Ivor	00:00:00	I'm here today in the home of Dr. Nadir Ali, overlooking the beautiful Clear Lake Texas. Beautiful home you got here Nadir, I'll have to say.
Nadir Ali	00:00:09	Thank you, Ivor. I'm glad that you're here today this afternoon.
Ivor	00:00:13	Ah, that was great. And we have a lot of the guys here earlier from low carb Houston, which is another fantastic conference you've pulled off three full days of excellent speakers.
Nadir	00:00:23	It's all because of the faculty and all because of the hard work that was put in by the university and by the speakers. I thought that it was a pretty engaging conference, that attendees were like, quite attentive to all the speakers and they participated vigorously, and I enjoyed it.
Ivor	00:00:44	Yeah, it was a real blast. And like you say everyone was highly engaged, and over 400 people.
Nadir	00:00:51	That's correct.
Ivor	00:00:53	And that's University of Houston. Clear Lake is the credited University.
Nadir	00:00:57	Yeah, right across the lake.
Ivor	00:00:59	Oh, yeah. I had to drive all the way around today.
Nadir	00:01:01	Right.
Ivor	00:01:03	So here you gave a fantastic hard hitting talk and I know a lot of it was around the actions of medications and all that kind of stuff quite technical. I thought today, maybe we'd take it up a level and talk around heart disease in general, you know, the cholesterol hypothesis versus insulin, what the real drivers are and what the real things you do to eliminate the chance of a future heart attack? Maybe slightly less medications and more into the mechanisms and the physiology.
Nadir	00:01:33	Sure. I think that for a long time, we've been focused on the LDL hypothesis for heart disease. And like you saying in many of your talks, we should move away from it and focus on the elephant in the room. And the elephant in the room could be defined in many different ways. But if you want to talk to a cardiologist, you should say, “Hey, I want to focus on lipoprotein quality.” And lipoprotein quality would be a surrogate marker of

		insulin resistance. So when I say low triglycerides and high HDL, that's actually an insulin sensitive person. And in fact, lipoprotein IR, which is like a protein index of insulin resistance, is based on those measures. So I think as cardiologists, we should focus a lot more on insulin resistance, on inflammation. And these are the primary drivers of vascular disease. These are also the primary drivers of hypertension and also diabetes. So I think, I would say, shift the focus away from LDL, and bring the focus more on to what is the real cause and the real cause being insulin resistance as you describe many years ago, in your talk at Breckenridge, with a graph classification, and that gives you an idea as to how insulin resistant someone is. And when I bring up the graph classification to my endocrinology colleagues, they have not even heard about it. So I think the local community that needs to kind of spread this message and invite people from various disciplines to come in and talk to us about how to properly evaluate the risk factors for heart disease.
Ivor	00:03:40	Yes, the most salient ones because everything's a risk factor, really. And I believe that last count, there's 300 risk factors for heart disease approximately, which is almost fatalism. There are so many risk factors, what do you do, but there's a top five or 10 and the ones you mentioned are at the top of the pareto stacked. LDL interestingly, and I liked the way you said that triglyceride over HDL, total cholesterol over HDL ratio, lipoprotein IR, and triglyceride, all of them all using cholesterol measures, but really to judge whether your insulin (resistance). So it's not really a cholesterol thing at all, but very few cardiologists would realize that I guess, or even endocrinologists.
Nadir	00:04:28	So I want to tell about my conversation with cardiovascular surgeon, and I know that you have shown several studies that correlate coronary calcification with various other risk factors. But when you look at coronary calcification and LDL, you really basically failed to find an association. But if I were to use a little bit of an analogy that lay person would understand and this is my CV surgeon told me is that, “Look, I have open the hearts of 10,000 patients. And I have looked into their coronary arteries to evaluate the degree of atherosclerosis,” which is basically plaque buildup and blood vessels of the heart of blood vessels of the body. And what he tells me is that there is no correlation in his mind in the 10,000 patients that he's operated on, in patients between low serum cholesterol and high serum cholesterol. So that was not a correlation. And when it came time for him to treat his cholesterol, he said, “I don't think that's an important risk factor. I don't want to take any measures

