COMMENTARY

7 Cardiology Trials to Look for in 2018

Robert A. Harrington, MD; C. Michael Gibson, MD

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Robert A. Harrington, MD: Hi. This is Bob Harrington on theheart.org | Medscape Cardiology.

Over the past couple of months, Mike Gibson and I have done a series of podcasts. We discussed the best trials of 2017 and commented on other issues in cardiovascular (CV) medicine outside of the trial world that our community is talking about. For this one, we thought we would look ahead and think about the data to come.

With that as background, let me introduce Mike Gibson, my friend and guest today. Mike is in interventional cardiology at Beth Israel Deaconess and a professor of medicine at Harvard Medical School. He is the CEO of the Baim Institute for Clinical Research and the founding director of PERFUSE. Mike, thanks for joining us here today on Medscape Cardiology.

C. Michael Gibson, MD: Good to be back with you, Bob.

Dr Harrington: We covered the landscape of 2017 and a number of colleagues asked, "What is going to happen next?". This is a great opportunity for us to reflect upon important trials in cardiology being done that will have results in 2018, or 2019 at the latest.

1. ODYSSEY (PCSK9 inhibitors)

Dr Harrington: Let's start with the important topic of lipids. In light of the FOURIER[1] results, one of our key trials from 2017, the ODYSSEY trial in acute coronary syndrome (ACS) is a big piece of news in 2018. I will preface your comments by telling our audience that I am a member of the executive committee for ODYSSEY. As we do this recording, I have not seen any data yet. Why don't you tell people what ODYSSEY is and what you are thinking about?

Dr Gibson: Thanks, Bob. This follows on the news we had about FOURIER last year. FOURIER was a slightly bigger study and had stable patients with, in many cases, multivascular disease. They had some peripheral artery disease (PAD) or stroke, and a prior myocardial infarction (MI). ODYSSEY differs from this in that patients have had a prior ACS event 1 month to 1 year before [enrollment in the study]. In contrast to FOURIER, where people got a fixed dose of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, there is uptitration of the dose in ODYSSEY. If you do not achieve an LDL-C of < 50 mg/dL, the dose is doubled and upwardly titrated.

Intellectually, that is important because many epidemiologists pushed back on the lipid field saying that no trial had been done that really targeted an LDL-C. This is clearly a trial targeting an LDL-C level of around 50 mg/dL; if it is positive, it will be very important when it comes to looking at the guidelines.

Another differentiating feature is the duration. While FOURIER was about 2.2 years, this is going to be 3 years. Of course, FOURIER was criticized for going too short [of time] to see a benefit, so ODYSSEY will give us a little more time to see a benefit. On the other hand, LDL-C is anticipated to be lowered at about 50% to 55% versus FOURIER, which was higher, at about 60%.

There is a slightly higher high-dose statin dosing in ODYSSEY, and that may erode the benefit; we will see. This is going to be a hot trial. It will be presented early on at American College of Cardiology (ACC) 2018. If it is positive, it will be the second big outcomes study [for PCSK9 inhibitors]. Hopefully, it will encourage insurers to be somewhat more liberal in allowing physicians to use this class of drugs that improves outcomes.

If [ODYSSEY] becomes the second of the big PCSK9 inhibitor outcomes trials, we will pretty firmly have three drug therapies that lower LDL.

Dr Harrington: I am totally with you, Mike. If this becomes the second of the big PCSK9 inhibitor outcomes trials, we will pretty firmly have three drug therapies that lower LDL: statins, ezetimibe, and PCSK9 inhibitors.

A lot of us are looking to see CV mortality outcomes. Were the ODYSSEY patients followed long enough to observe an effect on mortality that was not seen in FOURIER? We are looking forward to ACC and seeing these data roll out.

Dr Gibson: The good news is that these are higher-risk patients. The bad news is that there may be more thrombotic events early on after enrollment, where you may not see a benefit of the PCSK9 inhibitor. It's going to be interesting to see what the study shows.

Dr Harrington: In IMPROVE-IT,[2] that was part of the key issue with ezetimibe. In the early period of risk, we wanted to make sure that that was not necessarily ascribed to the randomized treatment. In fact, there was a longer period of follow-up after 1 month of therapy, whereby you could see more of what might be considered the LDL-C-lowering effect as opposed to some contamination by the thrombotic risk effect early on.

2. REDUCE-IT (Omega-3)

Dr Harrington: Let's stay in the lipid field but move from LDL-C to triglycerides with REDUCE-IT The notion of this trial is to determine whether reducing triglycerides with omega-3 fatty acids can improve clinical outcomes. This is an area where there is a lot of anecdote—small and observational reports—and no clear consensus as to whether lowering triglycerides actually improves CV outcomes. Do you want to comment on this one?

