200 patients or more.

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Coming up to Cope here, in 1997, not quite 200 patients but 189. He looked at consecutive patients having coronary-artery bypass surgery. Even though it was a retrospective review, it is useful because it is kind of a crossover. Albumin became in short supply so they had to switch to hetastarch. Subjectively, they observed that there was more bleeding once that occurred.

They eventually went back to albumin and eliminated the use of hetastarch, and they went back and looked at the patients four months prior to this period of time when they used hetastarch and four months after to come up with a comparison. They found what they believe is a significant increase in blood loss and the use of hemostatic agents associated with hetastarch use in the OR.

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These are their values. When patients went out of the OR into the ICU, at the first point in ICU they would get a bunch of labs, and one of them was the hematocrit. They found that in those patients who did receive or did not receive hetastarch there was a significant difference, a

crit of almost 34 to 31. Again, the prothrombin time was slightly prolonged, not a difference that would strike you clinically as overwhelming but, again, something that you would expect from the laboratory findings about its effect on fibrinogen and von Willebrand's factor but, again, there is no way at this point in time clinically to measure or assess what is happening to platelets in terms of their function. We can count platelets, but platelet counts alone don't do much to help you unless it is a very low number.

But what is very useful in this paper is that when they looked at the chest tube drainage, the rate of chest tube drainage in the first two and the first eight hours, it was statistically significantly more in those patients who had received hetastarch than those who did not receive hetastarch. The use of hemostatics refers to just, you know, when you are at a loss as to what is going on and because fibrinolytic process can be part of the bleeding difficulty in the OR, drugs like Amacar or Aprotinin may be used, some of which are very expensive. So, trying to resort to something to fix the bleeding problem, it was more frequently used in those patients who received

hetastarch than those who did not. Although the rate of patients who had to go back to the operating room for reexploration is not significant in terms of statistics, it is very significant in terms of the trend for those patients who had to go back again because of the increase in morbidity, mortality, expense, length of ICU stay and all that.

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Another study, by Lorraine Herwaldt at the University of Iowa, again, because of cost issues they were looking for something cheaper than albumin at the time. They had a period of time where the substituted hetastarch for albumin as part of the pump prime solution. They, again, noticed just subjectively that the bleeding rates in those patients increased substantially.

So, they did two case-control studies. In the first case-control study they looked at the risk factors associated with more bleeding and found that it was patient age greater than 60 or the use of greater than 2 mL/kg of hetastarch that was associated with bleeding in these patients. So, they reverted back to albumin; and it was the risk factor.

I think one of the values in this paper is that they carefully defined what bleeding was. They defined bleeding as any patient who had to go back for reoperation, with chest tube drainage of more than 800 cc over four hours, or if the surgeon, in his judgment, thought that the patient bled excessively and they wrote it in the chart.

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I will switch next to a paper by Jill Knutson at the Mayo Clinic, who had a surgeon there who read Cope's paper and, based on that observation, decided to stop using hetastarch during surgery, not as part of a pump prime but just to volume expand or to replace lost blood during the surgery. They eventually evaluated 444 cases during this period of time. So, they had 234 patients that received hetastarch and 210 that did not receive any hetastarch.

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When they looked at these 444 cases in this period of time when hetastarch was used, one of the advantages, even though it is retrospective, is one surgeon for the whole period of time, and they had this one distinct period of time when no hetastarch was used so, again, even though it is

retrospective it is also kind of a crossover. When they reviewed, they found that, again, when these patients left the OR, and this is just intraoperative use of hetastarch, when they got in the ICU the mean crit. was 32 in the patients who did not receive hetastarch but in those who did it was 27. I think that is a pretty significant number, not only because it represents a greater likelihood for patients to be transfused blood in the ICU but also that is right at the transfusion trigger that has been established for when you would expect this group of patients to be transfused. In this group, to keep their hemoglobin at 10 and hematocrit at 30 is a very reasonable thing. As well, the number of platelets were decreased as well.

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Looking at their data in terms of chest tube drainage, at each interval measured in the first 24 hours those patients who received hetastarch had more bleeding from their chest tubes than those who did not receive it. Again, part of the problem here is it is so difficult for the surgeons sometimes to make a decision as to when you take that patient back for reoperation because

of chest tube bleeding. It is not clear-cut; there is nothing out there that is a clear-cut trigger for them.

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The same thing you would expect, if you bleed more, it is more likely that these patients are going to receive blood and blood products, red cells, platelets and FFP. In each instance it was a very significant difference with those patients who received hetastarch.

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We have three studies, retrospective studies but that I think are very useful because they represent kind of a crossover design, where there is a strong association between the intraoperative use of hetastarch and more bleeding or excessive bleeding immediately after surgery. Although I haven't dwelt on all the details, it appears that in each of these studies there are no real differences between these groups.

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I think there are some real interesting points in Dr. Canver's paper, in his review first of all, because you are looking at patients having one surgery, bypass surgery, and a very large

number, 887 patients over this period from 1987 to the end of 1995. They classified their patients in different groups based on the kind of pump prime.

I had the opportunity to speak with several of the authors and co-authors of these papers, Greg Nuttle at the Mayo Clinic and Mr. Nichols, to get a little bit greater background on how the study was conducted. One of the problems with pump bypass priming solutions is that everybody has their own. There is no brand out there; everybody makes their own and it varies from time to time. Over a nine-year period, just knowing from our own experience, the formulations change.

I wasn't clear from reading the paper exactly how they formulated their pump prime. They used a volume of 20-100 cc and, apparently, what they did was just, once the patient was hooked up to the bypass, just added in one of these different reagents. They didn't have a constant volume per pump prime. I think the best you could say is for group one that received 500 ml of crystalloid, in addition to the 2200 for a total of 2700; group two, 500 of Hespan so a total volume of 2700; for group three, 25 percent albumin for a total volume

of 2250, etc., etc., as I understand it in this pump prime solution. Maybe we can clarify that in a minute.

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As has already been pointed out, I think there are significant differences between the group that received Hespan and the group that received albumin and a combination of albumin and Hespan, both in terms of the cross-clamp time which is that period of time when the heart and lungs are completely isolated and the bypass which encompasses the total time before you go on and completely come off, when you are circulating blood through that plastic circuit. To me, clinically as well as statistically there is a big difference between a two-hour pump run and a three-hour pump run. Even with the other groups too, I think that there is still some significant difference.

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As has already been pointed out, the groups that received platelets and the ones that received FFP, it looks like it was really much more in the Hespan group as opposed to albumin.

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In addition, over a nine-year period, even

if it is one surgeon, the technique is going to get better, a little more refined. Inevitably, in a teaching hospital you have other people involved over a nine-year period so there had to be other surgeons. I know there were certainly other anesthesiologists without real distinct transfusion protocols in mind. So, it is difficult retrospectively to standardize the practices. But I do think the blood product usage was different in these groups, and some of the endpoints are not real useful because the surgeons really didn't have control over them, like the length of ICU stay. That was an administrative decision, not based on a clinical decision. If there had been data like how long a patient was on a ventilator, and I assume they would come off the ventilator based strictly on a clinical decision, that might have been more useful.

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To wind this up, there are some comments from the authors, from Greg Nuttle from the Mayo Clinic. I should mention that in their study if they weren't getting a hetastarch solution it was their practice that almost all of their patients received albumin as intravascular volume

replacement. Although they didn't publish those numbers, it is behind the actual practice.

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I didn't show the data on this, but Cope also did a correlation in his study on intraoperative use of hetastarch, and they showed a positive correlation which I think was something like 0.4 between hetastarch dose and postop bleeding. So, the more you gave, the more you bled. So, that led them to think that even at a low dose, in this group of patients, intraoperative use of hetastarch may not be safe.

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In terms of what I think these are telling us and what these data are telling and advisory committee, it is that excessive bleeding and increased transfusion requirements are associated with intraoperative use of six percent hetastarch in these patients undergoing cardiopulmonary bypass; that there is evidence that there is an increased risk of reexploration in these patients following hetastarch use; and that, clearly, three major centers, Iowa, Mayo Clinic and UVA, are avoiding the use of hetastarch as pump prime in their bypass procedures.

That concludes the comments I want to make on this. Any questions?

DR. NELSON: Thank you. I have one question. The committee was asked, first of all, whether the evidence or the data would suggest a warning label and, as an alternative, they were asked should a prospective, randomized trial be done to answer the question. It seems, although it is not universal, that there are quite a number of surgical programs that are convinced that hetastarch does increase the risk of bleeding. Given that feeling, and I would like your opinion as to how widespread that feeling is, but given that feeling, it might be difficult to do a clinical trial. I think that surgeons would be reluctant to randomize patients to an arm when, even though it might be somewhat cheaper in the cost of what is being infused, the overall cost might be more and they might feel it was harming the patient. Given your contact with surgeons throughout the country in review of the literature, that it would be feasible to do a large clinical trial?

DR. HAYNES: There are two or three points there. First the clinical trial, it is going to be

very difficult for a couple of reasons. One is the cost, and I don't know who would fund this sort of thing. You are speaking not only to surgeons, and everybody's goal is obviously to minimize the complications. You have touched, as a number of people have touched on the issue of cost. You know, the cost of albumin a few years ago was much higher. Just general pricing policy for most academic hospitals is different but it is not that much different. In just ball park figures, and I am just saying this off the top of my head, you are talking roughly in the $15 to $20 range for 500 ml of hetastarch solution, at least for Hespan, and maybe about $30 for five percent albumin so you double that and you are looking at $60.

The point about drug cost, whether it is this or any other drug in the perioperative process, it is a small part of the big picture. The way we save money is not by using a cheaper drug; it is avoiding a complication because the complications are what are devastating and expensive for the individuals and for the institutions.

In terms of how you would do this study, yes, there would be a lot of reluctance on the part

of surgeons to randomize patients to something that they now think, based on these studies, might be dangerous to the patients, and also it would be very difficult to convince an IRB these days that the endpoint is going to the OR for an emergency reoperation.

DR. NELSON: Particularly if the only benefit was a small economic benefit. As you mentioned, a complication in five percent of the patients would wipe that out easily.

DR. HAYNES: Yes. Well, Herwaldt mentioned that in her analysis. They were trying to save a little bit of money but the cost of taking patients back to the OR quickly wiped that out. The minimum is like a $7,000 bill.

DR. LEW: In your talk you didn't make distinction between the two different products, the Hespan and the Hextend, although in your handout you started to show some differences and mentioned another study. There is, you know, some debate whether it is the hetastarch itself that is the problem versus the carrier, the combination of the hetastarch and a particular carrier.