		special, specifically pharmaceutical measures to take care of that." So that's the kind of analogy I think every physician should use and go a step further and start thinking as to why our body makes the LDL in the first place. Can I look at the biologic role of LDL? And we explored that a little bit. And I don't know if you want to kind of touch a little bit on that.
Ivor	00:06:19	Yeah. Actually, I would do Nadir, because cholesterol even though we don't see it as a primary problem and it's low down the list, the very fact that so many cardiologists In fact, the vast majority of people perceive it as the biggest risk. It's well worth exploring it so people can understand it. So yeah, the role of LDL where it came from, what roles it takes in the body, that'd be a great thing to go through a little.
Nadir	00:06:48	I'd love to do that. But before we say what an LDL is, we need to say that cholesterol is a fatty substance. Our blood is watery, so cholesterol will not mix with blood so the body needs to carry cholesterol in a package that dissolves in blood. So the lipoprotein is such a package or a carrier. The lipoprotein is made of phospholipid bilayer that dissolves in lard. It has certain identifying proteins that make it do a certain function in the body. And the cargo of that is cholesterol and triglycerides.
	00:07:28	So when you look at the LDL molecule, it was designed through millions of years of evolution for a specific purpose. And I think that purpose was getting fat soluble vitamins. That purpose was getting CoQ10. That purpose was to fight infections, bacteria and viruses. That function was for cell repair. That function was to deliver cholesterol to certain organs that don't make cholesterol so that they could convert it into hormones. The adrenal gland needs cholesterol to make stress hormones. The testis and the ovaries need cholesterol to make sex hormones and without the LDL cholesterol, they would not be able to make it. And I think the current epidemic of erectile dysfunction in some degree ties to the fact that we are trying to reduce the LDL cholesterol as our major goal to combat heart disease. And I think that is misplaced.
	00:08:43	So, when I cannot stock about the LDL hypothesis like this, it doesn't make sense to my colleagues because hardly any of them have really thought about as to why nature and evolution created an LDL molecule, they'd like to reduce it down to zero. And they use the argument that very low LDL correlates with a reduction in heart disease. And I don't find that argument that convincing.

	00:09:22	Let me take the example of abetalipoproteinemia. Now this is a condition in which the LDL is absent. So in other words, it's a genetic condition in which the body is incapable of making LDL. It's also incapable of making chylomicrons and VLDL which are very similar lipoproteins. So these are not produced by the liver. So in that situation, a person born with abetalipoproteinemia has either zero or 15 or 20 milligrams per deciliter of LDL. Normal is considered to be about 100. Some people consider 120 to be normal. So you would expect that people with abetalipoproteinemia should live should live indefinitely. Right?
Ivor	00:10:19	Almost.
Nadir	00:10:20	And these people get blindness because the lipoproteins carry vitamin E and vitamin A that are important for our vision. They get recurrent infections because LDL is in Borland? [Inaudible 00:10:34] fighting infections. They get ataxia. Ataxia is a movement disorder. Because cholesterol is important in milinating our nerve cells so that they function properly. And rather than living forever, they have a failure to thrive. They get fatty liver cancer, and most of these people are dead in their third or fourth decade, and hardly anybody survives into their fifth decade. So I want every physician when they are thinking about the LDL hypothesis, to think about this genetic condition in which LDL levels are low, yet there is so much biologic malfunction, blindness, ataxia, fatty liver, recurrent infections, so that when they are trying to drive the LDL low in a cardiac patient to say, “Hey, maybe, that may not be that good. Because Let me think about what damage I could be doing to these people.”
Ivor	00:11:45	Yeah, and it could be very long term problems as well. So won't show up in a few years with a quick trial. So point very well taken. And we did see with PCSK9 inhibitors, a 60% or so reduction of LDL, and yet only a 20% reduction in events and no real changes in mortality outcomes. So, yeah, the LDL hypothesis has been overstressed and depended upon, as the big thing, and yet they're kind of rolling out of benefits as they push lower and lower. And all this is against the backdrop of studiously avoiding, or not looking closely at all the major factors that you described. We do have a topsy turvy world in cardiac disease, don't we?
Nadir	00:12:36	Oh, I couldn't agree more. For the first 25 years of my practice, I would not want to see a patient in my office. I'm an interventional cardiologist, I open up the blood vessels of the heart with a stand. And the reason I did not want to see

patients in my offices because I thought I was completely ineffective. You know, I would not be able to make any difference in their hypertension and their obesity and their diabetes. And I could modulate the LDL cholesterol but I did not see a clinical difference. In my practice, I have done a coronary angiogram. To a layperson what a coronary angiogram is, you take a person to the cath lab, and you insert a little plastic tube through the blood vessel in the leg or the blood vessel in the hand and run it up to the heart and take pictures of the blood vessels of the heart. So I have seen people come in with an LDL level of 15 to 20, having a heart attack and having severe blockages of the blood vessels of the heart. On the other hand, I have taken people, elderly women, like in their 90s with a lifetime of LDL cholesterol over 200 and I have found clean coronary arteries. So for me, it is hard to reconcile that LDL could be such a major player, just like my heart surgeon when he came and told me that he does not believe because what he sees does not correlate with cholesterol.

Ivor 00:14:22 And actually, William Davis, MD, I remember his original Road to Damascus Conversion perhaps was exactly that, that he was interventional cardiologist. And he realized over time that the degree of arterial disease he saw bore no relation to the cholesterol values even outside of statiner or statin naive patients. In general, there was no correlation and that started his journey. And then he discovered exactly what you're saying. It's how many years ago is this where you began to realize what you're talking about? Like you're kind of ready relations that lead you to being so knowledgeable now and what really causes heart disease? Is that quite a few years back?

