DANNY LENNON: Welcome to the podcast, Dr. Bill Harris. How are you doing?

BILL HARRIS: I'm doing great. Good to be here.

DANNY LENNON: Thank you for taking the time. We have a lot of questions. So I'm not going to belabor the intro too much. Needless to say people, before we started talking, will have heard me introduce your extensive background in this area, and so, there's a number of details I want to get into related to some of the various trials that have happened with different omega-3 supplementation, maybe we can talk a bit about epidemiology, etc. But maybe a good place to start would be to lay down some definitions for people listening to understand the fatty acids that we're going to primarily bring up. Most of our discussion, of course, today is related to different types of polyunsaturated fats, and then from there, we're also going to focus in further on different types of subtypes. So can you maybe just clear up the picture in people's mind, when it comes to this group of fatty acids as polyunsaturated fats, and then, how we typically classify those into different subtypes, and then from there, maybe even more subtypes that come off the

back of that, what's the best starting point do you think for listeners?

BILL HARRIS: Well, typically, in nutrition, we have categorized fatty acids chemically by essentially how many carbons are in the chain, and, more specifically, how many double bonds are in a given molecule. So saturated fatty acids have no double bonds, and they're all the straight chains of carbon. Monounsaturates have one double bond, polyunsaturates have two or more double bonds, and those are the big bins that we categorize them in. It's probably not nutritionally proper, but that's the way it's been done for years. So the saturated fatty acids typically are ones that are, we'll say, solid at room temperature like butter, like lard, very rich in saturated fatty acids. Tropical cocoa butter is rich in saturates. Monounsaturates, classical one is the oleic acid, which is 18-carbon fatty acid double bond in the middle of it, position number nine, so it's called omega-9 fatty acid, and that's found in typically olive oil, canola, a fair amount of vegetable oils have oleic acid. And then, the polyunsaturates, generally we break into, from a food point of view, there's plant based, which would be like seed oils, corn oil, safflower oil, sunflower seed, etc. And then there are basically animal-derived omegas or animal derived PUFAs (polyunsaturated fatty acids) which are typically from fish, the omega-3 category of fatty acids.

So we have omega-6 and omega-3 are the two major classes in the polyunsaturated group, and they're called omega-6 and omega-3, based on the fact that all of the fatty acids in the omega-3 family have the same terminal carbon structure. They have a final carbon atom at the end, and that's the omega carbon, the first carbon is the alpha, and the last carbon is the omega carbon. And then, if you count in three positions, the third bond is a double bond, and that's characterized as all of the omega-3 fatty acids. And the omega-6 family, the first double bond counting from the end is in the sixth

position, so that's the whole family is like that. They have the same last name, the first name, the other side of the molecule can be longer or shorter, or have more double bonds or less than that first double bond from the methyl group categorizes the omega-6s and the omega-3s. And then within each of those, we have a subset of different fatty acids. In the omega-6 class, the two major ones are linoleic acid, which is an 18-carbon omega-6 two double bond, which is typically called the essential fatty acid, omega-6 fatty acid. And then, there's the other fatty acid in that class it's important, it's called arachidonic acid, and it's a longer, more highly unsaturated, more double bond. That's found in animal products, typically meat, and anything that really comes from an animal is going to have arachidonic. Arachidonic is not available in plant sources. Similarly, there's a very similar pattern on the omega-3 side. There's an omega-3 long chain, relatively long chain, 18-carbon three double bond called alpha linolenic acid, and that's a plant derived omega-3, kind of, analogous to the plant derived omega-6 linoleic acid And then, there's the animal derived marine omega-3s, long chain EPA DHA 20-20, two carbon fatty acids with many double bonds. So that's kind of the over layer, within the omega-6 and omega-3, there's a plant and an animal derived set of fatty acids, and they have different properties, different functions, but that's the general idea.

DANNY LENNON: Yeah, thank you for that, and we're certainly going to circle back to much of this later on. I have a few questions around the omega-6 fatty acids, but primarily, I think the bulk of our time will be on the omega-3s. And certainly looking at the comparison maybe between some of these different types of which many people listening will have heard of, EPA, DHA, ALA, and there's some interesting debates that have come up in Nutritional Science recently that we can maybe try and clarify on, maybe as a starting point though, before we start looking at the impact of these types of fatty acids on

certain outcomes, one of the things that I think is useful to think about is the omega-3 status, and what we actually mean by this, because if we're comparing different studies, what someone's omega-3 statuses, and then how that compares to certain health outcome, we need to know where that comes from. So one of the interesting things, I suppose, with omega-3s is that they're found in different compartments of the body, however, we can measure them in different places, although how commonly that is done probably differs. And then, we have a concept that people listening to this podcast regularly will have heard us mention before of this omega-3 index. So really, as a starting point, when we talk about omega-3 status, can you maybe give us some kind of ground basics of how do we measure omega-3, and then, what is the best way to quantify what someone's current omega-3 status is?