DR. HAYNES: Right.

DR. LEWIS: Can you expand on that?

DR. HAYNES: Right. It is interesting you bring that up because that was the one thing that really got my attention initially because the marketing information associated with the Hextend product--I want to be careful how I say this, I mean they just make the statement that it has been used in very large volumes. What we have been talking about and, again, what I think the common practice is among anesthesiologists and one that I learned in training is to stick with what Dr. Landow mentioned at the beginning, a dose of 10-20 cc/kg, which gets you out to about a 1500 cc daily limit on this. With Hextend, and that comes out of a paper where even in the title they suggest very large use of that product, and in the paper that refers to the use of up to 5 liters in some surgical cases, which I think is an enormous amount of product to use, yes, the difference really is--I don't know if somebody might be here from Abbott who markets that--I know in the paper where it was described, one difference was 550 molecular weight substance. I don't know if that was a misprint or if it really is the same hetastarch that is in the other product, Hespan. But the real difference is that it is just in a different carrier. I don't

see that study being based on a real difference in the solute; it is the solvent that is different in those solutions.

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I thought this issue might come up so I included a couple of slides at the very end. I was going to limit this just to a discussion of the cardiac surgery patients but this goes outside that to other general surgical patients. In the study that is quoted, they looked at general surgical patients. I think it was urologic, gynecologic and general surgery or orthopedic patients.

In this study they were comparing the two hetastarch solutions, Hextend which is an electrolyte solution compared to Hespan. When they invented Hespan years ago, I don't know why they put it in saline. It makes a certain amount of sense to put it in an electrolyte solution that is going to mimic normal plasma. In their study they were just infusing some lactated Ringer's throughout the surgery as a baseline and then they had certain hemodynamic targets: if a patient's blood pressure dropped they infused one of the study solutions. If their heart rate went up, they infused one of the study solutions. Then, they

also just estimated what the blood loss was and replaced it 1 cc for 1 cc of the study solution.

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What they were really comparing was an electrolyte solution with six percent hetastarch to saline with six percent hetastarch and the estimated blood loss was about the same. The total volumes given to the patients on the average were the same, although there is considerable variation. You can see that 35-40 percent of the patients received in excess of what I think is a safe dose of this material to use, with some patients receiving up to 5 L.

So, based on some of the information I have shown you already, I don't think it should come as any surprise that, because it is one form of hetastarch compared to hetastarch in just another solvent, they are going to have similar blood losses; similar hematocrits both at the beginning and end of surgery; and a little change in the prothrombin time.

I don't think that really tells us that when you conduct a study looking at one carrier for hetastarch versus the other, that then it is safe to give large volumes of a hetastarch solution to a

surgical patient. So, that is where that came from.

DR. LEW: I think this is going to be for discussion later, but I have concerns that we were given confidential information in our packets that clearly makes a huge distinction, but can we use that data, since it is marked confidential, in making our decision? It sounds like because it is marked confidential we can't discuss it and I think it needs to be discussed.

DR. NELSON: Well, if it was given to us I think somebody wanted us to look at it. This is a public hearing so I don't know.

DR. LEW: We are scrutinizing what has been published, but then we have confidential information which I think we ought to scrutinize because, certainly, the panel here has a lot of expertise.

DR. NELSON: Sometimes we have executive session, but this is a public hearing that I think is being recorded. So, whoever gave it to us, if they want it to be confidential, then we shouldn't discuss it.

DR. SMALLWOOD: The information provided to the committee that is marked confidential was

provided by those presenting in the open public hearing, which are sponsors. Those sponsors are here today. They may address that.

MR. WANGELIN: Speaking for the sponsors package, Abbott Laboratories, that Dr. Smallwood is referring to, the confidential stamp only meant that we didn't feel, prior to the meeting, the information should be published on a website, but it is for open discussion here in this meeting.

DR. NELSON: Thank you. Your name?

MR. WANGELIN: I am sorry, my name is James Wangelin, and I work in the regulatory affairs department at Abbott Laboratories.

DR. NELSON: Toby?

DR. SIMON: I think this was an excellent presentation, as were the two previous presentations. I think it is worth putting it in context, and that relates to a couple of the questions that I asked. This substance, hydroxyethyl starch, is, as the speaker pointed out, known to increase bleeding and the data have been published over many years. So, this is old data.

The question one might ask is if you are dealing with a surgery where bleeding is a prime

consideration, why would you use something that increases bleeding? A lot of this use began in the mid-1990s when, for a while, albumin was hardly available. It was in extremely short supply. Actually, the same thing happened in therapeutic plasma exchange. People had to do the procedures. They didn't have albumin so they began looking for something, and they also felt in that circumstance that colloid was superior to crystalloid. Indeed, I think that is true with therapeutic plasma exchange. So, people developed protocols using hydroxyethyl starch and seemed to observe that it worked and that the complications, in some people's hands, were acceptable.

Then albumin came back into supply. Originally it was quite expensive. Even though, as I think the speaker pointed out, it is a small percent of the expense in cardiac surgery, the overall expense to the hospital could be quite substantial, and in the managed care environment many hospitals regulate, as was pointed out, albumin and other such expensive pharmaceuticals to keep their overall cost down.

Now the albumin price has, I guess, come down and it is more available so it is an

interesting issue in that we wouldn't be discussing it if it weren't initially for the shortage and then the difference in cost. That is why I asked the prior speaker if albumin were the same cost would he use albumin. I believe the answer was yes.

The other interesting thing I think in the discussion was the heavy use of this word "may" in the various inserts and discussions. I believe it should be not that hydroxyethyl starch may cause bleeding but that it sometimes or often does, or whatever term is most appropriate. I think that might get at the issue that we want. But I think it is an interesting issue.

There is also the division between the issue of is there more bleeding with hydroxyethyl starch, and the answer is probably yes, but then is it clinically significant enough to require a warning, and there I think it is much more cloudy, grey and difficult to determine. Obviously, with a strong difference of opinion within the surgical community, with a lot of retrospective data and what prospective data we have, not as well controlled as we would like, I think it makes it difficult to answer that second question of whether

it is clinically significant.

DR. HAYNES: Do you want me to respond to that?

DR. NELSON: Go ahead.

DR. HAYNES: Again, it is going to be I think impossible to get a prospective study to get at that issue. I can share with you what I do and what my experiences are. I am not going to stand here and speak for the people at the Mayo Clinic, although I communicate with them most closely and know them and know what their feelings on the subject are, and they have clearly discontinued the use of hetastarch in surgery. Again, it represents a unique population because they are already at risk for several reasons. So, do you, in that situation, add some other factor that can make it worse, knowing that the worst scenario is that you are going to get your ticket stamped to come right back to the OR with all the risk and cost associated with that.

The other driver that you mentioned isn't only the issue of cost or availability, but we are looking at studies that span a 20-, 25-year period and there were many pressures in the 1980s and early 1990s to reduce any blood product use at all,

with it was correctly founded or not, because of the infectious disease risks associated with transfusions.

So, there are many variables, but this is what the experience is. My guess is that maybe 40 percent or so of medical centers use hetastarch intraoperatively for cardiac surgeries. I would say at least half or the majority are not, are getting away from it.

DR. SIMON: Those that use it could do a prospective study, couldn't they? They have already said that it is safe in their view. Why couldn't those, like Albany who do use it, do a prospective study?

DR. HAYNES: One, you have to have motivation and time and resources to do it. You know what happens in the real world, we are all busy. It is no secret that everyone in healthcare, surgeons and anesthesiologist in particular are working very hard and, you know, even in academic centers it is very hard to do this kind of research. It is certainly not going to happen in a community center, and what is out there is just this sort of gestalt that hetastarch has been safe; doesn't really cause a problem because most

surgeons and anesthesiologists are so busy they are not even going to have the time to sit down and read even the retrospective literature, much less do a prospective study. So, they are relying on agencies like yourself as well as academic centers and others to investigate this problem. When it comes to investigating the problem prospectively, it is going to be very, very tough, if it ever gets done. I don't see that happening.

DR. NELSON: I have one more question. One of the endpoints that seems to be sort of consistent in the studies, you said, is the estimated blood loss volumes. Those are measured in the chest tubes; I guess how much is in the bottle.

DR. HAYNES: Right.

DR. NELSON: But is there any variability related to loculation or poor drainage of fluid that actually is in the chest but not in the bottle? Is that a problem? Because you can record exact volumes, but it is not exactly a closed system, is that pretty reliable, do you think?

DR. HAYNES: That is a good question to ask because, first of all, when you talk about estimated blood loss--let's step out of the cardiac

arena for a second, estimated blood loss, like in this paper, is at best a guess. You see blood all over the field. Some centers will weigh sponges as an estimate. It is not very reliable. It is very difficult to measure intravascular volume in a research lab; it is impossible in a clinical setting. So, just looking at the surgical field sponges, drainage or suction intraoperatively, it is at best an estimate.

In a study like this where you are just replacing cc for cc, it kind of makes you wonder. So, you have to look at estimated blood loss with a very suspicious eye. In cardiac surgery, as pointed out, you have two, sometimes four chest tubes. Can they get loculated, or some trapped and not drained? Sure, it probably does from time to time. But these are pretty large drainage tubes; these aren't small drainage tubes. They are probably a half inch in diameter, three-quarters of an inch. At the same time, patients in ICUs are getting chest x-rays and you would see loculations of fluid, and you are closely studying this over a 24-hour period.

DR. NELSON: Right.

DR. LEW: Since you can talk about it, we

were provided three articles, some submitted, some in press, all three articles suggest that Hextend is quite different from the Hespan, suggesting that the problems with Hespan do not show up with Hextend. That is why I bring that up, because if we are talking about the package insert, are we talking about this for hetastarch and anything that has hetastarch is going to go, or is there really a difference between Hespan and Hextend? All the studies that you have shown, as far as I am aware, except for this last one, used the Hespan. Is that correct?

DR. HAYNES: Yes, as far as I know. It is described as six percent hetastarch in saline, and the only preparation I know of in the United States is Hespan. Now, if there is a difference, you will have to tell me because I don't know what it is, other than the solution.

DR. ALLEN: I have two questions. I know that the low molecular weight formulation is not available in the United States. If a prospective study were to be done, would you want to see mid-weight included as a comparison with the heavier molecular weight product that currently is licensed in the United States? Based on the

information from Europe and studies that have been published?