Nadir 00:15:07 So that transition happened right between 2012 to 2013. Tour de France was going on. And Chris Froome, although he was not… I'm a cyclist, and I work with the cycling team and I'm over 150 pounds now, but I used to be about 180, 185 pounds. And I didn't know if you knew that or no. But Chris Froome, there were some reports at that time in 2012-13 timeframe, he was a tremendous athlete, he was climbing mountains in France without any parallel, he didn't have any rival out there. And he was a low carb athlete. And I was listening to a podcast like December 25, 2012. This podcast was by Seshwan Adrian? [Inaudible 00:16:05] He's an Australian rugby physician. It was not a very good podcast, but he was talking about the biology and the biochemical mechanisms of why low carb works. And then I was struggling with trying to keep up with my cycling team. I was about 30, 35 pounds overweight. I'm a pretty determined guy could not lose that weight. So I said, "Let me try

this low carb." And within three to four months, I was down those 35 pounds. I was cycling better than I had ever done. I was feeling better, I had more energy. And then it dawned on me, "If it works in me, why should I not try it in my patients?" And then I started trying it on my patients. That's when I said," This is a transformative experience. I don't need to not see patients in my office. I just don't need to be a plumber in the cardiac cath lab. I don't need to put in the stands alone. I can take care of them in the office."

00:17:12 I don't know if you remember or no but '14, '15 and '16 was a timeframe in which there were very few players in this field. Peter Attia was one of them. And Jeff Volek was one of them. And my clinical experience was a little different than the clinical experience of these people because they came out and said, "Yeah, low carb is good, because it reduces insulin resistance." And I found that, there's no question about that, that it reduces inflammation. I found that, that it reduces triglycerides. There was no issues with that. And it increases HDL. People lose weight. They get off their diabetic medical Their blood pressure improves. So there were all these positives. But what they said was that one third of people keep their LDL the same, one third, the LDL goes down, and the other third, the LDL will go up. But they never talked about how high the LDL would go up. And my clinical experience was a little different. And the reason it was different is that I found that the more metabolically healthy one got, their LDL would go up.

00:18:40 And I struggled with that concept. I didn't know what to do about it. And in the '15, and '16, and even 2017 timeframe, we didn't know so much about lean mass hyper responders. And I think that if you are metabolically healthy,even though you will not be completely in the lean mass hyper responder phenotype but your LDL cholesterol will go up above guidelines. And I did not know what to do about it. And I guess a fair way to say is that none of us really know what to do about it. I don't know if you have reconciled the lean mass hyper responders, and we necessarily don't have to talk about lean mass hyper responders, but talk about when you put somebody on a low carb diet, when you make them go through intermittent fasting and all your biologic markers are improving but the LDL is going in the opposite direction of what guidelines consider to be good, what do you do about it?

Ivor 00:19:56 That's a common challenge and it is interesting, these lean mass hyper-responders you refer to, just for people who aren't aware, it's people who are quite lean, athletic, fit, low body fat

percentage, and when they go low carb and towards keto, they really conjunct their LDL like doubled. Huge numbers. And the interesting thing is, you mentioned there Nadir, that, you know, people who are less metabolically healthy and less fit and overweight, often they don't go up so much. They're happy guys. And I think they're typified by Dr. David Unwin in the UK. A lot of his patients are older, they're overweight, they're kind of diabetic, they're quite unhealthy, and would need those low carb, but then he doesn't see any rise in LDL. But again, he doesn't have younger, most killer lean people who are going quite hard keto. So they're the guys [Inaudible 00:20:54]

00:20:54 Now, the question again comes back to what does that mean, of course. That's the million dollar question. And Jeff Volek has published a paper last year, and he entitled The Paradoxical Rise in Lipids of Ultra Endurance Athletes. And he saw the same thing he saw a big increases in LDL P and particle numbers in LDL, ironically, in athletes who are getting more and more fit with excellent inflammatory markers. So this paradox is coming up all over the place. And you're right, what do we do about it? In our book, myself and Dr. Garber, Eat Rich Live Long, we got out of this bind by simply saying, look, if your LDL goes up a lot, and we explained that it happens, we gave an alternative diet, that softer low carb, you know, a milder low carb diet so that people can have an option to lower their LDL somewhat. If they're concerned, every person has to take responsibility for themselves. So we give this get out option. But that doesn't mean that we necessarily think that you should do that. We're just giving the option because it has to be a personal decision.