BILL HARRIS: Sure. That's a good place to start. So we kind of tackled this problem of how do you define somebody's omega-3 status almost 20 years ago now, and we came up with a blood test we call the omega-3 index. And that is a test that measures the amount of EPA and DHA, the two long chain omega-3s that characterize the fish oils typically. So how much EPA and DHA is in a red blood cell membrane, so it's the most common cell in the blood, easy to access, easy to get to, the omega-3s constitute a proportion of the fatty acids in the membrane, the more omega-3, more EPA and DHA a person eats, the higher the level of EPA and DHA in a red cell membrane. They pretty much replace the omega-6s, the omega-3s go up, the omega-6s go down. The omega-3 index then is expressed as a percent, so it's an EPA plus DHA as a percent of the total fatty acids in the membrane, and that will typically run from, say, 3% of total fatty acids on the low end to 10-12, even 15% we've seen. That's very unusual. The average American has around 5 to 6% omega-3 in their red cell membranes. The average Japanese around 9 to 10% EPA and

DHA, because they eat so much more fish than we do. And so, that's a major of status, one of the benefits there, and, as you mentioned Danny, there are many ways to measure omega-3 levels in the blood. And so, they can be done on dry blood spots, it can be done in plasma, it can be done in some of the lipid classes in plasma like phospholipids or cholesterol esters. Those are all places where you can measure omega-3 levels, and they pretty well correlate with each other fairly well. We think the red blood cell is the best way to do it, simply because it's the most stable over time within a given person. So there's not much – it's very much like hemoglobin A1C in measuring glycemic status diabetics. It's better than plasma glucose, which goes up and down a lot, hemoglobin A1C, which is measured in red blood cells, and expressed as a percent. That's a much more stable long term look at glycemic status. We're interested in omega-3 status, and we use the red blood cell to do the same thing. Again, the red cell changes very slowly, relatively slowly. If you want to see a really fast change in omega-3 levels FTC, increase your omega-3 intake, it'll reflect first in the plasma, but within a few weeks, three months to four months, it will eventually stabilize and the red blood cell level will come up to a new steady state, since it takes about four months for all the red blood cells to turn over. And so, that's what we kind of look at that three to four month.

DANNY LENNON: Yeah, and that throws up a couple of interesting things that I'm just going to open a tab on that we might circle back to later on, particularly, in the context of looking at the impact of certain interventions on health outcomes, and we look at very short term studies, knowing the kind of maybe expression of something like DHA in different cell membranes and so on is important to bear in mind. But for now, you've mentioned that we have this omega-3 index that can give us an indication of someone's status, it's relatively stable, it's measured as percent. In terms of

giving people an idea of relative to that average figure of maybe 5-6% in the population, is there a kind of clear set of guidelines we currently have now on what is advised for certain health outcomes, of seeing something around for cardiovascular disease, in particular, it seems to be something around 8% or above seems to be this kind of threshold where we see a lot of risk reduction, is that something that is replicated? Is there disagreement amongst what a target omega-3 index may be? What's the kind of lay on the land there?

BILL HARRIS: It certainly was defined early, when we first published our paper in 2004, where we kind of created the omega-3 index, and proposed that it would be a risk factor for, as you say, cardiovascular disease, we chose 8% based on the data that was available at that time, and it's held up really quite well I think, whether it's 7%-9%, it really isn't a threshold in the sense that, if you're at 7%, you're at much higher risk than you're at 8%. It's very much gradient, which you would expect. So if we see people get up to 7%, they're concerned that they're not at 8%, it's okay, 7% is way better than 4%. So it is a gradient. We think that even for mental health outcomes, it looks like roughly 8%, it would kind of make sense that there is sort of a sweet spot for all health across the board, whether it's hard brain, just general longevity, etc., anti-inflammatory properties. I think that 8% to 12% range is a really good range to be in.

DANNY LENNON: How reliably or repeatably can we see a certain change in someone's omega-3 index with, say, a certain intervention? In other words, how much interindividual variability do we see in response to either food intake or supplementation, and how that will actually affect that end number?

BILL HARRIS: It varies a lot, surprisingly. If you look in aggregate at large groups of people, taking more omega-3 definitely dries up the omega-3 index, no question. But any given person's

change in a response, say, to taking one or two grams of EPA and DHA seems to vary quite a bit. We've seen people that you give them like a gram and a half of EPA DHA, and their omega-3 index goes from 4% to 8%, which is great. That's what we expect. Some people go from 4% to 5%. Some go from 4% to 10%. What it is about the response, I mean, I think it's fascinating that there is that much variability, but it appears to be there even in controlled studies, where compliance has been guaranteed. We know that there's quite a – so that's an area of research, I think, in the future is to decide how much a given person needs to take to get to a certain omega-3 index. It's got to be genetic factors.