Dr Gibson: There are fascinating data from the GISSI group[3] showing some benefits in heart failure (HF). There are some animal data showing not just lipid changes, but stabilization of membranes and reduced arrhythmias. Of course, we know that the Japanese population and people in the Pacific Rim have higher fish consumption, and there may be some health benefits there. This trial is looking at EPA, or eicosapentaenoic acid (omega-3), at a pretty high dose of 4 g/day on top of a statin. The idea is to determine whether reducing triglycerides, which some people think are an independent risk factor, can improve outcomes.

This is a randomized, double-blind, placebo-controlled trial. You had to have an elevated triglyceride level of about ≥ 150 mg/dL and < 500 mg/dL to get in. You had to be on a stable statin dose with an LDL-C of 40 mg/dL to < 100 mg/dL and have some CV risk factors. Then, you are randomized to staying on the stable statin or getting Vascepa® (icosapent ethyl) on top of it.

The study started in 2011. There are 400 sites in 11 countries and it's event driven. A total of 1612 adjudicated events will be analyzed over 4-6 years. The events are CV death, MI, stroke, revascularization, or unstable angina. The endpoints of revascularization and unstable angina are a bit soft, but death, MI, and stroke are hard endpoints. The trial has completed enrollment and should hit the number of target events pretty soon.

Dr Harrington: A lot of us are awaiting this one. We all see coronary disease patients who have elevated triglycerides. The data have never been clear enough to mandate or to result in a high level on guideline recommendations to use triglyceride-lowering therapy in this range that you are talking about, which is not the excessively high, but it is certainly above the upper limit of normal. So, more to come on that one. There is a lot of interest in the general cardiology community, the preventive cardiology community, and the lipid community.

3. GLOBAL LEADERS (DAPT and DOACs)

Dr Harrington: Turning our attention to antithrombotic therapy, let's do both antiplatelets and anticoagulants. First off, the notion of dual-antiplatelet therapy (DAPT) post-stenting has always been thought to, at least over the past 15-20 years, require an adenosine diphosphate (ADP) inhibitor plus aspirin. Questions are being raised as to whether you need both agents for the long run and what that duration should be. Important trials like DAPT [4] have certainly asked that question. We expect to see two trials later this year or early next year: GLOBAL LEADERS and TWILIGHT. Do you want to try to put the field in context and then pull these two trials in as to what they are specifically looking at?

Dr Gibson: We used to give dextran, Persantine® (dipyridamole), aspirin, and warfarin with 8- to 10-French sheaths in someone we had put an old Palmaz-Schatz stent in. We both remember when ticlopidine was introduced, and aspirin plus ticlopidine turned out to be better than warfarin in the STARS trial.[5] That really cemented the role of DAPT.

Will dropping aspirin from DAPT and giving ticagrelor alone improve outcomes versus aspirin alone?

We have come a long way since then. We have newer stents that are less thrombogenic, and we also have drugs that are more potent than, say, ticlopidine. While there has been some studying of extending DAPT, most of the interest comes in shortening the duration of DAPT. There is a lot of recent interest in getting rid of aspirin. Remember that clopidogrel beat aspirin[6] when they were studied head to head. The question is, can we drop aspirin and still preserve good outcomes? Aspirin inhibits prostaglandin synthesis, causes gastrointestinal bleeding for that reason, and is a vasoconstrictor.

Our audience knows that in the WOEST trial,[7] the PIONEER AF-PCI trial,[8] and others where aspirin was dropped from triple therapy, we had less bleeding and as good, if not better, efficacy outcomes as well.

GLOBAL LEADERS is a big trial of about 16,000 patients and is an all-comer percutaneous coronary intervention (PCI) trial. People get the BioMatrix™ stent, and it's open-label with two arms. Everyone gets either

ticagrelor for 24 months or aspirin for 24 months. In the ticagrelor arm, you get aspirin for 1 month, so it's ticagrelor plus aspirin for a month and from there on out, ticagrelor. In the other arm, the conventional DAPT arm, you get ticagrelor plus aspirin for 12 months if you are an ACS patient or clopidogrel plus aspirin if you are a coronary artery disease (CAD) patient. Then, from 1 year on, it's aspirin monotherapy.

In other words, it's ticagrelor for the majority of time alone or a little mix of DAPT for 12 months plus aspirin monotherapy for another 12 months. This is going to be a tough lift. By dropping aspirin from the ticagrelor arm, they expect to show superiority in ischemic outcomes, mortality, and non-Q wave MI. For the bleeding side, they expect to show a reduction in BARC class 4 or 5 bleeds.

Will dropping aspirin from DAPT and giving ticagrelor alone improve outcomes versus aspirin alone? It's going to be interesting.

Improving ischemia is good, but not if it comes at a big cost of bleeding.