Nadir 00:22:09 Sure. I couldn't agree more. But what I would like to do is, I'd like to spend a little time if it's okay with you to talk about why LDL goes up in person like that who is getting metabolically healthier? A lean mass, an athlete, a hyper responder, whatever you want to call it, because I think that's my specialty. And the reason I dawn upon this is from two standpoints. One is that I had a couple of diabetic patients and these were type 1 diabetics. And they were running hemoglobin A1cs anywhere between 8 to 12. And you would be surprised that they had an LDL cholesterol of about 80, somewhere in the 70s, somewhere in the 90s. And when I made them rabidly low carb, and when by rabidly low carb meaning that they would take less than 20 grams of carbs, and they improve their blood sugar control. I would put them on freestyle every, which is like dex comments, continuous glucose monitor, and they would run very tight sugars in the 90s, always below 100, even postprandially.

Ivor	00:23:34	Nice!
Nadir	00:23:35	And they would take very small doses of insulin to control the sugars. And what I found is that if the LDL was in the 80s and 90s, as their diabetes got better, their LDL run up to 150. And as the hemoglobin A1cs dropped into the less than 5, and these are type 1 diabetics, maintaining a hemoglobin A1cs less than 5, Their LDL is were always above 200.
Ivor	00:24:03	Wow!
Nadir	00:24:04	So I said, Why is this happening? And I know you and I talked earlier that Dave had an energy model and energy delivery model and which basically stated that since you need to supply fat calories to the cells, that you would need to make work more VLDL. So what's happening is that the liver is putting out a boat that carries a lot of triglycerides fat in a particle and as the VLDL drops off its cargo, which is fat, to the muscles and other cells of the body, it gets converted to the LDL molecule. And you know, that famous interview he had with Peter Attia, in which he said, this cannot be possible because in a situation in which there is low insulin levels, there is clear biochemical evidence that the liver is not making VLDL. It's not making triglycerides, basically. And that to some degree is correct. And I'd get back to that, I want to be fair today, Feldman, because I think he's also partially right. But I think what's happening in that situation is that the liver is taking up free fatty acids, it's taking up triglycerides, breaking them down, and sending them through the mitochondria to make ketones.
	00:25:37	And this was at my Denver presentation, which says that the biochemical machinery to make ketones is exactly the same biochemical machinery that makes cholesterol. So when you jack up ketone productions a lot, like if you take a type 1 diabetic, and they're not eating any carbs, and you check the ketone levels and they are in their 2s or 3s or even higher, you would agree that they are predominantly burning of fat energy, right?
Ivor	00:26:10	Absolutely!
Nadir	00:26:11	So if they're burning of fat energy, they're making a lot of ketones in the liver, and hence they're also making a lot of cholesterol. So there is biochemical evidence from studies that I can, you know, point out to you, that shows that LDL production goes up, the liver is capable of making LDL directly without

		going through the VLDL pathway and then dropping fat to convert to LDL.
Ivor	00:26:40	Well, actually Nadir, that's fascinating. Because many years ago, I got a paper, and not many papers go through these pathways, but it showed that the LDL comes from the liver and then becomes IDL and then LDL as the cargoes dropped off. But there's also IDL direct from the liver and there's also quite a lot of LDL at times directly from the liver, depending on the person. Now, you've described a scenario where LDL is being generated directly from the liver appropriately, because of the state physiologic state, the person is, in a very fat burning stage creating ketones and also LDL.
Nadir	00:27:21	That's absolutely right. And I can give you further corroboration. There are papers that go through the synthesis of LDL in a fasted state, in a low carb state that showed that LDL production directly increases. There are also papers that show that your LDL receptor goes down in a low carb situation. And the reason for that is pretty simple. If the liver is making a lot of cholesterol, it doesn't need any cholesterol from the circulation. So it has to down regulate its LDL receptors. There is also evidence that when the liver is making a lot of cholesterol and the LDL receptors are down regulated, the liver is eliminating more cholesterol as bile that is not getting reabsorbed. Because like we talked about cholesterol is not a metabolic fuel, you can’t burn it, like you can burn fat like you can burn carbohydrates. So the elimination pathway for cholesterol is through bile.
	00:28:31	There is another pathway through which cholesterol is eliminated, which not many people know about and it's called TICE - trans-intestinal cholesterol elimination. And this pathway really takes up macrophages that have taken oxidized LDL and eliminated through the intestines. And another reason why all of this came to the forefront is because of the new advent of SGLT2 inhibitors. So a moment to talk about SGLT2. Are you aware of these?
Ivor	00:29:15	Oi, the glucose transporter, yeah, to help with diabetes by stopping the absorption of glucose or at least limiting it. But I believe those drugs, they send the glucose and the sugars down to the urine and cause urinary tract infections.
Nadir	00:29:32	Right. So basically, you're being sugared. But when you're being sugared, the body is very smart. It turns to fat metabolism.