DANNY LENNON: Of course, as with everything, genetics plays a huge role. So let's dive in maybe specifically into heart disease, because this has been traditionally where a lot of the research has been focused. We, of course, from, nutritional epidemiology, see a relatively kind of consistent finding of those with higher fatty fish consumption, or even if we go and look at the omega-3 index, those with higher omega-3 index relative to much lower tend to have reduced risk of coronary heart disease or cardiac events. You tend to see general recommendations that are consistent across a lot of guidelines around the number of servings per week of oily fish that are recommended for this risk reduction, and then, that kind of translates to a certain amount of EPA and DHA. So before we get into either the nutrition interventions or probably, more interestingly, the recent supplement trials, can you maybe just explain what the mechanism maybe, that we're seeing this association between higher omega-3 status or higher fatty fish consumption, and then, lower cardiovascular disease events or mortality, what are the main mechanisms put forward as to why we get this risk reduction?

BILL HARRIS: Yeah, and that's – it's quite a list of different types of mechanisms that the omega-3s – that

explain why omega-3s lower risk for a variety of outcomes, including total risk for death, for example, and total mortality. I think probably at the top of the list these days is an anti-inflammatory effect, where the omega-3 fatty acids not only will slow the initial inflammatory response to an insult of some sort, or an injury, or an infection, but they will also help turn off excess inflammation after the initial cycle has taken its proper course to increase inflammation, deal with the problem, and then the inflammatory markers will go down faster if you've got omega-3s on board. So there's an anti-inflammatory, pro-inflammation resolution sort of effect. There's also the kind of classic omega-3s, higher omega-3 associated with lower levels of triglycerides in the blood, and that's one of the, of course, lipoprotein risk factors, the omega-3s also will affect the way platelets function, and that makes your blood a little bit thinner. It's like taking aspirin in a way, it's safer than aspirin, but the same idea that the blood is less likely to clot inappropriately, which can cause, of course, a heart attack or a stroke. Those factors are there. Plus, we think the omega-3s also do something to the autonomic nervous system, particularly as is seen in the heart where just resting heart rate is lower in people with higher omega-3 levels, and that is something that's seen in a randomized trials as well as observational studies. So a slower heartbeat is a sign of a healthier heart to a point, of course. And so, those are some of the general mechanisms by which we think they're operating.

DANNY LENNON: I find omega-3s, and particularly the heart disease story, a really useful example in nutrition science that we see replicated in other places where we have a certain association found in epidemiology with a certain type of food, and we kind of look at the kind of main nutrient of interest there, and then we try and look at supplement trials, and then sometimes we see maybe some conflicting results. And in the case of omega-3 supplementation, we see a

really interesting story where we have conflicting results in the sense, at least, initially, on the initial look, it seems conflicting, of some trials having this really, really positive effect, and then, someone else will point to another trial that seems to show either no effect, or, at least, it doesn't have the same degree of effect. And this kind of story has really exploded over the last number of years, because we've seen, in a series, a number of really big omega-3 supplementation trials, whether that's VITAL, ASCEND, REDUCE-IT, STRENGTH, all that kind of came in kind of short succession, seeing some differences that are worth digging into the details here. So I don't know where the best place to start is here, but given that we see this kind of conflicting surface of reporting of different results here, there's probably a few key places that explain why we're seeing really positive effects in one place, null findings in the other. So of maybe those trials or others that you think is a good starting place, how do we start working through these really important, really large trials, and working out what exactly that data is telling us?

BILL HARRIS: Yeah, it's a long story, as you imply, because back in the late 80s and the 90s, it was really clear as we started doing randomized trials with omega-3 with cardiovascular disease and endpoint, that they were becoming, it was very clear, they were very effective. The GC prevention trial, the dark trial, jealous trial, and even just the heart failure, were all positive great trials. And then, people started trying to replicate the trials in the first decade of the 2000s, and then, in the 20 teens, I guess. And several trials were not replicating, were not showing the same result, and people were going, well, what happened. And I think part – many things happened, number one, background omega-3 intake is going up in the population in large. So that reduces the, of course, with omega-3s, you're not giving a product like you are with a drug that does not exist in the placebo group. Placebo group has

omega-3, just at different levels than the intervention group. And so, as the background levels go up, the difference between the active and the placebo is less and less in terms of blood levels. Also, just a general idea of taking people, and, I guess, the other thing to mention is what's happened over the last 20 or 30 years in cardiovascular disease is we've developed better drugs, better treatments, reducing the risk for serious adverse events of heart attacks, have made studies that have tried to reduce, you know, when you add omega-3 onto a statin, you're not going to get the same benefit, you're not going to see it as clearly as you put omega-3 versus placebo, and there's no statin in the background.