DR. HAYNES: Sure, it might be an interesting observation, but I think what would be more informative would be to compare any new thing with what is a common practice. You know, albumin has been mentioned; crystalloid has been mentioned; blood products. We don't replace intravascular volume with just any one thing, and when we are giving blood products, especially in terms of FFP, I mean you can call it fresh-frozen plasma and you can also call it a colloidal substance because it is. It is a collection of plasma proteins in an electrolyte solution.

Many anesthesiologists will replace intravascular volume with a combination. I know many who have used Hespan; I have used Hespan. We will use it but up to a certain limit. There doesn't seem to be any real limit on albumin, crystalloid. I mean, it depends on the circumstances, how much you have to infuse to keep the patient alive. But if there is something that has a limit, I think it might be more instructive, whether it is Hextend, Hespan or any new one that comes along, to treat both groups in the same

manner and have two arms, one that would continue with the way we do things normally with blood, FFP and albumin, and then continue on with the other arm of an experimental drug. That would be more informative to me.

DR. ALLEN: A second question I had, and perhaps Dr. Canver could respond also, I was confused by the volumes in each of the four groups that you alluded to in Dr. Canver's study, the priming-plus. You know, it suggests to me that the whole issue of the volume received is very highly variable and wasn't really reflected by the descriptive four groups.

DR. HAYNES: Do you want to respond to that?

DR. CANVER: The total pump prime was 2200 cc, and then additional substance was given.

DR. ALLEN: How much did you say?

DR. CANVER: The total circuitry, 2200 plus whatever each group is given.

DR. ALLEN: And, was the pump priming solution the same in all four groups, or did it vary?

DR. CANVER: It was 2200 cc, identical in all four groups.

DR. NELSON: Wait a minute, but the group with hetastarch was primed with hetastarch; the one with albumin was primed with albumin?

DR. CANVER: The way I understand it, the basic 2200 cc was identical in each of the four groups. In addition, they received Hespan, albumin or Hespan and albumin together.

DR. ALLEN: What was the 2200 pump prime solution that you say was the same in all groups?

DR. CANVER: It was a lactated Ringer's solution. I actually wanted to respond, if I am allowed--

DR. NELSON: Sure, go ahead.

DR. CANVER: Dr. Simon raised a very good issue. It depends on how you approach the issue. You may think that this agent has anything to do with the bleeding after cardiac surgery. I think it is so multifactorial because we don't use Hespan and we still have bleeding. The bleeding rate after heart surgery, which includes all types of procedures, is less than one percent.

I want to clarify, reexploration required for bleeding is less than one percent. That is extremely low. In fact, it is negligible in our hands. But that is only achievable by many

strategies, which I skipped in my initial part of strategies, and I think Gary really elaborated very nicely. We don't do only one thing. I think it would be very easy if you give Hespan or no Hespan and you are done with it, but all these patients, about 80 percent of patients come with aspirin the day before, emergency operations, have many, many other anti-platelet agents that they are on. Every hospital setup is different. Surgeons' techniques and their training is different; what they do is different. We also use a lot of hemostatic agents. We use fibrin glue, a lot of mechanical agents. Then, also, the amount of transfusions that an anesthesiologist gives also alone increases bleeding. When you look at this drainage from chest tubes, most of us now like them not to be visible because the patients like it. Our incisions are smaller and the chest tubes are now softer and sometimes we actually don't even put them in, in some simple cases.

So, essentially you are dealing with a very multifactorial issue. But I still feel, listening to all the arguments, that low molecular Hespan versus albumin in some sort of clinical trial, I think that would be something not done.

DR. DIMICHELE: Dr. Haynes, you really eloquently reviewed a lot of the literature that we were also given to review. I just need to ask your opinion, because I also had the question that Dr. Lew asked about what type of starch was actually used, but the other issues are the other variables that cause bleeding which you, again, so eloquently went over. It is unclear in the retrospective studies, in fact, in some of them, including pump time and things like that, you actually criticized in Dr. Canver's study, but among the other studies, the other retrospective reviews, can you feel confident that there were no other variables accounting for the results in those studies?

DR. HAYNES: Yes, and it varies among the studies, but going back to the Mayo Clinic because some of the things they did, one, it was one surgeon for all cases requiring coronary-pulmonary bypass, 565 patients from January of 1995 to December of 1998. It was the same group of anesthesiologists involved. It was conducted at a time when we had worked on guidelines for transfusion for a number of years. So, the transfusion triggers are well established. So, just because it was all condensed down in a fairly

limited period of time, many of these other confounding variables are not--

DR. DIMICHELE: But what about things like pump time? I mean, there seemed to be some uniformity in the other study as well. What about an issue such as pump time? You said, for instance, that pump time of two hours or three hours, and you do this every day, is quite significant.

DR. HAYNES: Right. Let's see, to answer your question simply, yes, I do feel confident that these groups were more comparable in the Virginia and the Mayo Clinic studies. I didn't quote all the details here. I think you have the papers there so you might be able to look at some of this data yourself, but I didn't find any significant variation between groups, between those who did or did not receive hetastarch, in terms of preoperative lab values, or in terms of patient demographic groups, or any of the other things. In terms of bypass duration, for instance, at the Mayo Clinic study it was a mean of 107 minutes versus 111 minutes. The time from end of bypass to out of the OR was 92 versus 99 minutes. These things were not significant. The lowest temperature on bypass,

29.9 versus 29.1. In table 1 of their paper they showed very nicely that there were very few differences, if any differences, between the patients who did and did not receive hetastarch.

DR. DIMICHELE: Thanks. My other question is there is an issue, it seems to me and maybe I am getting confused, of when exactly this substance is used in the procedure. In other words, even in the studies that you quoted there was less of a difference when the hetastarch was used actually postoperatively and not used intraoperatively or as a priming solution. Again, I need to ask you because we are going to be asked to make some decisions here. You know, the question is does it need to be specific to the timing in a certain preclinical, etc? These are nuances but they are very, very important.

DR. HAYNES: Yes, they are nuances and you are right. What I think I am trying to convey here as a message is that you have a unique surgical population having a specific kind of surgery where you are doing an awful lot of stuff to them that can interfere with coagulation. Then they survive the surgery, they go on, they start to recover. Those perturbations are resolving or diminished or

gone, not that the coagulation mechanism suddenly comes back to normal but do you add one other thing that can impair coagulation on top of those other four that could result in patients coming back for emergency surgery? Or, do you use it afterwards when homeostasis is starting to be restored and then some amount of hetastarch is probably not deleterious? I think there is a difference. Okay?

Also, if you stay within some acceptable, reasonable guideline because, you know, here we are dealing with hetastarch that is being given in reasonable amounts and there is still concern that it may cause bleeding. As I said earlier, what prompted my concern originally was the notion with some marketed materials that you could give whopping doses of this stuff whether it is cardiac or just general surgical patients, which I think would be very inappropriate today.

So, I think the difference is, yes, once somebody starts to recover and things come back to normal, is a little hetastarch going to get you in trouble? Probably not. But do you do it in a circumstance--and, as I pointed out, we don't use it in neurosurgical patients, we don't use it in liver transplant patients, and by analogy you have

a somewhat similar circumstance here with hypothermia, bypass, heparinization, all these things going on, if you add one more variable that could have a serious outcome.

DR. NELSON: Thank you very much, doctor.

DR. HAYNES: Thank you.

DR. NELSON: Stay around, we may have more questions.

DR. LANDOW: Before the committee undertakes a discussion of the questions that FDA has posed to them, I would like to present to you for your consideration nine reasons to be cautious about the data that you have seen today from these non-randomized trials, and not to jump to any conclusions.

[Slide]

The first reason is that the treatment arms may not be comparable across these different trials that we have heard today. For instance, and this is not a list that includes everything but there may be different inclusion and exclusion criteria, such as related to anti-platelet medications for a simple example. Also, there might be a difference in the severity of illness scores and how you adjust for those differences

between studies.

[Slide]

Second, even with sophisticated statistical techniques, and mainframe computers as the extreme, one can never be sure that key outcome predictors have been recognized and adjusted for. While we all realize that there are different risk factors in terms of age, gender and severity of illness, there are many that we are just now beginning to discover that may also play a role, and these include genetic predisposition and socioeconomic status.

[Slide]

Third reasons, standards of medical care change over time. We know that Dr. Canver's study lasted eight years and things do change in that time period.

[Slide]

Fourth, fluid management, apart from the hetastarch situation, can vary across particles. Knutson et al. state specifically in the manuscript that there were no specific transfusion algorithms used in the study period. Second, there were no rigorous guidelines for infusion of hetastarch, albumin or crystalloid. I think that is very

important.

[Slide]

Patient selection and treatment can be unintentionally biased. For instance, in Dr. Canver's study they stated that the decision to use a particular type of priming solution for bypass was arbitrarily made by the clinical perfusionist, which leaves open the question could hetastarch have been avoided in certain patient groups, such as older patients or patients with renal failure? We don't know that information.

[Slide]

Confounding is very likely. For instance, in the study by Knutson et al. the hetastarch group, as opposed to the non-hetastarch group, had lower temperatures on bypass, longer time on bypass, and higher frequency of preoperative anticoagulant use.

[Slide]

In the study by Cope at al. there were different volume expanders used at different points in the operation. There was a group where hetastarch was used only after bypass had been completed and the patient had been reversed; one where the patient got hetastarch only in the ICU;

and a third group where there was no hetastarch. But then you can look at the percent of patients receiving colloid post-bypass and those receiving colloid in the ICU and you see that there is a lot of information that is sort of fuzzy. We don't have a good handle on exactly what each of these patients received. So, it is hard to draw conclusions about the effects of hetastarch compared to the other products.

[Slide]

Confounding is likely also in the different pump primes that were used. Cope et al. used albumin and crystalloid. Knutson claimed that they did not use hetastarch at all. Canver gave you the four groups. So, we have different primes and we are trying to draw conclusions about a product, and I think it is very difficult to tease apart the effects of the solutions and the bleeding problem.

[Slide]

Reason number seven, adequate statistical power alone does not ensure that there is no bias or confounding taking place. You heard a quotation before that approximately 200 subjects are required to detect an absolute difference of ten percent

increase in blood loss. These studies meet those criteria, nevertheless, they all are subject to certain weaknesses that I have listed here. So, statistical power, by adequate sample size, does not solve our problems.

[Slide]

Another reason that is well-known is that the quality of the data is often uneven in these retrospective studies. The endpoints are defined differently and they are not prespecified. Many times the endpoints are chosen after the study is completed, although the manuscript, obviously, will not say that.