		Because since the body is getting rid of sugar, it makes you burn fat. And when you burn fat, you will make ketones, right?
Ivor	00:29:54	Yeah.
Nadir	00:29:55	And when you make ketones, you will also make cholesterol and LDL. So that's the pathophysiology that has been shown very clearly in an animal model of SGLT2 inhibitors as to why the LDL cholesterol goes up. And in addition that is corroborated by our clinical experience because when you use these SGLT2 inhibitors, you're fat burning, your sugars get better, you're being urine, but you have a substantial benefit in cardiovascular outcomes. Your cardiovascular outcomes, improve heart attacks, deaths hospitalizations. But I want you to guess what's happening to LDL?
Ivor	00:30:42	Yeah, I know. LDL has gone up, in concurrent with the improved outcomes, better health and everything working better, not about drug except for the infections. But LDL has gone up and the heart attacks and atherosclerosis go down.
Nadir	00:31:00	So that's another paradox, right?
Ivor	00:31:01	Yeah.
Nadir	00:31:02	Okay. But I think in all fairness today Feldman because, you know, I think that in large part I agree with him, because there is a component of energy delivery. And this might be a little bit for the geek, so if there are certain people who are not geeks in your audience, they can turn off and they don't need to watch the segment.
Ivor	00:31:24	But they got to turn back on in two minutes though.
Nadir	00:31:26	Okay. So really what's happening is that there is PCSK9 which you know, and then you know that there is an LDL receptor. So basically PCSK9 is a protein that the liver elaborates. And this protein comes in, binds to the LDL receptor and removes it from the liver by basically taking you through autophagy; it eliminates it. But the regulation of both the LDL receptor that reduces LDL cholesterol and the PCSK9 is coregulated by the liver through a certain signal. It's called SREBP2, we don't need to kind of really get into that. So the body creates a very homeostatic system in which it figures out, "Hey, this person is not eating," like fasting which is an extreme example of a low carb situation. And it tries to create a balance between energy delivery and energy removal from the circulation. So if you wanted to deliver energy, let's say you wanted to deliver energy

because you're not eating or you're in a stressful situation, you have an infection and you need more fat based energy into the circulation, you will increase the production of PCSK9 so that you remove the LDL receptors and then leave a lot of the LDL lipoproteins that are carrying the fat energy in the circulation.

00:33:09 So, Dave Feldman is not entirely wrong, because there is coregulation of these forces that are removing energy from the bloodstream. Worse this keeping it in there depending on the situation, whether you need it or not.

Ivor 00:33:26 Exactly. And this often occurs where there are multiple kinds of mechanisms tied into a phenomenon. So, I agree entirely. The energy delivery model makes sense in many aspects, but then of course, the biochemical ketone generation also generating LDL directly from the liver not only makes sense but in fairness, it's been demonstrated in animal models as you say. But all of these things both the energy delivery model and the ketone generation model of LDL rising, they're all completely physiologic, natural and right they are correct and right for the state the persons in. And the irony is that the state of fasting is invariably no one would contest this, fat fasting is healthy in every way. Animals live longer when you do more fasting, no one will argue with this. So a fasting healthy state has been demonstrated clearly in papers to raise right up the LDL particle count, raise the LDL, lots of other healthy states, the SGLT2 inhibitors, which lower heart events and lower vascular disease, also raise the LDL. How do we reconcile these paradoxes except that it's not really LDL that's the problem, it's just that LDL is connected to the problems.

Nadir 00:34:59 You know, we are preaching to the choir and you and I are on the same page. So I think that LDL needs a little bit of redemption. It needs the respect. The medical profession needs to give it respect that we should no longer call it the bad cholesterol. It is the good cholesterol. It is just the context in which you are viewing the LDL and the context that we are viewing the LDL is high triglycerides, low HDL insulin resistance. And in the beautiful work that you have done along with so many other people, you have clearly demonstrated that when you take into account insulin resistance, high triglycerides, low HDL, the LDL no longer remains a risk factor in any real increase in cardiovascular events or cardiovascular mortality. So I think that there should be a focus away from the LDL and more towards insulin resistance. And there should be a focus away from reducing LDL to 30 milligrams or below 50 milligrams per deciliter as it's happening now with PCSK9 inhibitors. So if I

were to give you an injection in your thigh, the PCSK9, the [Inaudible 00:36:20] once every two weeks, I can drop your LDL to 30 milligrams per deciliter.

Ivor 0036:29 From 70 or 80, maybe on the statin right down to 30. That kind of state.