So concomitant drug therapy is another thing that's changed over time, and made the omega-3s appear to be less beneficial. Doses are kind of low, typically, now around 800 milligrams, 900 milligrams of EPA and DHA is what's been used in many of those trials. And I think that's just too low, given the background of these other drugs that people are on. Another thing is the fact that we're taking people that are getting these trials are typically in their mid-60s, they've already got existing disease, they're certainly at high risk for disease, so trying to turn – and then, they're studied for maybe four or five years – and so, we're trying to turn around this battleship that's spent 60 years going in the wrong direction, we're going to do it with less than a gram of omega-3 on top of other drugs, and do it in less than five years. Well, it's just asking a lot for the nutrient. I mean, I think we're looking – we need to look at omega-3s as a lifelong, not a lifelong nutrient, a life, not something just to be given to the end of life to try to improve things. We want a high omega-3 index from minus nine months of age, all the way through. And when you look at that net population Epi, that's the kind of stuff we can see in more of the epidemiologic studies than the intervention studies. But I think these intervention studies fail, largely because they don't treat people

soon enough, they don't give them enough omega-3, and they do it on the background of other drugs that people are already reducing cardiovascular risk.

DANNY LENNON: Yeah, and I just want to reiterate a few things that you've said there, because they're really important for even people that want to critically analyze research generally across nutritional or health science, and there's some really important kind of meta lessons from that. One that you mentioned was around this increased kind of background fish intake within the population, and you made a really important point that we try and emphasize a lot here in relation to nutrition studies that there is no zero nutrient exposure in the same way that we would have with a drug. And so, you start getting into trouble when you start trying to look at some of these nutrient trials in the same way you would look at biomedical trials typically. You also mentioned that because treatments have got better, this may be a problem, and again, I suppose, from one side, it's great for people that there are less events and less people dying, but from a research point of view, that kind of tends to play havoc with your kind of effect size and so on.

BILL HARRIS: Right.

DANNY LENNON: And then, this intervention duration is particularly interesting and most poignant, because we're talking about heart disease, and when we think of that time course that you mentioned, we know that this is a cumulative exposure for a lot of these processes related to cardiovascular disease that happened over decades. And so, thinking that we can intervene and see some results in a short period of time is problematic. So with that, I did want to ask about a couple of those trials specifically, because I think they serve as a good example of what we've just said, and, I suppose, two of the big ones that get put forward on either side is, on one side, we have something like the REDUCE-IT trial where we

see these really big effect sizes, we see these massive results that seem to be completely change the game, and this could be a really, really important finding; and then, on the other side, the one that probably most people tend to look at then is something like VITAL where the most common, I suppose, at least, mainstream reporting of that is that there are null finding. And that's people, what they think of that, although there is probably some nuance to that. And there's some important differences in each of these trials that relate to some of the things you just said, one is around dose, so maybe if we start with the REDUCE-IT trial, could you maybe just give people an overview of some of the important things to know about that trial in terms of dose, some of those findings, etc., and then, we'll be able to compare it then with something like VITAL maybe in a few moments?

BILL HARRIS: Sure, yeah, REDUCE-IT was a trial that was done with a product called Vascepa, which is an EPA only product, doesn't have DHA in it. It's a drug that's been used in Japan for decades, but it's brought to the United States relatively recently. So that's one important factor, it's just EPA. Number two, it was a four grams of EPA, it was a five or six times higher dose than most studies done with omega-3s. It picked people that were high risk for cardiovascular disease, which is very typical for these trials, because they want to get as many events as they can too, and with as few people in a shorter period of time, because it's cheaper to get the drug approved that way. Another very important piece of the REDUCE-IT trial was that they used a placebo that's been kind of controversial. The placebo in their trial was not a vegetable oil or corn oil or soybean oil or something, but it was mineral oil, so it's not absorbed, which at one level is fine. But there's been considerable concern that the mineral oil actually made the placebo group look worse than they would otherwise have looked, which magnified the difference between the treatment group and the placebo group, because typically,

a placebo is supposed to be completely inactive, do nothing to risk. And there's been a fair amount of concern that some of the apparent benefit of EPA, and this was a very beneficial trial, as you mentioned, 25% reduction in risk for just about every adverse outcome in cardiovascular disease, which is great, but if it's caused in part by the placebo group getting worse, then you can't attribute all of that to the EPA. So it's been very controversial in that light. But it was an effective study and vital, if we can jump over to that, they had used a much lower dose, EPA plus DHA of about 880 milligrams. So that's about fivefold lower dose than just the EPA and reduce it. They used a, I think, more proper placebo, a vegetable oil based placebo, one capsule a day, which is going to do nothing, that's a very little dose of the non-omega-3 oils.