Dr Harrington: I have so many levels of interest in this. We are seeing an error with these antithrombotic trials of what I would call strategy. When you and I did trials throughout the '90s and early 2000s in this field, they were largely trials testing a drug against another drug or against placebo. Now, we are starting to see the optimal strategies and the optimal balance for patients. Improving ischemia is good, but not if it comes at a big cost of bleeding. How do you balance those two?

The final thing I'm sure our audience is thinking is, "Whoa—you're getting rid of aspirin?" Mike, how many times did we say over the past 25 years that we could not possibly get rid of aspirin because it is backbone therapy? A lot of interesting things will come out of a trial like GLOBAL LEADERS.

Dr Gibson: When you look at the history of aspirin, it was really launched with ISIS-2[9] showing an improvement in outcomes with a lytic agent; [the data are] a little more spotty outside of ISIS-2. We'll see, but it's not all good with aspirin. It does cause bleeding. It does cause some vasoconstriction.

4. TWILIGHT (Monotherapy vs DAPT)

Dr Harrington: Move us into TWILIGHT.

Dr Gibson: TWILIGHT is slightly different. It also is an all-comer PCI trial and has 9000 patients. Everyone gets 3 months of ticagrelor and aspirin, and then they get either ticagrelor alone or ticagrelor plus aspirin. I want to make it clear that everyone is getting aspirin for around a month in GLOBAL LEADERS, and everyone is getting aspirin for 3 months here, so it's not complete early withdrawal of aspirin but a shortened period.

The primary endpoint is bleeding and superiority in BARC 2, 3, and 5 bleeding for ticagrelor alone. The idea is that hopefully there will be noninferiority for the ischemic outcomes of CV death, MI, ischemic stroke, and ischemia-driven revascularization. That statistical design looks to be more within reach to show that you reduced bleeding by getting rid of aspirin, and that you preserved efficacy with noninferiority.

Dr Harrington: It also looks like it will be an easier comparison to understand, doesn't it? To me, this fulfills the classic definition of when noninferiority trials should be used, because you always give up something in noninferiority. The question is, what do you get in return? What you are trying to get in return here is less bleeding and less of the important bleeds. I like the construct, and we will see if they fulfill noninferiority in ischemia and benefit in bleeding.

5. VOYAGER PAD (DOAC vs Aspirin)

Dr Gibson: The other trial in the antithrombin space is more of an anticoagulant trial. The VOYAGER PAD study kind of builds upon what was seen in COMPASS.[10] In COMPASS, the rivaroxaban dose was reduced to 2.5 mg twice a day plus aspirin, a regimen that we studied back in ATLAS.[11] Obviously, both of those trials did quite well, including a reduction in mortality in both. This study looks at that regimen in the PAD patient. They are looking at people who recently had a peripheral arterial procedure distal to the iliac. Patients had to have symptomatic PAD and were randomized within 10 days of the revascularization. Again, it's a trial of low-dose rivaroxaban plus aspirin versus aspirin alone. It has 6500 patients and is event driven, with 1015 endpoints to be reached with about 30 months of follow-up. Results are being stratified by surgical or endovascular procedure and by clopidogrel use.

Finding something that works in the PAD population has been tough...

We'll see if results of the ACS and CAD side of things extend over to the peripheral interventional side of things. In COMPASS, the PAD cohort did well, but we'll see if the interventional cohort does well here. Not a lot of therapies have worked in the interventional side of the PAD population.

Dr Harrington: You hit the highlights of VOYAGER PAD, and I'll stress a couple of points. We have talked in these podcasts before that with anticoagulants against antiplatelet agents, one does not need to be paired up

against the other. There are some interesting observations that the anticoagulant, over time, seems to be emerging as a powerful addition to the postevent regimen, whether it is in coronary disease or other aspects of atherosclerosis.

The second point is that we have trials like EUCLID[12] that did not show any benefit of ticagrelor in a PAD population. Finding something that works in the PAD population has been tough, hasn't it?

Dr Gibson: It has. You and I both know that these people are frequent flyers, too. It's not just one event. The rehospitalization rate after these revascularizations is very high. So it's very costly, there are frequent flyers, and there is an unmet need. It's going to be interesting.

Dr Harrington: We'll learn a lot, and putting it into the context of other PAD trials will be an important thing to consider.

6. COMPLETE (Staged vs Culprit-Only Primary PCI)

Dr Harrington: There are two more trials to go—one from interventional cardiology and one from interventional electrophysiology. Let's do the interventional cardiology trial first.

In our 2017 discussion we talked about CULPRIT-SHOCK[13] and how interesting those results about shock-related artery revascularization versus more complete revascularization were. Now, the COMPLETE trial is looking at a broader cohort of patients undergoing PCI for acute MI and is looking at complete revascularization versus target revascularization. Would you give your thoughts on COMPLETE?