Nadir 00:36:33 90 milligrams to 30. And in a person who's probably not taking a statin, it would be about 120. And when you do a study like this, in 28,000 patients in one trial, 19,000 patients in another trial, so you have roughly close to 50,000 patients. And despite doing 50,000 patients and reducing the LDL to 30 milligrams per deciliter, you don't show a mortality benefit. I would consider that as abject failure. Not as partial success; that is abject failure. And the people who give presentations in favor of PCSK9 make an argument that, We are going to get your LDL down to what you had when you were a little newborn." Right, a little newborn. And they say, "Hey, this LDL in newborn are so good and we want to get you back to that level." And if I were not running this conference that we just ran, I would not be able to counter that argument. But now I can because there are a couple of smart people in the audience. When the PCSK9 presenter talked about how good the inhibitors can get your LDL down, he asked a very simple question, which is that newborns have the highest cholesterol synthesis. And that making LDL, so if you measure LDL synthesis, it's very high. The only reason LDL is so low is because it's being used. It's being used for cell repair, for making cells, the newborns are in a tremendous growth cycle. The cholesterol is needed for them. And as you get older, your growth rate reduces and the LDL is being used for other purposes. So I don't think you can make the argument that lower is better. In fact, I think that lower is dangerous. Because there was one study of PCSK9 inhibitor in which it was tracking vitamin E levels and in just as shorter span as 52 weeks, one year, there was a significant reduction in vitamin E levels. Which goes back to the genetic condition the abetalipoproteinemia, which gets were getting blindness, recurrent infections. And it argues that the LDL is a carrier of fat soluble vitamins.

00:39:22 Now, in an adult person, it might be much harder to figure out whether these people are getting vitamin deficient because they have a low LDL because it may take a lot longer to manifest. You're not in a growth phase. You're not a young child, you're not in adolescence. So I think that all these factors need to be taken into consideration because this nature is so homeostatic. And you cannot just take out one thing without a

lot of different consequences. And I don't know why we have this fascination with drug therapy whereas what we need to be modulating, is nutrition, lifestyle, intermittent fasting , exercise,. These re the things that have a huge impact have a major impact.

Ivor 00:40:17 Yeah. And if you add in then crucial vitamins and minerals, which many people are deficient in, and you add that to what you listed there, you could have an enormous, synergistic impact on future risk. A bit like as William Davis said, he has effectively eliminated repeat heart attacks even in his secondary prevention patients. They basically just disappeared when all of the low carb, magnesium, vitamin D, fish oil, and all the things you mentioned, were all put together in a package. The vascular disease just simply slows down and goes out at the dangerous. Whereas driving LDL down into their boots will only get us percentage reduction of events and not really affect mortality, even though it's reducing from 90 down to 30. So it's like this obsession with lowering it, if they put an ounce of the energy that we're doing to achieve that into some of the other things we're talking about, they get an enormously bigger bang for the buck. But I guess all the other things that you do to actually resolve vascular disease, none of them have any business model at all. So it's not really part of the challenge. There's no conspiracy. It's just that if it doesn't have a business model and a revenue generation capability, then the business of medicine doesn't really have an interest in it.

Nadir 00:41:48 That's where you come in, Ivor. And I think that the pharmaceutical industry has gone so far astray and the conflict of interest is pervasive in all of medicine. It's pervasive at the level of a clinical center where a drug is investigated. It's pervasive at the level of the central adjudicating committee, the CAC, that looks at all the data and decides whether a person on drug got an event or didn't get an event. It is pervasive at the level of the Data Safety and Monitoring Committee. These are the people who are charged to say, “Hey, should we stop the clinical trial because the drug is harmful?” And the reason I'm saying that and you know, there are many more components that I didn't get into, the reason I'm saying that is that every single one of these entities is paid for by the pharmaceutical industry. And if the pharmaceutical industry is paying them, then a person having an event on our drug, just giving you an example. Like let's say I'm taking a blood thinner drug, let's not even go towards cholesterol. And the blood thinner drug is made by the company and they want to make it look good. And if I have an event on that drug, me working for the company

		would try to find excuses to exclude me from being counted as an event. Has that happened? Do you think?
Ivor	00:43:29	Yeah, this is the problem with soft events. You know, that's why mortality is so important. And I know it's hard to power for that statistically. But it's why mortality or really hard heart attack events are so important. And the soft events like revascularization, they're almost subjective.
	00:43:50	One other thing that occurred to me, Nadir is these are meant to be blinded. And for people listening, it just means no one knows who's on the drug, no one knows who on placebo.
Nadir	00:44:01	That's not true.
Ivor	00:44:02	It cannot be true unfortunately with cholesterol lowering, because every doctor and every person involved from the pharma employees through to the non pharma employees in the trial, they know at one glance who's on the drug and who's not just look at their cholesterol. So all of these trials are by definition on blinded, which is not acceptable, usually, but there's nothing we can do about it. So those subjective decisions, everyone knows who's on the drug and who's not effectively.
Nadir	00:44:33	And actually you are a lot kinder to the pharmaceutical industry than I am. Unfortunately, I'm a little bit more of a cynic. Whether you know, it's good for me or not, I don't know I may find that out in the wrong way. But you talked about mortality being pretty difficult and point to fudge. But I don't think so, because the person who was making the decision, the person at the center adjudicating committee can look at a mortality in somebody and find reasons to exclude that from being counted in the treatment group. The reason I say this is because there is no third party verification of any of the clinical trial data. This third party verification is lacking. It's held by the company. This data is not something that the Cochrane Collaboration can view and make its own independent decision. Because what needs to be done is that every case report form that comes out of every patient should be open for public scrutiny.
Ivor	00:44:43	Yes.
Nadir	00:44:44	And that will be the only right way for me to say, I'm going to trust a clinical trial. Because the variability in clinical trials, the number of errors that have been shown in different trials, the Vioxx trial, for example, which was with arthritis medicine, or