Also, a big problem with these studies is that there is missing or inaccurate data, and it is very hard to pinpoint that in an article published in a medical journal. Finally, different variables are collected. Some are left out, some are included. It depends on which study you are talking about.

[Slide]

Another reason is reporting bias. It is well recognized that positive findings are much more easily accepted by medical journals than negative findings. So, we don't know what those

negative findings were.

[Slide]

The conclusion that we draw from this is that non-randomized clinical trials tend to exaggerate an effect size, in this case the incidence of bleeding in this population.

Now we come to the questions by the committee, or do we go to the open session?

DR. NELSON: There are a number of people so we will come back to that. So, stick around.

The other issue, it seems to me, is that the question that the committee is being asked is a little more complex in that there already is a label saying that there is no evidence that hetastarch causes bleeding. Are we to deal with that? I suspect that there may be some sentiment that that statement needs to be changed because it doesn't omit the reference to bleeding; it says there is no evidence. This isn't perfect evidence and I certainly agree with the weaknesses of this and the necessity to really be sure to do a randomized, controlled trial, but I am not sure it is accurate to say that there is no evidence that there are bleeding problems.

DR. CHAMBERLAND: I also need some

additional clarification, and I apologize if perhaps you have covered this in your introductory presentation which, regrettably, I had to miss. I think there are a number of issues that are at least confusing to me that I need some clarification on. Some of that will come out in the public hearing, but initially my approach to the material for this topic was to read it as it came, and the issue paper provided by FDA, the summary issue paper, and the articles that are referenced in that summary paper kind of initially led me to believe that these were sort of the primary papers, the important papers, whatever, but these were the important papers to consider.

There was also no reference to the fact that there are apparently a couple of different versions of this product out on the market, and these five papers that you just reviewed with respect to some of the issues that need to be considered really only addressed one version of this product. Then, as Dr. Lew mentioned earlier, the committee has also been supplied with a lot of additional materials coming from the sponsors and manufacturers of these various products.

So, I am a little confused as to what it

is that we are supposed to use in trying to develop some recommendations from the FDA and why FDA, in its own pulling together of the issue, at least to me, didn't seem to take into consideration additional literature and information about this whole other product. If someone could provide some clarification--I don't know if that is confusing to other members of the committee.

DR. NELSON: Yes, there are two different products and there could be two different labels I suppose. Do you want to comment on that, Dr. Landow?

DR. LANDOW: The clinical problem that has arisen from the medical community is bleeding associated with hetastarch. So, that is the reason this product is under discussion.

DR. NELSON: So, we are discussing hetastarch.

DR. CHAMBERLAND: Generic hetastarch.

DR. LANDOW: Yes, hetastarch in normal saline, but not in the lactated Ringer's solution, not the Hextend.

DR. NELSON: If that is the case, then it is not appropriate for any presentations on Hextend.

DR. HOLLINGER: That is very confusing. I thought this was just on hetastarch in general and to determine whether there are any particular differences that would require different warnings. I mean, otherwise I am not sure why we got this ton of information on hetastarch from Abbott. That is a lot of information to go over if we are not going to discuss it, if it is not going to be up for discussion.

DR. FALLAT: Isn't Hextend already on the market as well?

DR. NELSON: Since '99 I think.

DR. FALLAT: So, we really have to address it.

DR. NELSON: Does FDA want us to discuss labeling of Hextend as well?

DR. LANDOW: The reason that you got the literature about Hextend was because that pertained to the discussion of the open session, but it does not pertain to the discussion that we called you here to agree to. Now, if you want to discuss it among yourselves, I suppose that is your prerogative. I am just saying that the reason we are calling this meeting is because of a bleeding problem that the medical community claims is

occurring with the Hespan in normal saline.

DR. HOLLINGER: But that is the problem. The question talks about six percent hetastarch. You don't say Hespan in normal saline, and that is what the question should have said if that is what we are supposed to discuss.

DR. NELSON: Yes, I think it does make a difference. One of the problems we have is that a lot of people have airlines leaving at three o'clock, and what-have-you, and if we are not to discuss the Hextend at this point, then we probably shouldn't listen to additional material.

DR. CANVER: I just wanted to say that the Hespan is a trade mark given by the company. So, you cannot really say Hespan in normal solution; you can only say in medical scientific form six percent hetastarch in normal saline. I mean, that is the proper way of saying it.

DR. NELSON: Yes, but what if we were to talk about hetastarch and Ringer's lactate?

DR. CHAMBERLAND: FDA really needs to assist us with their question because the first question that we have been asked to consider is, is there evidence for excessive bleeding in cardiac surgery patients who receive six percent

hydroxyethyl starch, and there is no additional qualification of that with respect to the carrier, which I think you appropriately pointed out. So, we need some clarity as to what it is that we are being asked to consider.

DR. LANDOW: I will say once again that the medical community has alerted us to what they see as a problem with excessive bleeding with six percent hydroxyethyl starch in normal saline, trade name Hespan, as correctly pointed out. We have not been alerted to a problem with Hextend, which is hydroxyethyl starch in lactated Ringer's. The only reason you got that information is so you could be aware of what was being discussed in the open session.

DR. NELSON: Yes? Identify yourself, if you will.

DR. WEINSTEIN: I think actually we do need to make a further clarification. I think Paul Albersold, in our group here, will make a clarification of what we intend to do here. It turns out that Hextend and Hespan apparently, at this point in time, both have the same labeled indication. In fact, I have to amend the comments of my colleague, Larry. We will be talking about

both of these at this point.

DR. NELSON: So, you want us to discuss both?

DR. WEINSTEIN: Right.

DR. ALBERSOLD: At the time that the Hextend product was licensed the labels were essentially the same for the two products. There was no evidence one way or the other--the trial wasn't designed to test for any differences between them. It was designed to show that they could be used essentially interchangeably. The labels are essentially identical and the starch products are the same in them. So, FDA has no evidence that there is any difference between them. I think that in the public session Abbott wanted to present some information. I think the committee can ask what the status of those trials is, are they to support a labeling change? I can't reveal what is going on in their INDs.

DR. NELSON: Dr. Smallwood has a statement.

DR. SMALLWOOD: Regarding the open public hearing, I will try to clear up a little bit of confusion, that is, when topics come before an advisory committee for all of the affected products

or related sponsors, if anything that is being discussed will have any association with that, they are notified. They have the opportunity to present during the open public hearing. The FDA will identify what is the specific issue to be discussed, but that is the reason why the advisory committee members did receive information from the sponsors, and during the open public hearing individuals are permitted to make such presentations and we will use the information as we see fit with respect to the discussion.

I would also like to state before we go into the open public hearing that the information that was stamped confidential and was submitted to the committee cannot be discussed publicly unless there is a public statement by the sponsor, stating that the material may be discussed in this public setting and this material may be publicly posted on the FDA website. So, at this time, with the committee chairman's permission, I would like to ask those sponsors that submitted information stamped confidential to please come to the mike and state publicly that your information may be discussed at this meeting and that it may be posted on the FDA website so that we may have a record in

our transcripts. Thank you.

DR. NELSON: Do we have a volunteer?

DR. SCHMIDT: While somebody is volunteering, I am sort of irritated to see that this material was published in 1995, and most of it is in newsletters dated 2001. So, somebody puts a stamp "confidential" on it, which is an old Defense Department ploy but it shouldn't work in Gaithersburg.

[Laughter]

DR. FALLAT: I want a clarification. Was Hextend approved on the basis of comparability studies with Hespan? Could we have an answer to that question?

DR. ALBERSOLD: I believe if you look at the summary basis of approval you will find that the primary endpoint was volume comparison to show that they could be used essentially interchangeably. There were no prospective study endpoints for any differences between them, any advantage, no clinical benefit to one versus the other. It was strictly that they could be used interchangeably essentially with the same volume.

DR. FALLAT: So, it was a comparability study.

DR. ALBERSOLD: Essentially, yes, it was.

DR. FALLAT: Thank you.

DR. WAITZ: Can I speak? This is Harold Waitz, from Biotime, sponsor for Hextend. About the confidentiality, we just had a concern that there are papers that are not printed and approved, that they appear on the FDA website beforehand. There are copyright issues with that. But certainly a lot of the information in there I believe can be discussed. Some of this stuff has been given in various forums as abstracts and papers.

DR. NELSON: So you are saying it can or cannot be on the FDA website?

DR. WAITZ: I mean, the papers themselves shouldn't be posted, but I think we can discuss the information that we are going to present.

DR. NELSON: Well, whatever you are going to present is in a public hearing.

DR. WAITZ: It is basically the references to the information that we are going to discuss that we are concerned with.

DR. NELSON: I have my lawyer here!

DR. SMALLWOOD: The procedure is that once something has been discussed publicly in a public

setting, it has become public and, therefore, we can post it on the FDA website because it has been made public once it has been discussed in this forum.

DR. WAGELIN: James Wagelin, Abbott Laboratories. Our concern is that any information that has been published, of course, can be freely discussed and can be posted on the FDA website. Those articles which have not yet been published, those are areas where we have concern because there could be copyright infringement sort of issues.

DR. HOLLINGER: I think you will have to point out, as we often ask in many of these cases, which is proprietary because there are a lot of things that are documented as confidential, and some of them, you are saying, have already published and some of them were back in 1997 or 1999. So, which ones are going to remain confidential?

DR. CHAMBERLAND: We need clarification, I guess, from the FDA as to how you want to address this. I think all of us would understand that for pre-publication, things that are in peer review there are concerns about, having public dissemination of them on a website. However, do

the FDA regulations regarding advisory committees allow this sort of split, the distinction that we are being asked here, or does it have to be both? Do you have the ability to both discuss it in a meeting and it has to be on the website, or can it be either/or? We need to get clarification as to what we can discuss.

DR. NELSON: I don't think the publication is the issue. I don't think, in most journals, that would jeopardize publication.

DR. SMALLWOOD: We have Dr. Bill Freas here, who is the director of the scientific advisors and consultants staff, and I would defer that response to him.

DR. DIMICHELE: Can also ask another question that I would like him to address? That is, if this information can't be put on the website but can be used in our discussion, in our free discussion which will become part of the public record one way or another.

DR. HOLLINGER: It may become moot if we are not going to discuss these issues which are being talked about in our deliberations. If we are only dealing with Hespan basically or hetastarch in saline, then we can just listen to these issues and

not discuss anything further, and then just get to the questions.

