as well too, and what we need to look at is the totality of the evidence.

What we're putting together is sort of a giant jigsaw puzzle, but we don't have yet all the pieces and they keep adding new pieces to us as well, too, to try and assemble a complicated picture. And perhaps being a rabid advocate of one agent or another agent or one trial or another trial, really doesn't serve us but to recognize the complexity of the health care system, and how the strategies that we develop need to be based on the evidence that has come forward.

Thank you very much.