VITAL had 25,000 people in it, compared to 8000 people in REDUCE-IT. VITAL was also a study that was done in relatively healthy, you couldn't have heart disease at baseline, you couldn't have cancer at baseline. So it was not, unlike REDUCE-IT, it was not a high risk population. It was average American risk, which is somewhat still argued as high risk, but it's a different group. And in VITAL, I went five years. You're right that the, if you read the abstract of the study, it says that vital was – omega-3s did not reduce risk for the primary endpoint of the trial, which was a composite endpoint, which means that a non-composite endpoint would be something like the endpoint of this trial is number of heart attacks that the group has. That's very clear; or it's number of people that have a stroke, that's a single clear; or it's the number of people that die of cardiovascular disease, that's a very simple endpoint. But what they did in VITAL, and they do in many studies, they do composites, so if you had a heart attack, or if you had a stroke, or if you develop cardiovascular disease, or if you developed, you know, those are the primary ones, fatal, non-fatal stroke; fatal, non-fatal cardiovascular disease, heart attacks,

all bunched together into one endpoint. And the omega-3s did not significantly reduce the risk for that endpoint. But if you look at different elements of that endpoint, like heart attacks, myocardial infarctions, there was a significant reduction in risk for myocardial infarction in the omega-3 group, but the other components of that metric, stroke, fatal or non-fatal didn't change, and so washed out they blocked the effect, the visible effect of the heart attack. So that's the problem with using composite endpoints, where there may be some element of the outcome that really was important and was affected, but it gets lost in the wash of all these other endpoints that weren't affected.

DANNY LENNON: Yeah, and so, there's a couple of really important points there, and again, let me kind of try and reiterate them. You mentioned with VITAL here, we have this composite of these three different kind of endpoints, and when you look at those individually, when you look at myocardial infarction, specifically, you see this reduction, but once you pull the three of them together, then this is what gives rise this overall null effect. And so, this is where, yeah, at a surface level, there may be null effect, but that's just a reflection of what was chosen as that kind of primary endpoint as opposed to specific outcomes that may be of interest to us. And this is something that actually rears its head in some of the other studies that have similarly been reported as null findings. I think ASCEND had a kind of similar issue. The STRENGTH trial which was kind of more in line with the dose used in REDUCE-IT, but again, no significant difference, when it was, again, a composite of cardiovascular events. So given that there's all these nuances between dose, what kind of outcomes were selected, differences in placebos used, at the end, people are kind of like, okay, where are we now in terms of omega-3 supplementation and heart disease. And I think you can probably find a variety of different opinions. But, in your view, what is the most evidence based conclusion we

can come to right now based on all these trials taken together, and then, other lines of evidence that may indicate where we are of what exactly omega-3 supplementation specifically may do in the context of heart disease risk reduction? And we can also maybe put a few caveats on that in terms of what type we're talking about, so dose, pharmaceutical grade versus typical consumer products, etc. What are some of that kind of initial list of recommendations you think are evidence based to make as things currently stand?

BILL HARRIS: Well, I think you can't make – you can't put all of your eggs in a randomized controlled trial bucket. You can't decide whether omega-3s are good for your heart, writ large over your whole life, from a trial that's done at the end of life, for a lot of people who are high risk. That's a problem. So you need to look at other forms, I mean, they're not irrelevant, but they certainly need to be looked at in the context of also the prospective population based studies that look at omega-3 intake, or better yet, look at omega-3 blood levels, and follow then people over decades of life, and see who has the lowest risk for heart disease, for cancer, for death from anything. And in those studies, we see that very clearly a higher omega-3 level, higher omega-3 index, whatever metric you want to use, is clearly associated with a 10 to 15% lower risk of cardiovascular events, total mortality, cancer events, etc., even non-cancer, non-heart disease death is reduced. When people have high omega-3 for a long time, and we're only talking maybe a 15-year follow-up, 15 to 20-year follow-up, if you really could know omega-3 levels in people in their 20s, and do a 60-year follow-up, I think it would be even clearer that having a high omega-3 for a long time is very good for your health. So what I think is people need to stop thinking about the omega-3s as a drug to treat an acute problem, it's a nutrient that's going to reduce your risk for all kinds of inflammation based diseases going forward. And so, supplementation or eating fish I think is still a very good thing to do, but to start in

your 20s or 30s or teens, if you can, to get your omega-3 index up to that 8% level is fantastic. You could hold it up there for decades, I don't think it's any question that that's going to be very good for your long term health.

DANNY LENNON: With that, I think, probably the recommendation in food based terms is often easier to make or, at least, there's less resistance to people hearing of typical recommendations of one to two maybe servings of oily fish, for example, when it comes to supplementation, one of the, I suppose, potential concerns that I've recently seen and I don't think I've been able to find a good reason as to explain this finding, but it appeared in some of those high dose supplement trials that we just mentioned; and I think last year, there was actually a meta-analysis by Lombardi and colleagues that looked at those trials together, and suggested that, for whatever reason, that supplementation seemed to increase the risk of atrial fibrillation, without really being able to pinpoint what exactly is going on, we're just seeing this kind of finding, and noting that previous to that, in past papers, we've often seen an anti-arrhythmic effects of omega-3. So kind of seeing it in a positive light, and now, there's been recently this kind of speculation around increasing risk of atrial fibrillation from some of these findings. What is your take on those findings in those different studies, and that particular issue right now, is there any light that you can shed on that for me?