DR. WEINSTEIN: I want to reiterate that we will be discussing hetastarch in a broad sense, both Hespan and Hextend.

DR. HOLLINGER: That will be part of the question?

DR. WEINSTEIN: The question has to do with labeling of these products in general.

DR. HOLLINGER: So, there could be different answers for different products, depending on what information comes out, or they could be the same.

DR. WEINSTEIN: You can give us your advice on either.

DR. FALLAT: But if Hextend was approved on the basis of comparability, then it would seem to me that if we answer the question with regards to Hespan it should apply to Hextend as well.

DR. WEINSTEIN: Again, I think we can listen to the discussion about this. I don't want to categorically say that this will necessarily be the case. There apparently are perhaps distinctions between these products that will come out later on. There may be further trials that are

submitted to us and we will have to evaluate the evidence of those distinctions that are being perhaps claimed between the two products.

DR. FREAS: I will try to clarify it. FDA is under a law suit, and the law suit states that what is given to the advisory committee in open public session is required to be posted on our website. Now, FDA is doing its best to be in compliance with this law suit in order to keep the public informed. FDA is always caught between a rock and a hard place when we come to pre-publication issues. In that case, we are asking the sponsor, and we are putting responsibility on the people who submit the material to submit summaries of that material in advance of the meeting, and not stamp them confidential.

FDA cannot publish unpublished material. It can be discussed but, again, we need the permission of the source person who originated the material. If we don't have that permission, then it puts us in a very bad place because FDA's obligation is to make material discussed at open public meetings public.

DR. NELSON: Thank you. Dr. Lew?

DR. LEW: I just want to clarify what Bob had mentioned. A lot of times FDA will do comparability studies, particularly with antibiotics because that is what I am most familiar with, and compare one cephalosporin to another. But it is clear that some cephalosporins have more adverse effects and, as that occurs, you do change the package insert. So, I don't think they are obligated to put it in the package insert for both.

DR. BAKER: Dr. Mary Baker, Abbott Laboratories, pharmaceutical research and development. What we would like to remain confidential and not be posted on the FDA website is the resource by Dr. Anthony Roche. Anything else will be discussed by the researchers and has been published in abstract form.

DR. DIMICHELE: But then my question is that information cannot be used by us to help make this decision.

DR. BAKER: Dr. Roche has also published that information in abstract form. That is available for discussion, but we ask that his submitted publication not be posted on the website.

DR. DIMICHELE: But any of the details from those papers will not be brought up in any

discussion and cannot be used to help us make the decision.

DR. BAKER: I believe you have been furnished with the abstract as well.

DR. DIMICHELE: Right, but we can only use what is in the abstract, is that correct? I am asking the committee.

DR. NELSON: I think that is correct. Now we move to the open public hearing. If you can try to be concise as possible.

**Open Public Hearing**

MR. SPODEN: Thank you, Mr. Chairman. Good afternoon. My name is John Spoden. I am the associate director of regulatory affairs for B. Braun Medical. It is my privilege to speak before the committee on behalf of B. Braun today.

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I have prepared a brief presentation to address some of the important issues raised this morning relative to the use of hetastarch in cardiac surgery. Because I am not a clinician, B. Braun has arranged for Dr. William Shoemaker to attend this meeting to address any clinical questions the committee may have. Dr. Shoemaker is a professor of surgery, in the Division of Trauma

and Critical Care at the University of Souther California, and has studied these colloids and hemodynamics extensively. In the interest of full disclosure, B. Braun has paid for Dr. Shoemaker's transportation, lodging expenses and will reimburse him at his normal rate for his time.

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B. Braun is the holder of two new drug applications for Hespan, one in a glass container, the other in a flexible plastic container. The product in glass was originally approved by the FDA in 1972 for use as a plasma volume expander. The original NDA holder of this product was McGow Laboratories. Although ownership of Hespan has changed over the years and was, until recently, with Dupont, it has been manufactured by McGow since it was first approved. When B. Baun purchased McGow in 1998 and purchased Hespan from Dupont in 1999, Hespan in a way came home. I mention this bit of history because, as discussed this morning, there is a lot of confusion in the literature. Hespan is referred to as a product of American Critical Care, Dupont Critical Care and others, but Hespan has always been the same product, made by the sam manufacturer.

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Hespan is B. Braun's brand of six percent hetastarch in normal saline. It is one of several licensed hetastarches available in the U.S. for plasma volume expansion. As discussed earlier this morning, hetastarches are characterized by their molecular weight and their degree of hydroxyethyl substitution. The hetastarch used in Hespan has an average molecular weight of 6000 D. That is how it is listed in the current package insert. That differs from what has been presented earlier today due to improvements in the way we actually analyze the hetastarch in the laboratory. It has a hydroxyethyl substitution ratio of 0.75.

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Differences in molecular weight and degree of substitution have been shown to affect the influence of these starches on coagulation and bleeding. The association between alteration of coagulation in the use of hydroxyethyl starches is well documented, and has been studied for over three decades. The effects of Hespan on coagulation result from hemodilution and a direct effect on coagulation factors and platelets. These effects have been described extensively in the

medical literature.

Briefly, the hemodilution effect is largely determined by dose level, single or multiple infusions, and the frequency of infusion. Moderate doses may cause dilution of clotting proteins, but these proteins are usually still present in amounts adequate to ensure effective hemostasis. According to the literature, significant risk of bleeding is usually associated with greater than a 25 percent volume replacement. Above this dose platelets can appear abnormal and adhesion is decreased. Some clotting factors become abnormal. Fiber and clots are friable and lack their normal tensile strength. Factor VIII also appears to be decreased beyond levels attributable to hemodilution alone.

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Current Hespan labeling includes warning regarding these and other effects. If the existing warnings relative to bleeding beyond normal levels are heeded, it could be expected that the adverse events associated with excessive bleeding would be relatively low. Indeed, if we graph an annual number of adverse events related to excessive bleeding per 100,000 Hespan units, these types of

adverse events are relatively low. An absence of bleeding-related adverse events starting in 1998 may reflect the influence of several published studies that we have discussed this morning on the decision whether or not to use Hespan in some clinical situations.

[Slide]

Two studies already discussed this morning, specifically papers by Dr. Cope and others in 1997 and Knutson and others in 2000, raise questions regarding the use of hetastarch in cardiac surgery and its possible association with increased bleeding. Both studies were retrospective and both recommended that prospective studies be conducted in order to fully answer the questions raised.

It is the opinion of B. Braun that the retrospective nature and other shortcomings of these studies, as Dr. Landow summarized in his nine points, limit their scientific relevance and the claim of a causal relationship between the use of hetastarch and excessive bleeding in cardiac surgery. However, B. Braun is also of the opinion that the data presented does show some evidence of an association between bleeding beyond expected

levels and the use of hetastarch during certain periods of cardiac surgery.

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Therefore, in order to enhance patient safety and to provide clinicians with important information, B. Braun has submitted proposed changes to Hespan labeling to the FDA. These changes are under precautions, contra-indications, dosage administration and warning section of the package insert.

In the interest of time, I will only present some of the more significant changes that we have made. B. Braun has proposed that in the following statement to the warning section: Hespan is not recommended for use as a cardiac bypass pump prime or in the immediate period after the pump has been discontinued because of the risk of increased coagulation abnormalities and bleeding in patients whose coagulation status is already impaired.

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Addition to the dosage administration section has been provided as follows: Hespan is reported to be associated with increased bleeding when used immediately after cardiac bypass pump has been discontinued. However, this risk of bleeding

diminishes rapidly.

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This statement has been proposed for addition to the precautions section: Increased risk of coagulation abnormalities and bleeding is also associated with higher doses. Patients' vital signs and hemoglobin, hematocrit, platelet count, prothrombin time and partial thromboplastin time should be monitored closely.

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In conclusion, while the safety debate regarding an association between hetastarch and excessive bleeding during cardia surgery will continue, B. Braun has acted prudently in taking definitive steps to enhance Hespan labeling in a way that we feel will satisfy the needs of the patients and clinicians using our product. Because we are taking these steps, we feel that no further clinical trials are warranted.

I appreciate the opportunity to articulate B. Braun's vision this morning and thank you very much.

DR. NELSON: Thank you. Are there questions?

DR. ALLEN: Two questions. First, your

graph showing the Hespan bleeding adverse events, do you have an explanation for that drop off? Is it with change in usage?

MR. SPODEN: One thing I didn't include in there is the sales volume. We have seen a decrease in sales volume and, although we cannot pinpoint it, we are expecting that perhaps the results of these studies that were published may have influenced the use of hetastarch in certain situations.

DR. ALLEN: Thank you. The second question is what is the current status of action on your proposed labeling and when was that submitted?

MR. SPODEN: We have been talking with the reviewers at FDA since October. We formally submitted the proposal for the labeling changes in April of this year and they are still being reviewed by the agency.

DR. NELSON: Other questions?

DR. HOLLINGER: I think you are to be congratulated for a proactive stand in this.

DR. NELSON: The next speaker is Harold Waitz. No? Dr. Gan, please.

DR. GAN: Good afternoon, ladies and gentlemen. It gives me great pleasure to be here

today to share some of the information.

[Slide]

What I am going to present to you today is to answer the question, Hextend, is it different from Hespan? An alternative title would be are all starches created equal? I would like to present to you specifically on one aspect of the difference between Hextend and Hespan, and that is coagulation. Other speakers will present to you more important differences between Hextend and Hespan.

[Slide]

What I would like to do this afternoon is to present data on six specific randomized, controlled studies and it is important, in contrast to the unrandomized, retrospective study that you have heard this morning. The six studies I am going to present to you with regards to coagulation are the following: The first study is an in vitro study comparing Hextend versus Hespan and lactated Ringer's. In view of time, I would like to call them Hextend and Hespan as you know what I am talking about, Hespan being hetastarch in saline and Hextend being in a balanced electrolyte carrier.

The next study I am going to present to you is the Phase III study comparing Hextend and Hespan. That is followed by the next sty where a lactated Ringer's group was added to that study. The fourth study is again comparing Hextend and Hespan in a group of geriatric population undergoing general surgery. The next study is an important one, looking at four different fluids, Hextend, Hespan, albumin and lactated Ringer's in 200 patients undergoing cardiac surgery. Lastly, I am going to present to you a couple of studies that address comparison of Hextend and albumin, which is obviously one of the fluids of interest.