		the enhanced study that was there with a couple of cholesterol medicines have clearly demonstrated the amount of data tampering that has occurred in these clinical trials. So, the inconsistency of clinical trials in which the degree of reduction in cholesterol does not correlate with mortality outcomes or even cardiovascular outcomes. The carrying that further is that larger reductions in cholesterol do not produce a dose response reduction in events. And over time, the reduction in LDL cholesterol has increased. So if it was here 25% reduction, now in 2018, it's a 60% reduction. The improve burden mortality with a 25% reduction in 1994 was a lot greater. 3.3% over five years. The improvement with a 60% reduction is zero.
Ivor	00:47:16	So PCSK9 case has an extreme.
Nadir	00:47:19	Right. How do you reconcile that?
Ivor	00:47:22	Yeah, it is unusual that over the decades and certainly since tighter regulations in 2005, that the benefits against placebos seem to be falling away. Even though in some cases, as you say, it was a great for lowering in more effective drugs. One would have to be careful with the data. I think on fairness, Nadir, I mean, if you have a secondary prevention patient who's got serious level of disease, I mean, you do leverage these drugs to some extent, but I think you really inform each patient as to what the numbers are.
Nadir	00:47:58	I was hoping you would ask me that question to get me off the hook. What do you think? So, I'm going to answer it the most honest way possible. And the most honest way possible is that I think a physician has to recognize that a cholesterol reducing medicine is likely to be taken by an individual for 30 to 50 years. That's a very long treatment time. And Medicare, the American Heart Association, all these major societies are making sure and are promoting the use of informed consent. Informed consent means that what are your risks or benefits in making a decision whether it's drug therapy or a surgery or an intervention.
	00:48:53	So, for secondary prevention, there is the most robust data, but that robust data is before new clinical trial guidelines from 2004. Because before 2004, a company could do 10 trials, ignore the nine trials that showed no benefit and show the one trial that showed benefit. So for secondary prevention, the most robust data goes back to 1994 when scrutiny on clinical trials was not that high. So what I tell my patients is that, I want to go through a fact that you're going to be taking this drug for 30 to 50 years. This is the data on secondary prevention in the trials

done in 1994. This is the current data on primary and secondary prevention in 2018. There is a little bit of reduction in benefits over the years in clinical trial data, but you can go buy the best clinical trial data that's available and use the drug. But I'd also want you to be aware that there are possible myopathy side effects, there is possibly an increase in your diabetes. There's probably some neurocognitive effects that you can have. There are possibly effects on bone density and calcification of the coronary arteries."

	00:50:27	And so I'm let them make a decision based on informed consent. And many of my patients decide to take the drug, and I do write a prescription for them. And I also warn them that I have spent more time reviewing this literature. And perhaps my evaluation of the literature is a little biased. And then I tell them that, "Most of the cardiologist in the community would want you to take this drug. And so here is the prescription so I don't want you to be swayed by the information I'm giving you, I would like you to make an independent decision." And I feel that that is an ethically honest way to do things.
Ivor	00:51:15	Absolutely, I mean, sharing the best data. And I guess also, you're much more up to speed on the trial data and on all of this technology than the vast majority of cardiologists who really will probably just get the headline item from what the guidelines are asking for, and have no understanding beyond that. So you're informing the much more, which is even more ethical, you know, a more fully informed patient. I think that's fair to say.
Nadir	00:51:46	And the reason I'm going into that direction is because I'm spending a lot of time with engineers.
Ivor	00:51:54	The data. It's all about the data.
Nadir	00:51:57	No, it's not just that but its root cause.
Ivor	00:52:00	Ah, yeah.
Nadir	00:52:01	So I think that engineers think more in terms of root cause than physicians do these days, because physicians are more pharmaceutical drug therapy oriented.
Ivor	00:52:14	Yeah, and a lot of correlations unless of the logic, the root cause and the logic of what's really driving things. But we talked about that earlier in this conversation, what the real drivers are, but I think more and more people are understanding what the real

drivers are. And then coronary calcification is getting used a lot more and that's going to shed a lot of light on what we're talking about. Because the more people who get coronary calcification, which is the best measure of your extent of coronary disease, we're going to see people with huge cholesterol with zero scores and almost no disease. And we're going to see the people with low cholesterol coming in with shocker scores. So rather than having to open people up to see this lack of correlation, we're going to see the correlation in a simple 5 minute scan all over the world. The data is going to flow. And we've already seen people in their 60s with LDLs, over 300 milligram, including one family in the UK, where three siblings are in their 60s with LDL levels in the stratosphere like that, and zeros and even one of them with a CT angiogram with with no apparent disease.