BILL HARRIS: Well, right, it kind of popped up first with REDUCE-IT, and then, it was seen, to some extent, in a couple of other trials; it's not been seen in different trials. And whether it's because of the high dose of omega-3, whether it's the type of people they're using, we need to keep in mind that we're talking about a risk for AFib, going from maybe 2% of the population to 3%. So, I mean, this is not, we're not talking about something that's happening a lot, but still, it's surprising and it's concerning. I will say that we are working on a study right now,

getting ready to submit it, looking again at blood levels of omega-3 fatty acids across maybe 20 different cohorts, different population groups, and follow it up for 10 to 15 years for looking to see if people who have higher omega-3 levels at baseline are at higher risk for developing AFib over time. So outside of the context of a randomized trial, but in an observational biomarker based study, and we're finding that, number one, there's no increased risk for AFib; in fact, there's lower risk for AFib in people that have higher omega-3 levels in their blood, and for the long term. So I think this is going to help clarify a little bit or at least give people some assurance that within the normal ranges of omega-3 that we see in populations, higher levels of omega-3 are good. Now, whether taking four grams a day of EPA increases risk for AFib, that needs to be studied further because that drug is out there. But the exact mechanism – you alluded to previous studies saying there's lower risk, and that was typically for ventricular fibrillation, not atrial fibrillation, so there's a difference in the type of fibrillation. A big study was done 10-15 years ago, trying to actually reduce risk for AFib in a randomized trial, and they did not find omega-3s were able to reduce risk, but they didn't see any increased risk either. So it's a new mystery, we haven't figured it out yet, but people are digging away at it. I don't think it's any reason certainly from the population, from a nutritional point of view, not to take more omega-3, because that data says it's good for your heart and reduces risk for AFib.

DANNY LENNON: Sure. Maybe the final thing I'll ask about in relation to cardiovascular disease risk reduction is given the fact that there's been these trials that have used high dose EPA only, for better or worse, there's been a kind of reputation then that some people have ascribed to EPA being the one that is having this impact on cardiovascular health, however, we know that DHA obviously significantly impacts that omega-3 index which we're seeing these associations for. So what do you think is the

most accurate way for people to think about EPA and DHA and their roles in cardiovascular health overall?

BILL HARRIS: I think they're really partners, I think they work together very well. The whole, you know, the company that makes Vascepa, that's the EPA only product, has been very keen to vilify DHA to say that, oh, the reason why REDUCE-IT worked with EPA only is because it didn't have DHA, and DHA is bad effects. Well, that's a complete – your completely data free assertion, trying to make DHA containing products look bad, which is their competitors, of course. But there's no evidence for that. There really is no evidence for that, DHA, when they're compared head to head, EPA versus DHA, and you look at effects on cardiovascular risk factors, DHA affects many of them favorably, EPA affects many of them favorably, but neither one of them is adversely affecting cardiovascular, whether it's an inflammation or lipids, or blood pressure, or heart rate, or any of those things, they always seem to be down with either EPA or DHA and not increased by either one of them. So I definitely think the EPA and DHA come naturally together in fish; to me, they're supposed to be there, there's a purpose for having them together; and for supplementation, I really recommend having both of them.

DANNY LENNON: We see almost the converse get discussed in relation to things like brain health, cognition in later life, early child development, in which most of the interest generated tends to look at DHA primarily, although there is obviously a lot on omega-3s generally, but DHA tends to be a focus there, because of this known role of DHA in brain function, brain development and so on. In relation to this area overall of DHA, or we can even talk about omega-3s generally, and its role in the brain, which relates to cognition throughout life, and particularly that kind of crucial importance that you've already mentioned of early in life, even pre-birth during pregnancy, what are some of the most

important things for people to know about how it plays a role in these different areas?

BILL HARRIS: Yeah, above the neck versus below the neck, is the kind of how you think about it, right. And you're right, the focus on DHA for the brain originally came from the discovery that the primary omega-3 fatty acid, and one of the main polyunsaturated fatty acids in the brains is DHA, virtually no EPA in the brain. And so, the logical conclusion was, well, let's give people DHA if we want to make their brain work better; and it's not an irrational approach, it's just it's turned out that, number one, you can think about above the neck of brain issues; one is dementia, the whole, that loss of cognitive function, Alzheimer's disease, etc. Another side of it is mental disorders, which is not dementia, it's like bipolar disease, depression, these sorts of things, and they're completely different diseases, mechanistically completely different. And so, people have looked at, it's been easy to study things like depression, because the symptomatology is very well characterized – so people have done many studies of giving EPA and DHA in various ratios in people who are depressed, and they surprisingly found out that it looked like the more effective products for those that had higher ratio of EPA, more EPA than DHA in terms of reducing symptoms of depression, which was a surprise, people thought it would be DHA. But that's what you do science for, you do these experiments to find these things out. Now, why that would be, it could be an anti-inflammatory effect of EPA, because EPA, again, is not structurally present in the brain, it certainly circulates in the brain through the blood and through the capillaries, and so, there could be an anti-inflammatory effect there.