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I will not go into details of the composition of hetastarch because that has been addressed by previous speakers. But I think it is important to notice the difference between Hextend and Hespan, and that is in the electrolyte carrier. As you can see, hetastarch in saline is formulated in normal saline. However, Hextend is formulated, in addition to sodium and chloride notably in smaller concentration, 124 versus 154 in Hespan. In addition to that, it also contains a number of important electrolytes, notably calcium, potassium

and magnesium.

[Slide]

Many of the results I am going to present involve thromboelastograms. I know that there are a number or experts in the audience of thromboelastography but for those who may not be familiar, I am just going to take a couple of seconds to explain what a thromboelastogram is.

Thromboelastogram was widely used back in the 1970s because it was popular, especially in liver transplantation, to monitor coagulation. It is a dynamic coagulation monitor and you can get a result fairly quickly, much quicker than if you send it to the lab.

This is a new version of a thromboelastogram where you introduce a sample of blood into the cup, here, and there is a pin that is then lowered, and the pin is under constant rotation under the influence of the magnet, here. So, if there is no clot being formed, there is no resistance between the pin and the site of the cup. As a clot begins to form there is increasing resistance, and this increasing resistance and increase in torque between the pin and the cup is then translated into a pattern, which is on the

next slide.

[Slide]

This is a pattern of a thromboelastogram. It looks a little bit like the end of a party where you go and smash glasses, sort of an inverted champaign glass pattern. There are several important features that are important here. The first is called R time, which is the reaction time. Reaction time is the time taken from when you introduce the blood sample into the cup to when there is the first hint of clot formation. So, this is where you introduce the blood into the cup and as soon as there is a hint of clot formation this pattern opens up, like this.

K time is a little bit further on. It is defined as when there is a significant amount of clot formation. So, this is R time and this is K time, 20 mm apart. As it opens up, this coagulation monitor also tells you the speed of clot formation, how quickly the clot is being formed. This is measured by an angle called alpha angle. Once a clot is formed, it also measures the strength of the clot formation, which is donated by maximum amplitude. So, this is a dynamic coagulation monitor which tells us what is

happening to the patient's coagulation at that point in time.

[Slide]

First of all, I would like to present to you the results of a hemodilution study, an in vitro study that looked at what happens if you take a sample of blood and hemodilute it all the way up to 75 percent.

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If you hemodilute a sample of blood with lactated Ringer's which is a common crystalloid we all use, as you can see, as you hemodilute further you are going to get hypocoagulation because of hemodilution.

[Slide]

What happens if you hemodilute the same sample of blood with Hextend? Again, you can see it is very similar to what you would see with lactated Ringer's, slightly increased with further hemodilution.

The next one is what happens when you hemodilute with Hespan. Clearly, you can see if you hemodilute this blood sample with Hespan beyond about 30, 40 percent, which is very close to about 20 cc/kg, it is increased in our time, which is

measured on the Y axis here, beyond 40, 50 percent hemodilution with Hespan.

[Slide]

The next data I want to show you is from a Phase III study. A Phase III study was actually conducted to compare the efficacy between Hextend and Hespan. We obviously looked at all the other aspects of fluid management, coagulation being one of them.

[Slide]

Just to give you a summary of the study, there were 120 patients, a two-center study, non-cardiac surgery with an anticipated blood loss of more than 500 cc. They were randomized into either Hextend or Hespan. The perioperative fluid management is fairly standard, what we normally do when we give a patient a bolus of lactated Ringer's 7 cc/kg, followed by a crystalloid infusion. Based on the fluid algorithm, based on blood pressure, heart rate and urine output we administer either Hextend or Hespan. The anaesthetic is a balanced technique to incorporate isolfurane and fentanyl.

[Slide]

This is of particular interest in terms of coagulation between the two solutions. Because we

are concerned about the Hespan causing coagulation in the higher volume uses, therefore, we divided our patients into those who received less than 20 cc/kg or those who received more than 22 cc/kg. When we looked at the R time, which is the length of time taken fort he clot to form, on the Y axis the square represents those who received six percent hetastarch in saline, or Hespan. The circle represents those who received Hextend. The solid line represents those who received more than 20 cc/kg, and the dotted line represents those who received less than 20 cc/kg.

Let us look at the result at baseline and end of surgery. At baseline there is roughly similar R time. For Hextend and Hespan, for those who were given less than 20 cc/kg, as noted by the dotted lines here, as you can clearly see, there is really no significant change at the end of surgery compared to baseline. But if you look at the fluid given at more than 20 cc/kg or a larger volume used, you can clearly see a difference in that the Hespan patient had a significant increase in R time, the time taken for the clot to form, compared to the Hextend patient who maintained his R time at the end of surgery compared to baseline.

[Slide]

This is K time. As you remember, it is the time taken for a significant amount of clot being formed. Again, you see a very, very similar picture. Over 20 cc/kg of Hespan, the K time is significantly longer compared to an equivalent volume of Hextend.

[Slide]

Does that translate into a difference in blood loss? Well, if we look at the overall blood loss there is no statistically significant difference between the Hespan and the Hextend group. The Hespan group is in yellow and the Hextend group is in red. There may be a slight trend but there is no significant difference.

But if you look at the subpopulation who received red blood cells, indicating that these patients lost more blood and therefore required transfusion of red blood cells, there was a significant difference in terms of the red blood cell transfusion. That is, blood loss in the subset or red cell transfused patients, on average the Hextend patients needed about 1500 cc compared to the Hespan patients who lost about a liter more of blood compared to the Hextend patients.

[Slide]

This is a table that shows you that in the transfused subset of patients, those patients who lost more blood, they lost more blood in the Hespan group. They also needed on average 500 cc more red blood cells when they received Hespan compared to Hextend. Likewise, the blood product utilization appeared to be less with Hextend compared to Hespan.

[Slide]

This study looked at when we added a third group of patients who received lactated Ringer's, a commonly used crystalloid in non-cardiac surgery. So, this is Hextend and Hespan, and this is the lactated Ringer's group which predominantly had LR administered during surgery.

[Slide]

Looking again at the thromboelastogram comparing the three groups, Hespan, Hextend and Lactated Ringer's, this is the percent change of R time from baseline and end of surgery. In this study we also looked at 24 hours after surgery.

If you look at the Hextend group, which is a square in yellow, and the lactated Ringer's group, in the triangle here, you can see very, very

similar coagulation profiles between Hextend and lactated Ringer's. However, if you look at the patient who received Hespan, there is a significant increase, about 40 percent increase in R time and this persisted beyond 24 hours. So, clearly, there are differences between Hespan and Hextend in terms of coagulation.

[Slide]

Next I want to move to the geriatric study. This was conducted in the United Kingdom. It was non-cardiac surgery with an anticipated blood loss of more than 500 cc. In this study the comparison was Hextend and lactated Ringer's being the colloid and crystalloid groups, compared with Hespan and normal saline, again colloid and crystalloid. The fluid algorithm again is very similar, with some bolus of fluid up front and then carried on with crystalloid infusion intraoperatively. The fluid administration is very similar to the previous study where it was based on an algorithm.

The primary hypothesis of that study was looking at acid-base changes. I am not going to present that aspect of the study; another speaker will present that. I am going to concentrate just

on the coagulation aspect.

[Slide]

In that study they planned to study 60 patients. However, the study was stopped when 47 patients were enrolled because they were concerned about severe acidosis in some of the patients in the study. When they did the 47th patient, the patient didn't do very well, developed severe acidosis. There was concern among surgeons and anesthesiologists and, therefore, the study was stopped. The blind was broken to say whether they had reached the primary hypothesis which, indeed, it had. There was a difference in acid-base balance between the two study groups and, therefore, the study was stopped. The mean age was over 70. The mean volume of study fluid given was over 4 L.

[Slide]

This is the TEG R-time result I showed you earlier. You can see that there was a statistical difference between the Phase III study. In the geriatric study they also did TEG comparing the Hextend and the Hespan group.

[Slide]

You can see that there was statistical

significance in the Phase III study. However, you also see a trend in the geriatric study but because the number in the study was smaller, 34 patients, therefore, that did not achieve statistical significance. But clearly you can see similar trends between the two studies.

[Slide]

This next study was done in cardiac patients. It was done in Columbia. There were 200 patients. They were randomized into four different groups, receiving lactated Ringer's, Hextend, Hespan or albumin. These were cases of coronary-artery bypass or valve. Most of the patients had been on cardiopulmonary bypass and there were some off-pump.

[Slide]

Just to give you some detail about the study. It is an intraoperative study. The study fluid for treatment of hypovolemia. A liter of the study fluid was added to the pump prime. There were no volume limitations in that study. They looked at several outcomes, renal function, bleeding, coagulation. Again, I just want to emphasize or just want to concentrate on the coagulation aspect of this study.

[Slide]

The median volume of the study fluid was about 3.4 L, except LR, obviously being crystalloid, so a larger volume was given. The total volume of fluid is about 5 L. There was essentially no difference in hemodynamics, cardiac output, blood pressure and urine output.

[Slide]

This slide shows you the bleeding outcome among those four groups. To recap, hetastarch and saline or Hespan, Hextend, albumin and lactated Ringer's. The first row is the amount of red blood cells transfused. In the Hespan group, on average it was about four units, whereas in the Hextend, albumin and lactated Ringer's groups it was about 2.0 to 2.5 units. This was a statistically significant difference. The FFP again was different, 3.8 units in the Hespan group; 2.5 in the Hextend group; albumin 1.8; lactated Ringer's 0.5 Platelet transfusion, 6.3 in the Hespan group; 4 units, Hextend; 3.7, albumin; and 2.2, lactated Ringer's.

What is more interesting is if you look at the percent of patients receiving either coagulation factors, FFP or platelets, about 70

percent of the patients who received Hespan had to have some coagulation product. However, 47 percent in Hextend and about 42 in albumin. If you look at the number of patients who returned to the operating room, about 10 percent in the Hespan group; 2 percent each in the Hextend and albumin group; and none in the lactated Ringer's group.

[Slide]

The next two studies that I would like to present to you are comparing Hextend and albumin. This first study comparing the two procedures is in radical retropubic prostatectomy and radical nephrectomy. These are, again, general urological procedures. They were either randomized to Hextend or albumin according to a fluid algorithm.

Baseline blood samples were collected at the beginning of surgery, end of surgery and 24 hours following surgery. Because we are concerned about platelets and some of the Factor VIII issues, we measured platelets. We did PT, PTT as well as looking at Factor VIII and von Willebrand's factors.