Nadir 00:53:27 Is that a low carb family or that's a…?

Ivor 00:53:29 No, they're an FH, kind of Familial Hypercholesterolemia. But I mean, this is the data we're going to see and we're going to see that correlation does not causation make. And hopefully people that asked, "Well, what is common to the people with high calcification?" and what we'll see as it's insulin resistance, it's autoimmune conditions, it's hypertension. It's low HDL, it's high triglycerides. It's bad cholesterol ratios. That's what's going to make up the lying share of the high calcifications scan results generally. And then maybe people will move a little away from the LDL, like you say and say okay correlates, but it's all context dependent, doesn't it? It's all the context.

Nadir 00:54:16 I couldn't agree more. I'd also like to kind of go over one final point if it's okay, is the power of N=1. I don't know if you were there, but when Dr. [Inaudible 00:54:32], the saw the physician from California was talking about his story of being 100 pounds overweight, having hypertension, pre diabetes, and really not doing very well, and with the combination of low carb and fasting, he lost 90 pounds in 100 days and improve all his biochemical markers. So the power of an intervention to improve all these significant variables in one individual is so high. So my point that I'm trying to make is that if a treatment works, you don't need 28,000 patients to show a difference and outcome.

00:55:27 Now, I grant you these are surrogate endpoints. But I think that the public should put pressure and the physician should put pressure that if a pharmaceutical intervention needs 30,000 patients to show a half a percent difference in an all cause

mortality outcome, we should not even do that clinical trial. Because it could just be noise. Because you need to remember to collect 30,000 patients, you have to do the trial in 25 countries in about 1000 plus centers, gather all this information with the biases that come into play. And there is so much potential for the data to go the wrong way with just small changes, tweaks, one or two patients one way or the other. So it's very important for healthcare professionals to understand this. And for us to get this on to the public so that they understand that a 30,000 patient study is not necessarily that powerful when it's trying to look at a small magnitude of difference. If your intervention is only capable of doing that small magnitude of difference, it's not worth pursuing. Come up with a treatment in which you can see a better improvement before you waste all these dollars to do this clinical study, and then you would need a return on investment, and there would be a lot of bias and trying to manipulate the data.

Ivor 00:57:14 Yeah, and the n equals ones like [Inaudible 00:57:19] there, he was jumping off the stage was really good. Those n equals ones, we've now got 10s, or heading towards maybe 100,000 people getting a dramatic shift in all the important markers in the right direction, a synergistic combination of triangulation of all important markers and blood pressure, all getting better. So we kind of have our trial, it's just not published. We know low carb and these correct interventions are dramatically reducing people's risk. We don't really need a trial but it'd be great if we could do on some day.

Nadir 00:57:54 I would agree with that. But until we come up with a trial like and say, in closing, that I have 5 medical assistants, 2 nurse practitioners. And we see between 30 and 40 patients on a regular basis, per day. And we feel a tremendous sense of gratification because we have 90-year-olds, 80-year-olds, 70-year-olds, who have lost between 30 and 50 pounds of faith, who have gotten off their wheelchairs, who are no longer on their diabetic medications. They have had a significant reduction in their blood pressure medications, their quality of life has improved. And the only intervention that we have done on them is a low carb diet, which is reinforced with intermittent fasting. And then my people see this in their patients. There is a patient and health care provider can And that makes us feel relevant. And you saw that at the local Houston conference that we ran that all the people from my office, they were so enthusiastic about the whole program and how they were involved and engaged in listening to and learning from all the

		speakers. So I feel that for the first 25 years, I was not as relevant as I have been in the last five to six years.
Ivor	00:59:32	Yep. And that's what it's all about. So you're doing an amazing job Nadir, not just in your practice with all your people, as you say is a highly engaged now, because they're seeing these transformations in patients, which you just don't see with generic drug treatments, but also with low carb Houston gone from 250 up to over 400 people. Way more speakers double the duration. So it's going from strength to strength, fantastic conference, one of the biggest in the US, and I hugely enjoyed being at it and speaking at it so thank you very much Nadir.
Nadir	01:00:05	Thank you, Ivor. It was a pleasure talking to you and I hope the surroundings work for your cameras.
Ivor	01:00:11	Well, yeah, I mean, this camera probably hasn't got great backlight control so you can see how beautiful it is here in your home, but we're probably not that clear. So I just finish up with asking as always, ihda.ie, our charity website, free information on the calcification score, which you of course are huge proponent of as well. And to get that information out for middle risk middle aged people, to get the wake up call with a five minute scan. So share the website if you can first and till next time.
Nadir	01:00:43	Thank you, Ivor.
Ivor	01:00:46	Thanks, Nadir.