When you look at the other side of things, cognitive function, loss of – development of dementia or Alzheimer's disease, it looks like, first of all, it's much harder to study than is something like depression or bipolar. And because it takes so long to develop, and so,

that's where nutritional epidemiology can step in, and we are beginning to see, we're getting ready to again submit a paper looking in the Framingham study at the relationship between the omega-3 index, really actually DHA, as it turns out, red cell DHA is pretty strongly correlated with – inversely correlated, higher levels of red cell DHA predict a lower rate of developing dementia or Alzheimer's disease in Framingham. And this is a second study that's – two different Framingham cohorts are now seeing the same thing. So having a higher level of red cell DHA or having higher DHA status does look like it is associated with, can't say it causes, it's associated with lower, slower loss of cognitive function. And again, that 8%, looks like it'd be a reasonable target to achieve that.

DANNY LENNON: Yeah, one of the reasons I ask this, and it's, I suppose, one of these questions now debated a lot within nutrition circles, when it comes to omega-3 and particularly getting direct sources of EPA and DHA relates to those who may be other don't consume fish, or who are following, say, a vegan diet and vegan lifestyle, and therefore, won't even consume an omega-3 supplement from a fish oil, now that, of course, there are vegan friendly versions of that from algae and so on. But the question then comes up, if someone is following a plant based diet, and is not getting sources of EPA, DHA, is that putting them at increased risk, because, I suppose, on one side, someone will say, well, look, we can get a source of omega-3 through ALA in various different plants, and we can convert some of that in the body. Then we get into this whole discussion around conversion rates and how much actually gets converted, and what is going to be useful. So with this kind of whole area, and there's many routes we can go down here, maybe as an initial probing question to get started, do you feel, based on current evidence that a direct source of EPA and DHA is necessary for, let's say, optimal health, and I know that's a very strange term that maybe doesn't mean much. But, in other words, if someone currently doesn't have a

direct source of those, and is relying solely on ALA, would their health in any way benefit from a direct source of EPA and DHA, in your opinion?

BILL HARRIS: Yeah, I think it would, that's not to say that you don't derive benefit from higher ALA intake. But whether you say, if it's a question of just ALA or ALA plus EPA-DHA preformed, I think the evidence is pretty strong that you will do better if you take the preformed ones. But there's a recent review now, just came out on ALA and cardiovascular health, and it's, there's some evidence, reasonable evidence that it's beneficial too. Is it as beneficial as EPA plus DHA? No. But it's still, I think, optimal to try to get EPA and DHA preformed and, of course, as you alluded to, you can get these in algal forms that a vegan or a vegetarian, or somebody who's just concerned about more ecological issues, vis-à-vis fish and toxins in fish, etc. You can get algal preparations in there are more coming. And there is research on not just algal forms, but actually plant based genetically modified plants like soybean, like camelina, these are things that grow out of the ground, and they're not algae that have been genetically modified to produce EPA and DHA. So if we can get past the GMO concerns, and the time will come, and we'll be able to grow plants and harvest EPA and DHA out of them, and won't have to take any fish. So that's coming in the future.

DANNY LENNON: Yeah, and I think that's something that can be so exciting and can change something, it only becomes an important reality then when we can have some agreement on, in the first place, it's actually better to have this higher omega-3 index and have these direct sources of these fatty acids. So with that, I suppose two quick questions to recap on what you said. One is, the problem from relying on ALA is that's simply a function of it is the amount that would be needed to get an appreciable level of EPA and DHA within the body to move up to omega-3 index appropriately, it's just too great, that it's

very, very difficult to have, let's say, an omega-3 index above 8%, if you're relying solely on ALA intake. Would that be a kind of fair conclusion?

BILL HARRIS: Right.

DANNY LENNON: And then, secondly from that, you mentioned that ALA itself can have benefits, are some of those benefits unique to ALA that seem to be distinct from EPA and DHA?

BILL HARRIS: That's a great question, and I don't think we can know that. I don't think we do know that at the moment. You would have to do some pretty fancy footwork to show that the benefits of ALA are there, even in the presence of no different, no changes in EPA and DHA levels. And I'm not sure anybody's actually done that, but it could certainly be that ALA, other than being converted to EPA and DHA, has some role in biology that we haven't discovered yet, and that's certainly open to that possibility. So there's lots to do in this area.

DANNY LENNON: Let me ask kind of one final thing, because I did want to get to this topic, because I couldn't let you go without bringing this up, given your expertise in the area of fatty acids, and one thing that has, for some reason, become a topic of conversation within nutrition circles, at least, on the internet, and in the blogosphere, has been this strange demonization of omega-6 fatty acids, particularly linoleic acid tends to get focused on, and/or people talking about seed oils or vegetable oils and so on. But this, I suppose, really hyped up demonization to the point of this is the number one problem with our food supply, and you just need to get this as low as possible. Can you maybe talk to any of that type of rhetoric that you've seen, what are your kind of thoughts on how we should just accurately think of omega-6 fatty acids as a nutrient within the diet, and is there any, in your opinion, is there any validity to this real worry about having an omega-6 fatty acid intake that is above some sort of minimal level?