[Slide]

The following few slides are the results from this study. This is comparing Hextend and

albumin platelets at baseline, in yellow; end of surgery, in red; and 24 hours following procedures in the Hextend group and the albumin group. Again, there was no statistical significance between platelet counts between these two groups.

[Slide]

This slide shows the PT and PTT time between the two groups, PT in the Hextend group, APTT in the Hextend and PT and PTT in the albumin group, again, baseline, end of surgery and 24 hours and again you see no difference between albumin and Hextend in terms of PT and PTT.

[Slide]

This slide shows you some of the coagulation factors, for example Factor VIII and von Willebrand factors antigen, as well as the collagen ADP, a much more subtle measurement of what happened to those Factor VIIIs as well as von Willebrand's Factor. Again, comparing Hextend and albumin, this is baseline, end of surgery and 24 hours and you can see, again, there is really no significant difference between those who were given Hextend or albumin. The average volume that was used in this study is between 2.5-3 L of either Hextend or albumin.

[Slide]

A recent study again looking at Hextend versus albumin in cardiac patients found no difference in chest tube output, post and preoperative hematocrits, as well as TEG differences and blood product usage.

[Slide]

In summary, comparing Hextend and Hespan, Hextend-treated patients seem to lose less blood. It seems to have a lower requirement for blood and blood products; better coagulating factors, as evidenced by thromboelastogram; better preserved renal function; less acidosis, which the next speaker will talk about in greater detail.

[Slide]

When compared to albumin, there appeared to be a very similar amount of blood loss between Hextend and albumin; required similar blood and blood products and an equivalent effect on blood coagulation, as noted by PT, PTT, von Willebrand's factor as well as TEG.

[Slide]

In conclusion, I believe that Hextend is different from Hespan, and I believe that as far as coagulation it is superior to Hespan bleeding and

patient outcome. I also believe that, based on the data that I presented, that Hextend is very similar to albumin in terms of coagulation.

The important question is when you look at data and ask yourself how does it change our clinical practice, at Duke, about a year and a half, two years ago, we changed all our Hespan to Hextend. I believe that at Mayo Clinic, that Dr. Haynes talked about, they also stopped using Hespan and are now using Hextend for their patients. Thank you very much for your attention.

DR. NELSON: Thank you, Dr. Gan. Questions? Don't go away.

DR. GAN: We will be happy to answer any questions.

DR. HOLLINGER: Just out of interest, if you look at your cardiac surgery patients, it would look like Ringer's lactate, which is even cheaper than anything else, is actually pretty darned good. I would then say that for this study one should probably go and use Ringer's lactate instead of either one of the hetastarches. That is what that data shows on that blinded, randomized clinical trial of 200 patients.

DR. GAN: I think you are right. That is

why we are still using Ringer's lactate. I think it is important to notice that that is part of the coagulation picture. We know that Ringer's lactate tends to cause hypercoagulation postoperatively, and that has been shown for many years.

One aspect which I think was pointed out earlier is that in that study they also looked at postoperative outcome in terms of incidence of edema and how long they stayed in the hospital. What they found is that patients who received lactated Ringer's had a significantly high incidence of edema, nausea and vomiting, probably because of gut edema. So, you know, you always have to trade the pluses and minuses.

DR. DIMICHELE: Actually, Dr. Hollinger asked my main question, but in looking at the data--you went through it very quickly and I was trying to kind of keep up with you, but what was very interesting in your Hextend-albumin comparison studies is that, certainly, there was a trend toward there being lower values in everything that you measured in Hextend compared to albumin, and you said it wasn't statistically significant, but if you look at, for instance, platelet counts--again, I don't know exactly what is not

statistically significant, the level or the decrease; I am not exactly sure what you were referring to, but if you actually look at the level of platelet count at the end of surgery with your Hextend, it is about 100,000 which is getting very close to the level for platelet transfusion, whereas it wasn't for albumin. Certainly, the trends are there.

DR. GAN: I certainly would be happy to comment on that. You will also see that the Hextend patients actually started off with their platelets lower as well.

DR. DIMICHELE: Yes, I know. But you are saying there are no differences. That is why I am saying I don't know what is not statistically different in terms of the level. The other thing about coagulation is that there are no absolutes here. It depends on what the level you end up at is. In other words, if you start out with a slightly lower platelet count the question is would you use Hextend. That is my question to you. I mean, given the drop in platelet count, if a patient goes into surgery with a slightly lower platelet count, given that the platelet counts that we ended up with were lower, would you do that?

DR. GAN: Let me give you my perspective. Just to answer the previous question, the important point to note also is that the Hextend patients on average received about 500 cc, 600 cc more Hextend compared to albumin patients.

DR. DIMICHELE: Yes, I saw that.

DR. GAN: So, I think that may also be an effect, which I think is an important consideration.

DR. DIMICHELE: Well, that was one of my questions as well because if the colloid advantage is the same for both, why did they?

DR. GAN: I think because Hextend, we know, is a larger molecule and I think it stays within the intravascular space for a longer period of time compared to albumin. The average molecular weight of Hextend is about 450, as we know, whereas the albumin is only 50,000. So, I think for those long procedures that may be the reason why one received more than the other.

To answer your second question about whether I would use Hextend in a patient with low platelets to start off with, I do a lot of liver transplant and now I use exclusively Hextend for my liver transplant. Yes, I do use Hextend and I use

Hextend exclusively. I used to use albumin for liver transplant.

DR. DIMICHELE: May I ask one more question? In the comparison study between Hextend and the other product, you said that basically the differences you found in the two products were mainly in the red blood cell transfusion group. Is that correct in terms of bleeding, etc? Not bleeding, but the differences that you did mention were in the packed red cell transfusion group. The question is that whole study had 120 patients, how many of those patients were in the subgroup that you went on to analyze in which you found the greatest differences?

DR. GAN: Yes, there were trend differences if you look at the overall comparison. I mentioned that the red cell transfused group, which formed about 35, 36 percent of the overall population, did show statistical significance not only in blood loss but also in the red blood cells transfused.

DR. DIMICHELE: Right, that is what I was trying to get at. They represented 36 percent of the total group.

DR. GAN: Right.

DR. SCHMIDT: There was a point that wasn't answered before Dr. Gan made his thorough presentation. That is, if the manufacturer of one product voluntarily wants to put a warning label on his product, it seems to me it is sort of an administrative decision on the part of the FDA as to whether this other product has to have it also. They are the people who decided that they both have to have the same package information. If that is the case, it probably doesn't relate to this committee. You didn't ask us that question. But if one wants to do it voluntarily and the other one doesn't, why can't they have two separate package inserts? I don't know that this committee is the place to answer that question. So, does the FDA have an answer for that?

DR. WEINSTEIN: I think that depends on the information that is received by the FDA as to how we would label the product. Perhaps the industry would like to comment on where this information is with regard to the FDA, the information that you have presented to us.

DR. GAN: With regards to--I am sorry, is that a question directed to me?

DR. WEINSTEIN: Yes.

DR. GAN: Maybe the industry people can better answer that question. I am here to present to you the data that I have.

DR. WEINSTEIN: Well, we have to evaluate the information that is presented to the FDA.

DR. GAN: You mean in terms of the availability of that information?

DR. WEINSTEIN: No.

DR. NELSON: I think that the FDA might still be involved in that because although the industry would say that they voluntarily put this or that label on it, I think the FDA would have to approve--

DR. WEINSTEIN: Yes, we have to review data and approve--

DR. NELSON: --review whatever labeling was done. So, you know, we don't take the FDA out of the loop by voluntary labeling by industry. Isn't that right?

DR. WEINSTEIN: Right. But it is dependent on data that we receive--

DR. NELSON: Yes, exactly. You have to evaluate the basis for a label or a non-label. That is why we are here.

DR. WEINSTEIN: That is right.

DR. FALLAT: I take it the FDA has not received this data formally yet. Is that right? Is that what you are saying?

DR. WEINSTEIN: It is appropriate for the company to comment on that.

DR. BERMAN: Keith Berman, Health Research Associates. My specialty area is blood products and biotherapeutics market research and clinical development. I have a few points.

DR. NELSON: You are with Biotime?

DR. BERMAN: I am here, retained by a major distributor of plasma products.

DR. NELSON: We wanted somebody from Biotime to speak. They don't have to.

DR. CHAMBERLAND: While the sponsor is coming to the mike, I need a point of clarification. What is the relationship between Biotime and Abbott? We got similar but different packets of data from Abbott and Biotime and I am unclear about how the two are related.

DR. WAITZ: Biotime is the holder of the NDA and Abbott Laboratories is our manufacturer and distributer. So, we work together. We license Hextend to Abbott.

DR. CHAMBERLAND: So, who is the sponsor?

DR. WAITZ: Biotime. Biotime is the NDA holder.

MR. WANGELIN: I just wanted to make one point of clarification for the record. Abbott is not at this point seeking any package insert label revisions for the Hextend product.

DR. WAITZ: As the NDA holder, Biotime is not asking for any label change.

DR. NELSON: I know you are not.

[Laughter]

DR. WAITZ: I just wanted to make that clear.

DR. LEW: I just wanted to get back to the study. I didn't get the number of patients that were enrolled in your prostate/kidney study that did show kind of a trend with Hextend having more increased PTT and lower von Willebrand Factor.

DR. GAN: It was a 30-patient study. So, it was a relatively small study.

DR. LEW: that may be why you don't have the N.

DR. GAN: Right, correct.

DR. LEW: With a small study like that, the trend looks kind of interesting--

DR. NELSON: Even in the larger one where

there were 120, that would be 30 in each arm. Right?

DR. GAN: No, 60 in each arm.

DR. HOLLINGER: I think, Ken, all this is important information because it gives us a broader view of the two, but I think the committee has been asked a very focused question with regard to cardiac bypass surgery with these two agents and the information does give us a global view of the things.

DR. CHAMBERLAND: That is a nice segue. I was actually focusing on your two cardiac surgery studies that you presented, and I had a couple of questions. The first cardiac surgery patient study with 200, and a lot of this went by very quickly so I am trying to catch up here, there were four arms. How many patients were in each arm?

DR. GAN: Sixty patients in each arm.

DR. CHAMBERLAND: Did you assess comparability in each of the arms in terms of preop. characteristics and what differences were found, and also intraoperative characteristics like cross-clamp, time on pump, etc.? I am assuming that is going to be very difficult in the kind of format that we have, but these are the kinds of

details that I think need to be made available to make a truly informed decision.