Dr Gibson: Like you said, it has a broader population. All or most of all of us concluded after CULPRIT-SHOCK that it may not be a good idea to do complete revascularization in shock. This is a broader STEMI population with primary angioplasty. It's a staged PCI approach rather than immediate PCI in the nonculprit vessel. The endpoint is rigorous—CV death and MI. Many of the studies in the past had just used revascularization as an endpoint. This uses tougher endpoints. It's a big study with 3900 patients and it's open-label, so everyone is getting aspirin and ticagrelor.

To be revascularized, you had to have a 70% visual stenosis in a nonculprit vessel or a 50% blockage with a fractional flow reserve (FFR) of < 0.8. It's interesting to see in this study the introduction of FFR as qualifying criteria. It'll be interesting to see if it complements CULPRIT-SHOCK or if there is a different answer.

It's interesting to see in this study the introduction of FFR as qualifying criteria.

Dr Harrington: I agree with you on the FFR inclusion. Really understanding whether there is functional ischemia is becoming more and more important to the interventional community. Trying to make decisions on the basis of FFR abnormalities is becoming part of standard practice. As you know, in the ISCHEMIA trial, we provided guidance for that group of patients undergoing revascularization that they should be completely revascularized using FFR to guide. In this setting of acute MI with ST elevation, COMPLETE is going to give us some interesting insights. What do you need? Do you need to get completely revascularized or is dealing with the culprit enough? Certainly, SHOCK made interventional cardiologists take pause and reflect on how much should be done in the acute moment. The answer is to probably just get in there, open up the vessel that is causing the problem, and get out of there.

Dr Gibson: Having looked at many thousands and thousands of these STEMI films over 30 years as a core lab, I have seen all of those "misadventures" when people went around dilating the other vessels. I was not surprised at all on the results of CULPRIT-SHOCK. I am skeptical that this will show a benefit, but we will see what it shows.

7. CABANA (Ablation in AF)

Dr Harrington: Our last trial, CABANA, is an NHLBI-sponsored trial with some industry support, looking at atrial fibrillation (AF) ablation versus medical therapy for AF. It's looking at clinical outcomes, as opposed to some smaller trials in the ablation world which just looked at persistence of quieting down the rhythm. This is an interesting one, given that there are a lot of procedures being done on a fairly limited evidence base.

If this trial were designed today in 2018, I think you would see a lot of people push for a sham control.

Dr Gibson: In comparing and contrasting the interventional world to the electrophysiology (EP) world, I am somewhat confused about the evidence base for ablation. It seems limited. This, of course, builds on CASTLE-AF, where catheter ablation in AF patients with HF reduced death and worsening of HF. CASTLE-AF was criticized because it was underpowered, and some of the positive results may not be real but may be somewhat spurious.

This is a bigger trial. This is 2200 patients, not with HF but with documented AF, who will receive either left atrial ablation or state-of-the-art rate or rhythm control. It is open-label and follow-up is for 5 years, which is a good

period. The endpoint is going to be total death, disabling stroke, bleeding, or cardiac arrest. They will also look at cost and quality of life. It's good to see this widely used procedure held up and tested rigorously.

Dr Harrington: I noticed that you paused and said that it was open-label. One of the things I learned from ORBITA[14] is that you can do sham-controlled procedures in a group of patients undergoing a contemporary CV procedure. Should that be the standard? CABANA was certainly started many years ago. But if you were to do it today, would you think maybe we ought to do a sham procedure?

Dr Gibson: I certainly would. We lived through the vascular endothelial growth factor (VEGF) days, where finally doing sham procedures was really important. We lived through the days of transmyocardial revascularization and drilling holes with lasers. Both of those were positives in "randomized" trials but were negative when you did a sham control.

Dr Harrington: Or when you did a trial that was big enough to get the clinical outcomes.

Dr Gibson: Yes. If this trial were designed today in 2018, I think you would see a lot of people push for a sham control. I certainly would. I might be in the minority there, but we need to do more sham-controlled trials with these devices.

Dr Harrington: Renal denervation is another example where the sham-controlled trial found no effect of the therapy compared with control.[15] It's humbling and a good example for potentially utilizing more sham controls in these procedures.

Mike, we had a great time looking back at 2017, and now we had a good time thinking about some trials to look forward to in 2018. I remain impressed that cardiologists demand evidence to change practice. It remains inspiring that so many trials are being done by people around the globe trying to answer these questions.

Dr Gibson: I agree. It's going to be an interesting year ahead.

Dr Harrington: My guest today has been Mike Gibson, professor of medicine at Harvard Medical School, interventional cardiologist at Beth Israel Deaconess, and the CEO of the Baim Institute for Clinical Research. Mike, thanks for joining us here on Medscape Cardiology.

Dr Gibson: Thanks for having me.

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