BILL HARRIS: Yeah, you're right, it is controversy, and it gets hot, and it's captivating for a lot of people, and it's lovely, it's fun to have a black hat and white hat, a good guy and a bad guy. And so, it's a complicated – it's not that complicated, actually. It all started out by discoveries back in the 60s and 70s that EPA, or rather that the omega-6 and omega-3 linoleic and linolenic acid compete with each other for the same enzymes for conversion to the longer chain products. So you have your higher omega-6 linoleic acid intake, you'll not convert as much ALA to EPA and DHA. Fine, that's true. And we know that typically the omega-6 derived products from arachidonic acid tend to be more proinflammatory than the ones from omega-3 fatty acids. Okay, that's true. But at the end of the day, the thing I think you need to look at is what does the epidemiology say, what does a randomized trial data say about omega-6 fatty acids; and we've looked in a consortium of 20 and 30 different studies, all put together in one big trial to look at the relationship between blood levels of linoleic acid omega-6, and risk for either cardiovascular disease or risk for diabetes over many, many years; and if the omega-6 is bad for you, hypothesis is true, then you would say, you would suppose that people have the highest levels of omega-6 linoleic acid in their blood; and don't worry about the diet, let's just look at the blood, because that's really what your tissues are exposed to; then you would say those people should be at higher risk for cardiovascular events, from proinflammatory mechanisms and for diabetes, because it's just a bad disease anyway. Unfortunately, that's not the way the evidence shows out. What we've published, it's very clear, the highest levels of linoleic acid in the blood are associated over time with lowest risk of cardiovascular disease, and the lowest risk of diabetes. So the hypothesis is not supported that omega-6 is bad, it's good. And then we look at the other omega-6 in the blood, arachidonic acid, and we see for that one, that there's no relationship between higher or lower

arachidonic, and increased risk for cardiovascular disease or diabetes. So it's kind of neutral in that regard, so the evidence, I think that's the most compelling – and again, it's hard to do randomized trials, long term, changing omega-6 and omega-3 or omega-6 levels. There's so much of it in our diet, it's very hard. So that evidence that prospective biomarker based epidemiology, linking higher levels of linoleic acid to better outcomes with the major diseases of our culture, says to me that the burden of proof is on those who would say it's bad for you, to tell me why these data should be ignored. And people don't, you know, people who hate omega 6 don't want to go there, they only want to talk about it; because all they want to do is point to some other study in a rat where higher omega-6 was bad for the rat. Okay, fine. Let's focus people, look right, look at the data that we have, and tell me why that should not be compelling evidence that a higher linoleic acid is better for you than low.

DANNY LENNON: Yeah, there's nothing more to add to that, I don't think.

BILL HARRIS: Yeah.

DANNY LENNON: Dr. Harris, before I let you go, is there any place on the internet you would like to have people's attention, where they can find either more of your work, anything you'd be involved with or anything that might be of use?

BILL HARRIS: Sure. Yeah, about a year and a half ago, we started a new nonprofit research organization called the Fatty Acid Research Institute, FARI; and we have certainly links to my bibliography and some of the work that we've done, you can find that there, and the URL is www.faresinst.com, so that's the Fatty Acid Resources Institute. You can just Google my name, and you'll find it too, that's probably the easiest thing. And also, OmegaQuant Analytics is the laboratory that we founded some 12 years ago now that analyzes omega-3, and there's a lot of data, and a lot of podcasts, and a lot of,

variety of – a lot of information there about omega-3s, at omegaquant.com.

DANNY LENNON: Fantastic. And for everyone listening, they will be linked in the show notes of this episodes, you can go and click through to those. With that, Dr. Harris, I'll leave you this final question, very quick one, to do with anything even outside of what we've discussed today. And it's very simply: if you could advise people to do one thing each day that would have a positive impact on any area of their life, what might that one thing be? And apologies for putting you on the spot with such a broad, generic question, but I would be interested to see what the first thing that comes to mind is.

BILL HARRIS: Well, I mean, I am kind of a one-trick pony, when it comes to those, because, to me, the biggest nutritional deficit we have in America is omega-3, EPA and DHA. So if people can simply focus on getting enough EPA and DHA, whether it's fish or supplements in their diet, that would be the one single thing. It's not going to cure every disease, but it's the one single thing I would do to improve health.

DANNY LENNON: Fantastic. Dr. Harris, thank you so much for giving up your time today to come and talk to me, and thank you for all the information you've given. It's been a pleasure.

BILL HARRIS: Great questions, Danny, you're much more up to date on the background of this stuff than most people I talk to, so nice job.

DANNY LENNON: Oh, very kind. Thank you.

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