DR. GAN: Absolutely. I think that is a very important question. But in view of the time, I wasn't able to present all the data. Suffice it to say that there was no difference in the intraoperative as well as preoperative on hemodynamics. There was no difference in renal function. There was no difference in coagulation, to start off with.

DR. NELSON: To follow-up on that, I think the question I think Mary asked, which was a good one, is the pump time and the cross-clamp time. Those are two questions that I think you didn't answer.

DR. GAN: Again, I believe they were similar. There was no difference.

DR. CHAMBERLAND: So, we have to be provided data in detail for each factor or characteristic that was examined.

DR. NELSON: Yes, because I think even in the earlier published study, even though the conclusion was that they were the same, they weren't the same.

DR. STUVER: Can I follow-up on that? I

think we do need to look at the data because if you only have 50 in each group, even if they are different they are probably not going to be statistically significant because the sample size is so small. So, it is nice to see the data so you can get a feel for it. I mean, you can't just say they are not different because they are statistically significantly not different; you need to look at the data.

DR. GAN: I would agree wholeheartedly. I believe the information is available. I believe this article has been accepting; I think it is pending publication. So, this information should be available.

DR. NELSON: Also some details about the randomization are important.

DR. CHAMBERLAND: It would be helpful.

DR. GAN: I think you bring up a very good question. I think this study, which I consider is truly randomized because to each of the fluids a dye was added, which makes it look tinged yellow, very similar to albumin. So, from the point of view of looking at color, obviously, the differences in viscosity as well as the color, it was as truly randomized as it could possibly be.

DR. CHAMBERLAND: One other question, the outcome measurements that you provided for this randomized, four-arm trial of 200 did not include postoperative blood loss in terms of rate, cc per hour or volume measured in chest tubes at certain intervals, and in the literature that was discussed in great detail by the FDA that was an important factor that emerged in some of these retrospective case-control studies. Can you tell us any information about not estimated blood loss but actual measured postoperative loss in each of the arms?

DR. GAN: I haven't looked at this study for a little while. I know there was information on chest tube drainage postoperatively. I just cannot quote you the number, but I believe that it was measured. But I think I did present to you the intraoperative blood loss.

DR. CHAMBERLAND: It was mentioned descriptively in the second study as no difference in chest tube output, but obviously the big issue with that second study is that it is 28 patients. So, it is clear that we need more detailed information. Certainly, FDA will need that as well.

DR. GAM: Sure.

DR. NELSON: Question?

DR. PIERCE: Yes, Ross Pierce, FDA. I am a little bit confused because we have been talking about details of these studies and I thought the question asked earlier was if the details of these studies had been submitted to FDA; essentially, has a final study report for any of these studies been submitted to FDA, and I heard Dr. Weinstein say that it would be appropriate for the sponsor to comment on that, and there was some confusion among the committee members as to who the sponsor was. It was clarified that that was Biotime. We heard Biotime speak but I just want to make sure I didn't have an absence moment because I didn't hear the question answered that the committee seemed to be interested in as to whether the details of these studies, including the raw data, in a final study report had been submitted to FDA. So, I just wanted that clarified for the record.

DR. BAKER: May Baker, Abbott Laboratories. The study by Dr. Bennett-Guerrero was an investigator-initiated study. We do not have the raw data. That paper has been submitted for publication. We don't have the manuscript and

the committee does not have the manuscript either, but that is an investigator-initiated study. The abstract of that study is available on the ASA website.

DR. SIMON: So, the answer is no. Is that right?

DR. HARVATH: The data has not been submitted to FDA? Is that your answer?

DR. BAKER: The data has not been submitted to FDA. Dr. Bennett-Guerrero is in possession of the data.

DR. HARVATH: Thank you.

DR. NELSON: If there is nothing else pressing, I would like to move on. Dr. Shaugnessy?

DR. SHAUGNESSY: For what it is worth, I may be going into a lot of the questions that you just asked concerning that second study.

Good afternoon. My name is Dr. Thomas Shaugnessy, and I am an associate clinical professor of anesthesia and perioperative care at UCSF Medical Center in San Francisco.

[Slide]

I would like to discuss two topics with you today that I feel would be of interest, definitely of interest to the committee. The first

that I would like to discuss deals with a recently published clinical study that deals with the exact issues that you are having in question today. Second, I am going to review some of our clinical experience at UCSF in reference to the use of Hextend as a substitute for albumin.

[Slide.]

The first study that I would like to present, that I would like to refer to was recently published in Anesthesiology in 2001. It is an unsponsored, randomized, prospective clinical trial that addresses the use of albumin compared with the use of Hextend as a plasma-volume expander in the perioperative period after cardiac surgery.

In an effort to limit the potential bias that can be introduced by the patient population, it was decided to eliminate from study those patients who had re-do procedures, those patients who were on anticoagulant therapy at the time as well as those patients who had any renal or hepatic dysfunction. I think we have gone through exactly why some of those issues, in terms of patient population characteristics, can impact on retrospective studies.

In any case, the major outcome

measurements for this study were thromboelastogram data which has been considered an excellent in vivo method of monitoring the coagulation cascade and the integrity of that cascade as well as monitoring more clinical parameters such as perioperative hemorrhage as monitored by chest-tube output for this specific patient population. In addition, blood-product utilization was also monitored.

[Slide.]

Twenty-eight patients were taken into consideration for this study. They were randomized into groups of fourteen. One group received exclusively 5 percent albumin as the sole colloid plasma-volume expander in the perioperative period. The other group received Hextend for the same purposes and it was done according to a certain protocol with parameters for central-venous pressure and blood pressure.

[Slide.]

These patients, as you can see in some of these results, are relatively well-matched in terms of age, sex, the amount of time spent on cross-clamp as well as cardiac-bypass time and the amount of colloids given, colloids transfused.

It should also be mentioned that they were

also the same in terms of preoperative hematocrit as well as thromboelastogram characteristics.

[Slide.]

To make a long story short, essentially this study showed no significant differences in terms of intraoperatively or on postoperative Day 1 in terms of the pre- and postoperative hematocrits, the thromboelastogram data, or the blood-product utilization.

[Slide.]

I am going to go into a little bit of detail in terms of what some of these graphics look like for these various, albeit negative, studies. As you can see, the preoperative hematocrits were about the same in both study groups. The preoperative hematocrit was about the same in both study groups and the postoperative hematocrits were slightly lower but comparable in both study arms.

[Slide.]

I think probably one of the most compelling aspects of this negative study is in the thromboelastogram data because the study was sufficiently powered to detect relatively small differences in thromboelastogram resolution. In this particular example, the R times, which

represent the initial clot formation show that, from the pre-bypass period to the post-bypass period and all the way into the first postoperative day, there is no real difference between the 5 percent albumin-treated and the Hextend-treated patients in both study arms. Once again, there are no significant differences.

Also, in terms of the K time which is the monitor of the rate of clot formation; once again, no significant differences in the post-bypass period or the first postoperative day. However, you can see a particular trend, in terms of an upward trend, at the post-bypass period but it tends to be the same in both the albumin group as well as in the Hextend-treated patients.

This was felt to be partially due to the fact of hemodilution which is probably an under-accounted-for aspect in terms of perioperative hemorrhage in a lot of patients but hemodilution may account for the fact that the K times have increased here. But they certainly do return to normal by the first postoperative day.

Finally, the maximum amplitude, on the next slide, which is a marker of the overall clot strength as well as platelet function, that tends

to show that, once again, there are no significant differences in the post-bypass period or the first postoperative day for either study arm.

[Slide.]

In terms of a little more clinical marker such as perioperative hemorrhage, that is monitored by the chest-tube output for this particular patient population. We are actually able to get quantitative numbers in this particular patient population about their perioperative hemorrhage.

For this group, what you can see is that, for every stage of their recovery period, there are no real differences in perioperative hemorrhage between the 5 percent albumin patients as well as the Hextend-treated patients.

[Slide.]

In terms of blood-product utilization, this study was slightly underpowered to detect any meaningful differences in blood-product utilization. However, it should be noted that, while 20 patients in the albumin-treated group required red-cell transfusions, only eight units were required in the Hextend-treated patients.

Also, it should be noted that, in this study, there was no significant morbidity or

mortality associated with the use of either of these agents in either study arm.

[Slide.]

In my role, and this is more an anecdotal topic, this is the second point I would like to make--in my roll as the Vice-Chairman of our Pharmacy and Therapeutics Committee at UC, we undertook the approval of Hextend in our formulary for the use of supplementing our use of albumin which, back in 1999, had reached the level of about 9,000 units a year.

We are an academic tertiary-care center so we do a heck of a lot of liver work as well as transplants. As you can see from the demographics that we have, we spent most of our albumin on the transplant population but we also have a relatively significant portion being used in our cardiac population as well as in our major spine surgery, in our Orthopedics Department.

[Slide.]

We actually undertook a major initiative. What we did is we place Hextend in our operating room right next to the albumin and actually promoted its use, through an educational effort, basically bringing clinicians' awareness of the UHC

guidelines, University Hospital Consortium guidelines, which state that hetastarch should be a preferred plasma-volume expander in the perioperative period--in most cases, that is a first-line or second-line agent--as opposed to albumin which tends to be reserved as a second-line or third-line agent.

So, with that educational effort underway, the Hextend being placed in the hospital formulary and in the operating rooms, we actually then ubiquitously placed a requisition form throughout the operating rooms to just track our albumin use over time.

What we found, at the end of a year of doing this, is that, before our intervention, where we were using 9,000 units a year, we actually decreased our albumin use to the point of about 2,600 units of albumin a year. The difference between those two, in terms of plasma-volume-expander usage, was made up, for the most part, with Hextend.

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This was a global, institutional change for us. So it affected many different clinical service lines all at the same time. When we looked

back at things, we looked at global clinical markers to assess the impact of this change on our clinical practice.

One example of this is the use of our blood-product transfusions during those two years. As you can see, in our operating rooms, we actually noticed an increase in our case volume from 1999 to 2000, just a modest increase. But, actually, what we found out was--when we looked at the amount of the total blood products used in our OR, we actually saw a slight decrease in the total amount of blood products used.

Actually, when we teased out the amount of packed red blood cells that were being used, we found also a slight decrease in their red-cell transfusions. Now, I am not going to hold this up to scientific rigors or anything, but our impression of it was that there was no real change in our transfusion requirements because of this change we made in terms of our colloid practices.

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In addition, when we looked at perioperative morbidity and mortality types of issues, we also found some surprising findings from one year pre-intervention to post-intervention. In